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THE FIMBRIA-FORNIX/CINGULAR BUNDLE PATHWAYS: A REVIEW OF NEUROCHEMICAL AND BEHAVIOURAL APPROACHES USING LESIONS AND TRANSPLANTATION TECHNIQUES

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Abstract—Extensive lesions of the fimbria-fornix pathways and the cingular bundle deprive the hippocampus of a substantial part of its cholinergic, noradrenergic and serotonergic afferents and, among several other behavioural alterations, induce lasting impairment of spatial learning and memory capabilities. After a brief presentation of the neuroanatomical organization of the hippocampus and the connections relevant to the topic of this article, studies which have contributed to characterize the neurochemical and behavioural aspects of the fimbria-fornix lesion "syndrome" with lesion techniques differing by the extent, the location or the specificity of the damage produced, are reviewed. Furthermore, several compensatory changes that may occur as a reaction to hippocampal denervation (sprouting, changes in receptor sensitivity and modifications of neurotransmitter turnover in spared fibres) are described and discussed in relation with their capacity (or incapacity) to foster recovery from the lesion-induced deficits. According to this background, experiments using intrahippocampal or "parahippocampal" grafts to substitute for missing cholinergic, noradrenergic or serotonergic afferents are considered according to whether the reported findings concern neurochemical and/or behavioural effects. Taken together, these experiments suggest that appropriately chosen fetal neurons (or other cells such as, for instance, genetically-modified fibroblasts) implanted into or close to the denervated hippocampus may substitute, at least partially, for missing hippocampal afferents with a neurochemical specificity that closely depends on the neurochemical identity of the grafted neurons. Thereby, such grafts are able not only to restore some functions as they can be detected locally, namely within the hippocampus, but also to attenuate some of the behavioural (and other types of) disturbances resulting from the lesions. In some respects, also these graft-induced behavioural effects might be considered as occurring with a neurochemically-defined specificity. Nevertheless, if a graft-induced recovery of neurochemical markers in the hippocampus seems to be a prerequisite for also behavioural recovery to be observed, this neurochemical recovery is neither the one and only condition for behavioural effects to be expressed, nor is it the one and only mechanism to account for the latter effects.

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ABBREVIATIONS

Ach	acetylcholine
AChE	acetylcholinesterase
AD	Alzheimer's disease
AF64A	ethylcholine mustard aziridinium
BDNF	brain-derived neurotrophic factor
ChAT	choline acetyltransferase
CNS	central nervous system
DBB	diagonal band of Broca
DOPA	3,4-dihydroxyphenylalanine
DOPAC	3,4-dihydroxyphenylacetic acid
DSP4	N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine
ED	embryonic day (developmental age in days after fecondation)
5,6-DHT	5,6-dihydroxytryptamine
5,7-DHT	5,7-dihydroxytryptamine
GABA	gamma-aminobutyric acid
HACU	high affinity choline uptake
HASU	high affinity serotonin uptake
5-HIAA	5-hydroxyindolacetic acid
HPLC	high performance liquid chromatography
5-HT	serotonin
HVA	homovanillic acid
KCl	potassium chloride
MS	medial septum
NA	noradrenalin
NGF	nerve growth factor
6-OHDA	6-hydroxydopamine
8-OH-DPAT	8-hydroxy-2-(di-n-propylamino)tetralin
PCA	parachloroamphetamine
PCPA	parachlorophenylalanine
PD	Parkinson's disease
QNB	quinuclidinyl benzilate
TTX	tetrodotoxin

1. INTRODUCTION

The idea of having recourse to brain tissue transplantations as a potentially therapeutical means to battle with symptoms due to brain disease or injury is usually traced back to the turn of the last century (e.g. Thompson, 1890; Forssman, 1900; Saltykow, 1905; for historical reviews, see Björklund and Stenevi, 1985; Gash, 1984; Sladek and Gash, 1984). However, a few years ago, Finger (1990) has

anecdotely reported a note suggesting that this idea may be at least three hundred years older. The idea was from a patient of the French physician Ambroise Paré (1510–1590). Because this patient was convinced that his brain was rotten, he besought the king to warrant his physicians to replace his ill brain by a healthy one. If nobody would contest that this ingenuous entreaty was and still is completely unrealistic in human beings, it is nowadays extremely well established that fetal neurons can survive transplantation in the central nervous system (CNS) of adult mammals.

Although sporadic experiments were attempted during the first six decades of the twentieth century (e.g. Björklund and Stenevi, 1985; Gash, 1984), genuine and significant progress in grafting neural tissue into the brain of adult mammals really began in the early seventies, with initial contributions of Sweedish and American research groups (e.g. Björklund and Stenevi, 1985; Gash, 1984). Within two decades, research on intracerebral grafting has undergone a radical ascent, accumulating an enormous amount of data that indisputably showed that intracerebral grafts of various anatomically- and/or neurochemically-defined fetal nervous tissues can survive and grow in the mature mammalian brain, contribute to structural reconstruction and foster functional recovery in various paradigms of brain damage. Most of these paradigms were inspired by current knowledge about the neuropathological characteristics and/or the functional disturbances associated with a series of neurodegenerative diseases in humans. For instance, 6-hydroxydopamine(6-OHDA)-induced lesions of the ascending nigrostriatal dopaminergic pathways in rats or monkeys have been used extensively as an experimental model of Parkinson's disease (PD). This lesion paradigm allowed comprehensive investigation of both the morphological features and functional effects of fetal dopaminergic neurons grafted into the denervated striatum. Although not unanimously acclaimed (e.g. Landau, 1990), the successes encountered by such approaches in animals rapidly led to the application of surgical grafting techniques in patients with PD (e.g. Lindvall, 1989, 1994a, 1994b; Lindvall *et al.*, 1990; Quinn, 1990).

Other types of brain lesions were developped and utilized as an experimental paradigm of Alzheimer's disease (AD). These lesions, which mainly consisted of depriving major central cholinergic targets such as the hippocampus or the fronto-parietal cortex of their cholinergic innervation, were useful to investigate the effects of intrahippocampal or intracortical grafts rich in fetal cholinergic neurons. Here also, the morphological characteristics and many functional properties of such grafts have been identified. So far however, and to our knowledge, this approach has not led to clinical application of the technique in patients with AD.

As concerns the paradigm of hippocampal denervation, many experiments have addressed the problem of the functionality of intrahippocampal grafts with, in the background, the conceptual view establishing a crucial involvement of the cholinergic component of the septohippocampal pathways (see below) in spatial learning and memory functions. In numerous experiments reported so far, the hippocampus was denervated using unspecific lesion techniques (aspiration, transection or electrolysis of the septohippocampal pathways) and cholinergic neurons from the fetal basal forebrain were implanted in the hippocampus to substitute for the missing cholinergic innervation. Such unspecific lesion techniques also disrupt neurochemically-defined hippocampal afferents other than the cholinergic ones (e.g. noradrenergic, serotonergic) and the substitution for these afferents has revealed possible with grafts prepared from the locus coeruleus, a noradrenergic nucleus, or the mesencephalic raphé, a serotonergic nucleus. To address the question of the functional involvement of cholinergic, noradrenergic and serotonergic hippocampal afferents, research has also been conducted with lesion techniques using neurotoxins that produce more selective damage of neurochemically-defined cell populations. Also such more specific techniques have been utilized to explore the extent to which intrahippocampal grafts of neurons from the fetal brain could foster recovery from hippocampal dysfunctions.

The major topic of this article is to review the studies which used intrahippocampal grafts rich in cholinergic, noradrenergic and/or serotonergic neurons in order to characterize their effects from both a neurochemical and behavioural point of view. After a brief presentation of the neuroanatomical organization of the hippocampus, its principal connected structures and the relevant pathways, we will consider the hippocampal denervation paradigms relying upon anatomically- or neurochemically-defined lesion techniques of/in the fimbria, the fornix and the overlying cingular bundle in the rat. These lesion paradigms are described according to: (i) their neurochemical consequences in the hippocampus; (ii) the structural and functional compensatory or reactive changes which may occur spontaneously over the postsurgical survival time; (iii) the behavioural (essentially cognitive)modifications which they produce. Each of these modifications may be used as a control in assessing the functional effects of various types of grafts placed into the denervated hippocampus. These effects are dealt with in the following section with distinction made according to the neurochemical specificity of the grafted cell preparations (cholinergic, noradrenergic, serotonergic and co-grafts) and, within each of these categories, according to whether the reported findings concern neurochemical or behavioural effects. In the last part of this article, the extent to which the neurochemical effects of the grafts may contribute to the aleviation of some behavioural dysfunctions induced by various types of lesions is discussed briefly.

2. NEUROANATOMICAL CONSIDERATIONS AND PRELIMINARIES

2.1. The Hippocampus

In the adult rat, the hippocampus (i.e. the dentate gyrus and the Ammon's horn, see below) is a large,

complex and layered sausage-shaped allocortical structure (Fig. 1A), measuring approximately 10 mm in the anteroposterior plan, 3.5 mm in the mediolateral plan and 1.5 mm in the dorsoventral one. Its anterior extremity, also called the septal pole, is localized dorsally in the brain and is contiguous to its contralateral homologue. Laying just behind the septal region, right above the dorsal thalamus and underneath the corpus callosum, the anterior extremity of the hippocampus is dorsally and laterally bordered by the parietal cortex. From there, the hippocampus bends both ventrally and laterally up to a posterior extremity, also designated as the temporal pole. This extremity is anatomically separated from its controlateral homologue, extends up to the ventrolaterally located amygdaloid area and, roughly, is bordered dorsolaterally by part of the occipital, temporal and perirhinal cortex and, more ventrally, by the entorhinal cortex.

Typically, the hippocampus consists in two U-shaped interlocking subregions (Fig. 1B) which can be identified over the whole anteroposterior extent of the structure. One, called *cornu Ammonis* or "the hippocampus proper" is usually further divided into four subregions that Lorente de No (1934) has designated as regions CA1, CA2, CA3, CA4 on the basis of more or less subtil neuroanatomical differences in terms of cell morphology and/or fibre projections. In the *cornu Ammonis*, the main population of neurons is constituted by large cells having pyramid-like characteristics. The other U-shaped region is called the *gyrus dentatus*. It is subdivided in a molecular zone, a granule cell zone and a zone of polymorphic cells (the hilus). Both the pyramidal and granule cells are organized in a compact layer of cell bodies which almost strictly parallels the external border of its respective U-shaped subregion.

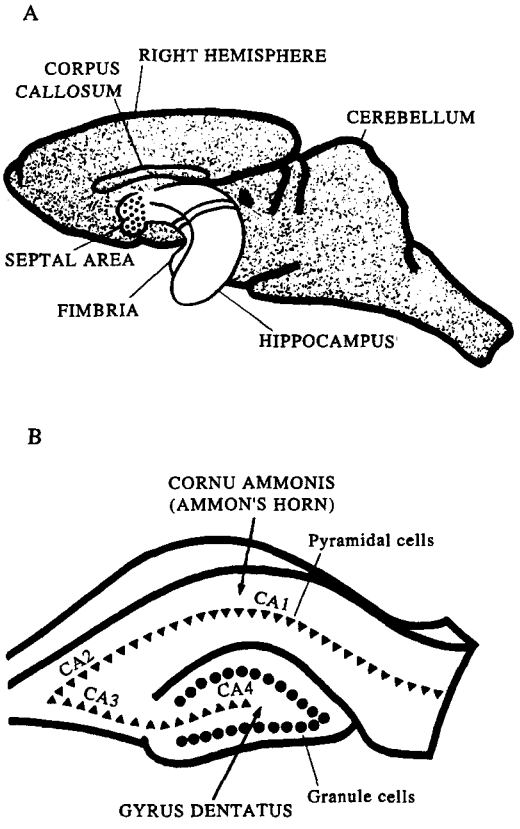

Fig. 1. (A) shows a drawing of a sagittal view of the rat brain previously deprived of all left forebrain structures (right hemisphere, colliculi, cerebellum,... in greyish are intact) in order to free the left hippocampus (curved blanck structure with the fimbria in the concave part) which is in contact with the septal are (stippled structure). (B) shows a drawing of a transverse section through the hippocampus at the level indicated in (A) by the arrow. (A) and (B) are redrawn after O'Keefe and Nadel (1978).

Beside the fibres constituting a dense intrinsic connection circuitry (intra- and inter-hippocampal connectivity networks), one may distinguish fibres connecting the hippocampus to other target regions of the brain (efferents) and fibres connecting several source structures to the hippocampus (afferents). Although most hippocampal efferents originate in the subicular complex (in which they relay), it may be reasonably accepted that the main hippocampal (indirect) efferents project to the lateral preoptic and hypothalamic areas, the septal region, the nucleus accumbens, the thalamus, the mamillary bodies, the rostral midbrain as well as on both the subiculum and the entorhinal cortex. Most of these terminals may use or are likely using glutamate as their neurotransmitter. The main afferents originate in the medial septum (MS) and the diagonal band of Broca (DBB: Cholinergic and GABAergic fibres), the *raphe* nuclei (serotonergic fibres), the *locus coeruleus* (noradrenergic fibres) and the entorhinal cortex (glutamatergic fibres). To review the entire hippocampal connectivity is beyond the scope of this review. The systems considered hereafter have been selected because of their importance in the transplantation experiments considered in this article. Actually, in most studies using intrahippocampal transplants in order to substitute for missing afferents, the cell preparations that have been implanted were rich in cholinergic, noradrenergic and/or serotonergic neurons. Thus, among all the structures connected to the hippocampus, the ones selected according to the topic of the present review are the septal area (used to designate both the MS and the DBB in the following), the *locus coeruleus* and the *raphe* nuclei, with particular focus on the cholinergic, noradrenergic and serotonergic innervation of the hippocampus. The GABAergic afferents from the septal region have not been studied as extensively as the three other types of afferents coursing rostrally and will be considered briefly in a separate section (Section 2.5).

2.2. The Hippocampal Cholinergic, Noradrenergic and Serotonergic Afferents: Sources

The cholinergic innervation of the hippocampus mainly originates in three major cholinergic nuclei of the basal forebrain, namely the MS (Ch1 in the nomenclature of Mesulam *et al.*, 1983) and both the vertical (Ch2) and the horizontal (Ch3) limbs of the DBB. A few cholinergic terminals (less than 10% of the entire hippocampal cholinergic innervation) are from interneurons located within the hippocampus,

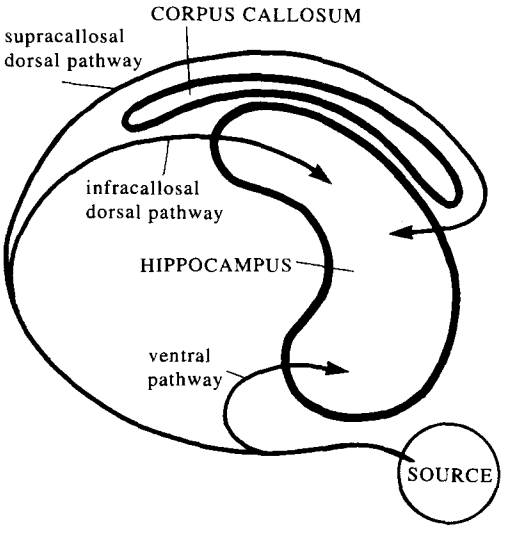

Fig. 2. Schematic drawing of a parasagittal view of the hippocampus and distribution of the main afferent routes through which the cholinergic, noradrenergic and serotonergic axons reach the hippocampus (source is referring to the medial septum/diagonal band of Broca, the locus coeruleus and the mesencephalic raphe, respectively).

most of which being found in the stratum lacunosum-moleculare of region CA1 (e.g. Frotscher, 1988). The noradrenergic innervation is exclusively of extrinsic origin and arises from neurons located in the dorsal part of the locus coeruleus (A6 in the nomenclature of Dahlström and Fuxe, 1964). Also the serotonergic innervation is exclusively of extrinsic origin. In majority, it arises from brain stem neurons located in the median *raphe* nucleus (B5 and B8 in the nomenclature of Dahlström and Fuxe, 1964), the remaining part originating in neurons from the dorsal *raphe* nucleus (B6 and B7). Conversely to the aforementioned basal forebrain nuclei which principally if not exclusively innervate the hippocampus, the locus coeruleus and the *raphe* nuclei provide massive innervation to several brain regions other than the hippocampus (e.g. cortex, spinal cord, thalamus, etc.).

2.3. The Hippocampal Cholinergic, Noradrenergic and Serotonergic Afferents: Pathways and Fibre Dispatching

It is now well established that the hippocampal afferents from the septal area, the locus coeruleus and the *raphe* nuclei course in three anatomically distinct routes (Fig. 2), namely the cingular bundle (overlying the corpus callosum), the fimbria-fornix complex (infracallosal dorsal afferents) and a ventral pathway whose exact anatomical location is not well known at present but which might reach the hippocampus by passing in the vicinity of the amygdalar complex. Both the cingular bundle and the fimbria-fornix pathways will be designed herein as the rostrally coursing dorsal afferents of the hippocampus.

Since the mid-1960s, it is known that the transection of the medial forebrain bundle produces dramatic depletion of serotonergic and noradrenergic markers in the hippocampus (e.g. Moore *et al.*, 1965; Heller *et al.*, 1966; both cited in Storm-Mathisen and Guldberg, 1974), and that the disruption of the fimbria and the fornix results in cholinergic denervation of the hippocampus (Lewis *et al.*, 1967). Fuxe (1965) (cited in Storm-Mathisen and Guldberg, 1974) had already reported that the noradrenergic fibres reached the hippocampus along three distinct routes and these data were confirmed later on by other groups (e.g. Lindvall and Björklund, 1974). Whatever of these systems is considered, most fibres project on the ipsilaterally located hippocampus and only 10-15% cross the midline to innervate the controlateral hippocampus (e.g. ACh: Peterson, 1989; NA: Room *et al.*, 1981; 5-HT: Jacobs and Azmitia, 1992). Storm-Mathisen and Guldberg (1974) have reported that, just before entering the hippocampus of the rat brain, most of these three neurochemical categories of hippocampal afferents were coursing commonly in the two dorsal and in the ventral pathways. They also demonstrated that the cholinergic, noradrenergic and serotonergic innervations of the hippocampus were essentially of extrinsic origin. From their study, the authors concluded that: (i) the largest part of cholinergic afferents were coursing through the fimbria-fornix pathways (approx. 75%), the supracallosal and ventral pathways contributing only a rather small part of the cholinergic hippocampal innervation (approx. 25%); (ii) the largest part of the serotonergic afferents were located in both dorsal pathways (approx. 75%), with a majority of these fibres coursing through the fimbria-fornix (approx. 50%); (iii) more than half the noradrenergic afferents reached the hippocampus via the ventral route (approx. 60%). Part of these findings are at some variance with data reported ten years later by Gage *et al.* (1983a, 1983c)) who, using other differential lesion techniques, found the supracallosal pathways to carry 30% of the cholinergic, 45% of the noradrenergic and 50% of the serotonergic afferents, the infracallosal pathways to carry 55%, 15% and 30% of them, respectively, the ventral route being in charge of the remainders. Finally, according to data of an experiment in which we assessed the neurochemical effects of electrolytic lesions restricted to the fimbria and the dorsal fornix (Jeltsch *et al.*, 1994a), we found the infracallosal pathways to carry about 55% of the serotonergic afferents of the hippocampus and about 60% of the cholinergic ones. Due to the fact that we have not assessed the neurochemical effects of the lesions at a very short postsurgical delay and because we did not prevent sympathetic sprouting and thus the contribution of reactional ingrowth of peripheral noradrenergic fibres [see below, Section 3.2.2.2], this experiment did not allow us to assess the proportion of central noradrenergic afferents coursing through the fimbria and the dorsal fornix. These variances in the relative amounts of neurochemically-defined fibres found to course in each of the three routes are likely due to differences in the respective lesion techniques (e.g. transection, aspiration, electrolysis), dissection and tissue preparation procedures (e.g. subdivisions of the hippocampus and regions used) or other factors (e.g. species, gender, age...). However, beyond these

variances, one clear-cut and important conclusion common to all these experiments is that the majority of the cholinergic and serotonergic afferents of the hippocampus are unquestionably, although not exclusively, coursing through both dorsal pathways. This is noteworthy because, regarding the easy access to these pathways (they are superposed, separated by only the corpus callosum and lay just underneath the cortical surface), the production of massive cholinergic and serotonergic hippocampal denervations may be relying upon a rather simple and rapid surgical procedure such as, for instance, knife-cut transection or aspiration of the tissue. To complete this section, it should also be stated that, in some respects only, one finds a heterogeneity in the topographical distribution of the cell bodies from which the serotonergic and the cholinergic pathways arise. It is known at present that serotonergic fibres originating in the dorsal *raphe* nucleus reach the hippocampus by the supracallosal and the ventral pathways, whereas the fibres originating in the median nucleus reach the hippocampus by both dorsal pathways (e.g. Azmitia, 1978; Steinbusch, 1981). Also, as regards the cholinergic afferents, Peterson (1994) recently showed that cholinergic neurons in the MS and the ventromedial region of the vertical limb of the DBB project to the hippocampus via the fimbria and the dorsal fornix, whereas the fibres arising from cholinergic neurons of the dorsolateral region of the vertical limb of the DBB reach the hippocampus via the supracallosal stria. Concerning the ventral route, it seems that the cholinergic fibres arise from neurons located in the vertical and horizontal limbs of the DBB (e.g. Gage *et al.*, 1984a; Milner and Amaral, 1984).

2.4. The Hippocampal Cholinergic, Noradrenergic and Serotonergic Afferents: Terminal Fields

Although there may be some variations according to the neurotransmitter system considered, the distribution of the terminal fields of the cholinergic, noradrenergic and serotonergic hippocampal afferents are summarized herein in relation to their routes of *passage*. It is established that, in some respects, there exists a heterogeneity not only in the mediolateral distribution of these fibres (Dravid and Van Deusen, 1983, 1984; Gasser and Dravid, 1987), but also in the topographical distribution of their terminal fields within the hippocampus (e.g. Gage and Björklund, 1986b; Gage *et al.*, 1983a, 1983c; Hörtnagl *et al.*, 1991b). Overall, there is a septo-temporal gradient in the distribution of the neurochemical markers along the septo-temporal axis of the hippocampus, the lowest terminal density being found in the septal pole of the hippocampus. This gradient appears to be less pronounced regarding the cholinergic innervation (+ 30% in the ventral pole as compared to the dorsal one (e.g. Gage and Björklund, 1986b; Jeltsch *et al.*, 1994a) than for the two other innervation systems (from the septal to the temporal extremities, the noradrenergic markers exhibit a three-fold and the serotonergic ones a two-fold increase; e.g. Gage and Björklund, 1986b). Although the terminal field of the fibres coursing dorsally and ventrally are partially overlapping, it is well known that the ones coursing dorsally enter and primarily innervate the dorsal hippocampus, while the largest amount of fibres in the ventral pathway enter and innervate the ventral hippocampus. Additional distinction can be made according to whether the dorsally coursing fibres are in a medial (close to the midline: Cingular bundle and medial fimbria) or a more lateral (mainly the lateral half of the fimbria) position. Actually, Gasser and Dravid (1987) showed: (i) the cholinergic fibres coursing medially and laterally to contribute a similar proportion of hippocampal innervation provided by the dorsal pathways, with terminals distributed along the whole septo-temporal extent of the hippocampus; (ii) the noradrenergic fibres coursing medially to contribute 80% of the innervation provided by the dorsal pathways with terminal fields found exclusively in the dorsal hippocampus, while the fibres coursing laterally (20% contribution) had terminal fields exclusively in the ventral hippocampus; (iii) the serotonergic fibres coursing medially to contribute 60% of the innervation provided by the dorsal pathways, the ones coursing laterally contributing the remainder 40%, with terminals of both found along the whole septo-temporal extent of the hippocampus. If one takes into account the percentages of the dorsoventral dispatching of the fibres (Gage and Björklund, 1986b) and further subdivide them according to the mediolateral distinction introduced by Gasser and Dravid (1987), one may propose the synthetic picture shown in Table 1.

A final distinction in the terminal fields of these neurochemically-defined afferents concerns their distribution in the different hippocampal subfields or

Table 1. Distribution of the Afferents from the Septal Area (Cholinergic), the Locus Coeruleus (Noradrenergic) and the Mesencephalic Raphé Nuclei (Serotonergic) in the Dorsal Supracallosal Pathway (Supracallosal Striae), the Dorsal Infracallosal Pathway (Fimbria-Fornix Complex) and in the Ventral Route with, where Possible, Particular Distinction as to Whether the Fibres Course Close to the Midline (Medial) or More Laterally (Lateral).

	Neurotransmitter					
	Acetylcholine		Noradrenaline		Serotonin	
Pathway	Medial	Lateral	Medial	Lateral	Medial	Lateral
Supracallosal striae	30%	–	45%	–	50%	–
Fimbria-fornix	30%	25%	10%	< 5%	20%	10%
Ventral route	15%		40%		20%	

This table was constructed by further subdivision of the data reported by Gage and Björklund (1986a) on the dorsoventral distribution of these pathways and according to data reported by Gasser and Dravid (1987) on the mediolateral distribution of these fibres in the two dorsal pathways.

layers. The density of the cholinergic terminals is highest immediately underneath and above the granule cell layer in the dentate gyrus, and approximately the same picture is found around the pyramidal cell layer in the Ammon's horn. The densest noradrenergic innervation is found in the hilus of the dentate gyrus, with terminals also present in the molecular layer of the dentate gyrus as well as in regions CA1 and CA3 of the Ammon's horn where they are in close proximity to the pyramidal cell bodies and their apical dendrite. For both systems, there does not appear to be a particular relationship between the layers in which the axons establish synaptic contacts and the pathways in which they course. This is not exactly the case as concerns the serotonergic terminals (Gage and Björklund, 1986b). The axons of the supracallosal pathway synapse preferentially in the polymorphic area of the dentate gyrus and in region CA3. Those of the fimbria-fornix pathways preferentially synapse in region CA1 and, although with a weaker density, in the polymorphic area and the molecular layer of the dentate gyrus. Finally, the axons of the ventral route synapse primarily in the molecular layer of the dentate gyrus.

2.5. The Hippocampal GABAergic Afferents: A Few Words

Kiss *et al.* (1990) reported the MS and the DBB to contain many neurones immunostained for parvalbumine, a calcium-binding membrane protein which is specific of a subpopulation of GABAergic neurons. That these septal GABAergic neurons project to the hippocampus has been demonstrated by Köhler *et al.* (1984) and, later on, by Freund and Antal (1988). In their article, the latter authors describe some morphological features of the GABAergic terminals which, in virtually all regions of the hippocampus, show large and multiple *en passant* boutons. More recently, Freund (1992) showed that the GABAergic terminals in the hippocampus preferentially synapse with inhibitory interneurons of the hippocampus (see also Freund and Antal, 1988). The anatomical distribution of the GABAergic fibres is not as well characterized as is the distribution of the three aforementioned neurotransmitter systems, but it is possible that part of it reach the hippocampus via the same pathways as those of the other fibres.

2.6. Conclusions and Summary

The hippocampus appears to be a well characterized structure of the telencephalon, both from a morphological and a neurochemical point of view (but also a few other structural and functional ones), and whether it is considered on the side of its intrinsic architectural organization, or examined on that of its connectivity network with other brain structures. This is a major advantage when one wishes to set up lesion paradigms in order not only to investigate the structural links and the functional implications of a given brain structure within a larger system, but also to test the efficiency of experimental manipulations such as the ones relying upon grafting techniques. According to all aforementioned data, it can be expected that the disruption of the rostrally-coursing dorsal hippocampal afferents (cingular bundle and fimbria-fornix) will be sufficient to induce massive cholinergic and serotonergic denervations in at least the two dorsal thirds of the hippocampus, while the noradrenergic hippocampal innervation should also be affected, but to a lower degree. Even damage to only the medial part of the dorsal pathways should be sufficient to massively denervate the hippocampus from its cholinergic and serotonergic inputs (see Table 1). However, important enough to be emphasized is the fact that even after massive disruption of the dorsal pathways, an aspiration or a knife-cut transection of the fimbria, the dorsal fornix and the cingular bundle is nothing more than a partial denervation paradigm (i.e. the ventral route is always spared as are other afferent and efferent pathways such as, for instance, the perforant paths originating in the entorhinal cortex).

3. THE PARADIGM(S) OF FIMBRIA-FORNIX/CINGULAR BUNDLE LESIONS: NEUROCHEMICAL EFFECTS, SPONTANEOUS REACTIVE COMPENSATIONS, AND BEHAVIOURAL EFFECTS

3.1. Why Such an Interest in the Fimbria-Fornix Lesion Paradigms?

Since many years, the fimbria-fornix pathways have been one of the privileged targets in experimental studies that used lesion techniques in order to investigate the functional implications of the hippocampus and its connected structures, or to characterize the possibilities to repair the functional consequences of hippocampal denervation by the means of drug treatments, administration of neurotrophic factors or intracerebral transplants. Although there are certainly many other reasons for analysing the functional implications of the fimbria-fornix pathways (e.g. Dutar *et al.*, 1995 and part 4.2. of this review), interest in these pathways begun to increase exponentially in the mid-1970s, when three independent research groups reported that the basal forebrain from patients with AD exhibited dramatic degeneration of the cholinergic neurons (Bowen *et al.*, 1977; Davies and Maloney, 1976; Perry *et al.*, 1977a, 1977b; White *et al.*, 1977) and showed that the extent of this degeneration was, in some respects, correlated with the extent to which cognitive functions were altered. At that time, AD was considered to be a cholinergic disease and there was a crucial need of psychopathologically and neurochemically reliable experimental animal models of AD in order to test some potentially useful therapeutical measures (e.g. symptomatic drug treatments). However, until very recently, there was a lack of a neurotoxic compound capable of damaging the cholinergic neurons in the CNS with an acceptable degree of specificity. Although AF64A has been claimed to be such a compound, its specificity failed to unanimously convince the scientific community (see below, Section 3.4.1). Therefore, a large majority of experimental studies relied upon lesion paradigms which consisted of destroying more or less

extensively well delineated regions of the brain known to contain cholinergic cell bodies (nuclei in the basal forebrain) or cholinergic axons (pathways arising from these nuclei). Classically, the lesions of the cholinergic hippocampal afferents were performed with a large variety of techniques including electrolytic or radiofrequency lesions of the septal area and the DBB, intraseptal injections of ibotenic, quisqualic or kainic acid, colchicine or other nonspecific neurotoxic compounds, as well as aspiration, transection or electrolysis of the fimbria-fornix pathways (e.g. Collerton, 1986; Dunnett, 1990; Fisher and Hanin, 1986; Olton and Wenk, 1987). Whatever of these techniques was used, it always induced a dramatic cholinergic denervation of the hippocampus (e.g. Collerton, 1986; Dunnett, 1990) and severely altered cognitive functions, especially those supposing spatial information to be memorized and appropriately used (e.g. Collerton, 1986; Dunnett, 1990; Dutar *et al.*, 1995; O'Keefe and Nadel, 1978; Olton *et al.*, 1979). Nevertheless, neither of these lesion paradigms was considered to be a satisfactory model of AD, primarily because there were two major technical drawbacks. First, the surgical destruction of cholinergic nuclei does not discriminate between different neurochemical categories of cell bodies, nor does it distinguish cell bodies and fibres and, therefore, unavoidably resulted in damage to noncholinergic neurons and fibres *en passage* in the vicinity of the lesion locus. Second, due to their scattered distribution among other neurochemically-defined fibres within anatomically-circumscribed pathways (e.g. the fimbria and the dorsal fornix), the disruption or transection of cholinergic axons without concomittant damage to axons of other neurotransmitter systems was simply not feasible with such classical tools. Thus, in both approaches, the attribution of the functional changes induced by the lesions to only the disruption of a cholinergic component remained a very debatable interpretation, even though some of these functional changes could be closely mimicked by local or systemic administrations of anticholinergic agents (e.g. Collerton, 1986). Some more recent findings on the neuropathological characteristics of AD (e.g. Bowen *et al.*, 1983; Haroutunian *et al.*, 1990; Mann and Yates, 1986) might, however, contribute to partly circumvent the drawbacks of the lesion paradigms just mentioned, mainly because some of the undesirable noncholinergic effects of such lesions are actually alterations also found in the brain of AD patients. In fact, AD is no longer considered as a matter of exclusively cholinergic degeneration, and memory no longer as a matter of only cholinergic functions. Other systems of neurotransmitters are also dramatically affected by the disease, some of which having, more or less directly, a cognitive relevance (e.g. Cassel and Jeltsch, 1995; Decker and McGaugh, 1989; Sirviö *et al.*, 1994; Steckler and Sahgal, 1995). For instance, histopathological studies have shown the functional integrity of the 5-HT system to be altered in patient with AD. Therefore, it is possible that paradigms of selective cholinergic lesions are indeed not as appropriate animal models of some of the neuropathalogical and cognitive characteristics of AD as are lesion (or pharmacological) paradigms producing simultaneous alterations in several neurotransmitter systems. Interestingly, fimbria-fornix lesions, whether extensive (aspiration, transection) or more limited (electrolysis), are able not only to produce a multitransmitter denervation in the rat hippocampus, but also, as reviewed in the next section, to induce some of the compensatory structural and functional changes as well as some cognitive perturbations which resemble part of those found in patients with AD (e.g. Aubert *et al.*, 1992; Collerton, 1986; Flynn *et al.*, 1995a, 1995b; Gertz and Cervos-Navarro, 1990; Kalaria *et al.*, 1989; Olton and Wenk, 1987; Porsolt *et al.*, 1995; Probst *et al.*, 1988; Vogt *et al.*, 1991; Zilles *et al.*, 1995).

3.2. Neurochemical Effects of Non-Specific Fimbria-Fornix/Cingular Bundle Lesions

3.2.1. *Cholinergic, Noradrenergic and Serotonergic Denervations of the Hippocampus*

3.2.1.1. *Cholinergic markers*

Using a procedure of non selective damage to the fimbria, the dorsal fornix and the overlying structures (i.e. corpus callosum, cingular bundle and part of the parietal cortex), it could be demonstrated that the disruption of these pathways resulted in dramatic depletion of cholinergic, noradrenergic and serotonergic markers in the hippocampus. *In vitro/ex vivo*, the assessment of the effects of such lesions on the cholinergic hippocampal innervation essentially used: (i) determination of choline acetyltransferase (ChAT) activity, the enzyme responsible for acetylcholine synthesis and which is found in both the cell body and the axons of cholinergic neurons; (ii) determination of acetylcholinesterase (AChE) activity, the enzyme responsible for the degradation (rapid inactivation) of acetylcholine and which is found in close proximity of the synaptic cleft, but not exclusively in the cholinergic neurons (although in the hippocampus there is a 95% correlation between AChE and ChAT activity; e.g. Levey *et al.*, 1983; Mesulam and Geula, 1992); (iii) measurement of high affinity [^{3}H]choline uptake by hippocampal synaptosomes, a rather specific marker of the axonal terminals (the uptake sites being located on these terminals); as well as (iv) [^{14}C]acetylcholine synthesis from [^{14}C]glucose in hippocampal tissue preparations, a marker which is more functionally oriented as it closely depends on the metabolic activity of the cholinergic neurons. Whatever marker was considered and depending upon the experiment considered, the lesions generally induced a 70% to more than 90% reduction of cholinergic markers in the septal pole of the hippocampus, the reduction in the temporal pole being usually slightly less pronounced (e.g. Björklund *et al.*, 1983a; Gage *et al.*, 1983a, 1983c, but see Cassel *et al.*, 1993b). Measurements of cholinergic markers in the hippocampus have also been performed *in vivo* on awake rats, the most recent technique consisting in the intracerebral implantation of a microdialysis probe with the permeable portion of the probe inserted in the hippocampus, collection of a buffer slowly pumped through this probe, and HPLC detection of choline and acetylcholine

concentrations in the collected dialysat. After extensive fimbria-fornix lesions, the cholinergic markers assessed *in vivo* by such means were also reduced by about 80% to more than 90% of normal in the dorsal hippocampus, some values being often below the detection limit of the HPLC system (e.g. Leanza *et al.*, 1993a; Nilsson *et al.*, 1992a).

3.2.1.2. *Monoaminergic (noradrenergic, serotonergic) markers*

As regards the noradrenergic and the serotonergic innervation of the hippocampus, the techniques used were similar to the ones used for measuring cholinergic markers, whether *in vitro* or *in vivo*. These included determination of the concentration of NA, 5-HT or 5-HIAA in hippocampal homogenates, measurement of high affinity uptake of [^{3}H]NA and [^{3}H]5-HT by hippocampal synaptosomes and microdialysis coupled to HPLC measurements of the neurotransmitters, their precursors or their metabolites. With such techniques, the lesion-induced hippocampal serotonergic denervation was also found to be dramatic. Indeed, the different serotonergic markers reached values lower than 20% of normal, these effects being usually less pronounced in the temporal than in the septal pole of the hippocampus. The initial effects of the lesions on the noradrenergic markers were not as dramatic as on the markers of both other neurotransmitter systems, essentially because the dorsal pathways carry a lower proportion of the noradrenergic afferents (see above) and not all approaches took the precaution of removing the superior cervical ganglia in order to prevent sympathetic sprouting, an aberrant reactional phenomenon that provides some subregions of the hippocampus with a peripheral noradrenergic reinnervation (see below, Section 3.2.2.1). This sympathetic sprouting response is not the only technical problem which may arise when one makes fimbria-fornix lesions to investigate the relationships that may exist between neurochemical alterations in the hippocampus and behavioural changes in the animal. During a long time, starting with Cajal's verdict against the regeneration possibilities in the adult brain (Cajal, 1928), it was thought that the brain was a rigid inflexible structure in which any damage would result in definitive structural and functional alterations. Fortunately, this conception has been shown to be erroneous. Even in the adult brain, there exists many compensatory mechanisms (e.g. Cotman *et al.*, 1981; Finger and Stein, 1982; Marshall, 1984, 1985; Stein *et al.*, 1995) after brain injury, some operating at the level of more morphological or neuroanatomical manifestations (e.g. regenerative or collateral sprouting), others at that of more functional ones (e.g. upregulation of receptors in target structures). From a strictly experimental point of view, such compensations might be a major drawback because, in some lesion paradigms, they may lead to misinterpretations of experimental data or unqualified conclusions, especially in experiments running over long postsurgical periods. Such a risk, as summarized in the next section, is also present in experimental approaches relying upon a certain type of fimbria-fornix lesion paradigms, in which both central and peripheral regrowth processes may contribute to structural and functional compensations.

3.2.1.3. *GABAergic markers*

Due to the very high levels of GABAergic markers which, within the hippocampus, are related to the intrinsic GABAergic neurons and glial cells, it is extremely difficult to biochemically detect the GABAergic denervation due to disruption of the extrinsic afferents. In a recent report, Lahtinen *et al.* (1993) have assessed the hippocampal concentration of several amino acids in rats given extensive fimbria-fornix lesions and found the concentration of GABA to show modest (-11%) but significant reduction in both dorsal and ventral parts of the hippocampus at a postsurgical delay of four months. Nevertheless, whether this reduction resulted from loss of extrinsic GABAergic afferents or intrinsic GABAergic neurons, whose number may also decrease subsequently to fimbria-fornix lesions (Chen *et al.*, 1989), is still unclear. In a pilot experiment which used an *in vivo* microdialysis technique (probe implanted in the dorsal hippocampus), we have not been able to find any modification of the hippocampal GABA concentration after aspiration lesions of the fimbria and the dorsal fornix (Whishaw *et al.*, unpublished results). In another experiment based on electrolytic lesions of only the fimbria and the dorsal fornix, there was no lesion-induced modification of the GABA concentration assessed in hippocampal homogenates (Jeltsch *et al.*, 1994c) 10 months after lesion surgery.

3.2.2. *Reactional Sprouting*

In a paradigm of fimbria-fornix lesions, the structural compensatory changes which occur in the hippocampus may result essentially from two types of reactional sprouting phenomena, one termed regenerative sprouting and referring to regrowth of damaged axons, the other one termed collateral (or terminal) sprouting and referring to growth of additional collaterals and terminals from unsevered axons. Collateral sprouting is further distinguished according to whether it originates on fibres that normally innervate a given structure (homotypical sprouting) or on fibres that do not normally project to the structure or the subregion which they invade after the injury (heterotypical sprouting). Interestingly, such sprouting responses are also observed in the brain of AD patients (e.g. Booze *et al.*, 1993; Cotman *et al.*, 1990).

3.2.2.1. *Homotypical reactional sprouting*

As shown by Gage *et al.* (1983b, 1983c) and summarized in Fig. 3, collateral sprouting subsequently to extensive disruption of both dorsal pathways (Fig. 2) mainly originates in the undamaged fibres of the ventral route and concerns the cholinergic, noradrenergic and serotonergic afferents of the hippocampus. The terminals of the fibres in the ventral route are normally confined to the temporal portion of the hippocampus. The degree to which this

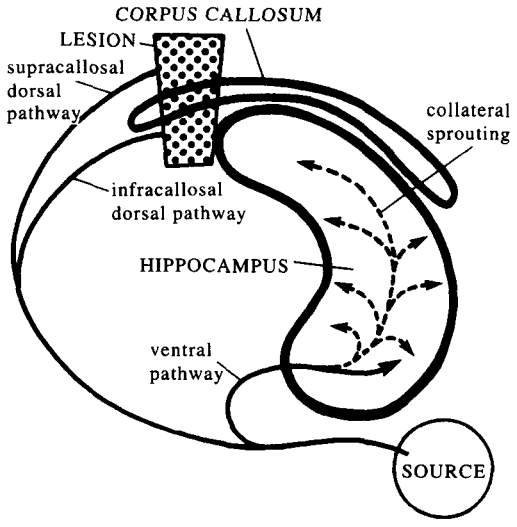

Fig. 3. Illustration of the collateral sprouting phenomena originating in the ventral route after disruption of the supracallosal and the infracallosal dorsal pathways (other sprouting phenomena induced by such lesions are not shown on this figure).

sprouting may provide the hippocampus with a new innervation as well as the topographical completeness of this innervation are both closely dependent upon which dorsal hippocampal afferents have been initially severed and the time elapsed since the lesion surgery (e.g. Dravid and Van Deusen, 1983, 1984; Gage and Björklund, 1986b; Gasser and Dravid, 1987). Common to the three systems of neurotransmitters, when the lesion disrupts both the cingular bundle and the fimbria-fornix pathways, this sprouting response has a rather slow onset and needs several weeks to a few months before significant neurochemical effects can be detected (Gage and Björklund, 1986b; Gage *et al.*, 1983a). Conversely, when the lesion is restricted to the cingular bundle, sprouting occurs more rapidly and neurochemical effects can be detected within only a few weeks (Gage *et al.*, 1983b, 1983c).

Gage *et al.* (1983a, 1983c) showed that ten months after disruption of both dorsal components (cingular bundle and fimbria-fornix) of the hippocampal afferents, the ChAT activity, intially (within one week) reduced to less than 5% of normal in the septal portion of the hippocampus, had increased to slightly more than 10% (two-fold increase), whereas, in the temporal portion, in which it was initially reduced to 15% of normal, it had reached 45% of normal (three-fold increase). As regards NA uptake by hippocampal synaptosomes at the same postsurgical delay, the initial reduction to 20% of control or even less in the most septal portion had been compensated for to a higher degree than ChAT activity, with values reaching 70% to 80% of control. This partial compensation was due to the sprouting of central noradrenergic fibres as Gage *et al.* (1983a, 1983c) had removed the superior cervical ganglia several days prior to the sacrifice of the rats (see Section 3.2.2.2). In the most temporal pole, the reduction of NA uptake due to the lesion was weak and failed to be significant. Unfortunately, the effects of fimbria-fornix lesions on 5-HT markers in the hippocampus have not been assessed in this paper. Evidence that undamaged serotonergic afferents of the hippocampus may sprout and attenuate the initial lesion-induced serotonergic deficit was reported by Azmitia *et al.* (1978), Zhou and Azmitia (1984) and Gage *et al.* (1983a). The former used a technique of 5,7-DHT-induced lesions of the supracallosal serotonergic pathways, while the latter used a suction technique. Both types of approaches allowed to demonstrate that compensatory collateral sprouting may account for partial recovery of serotonergic markers in the hippocampus. To give just one illustration, after aspiration of the cingular bundle, Gage *et al.* (1983a, 1983c) have shown that the high affinity 5-HT uptake by hippocampal synaptomoses from the dorsal third of the hippocampus was reduced to about 35% of control 2 weeks after lesion-surgery and, four weeks later, had recovered to about 60% of normal, a level at which it remained stable for 1,5 year.

3.2.2.2. *Heterotypical reactional sprouting*

Although several examples of heterotypical reactional sprouting have been demonstrated in the hippocampal formation (e.g. Azmitia and Whitaker-Azmitia, 1995; Goldberger and Murray, 1988; Marshall, 1984, 1985; Steward, 1989), this part will exclusively consider the phenomenon termed sympathetic sprouting which, regarding some of the graft-induced neurochemical effects presented further on, clearly deserves a few lines of presentation and comments. Noradrenergic sympathetic fibres are commonly found in association with some large blood vessels in the CNS (e.g. Crutcher, 1987), but they also innervate other peripheral targets such as, for instance, the cardiac muscle, the iris or the salivary glands. In the CNS, the sympathetic axons, which have terminals in structures such as, for instance, the choroid plexus or the pineal gland (Crutcher, 1987), are also found to be associated with longitudinal parahippocampal blood vessels. The latter terminals arise from the superior cervical ganglia and provide the densest vasculatur innervation near the temporal pole of the hippocampus (Crutcher, 1987). Sympathetic sprouting in the hippocampus designates the invasion of the hippocampal parenchyma by such peripheral noradrenergic fibres subsequently to a rostral denervation of the hippocampus. A *sine qua non* condition for sympathetic ingrowth to occur in the hippocampal parenchyma is that the hippocampus must be deprived of at least a part of its cholinergic innervation, whether by lesioning the cell bodies or by disrupting the afferent fibre tracts (e.g. Björklund and Stenevi, 1981; Cassel *et al.*, 1992b; Loy *et al.*, 1980). As to which mechanism(s) might account for this aberrant sprouting response, a problem that is beyond the scope of this review, the reader is referred to review articles by Crutcher (1987, 1990). Following cholinergic denervation of the hippocampus, sympathetic fibres begin to grow within the temporal pole of the hippocampus, mainly into the hilus of the dentate gyrus and along the pyramidal cell layer in

subregions CA4 and CA3 of the Ammon's horn (e.g. Crutcher, 1987; Crutcher and Davis, 1981). This ingrowth has a rapid onset (evidence for sympathetic terminals in these regions can be found within a few days after the lesions, e.g. Milner and Loy, 1980) and seems to continue during the whole postsurgical life span of the lesioned animal, as suggested by the observation that over up to 10 months, the hippocampal NA concentration increases slowly but inexhaustively (e.g. Madison and Davis, 1983; Jackisch *et al.*, 1995). Madison and Davis (1983) investigated the time course of the recovery of noradrenergic markers in the hippocampus following septal lesions that also disrupted part of the central noradrenergic hippocampal afferents. In part of their rats, they additionally performed removal of the superior cervical ganglia in order to be able to estimate the degree to which collateral sprouting of central fibres contributed to the recovery of noradrenergic markers. Madison and Davis (1983) found that two weeks after the lesions, there was an approximatelty 50% decrease of the hippocampal NA concentration (entire hippocampus), whether the rats had been ganglionectomized or not. As evident from the rats which sustained bilateral ganglionectomy, sprouting of the non-severed central noradrenergic fibres had contributed to normalize both the concentration of hippocampal NA and the high affinity NA uptake by hippocampal synaptosomes (a better marker for the density of the terminals) by 12 weeks after surgery. In the rats which did not sustain a ganglionectomy, the NA concentration was near-normal after already four weeks and, 16 weeks after surgery, it exceeded control values by more than 100%. In the experiment by Jackisch *et al.* (1995), the lesions consisted of aspiration of the fimbria-fornix and overlying structure, no ganglionectomies were performed and the postsurgical delay was extended to 40 weeks with several intermediate delays. After the 40-week survival time, we found the concentration of NA to largely exceed that found in the intact control animals, with a maximal effect in the two temporal thirds of the hippocampus (about + 200%). Thus, conversely to collateral homotypic sprouting of hippocampal noradrenergic afferents which at most normalize noradrenergic markers of the hippocampus, the sprouting of noradrenergic axons from the peripheral nervous system may contribute to largely overcompensate the depletion of some hippocampal noradrenergic markers which follows septal lesions or disruption of the dorsal septo-hippocampal pathways.

3.2.3. *Supersensitivity and Metabolic Reactions*

In addition to the compensatory changes due to sprouting and/or regeneration, there is also a series of perhaps more functional modifications which are generally more rapid in that they produce detectable effects within a few days after lesion surgery. Such compensations may occur at essentially three levels of the neuronal communication, two of which being operating on the presynaptic side, the remaining being found postsynaptically. Presynaptically, these compensations may affect the metabolic machinery in the spared neurons (e.g. acceleration of neurotransmitter synthesis), as well as the amount of neurotransmitter released by the spared terminals (they release more and/or show downregulated autoinhibitory mechanisms). Postsynaptically, the changes essentially concern the status of the receptor towards its ligands. Such compensatory phenomena were first described in the dopaminergic nigro-striatal system and were found to also operate in patients with PD (Bernheimer and Hornykiewicz, 1962). After experimentally-induced degeneration of the nigrostriatal pathways, the residual dopaminergic neurons synthetize and release more dopamine than normal ones (e.g. Hefti *et al.*, 1980), and this dopamine acts on upregulated receptors (e.g. Creese *et al.*, 1977; Ungerstedt, 1971).

Supersensitivity is a term which designates a phenomenon by which postsynaptic receptors increase their sensitivity to chemical agents in reaction to (sub)total denervation. Such an adjusting mechanism was known for a long time in the peripheral nervous system (glands, muscles...). In the CNS, one of the clear-cut demonstration of one previously suspected mechanism (Ungerstedt, 1971) underlying such an adaptative event was by Creese *et al.* (1977). Using the so-called "Ungerstedt" (e.g. 1971) model of PD, these authors found that following a unilateral lesion of the dopaminergic nigrostriatal pathway, rats injected with apomorphine, a dopaminergic agonist, repeatedly turned in a direction opposite to the side of the lesion, a side on which they also found the striatal [^{3}H]haloperidol binding sites to be increased dramatically as compared to the controlateral unoperated striatum.

More recently, the aforementioned mechanisms have also been identified in the residual hippocampal innervation systems following partial denervation, perhaps more particularly as regards the sensitivity of the cholinergic, noradrenergic and serotonergic receptors.

3.2.3.1. *Cholinergic system*

As concerns cholinergic neurons, Lapchak *et al.* (1991), using partial or complete fimbria-fornix transections in the rat, have compared the effects of both lesions on hippocampal cholinergic markers, with evaluations performed 3 weeks postsurgery both *in vitro* (determination of [^{3}H]acetylcholine synthesis in hippocampal slices, ChAT activity and synaptosomal uptake of choline) and *in vivo* (hippocampal acetylcholine and choline content, newly synthetized acetylcholine and rate of acetylcholine synthesis). These authors found both lesions to deplete all *in vitro* markers, with the depletion being less dramatic after partial (− 35% to − 60%) than after complete lesions (− 70% to − 90%). Whereas the *in vivo* markers were depleted as severely as the *in vitro* ones following a complete transection, they were not significantly modified after a partial transection. The latter finding clearly demonstrates that surviving cholinergic neurons in the septo-hippocampal pathways may functionally compensate for the partial loss of cholinergic hippocampal innervation by increasing the synthesis and the release of acetylcholine. Using an *in vivo* microdialysis technique, Leanza *et al.* (1993a) have reported that

subsequently to fimbria-fornix transections relatively more extensive than in the case of the partial lesions used by Lapchak *et al.* (1991), the acetylcholine turnover can be increased dramatically in the denervated hippocampus. Another adaptative mechanism in cholinergic neurons surviving a lesion may consist in the modification of their sensitivity to neurotrophic factors. Such a possibility has been recently suggested by Willson and Hanin (1995) who used AF64A-induced lesions of the hippocampal cholinergic afferents followed by intraventricular administrations of NGF which was continued over two weeks. In their lesioned rats, Willson and Hanin found the surviving cholinergic neurons to exhibit an increased sensitivity to NGF treatment, as both the ChAT and the AChE activities were increased by about twice as much as in the NGF-treated unlesioned control rats. Wall *et al.* (1994) have also reported some changes at the postsynaptic level. After basal forebrain lesions, Fuji *et al.* (1993) found the number of [^{3}H]QNB binding sites to be increased in the hippocampus, an indication for occurrence of muscarinic hypersensitivity. That a cholinergic denervation of the hippocampus may induce an upregulation of muscarinic receptors seems to be a well documented fact, even if a small number of studies failed to find the sensitivity of hippocampal muscarinic M1 receptors to be affected by medial septal (Bauer *et al.*, 1992) or partial (Araujo *et al.*, 1993) as well as extensive (Cassel *et al.*, 1991a) fimbria-fornix lesions.

Following unilateral aspiration of the dorsal septohippocampal pathways, Araujo *et al.* (1993) showed that 10 to 24 days after surgery, the total amount of hippocampal muscarinic receptors had increased by 17%, with the density of the M_1, M_3 and M_4 subtypes being increased by 14%, 77% and 29%, respectively, and that of the M_2 subtype being decreased by 22% (probably because of their partly presynaptic location). It is noteworthy that the number of hippocampal M_2 receptors was also decreased after lesions of the MS (Bauer *et al.*, 1992), but that the affinity of the remaining M_2 receptors was actually increased (Kolasa *et al.*, 1995). These data are in line with a more recent report by Levey *et al.* (1995) who found M1 and M4 receptors to be upregulated in the hippocampus subsequently to fimbria-fornix lesions, but not subsequently to lesions produced by the immunotoxin 192-IgG which is specific to cholinergic neurons (e.g. Wiley, 1992; Wiley *et al.*, 1991, 1995; but see also Rossner *et al.*, 1995; Walsh *et al.*, 1995; and Section 3.4.1). That some of these adapative changes (M_1 upregulation) may be lasting for several weeks or months after lesion surgery has been shown in earlier reports (e.g. Benson *et al.*, 1989; Dawson *et al.*, 1989; Joyce *et al.*, 1989). An upregulation of the muscarinic receptors in the denervated hippocampus has also been found with a technique assessing the metabolic cascade of the second messengers associated with the activation of these receptors. The postsynaptic muscarinic receptor is linked to a second messenger system in which phosphatidylinositol is hydrolyzed into diacylglycerol and inositol triphosphate. The latter compound can be measured in response to carbachol-induced activation of the receptor. Using such an approach, Connor and Harrell (1989); (see also Harrell *et al.*, 1992) demonstrated that 4 months after large septal lesions, the carbachol-induced formation of inositol triphosphate in hippocampal slices was still increased by 60%, a result showing that these receptors had undergone a lasting upregulation in response to cholinergic denervation. Also Lapchak *et al.* (1993); but see Cassel *et al.*, 1991a) found that after partial fimbria-fornix lesions, the carbachol-evoked production of inositol triphosphate (involved in the second messenger cascade of M_1 receptor activation), was upregulated in the hippocampus ($+80\%$), whereas the density of M_1 and M_2 receptors was not affected. Alterations in muscarinic receptor sensitivity have also been found in the hippocampus of aged rats (Fordyce and Farrar, 1991) as well as in some brain regions of patients with AD (Flynn *et al.*, 1995a, 1995b; Nordberg *et al.*, 1983). Interestingly, not only muscarinic receptors may undergo functional changes after cholinergic hippocampal denervation. Actually, using AF64A-induced lesions of the hippocampal cholinergic afferents, Potter and Nitta (1993) have found that two weeks after surgery, the inhibitory muscarinic autoreceptor of the cholinergic terminal had undergone downregulation, whereas the facilitatory nicotinic autoreceptor had undergone upregulation, a finding confirmed by a subsequent experiment (Thorne and Potter, 1995). Interestingly, both these changes might underly some of the aforementioned findings reported by Lapchak *et al.* (1991) in the partially denervated hippocampus. Finally, there is evidence that cholinergic denervation of the hippocampus increases the transcription of mineralo- and glucocorticoid hippocampal receptors. It is also noteworthy that some of the aforementioned lesion-induced changes in receptor sensitivity, especially as regards the muscarinic receptors, can be partially altered (generally attenuated) by the ingrowth of sympathetic noradrenergic fibres originating in the superior cervical ganglia (e.g. Harrell *et al.*, 1994, 1995; Kolasa *et al.*, 1995).

3.2.3.2. *Noradrenergic system*

Gage *et al.* (1983b) performed bilateral fimbria-fornix aspirations which, three weeks later, had decreased the NA concentration by 90%, 55% and 20% in the dorsal, "middle" (a part intermediate between the dorsal and ventral thirds of the hippocampus) and ventral hippocampal regions, respectively. Estimations of the DOPA/NA ratios were used to determine the turnover of noradrenaline in the spared noradrenergic terminals. These estimations showed a dramatic increase in the dorsal hippocampus, a less pronounced one in the middle part and no significant change in the ventral hippocampus. Interestingly, this adapatation of the metabolic machinery was no longer observed seven months later, when the NA concentration had recovered a near-normal level. Evidence for a transient upregulation of the noradrenergic turnover in undamaged neurons after fimbria-fornix lesions has also been obtained using *in vivo* microdialysis methods with the dialysis probe implanted in the denervated hippocampus at various postsurgical delays. Indeed, Leanza *et al.* (1993a) have reported

that four weeks after a fimbria-fornix transection, the NA turnover showed a 3-fold increase in the dorsal hippocampus (estimated as the dialysate level/tissue content ratio). Concerning the noradrenergic innervation of the hippocampus, Zahniser *et al.* (1986) found that one to two weeks following specific DSP4-induced destruction (see Section 3.4.2) of the hippocampal noradrenergic afferents, the number of hippocampal β-adrenergic receptors was increased by 20 to 25%. This upregulation seems to last for several months and to be still detectable one year after DSP-4 treatment, a delay at which the markers for noradrenergic function in the hippocampus had recovered a near-normal level (Wolfman *et al.*, 1994). Interestingly, an upregulation of β_1 and β_2 receptors was also observed in the hippocampus of patients with AD (Kalaria *et al.*, 1989). All these data showing an adrenoceptor supersensitivity due to noradrenergic denervation of the hippocampus are in line with two earlier reports relying upon different lesion paradigms. Morrow *et al.* (1983) performed unilateral or bilateral transections of the fimbria and the fornix or radiofrequency lesions of the septal area (through which part of the hippocampal noradrenergic afferents are coursing) and, with both lesions, found a subpopulation of hippocampal adrenergic receptors (presumably from the α type) to be enlarged for at least one month after surgery, with the enlargement being detected as early as 6 days after surgery. There is also evidence that the sensitivity of hippocampal noradrenergic $\alpha 2$ receptors can be modified (downregulated in the dorsal hippocampus and upregulated in the ventral hippocampus) after partial fornix transection (e.g. Dyon-Laurent *et al.*, 1993, 1994) and that DSP-4-induced lesions which decrease the noradrenergic markers in the hippocampus may produce behavioural supersensitivity mediated presumably by α_1 and α_2 receptors. In another study, Heal *et al.* (1993) showed that subsequently to DSP-4 lesions, there was an initial reduction of the hippocampal α_2 adrenoceptors (-18% 3 days after administration of the neurotoxin) followed, 12 days later, by an increase to a slightly above-normal level ($+8\%$). Finally, there is evidence that after DSP-4 or 6-OHDA lesions of central noradrenergic fibres, the number of hippocampal corticosteroid (Maccari *et al.*, 1992) and cholecystokynin receptors (Harro *et al.*, 1992) is increased, whereas that of somatostatin binding sites is decreased (Lopez-Sanudo and Arilla, 1992).

3.2.3.3. *Serotonergic system*

Similar changes may occur in spared serotonergic neurons. It has been repeetedly reported that a serotonergic denervation of the hippocampus induced an increase of the 5-HIAA/5-HT ratio, an indicator of the 5-HT turnover in the spared neurons. For instance, 5,7-DHT-induced lesions of the hippocampal serotonergic afferents increased this turnover by approximately 30% (e.g. Daszuta *et al.*, 1988; see also Auerbach *et al.*, 1985). Aspiration lesions of the supracallosal and infracallosal pathways were found to increase this ratio in the dorsal hippocampus to about 400% of normal (Cassel *et al.*, 1993b) and electrolytic lesions restricted to the infracallosal pathways to about 250% (Jeltsch *et al.*, 1994b). As regards the status of the 5-HT receptors in the denervated hippocampus, previous studies have reported the density of the hippocampal 5-HT_1 receptors (with no distinction of the subtype) to be reduced by approximately 50% after fimbria-fornix lesions (Quirion and Richard, 1987) and the binding to non-5-HT_{1A} sites to be reduced by 20% after septal lesions (Kiedrowski *et al.*, 1990). Such results, however, rather than indicating compensatory mechanisms, might be regarded as reflecting a decrease in the number of 5-HT receptors located on the severed terminals of serotonergic or even other types of neurons such as the cholinergic ones (e.g. Cassel and Jeltsch, 1995). At the level of the spared serotonergic terminals, receptors mediating autoinhibitory mechanisms of 5-HT release were shown to undergo downregulation (Chaput *et al.*, 1990). Conversely, after serotonergic denervation, the postsynaptic hippocampal 5-HT receptors may be upregulated: In that concern, Nelson *et al.* (1978) found that after 5,7-DHT-induced lesions (i.c.v. injection; see Section 3.4.3) of the serotonergic system, the [^{3}H]-5-HT binding in the hippocampus was increased by about 40% within a few days as compared to noninjected control rats, a finding that was confirmed later in two other studies using 5,7-DHT-induced lesions (Morrow *et al.*, 1985; but see Quick and Azmitia, 1983) or fimbria-fornix transections (e.g. Morrow *et al.*, 1985). However, again with 5,7-DHT-induced lesions of the serotonergic system, Fischette *et al.* (1987) found that, in the hippocampus, there was no apparent upregulation of either 5-HT_1 or 5-HT_2 receptors, a result also supported by the data of Miquel *et al.* (1992). Absence of hippocampal 5-HT_{1A} receptor alterations have been reported in 5,7-DHT-treated neonates (Pranzatelli *et al.*, 1994) and in adults given intrahypothalamic injections of 5,7-DHT (Frankfurt *et al.*, 1993). Evidence that 5-HT_6 receptors are not altered in 5,7-DHT-treated rats has been obtained more recently (e.g. Gerard *et al.*, 1996). In rats given intracisternal injections of 5,7-DHT, the number of hippocampal 5-HT_{1A} receptors was, however, increased (Pranzatelli, 1994), as was that of 5-HT_{2C} (5-HT_{1C} in the authors' terminology) binding sites after intracerebroventricular administration of the neurotoxin (Rocha *et al.*, 1993). In another recent report, Sijbesma *et al.* (1991) showed that subsequently to 5,7-DHT-induced destruction of the serotonergic neurons in the dorsal and the median *raphe* nuclei, rats exhibited an increased 5-HT_1 receptor binding in various subregions of the hippocampus ($+13\%$ to $+27\%$), as well as in various other regions of the brain (see also Frankfurt *et al.*, 1993). Finally, using microinjections of 5,7-DHT directly into the cingular bundle and the fimbria-fornix pathways, Patel *et al.* (1995) reported, that two weeks after surgery, the 5-HT_{1A} immunoreactivity was significantly increased in the dentate gyrus and region CA1 of the hippocampus as compared to that seen in virtually intact rats. Some of the discrepancies among these different reports might be due to the differences in the lesion techniques used (location, extent, amount of neurotoxin injected), the age of the animals (neonates *versus* adults) or other factors such as, for instance,

the duration of the postsurgical delay. This comment also applies to the discrepancies in the results of the studies mentioned in previous sections (3.2.3.1 and 3.2.3.2). Finally, central 5-HT depletions were found to decrease the transcription and the number of hippocampal mineralo- and glucocorticoid receptors (Yau *et al.*, 1994; Novotney and Lowy, 1995) and to increase the number of glutamate binding sites (Mennini and Miari, 1991), initially in subregion CA3 and, later on, in all hippocampal subregions. The latter effect is not found in 5-HT-depleted neonates (Ogawa *et al.*, 1994).

3.2.3.4. *Conclusions*

Taken together, these results (summarized in Table 2) show that, among the different functional compensation possibilities which may occur in the partially denervated hippocampus, neurons spared by fimbria-fornix lesions may upregulate their metabolic machinery, downregulate presynaptic receptors involved in a tonic inhibitory regulation of neurotransmitter release and, should the case arise, upregulate the presynaptic receptors mediating an autofacilitation of neurotransmitter release (e.g. nicotinic receptors on cholinergic terminals). In addition, at the postsynaptic level, the cholinergic, noradrenergic and serotonergic receptors may become hypersensitive to their endogeneous ligand. There is also some evidence suggesting that the alteration of one specific neurotransmitter system afferent to the hippocampus may induce modifications of receptor sensitivity in other neurotransmission systems (e.g. Alonso and Soubrié, 1991; Donnerer *et al.*, 1992; Maccari *et al.*, 1990, 1992). Obviously, these adaptative modifications in receptor sensitivity and neurotransmitter turnover have an earlier onset and a less protracted timing than the modifications briefly described in Section 3.2.2 (sprouting). In some respects, one might consider that the adaptative changes described above might even be in a balanced relationship as it was shown that the receptor upregulations resulting from denervation are progressively attenuated by the protracted ingrowth of sprouted fibres originating in the spared neurons and by that of sympathetic fibres from the superior cervical ganglia.

3.3. Behavioural Effects of Non-Specific Fimbria-Fornix/Cingular Bundle Lesions

In behavioural neurosciences, the notion of *behavioural task* can be roughly regarded as referring to a particular situation (using a specific apparatus and a particular procedure) in which the animal is supposed to do something in relation to the experimenter's expectations and the experimenter to

Table 2. Summary Table of the Neurochemical and Pharmacological Consequences of Lesions in the Fimbria-Fornix/Cingular Bundle Pathways with Focus on the Associated Neurochemically-Defined Hippocampal Denervations, Functional Compensations and Structural Changes

Denervation*	Rapid compensatory lesion-induced changes	Slow protracted compensatory lesion-induced changes
Cholinergic	–synthesis and release of acetylcholine increased in spared neurons –sensitivity to neurotrophic factors increased in spared neurons –upregulation of postsynaptic receptors (e.g. M1, M3, M4)† –upregulation of presynaptic facilitatory nicotinic receptors –upregulation of mineralo- and glucocorticoid receptors –downregulation of presynaptic inhibitory autoreceptors (e.g., M2) and heteroreceptors (e.g., 5-HT1B)	–collateral homotypic sprouting of spared axons –regenerative homotypic sprouting of damaged axons –nonregenerative heterotypic sprouting of sympathetic fibres
GABAergic	–no data available so far	–no data available so far
Noradrenergic	–noradrenaline turnover increased in spared neurons –upregulation of α_1, α_2, β_1 and β_2 receptors –upregulation of corticosteroid and cholecystokynin receptors –downregulation of somatostatin receptors	–collateral homotypic sprouting of spared axons –regenerative homotypic sprouting of damaged axons
Serotonergic	–serotonin turnover increased in spared neurons –upregulation of 5-HT_{1A} and 5-HT_{2C} receptors‡ –upregulation of glutamatergic receptors –downregulation of mineralo- and glucocorticoid receptors –downregulation of autoinhibitory serotonin receptors	–collateral homotypic sprouting of spared axons –regenerative homotypic sprouting of damaged axons

* Extent of the denervation depending upon the lesion extent with maximal effects on cholinergic and noradrenergic markers, intermediate effects on noradrenergic ones and weak effects on GABAergic ones.

† Some of these changes can be altered by sympathetic ingrowth.

‡ The occurrence and subtype of receptor(s) concerned are still subject to controversy and regulatory phenomena seem to be absent in neonate rats subjected to serotonin depletion.

record something in relation to the animal's behavioural capabilities. The constraints of this situation are defined such as to induce the animal to do something particular which the experimenter will record in terms of quantitative or qualitative data and from whose the latter will be able to infer knowledge about the animal's capabilities. When one considers a behavioural variable (e.g. latency to find an submerged platform in a water tank), one has to keep in mind that all testing situations irrevocably involve a large series of psychological processes covering motivational, attentional, perceptual, sensory-motor, cognitive... processes and that, therefore, the risk of interpretational bias is omnipresent. Nevertheless, such a risk might be minimized by analyzing the behavioural consequences of a given brain lesion using an as large as possible battery of tests, with each test being more sensitive to one of these processes than to all other ones. It is clear that all behavioural perturbations associated with lesions in the fimbria-fornix and cingular pathways are potential concerns in studies aimed at characterizing the possibilities of intrahippocampal grafts to foster functional recovery. Regarding the behavioural effects of fimbria-fornix lesions reported so far in the literature, most studies have focused attention on the mnesic sequelae of such lesions (some reasons to that may be found in Section 3.1) and only a few were concerned by behavioural aspects in which the mnesic component may be considered more negligible.

3.3.1. *Maintenance Behaviours*

Maintenance behaviours cover eating, drinking, moving, perceiving and, in some respects, sexual, social and maternal behaviours. Though having a cognitive dimension which one should not ignore, it may be considered that the mnesic/cognitive load of such maintenance behaviours is rather low as opposed to the cognitive demand of, for instance, a large variety of maze learning problems. The effects on such behaviours of a disruption of the septohippocampal pathways have not been subject to systematic investigations during the last twenty-five years. Furthermore, when examined, most studies relied upon more or less extensive lesions of the hippocampus rather than of the afferent or efferent hippocampal pathways. In one of the last reviews in which this topic was dealt with, namely that by O'Keefe and Nadel (1978), it has been concluded that lesions affecting the integrity of the hippocampal formation (in its broadest sense) do not result in critical or major perturbations of the aforementioned behavioural aspects. Nevertheless, according to some early reports and to a few more recent ones, an alteration of the hippocampus may produce more or less subtle consequences on several aspects of maintenance behaviours or some underlying regulatory mechanisms such as, for instance, circulation, modulation or emission of hormonal information. Although the majority of studies have investigated the effects of different hormones on functional or structural, sometimes ontogenetic, aspects of the hippocampus or, more generally, of various brain structures (e.g. McEwen and Parsons, 1982), there exists a few experiments suggesting that hippocampal lesions may result in alterations of regulatory processes based upon hormonal communication, especially as regards the hypothalamic-pituitary-adrenocortical axis (e.g. Jacobson and Sapolsky, 1991). For instance, Soulairac and Soulairac (1978) have reported that in male rats, the hippocampus is an important relay structure in the circuits involved in regulation of emotional and sexual aspects of behaviour, a statement which is in line with the report by Kim (1960) who showed adult male rats given hippocampal lesions to exhibit exagerated copulatory activity (see also Bermant *et al.*, 1968). In female rats, hippocampal damage induces perturbations in estrus cycle (e.g. Borker and Mascarenhas, 1990 but see Capobianco and Hamilton, 1973). Hippocampal lesions are also able to transiently alter the circadian rhythm of plasma corticosteroids (e.g. Mason, 1958), and so are lesions of the fimbria-fornix (e.g. Nakadate and de Groot, 1963), or to perturbate the responsivity of the pituitary-adrenal axis to mildly stressful situations (e.g. Coover *et al.*, 1971). However, whether these modifications in the functional integrity of hormonal systems may influence behaviour does not appear to be a major concern in the literature.

Lesions of the hippocampal formation in female rats were also found to increase food intake and hoarding behaviour, thus accelerating weight gain (Borker and Mascarenhas, 1990; King *et al.*, 1994). Such alterations are not observed in hippocampal male rats (Forloni *et al.*, 1986), although male rats with hippocampal damage were found to be impaired in using information provided by their "hunger state" (Davidson and Jarrard, 1993). Male rats with fimbria-fornix lesions show abnormal patterns of consummatory behaviour in that they drink and eat more frequently than their unlesioned counterparts with, however, an unchanged total amount of food and water intake (Osborne and Dodek, 1986). The latter findings might be in some respects explained by the fact that fimbria-fornix lesions result in an overall increase of activity.

Actually, regarding locomotor activity, it is well established that hippocampal as well as fimbria-fornix lesions induce a dramatic increase in locomotor activity in both familiar (e.g. the home cage) and unfamiliar (e.g. an open field) environments (e.g. Capobianco and Hamilton, 1976; Cassel *et al.*, 1991b; Dunnett *et al.*, 1982; Jeltsch *et al.*, 1994a, 1994b). Hippocampal lesions also attenuate the cyclic activity changes (Jarrard, 1968). Other aspects of maintenance behaviour such as, for example, maternal behaviour (Kimble *et al.*, 1967) and social interactions (Kolb and Nonneman, 1974) may also be altered by hippocampal lesions. Finally, it seems that sensory-motor capabilities are not disrupted by hippocampal lesions when the lesion is bilateral. When made on only one side, as is the case with unilateral lesions of many other brain structures, hippocampal lesions induce a sensory-motor deficit that consists in ipsilateral turning and orienting biases. Using two types of fimbria-fornix lesions (aspiration versus electrolysis), we recently found (Hofferer and Cassel, 1996) that, whereas both lesions induced qualitatively similar cognitive deficits, the lesion made by aspiration induced a sensorimotor

deficit (presumably due to the partial damage to the medial parietal cortex) which the otherone did not.

As briefly summarized in this section, hippocampal lesions may alter more or less subtly maintenance behaviours. For most of them, the question of whether fimbria-fornix lesions do mimick the effects of hippocampal lesions remains to be addressed more directly than was done in the past. A major drawback with such effects is that part of them might introduce some bias in the accuracy of the various procedures used to assess cognitive functions. However, one may assume that the impact of such effects may be minimal when test situations used to assess cognitive capabilities are designed in such a way as to reduce the influence of maintenance behaviour upon the accuracy of cognitive performance or, should the case arise, to get this influence under sufficient experimental control to enable the measurement of the importance of the bias and to do appropriate corrections.

3.3.2. *Learning and Memory*

In 1957, Scoville and Milner (1957) reported the now famous H.M. case, an epileptic patient who exhibited a severe anterograde amnesia subsequently to bilateral resection of several temporal lobe structures including the amygdala and most of the hippocampus. Since that time, a majority of studies investigating the behavioural functions of the hippocampus with lesion or stimulation techniques have focused attention on the implication of the hippocampus and some of its connected structures in mnesic processes. As to which mnesic processes are affected by hippocampal lesions or denervations has become a large debate in which controversy is fed with competition between theories, more or less subtle differences between conceptual views, and the fact that findings in one species or with one given task cannot be generalized to another species or another task without qualification (e.g. Eichenbaum, 1992; Eichenbaum *et al.*, 1994). Even in the rodent literature, there is no consensus yet, neither as to which type of memory the hippocampus is mainly dealing with (constructing and learning spatial representations, storing and managing information in the working memory, memorizing contextual attributes, establishing configural associations, etc.), nor as to which theoretical categorization of the memory types related to hippocampal function may be considered as having the highest heuristical value. For extensive reviews relative to all these aspects (including the controversies) the reader is referred to, e.g. Eichenbaum, 1992; Eichenbaum *et al.*, 1992, 1994; Gray and McNaughton, 1982; Kesner, 1984; O'Keefe and Nadel, 1978; Olton *et al.*, 1979; Squire, 1992; Sutherland and Rudy, 1989. Therefore, we would like to only summarize a few simple ideas along which neurobiologists using intrahippocampal transplants have addressed the question of whether the grafts of fetal brain tissues may contribute to foster recovery of cognitive functions such as learning and memory, which are impaired by various lesions in the hippocampal system.

3.3.2.1. *Lesions of or in the fimbria-fornix fibre track and mnesic consequences*

A brief review of the intrahippocampal transplant literature (see also below) clearly shows that essentially three types of testing situations having a more or less prominent spatial load were used extensively: The food-rewarded (learned) T-maze alternation, the radial arm-maze and the Morris water-maze tasks. In the two latter situations, a distinction was made sometimes between the so-called working memory and reference memory performances (see below). Behavioural tests relying upon passive or active avoidance retention, operant conditioning tasks or others based on resolving maze-learning problems different from the aforementioned ones (e.g. Hebb and Williams maze) have also been used occasionally in intrahippocampal grafting experiments.

The food-rewarded alternation task uses a T-shaped maze. Although there are several variants of the testing procedure, the basic principle of this test can be summarized as follows: A trial is conducted in two steps. In the first step, a rat previously subjected to a restricted food or water diet is placed at a start point in the central alley and, from there, is allowed (or forced) to visit one of both arms at the extremity of which he will be reinforced with a food-pellet or a small amount of water placed in an excavation so that the rat cannot see the pellet or the water from the choice point between the goal branches of the maze. In the second step (which can be separated from the first one by a delay of variable length), the rat is returned from the just visited arm to the start point. From there, he has the possibility to visit either arm, but only the visit of the arm that was not visited in the first trial is reinforced. Over repeated trials, normal rats learn easily the task and may reach stable alternation rates approximating 100%.

The radial maze typically consists of a central platform from which radial arms (most often eight) extend over a few tens centimeters (e.g. Olton *et al.*, 1978). At the extremity of each arm, a pellet of food is placed into a small excavation. For a given trial, a food-deprived rat is placed on the central platform and allowed to choose freely among the arms and to collect the pellet in each arm. In each arm, the collection of a food pellet is possible only once within a given trial. With such a procedure, a normal rat progressively learns to consume all food pellets with a minimum of arm choices, and thus a minimum of errors; errors are defined as the re-entries within a given trial into already visited arms. Without any other constraint, this task is considered as measuring typically spatial working memory. Modifications of this standard testing protocol allow to distinguish between errors due to either working memory or reference memory failures (e.g. Jarrard *et al.*, 1984b for more details on the protocol). Briefly, according to Olton's theory (e.g. Olton *et al.*, 1978), the notion of working memory is considered to refer to mnesic processes encoding items related to the temporal/personal context of an event or a test situation, whilst reference memory encodes context-independent rules and procedures that are specific to a given situation and which remain valid each time this given situation

is encountered. To illustrate these memory categories by a concrete example, one may consider four persons playing cards. In their reference memory, these persons have memorized the rules of the game (pinocle, tarot, bridge or whatever). Their working memory will be utilized to remember the cards that are played in each turn. When all cards have been played, informations stored in their working memory are not longer meaningful, and thus can be "deleted". Conversely, the rule of the game stored in the reference memory will be the same for the next and all subsequent deals.

The Morris water maze task (e.g. Morris, 1983) uses a large circular pool of water in which an escape platform is hidden just underneath the water surface. Generally, water is made opaque with addition of powdered milk. From whatever position it is released in the pool, the rat has to find this hidden platform which he uses as a refuge. When the location of this platform is kept stable over trials, normal rats quickly learn to navigate directly to the appropriate position right after having been released in the pool and they are able to do so regardless of the position from which they are released. According to O'Keefe and Nadel's theory (O'Keefe and Nadel, 1978), this task is a typical place learning task (as opposed to a taxon learning task) requiring an intact ability to construct and use a cognitive map, i.e. an allocentric representation of their environment. In Olton's view (e.g. Olton *et al.*, 1978), this task requires intact (spatial) reference memory operations (as opposed to working memory operations) through which rats have to learn a given rule (the platform's location) that remains efficient as long as the location of the platform is constant. Modifications in the aforementioned standard testing protocol allow to distinguish between impairments due to either working memory (the platform is placed in a new location each other day) or reference memory dysfunctions the platform is kept at the same location from day to day).

In each of these three test situations, rats with a disrupted fimbria-fornix system show clear-cut deficits, whether after partial or extensive lesions of the pathways, after lesions restricted to nuclei such as the MS or the DBB, or after lesions performed with more (e.g. AF64A, IgG 192-saporin; see below, Section 3.4.1) or less (ibotenic, kainic or quinolinic acid) specific neurotoxic treatments (e.g. Olton and Wenk, 1987; MacDonald and Sirviö, 1993). Almost always, these deficits have been interpreted as due to disruption of the ability of the rats to handle, remember and/or appropriately use spatial information (e.g. O'Keefe and Nadel, 1978) to be processed in the working memory compartment (e.g. Olton *et al.*, 1979). This interpretation certainly applies to the deficits found in the T-maze alternation task and in the radial maze task used with a standard testing procedure. There is, however, evidence that operations in the reference memory compartment are also altered. Indeed, the deficits found in the Morris water maze do typically reflect an impairment of spatial reference memory, a finding which has also been observed in the radial maze task performed with the procedure described by Jarrard *et al.* (e.g. Jarrard *et al.*, 1984b).

As stated above, the disruption of the fimbria-fornix pathways deprives the hippocampus of several neurochemical types of afferents. Thus, an interesting question is which of these neurochemical systems accounts for the modulation of the cognitive operations altered following fimbria-fornix lesions? There is a series of converging arguments consolidating the view of an important role of the cholinergic component of these pathways. Actually, most mnesic deficits found in nonspecific lesion studies can be mimicked by systemic or local administration of antimuscarinic compounds such as, for instance, atropine, pirenzepine or scopolamine (e.g. Cassel and Kelche, 1989; Collerton, 1986; Hagan *et al.*, 1987). In addition, there is evidence that these deficits can also be attenuated, in some respects and under some conditions: (i) by the acute administration of cholinergic agonists such as, for instance, the muscarinic agonists oxotremorine and pilocarpine (e.g. Matsuoka *et al.*, 1991; but see Greene *et al.*, 1994); (ii) by the administration of neurotrophic factors acting more specifically on the central cholinergic system (e.g. nerve growth factor; Pallage, 1990; Pallage *et al.*, 1986; Will and Hefti, 1985); (iii) as reviewed hereafter, by the implantation into the denervated hippocampus of grafts rich in cholinergic neurons (e.g. Dunnett, 1990; Sinden *et al.*, 1995; Tarricone *et al.*, 1996). Furthermore, AF64A-induced or IgG 192-saporin-induced lesions (e.g. Berger-Sweeney *et al.*, 1994; Book *et al.*, 1994; Heckers *et al.*, 1994; Nilsson *et al.*, 1992b), which both are or have been claimed to alter more specifically the cholinergic afferents of the hippocampus with only minimal damage to other neurochemical fibre systems (e.g. Book *et al.*, 1994; Hanin, 1990; Heckers *et al.*, 1994; see also below, Section 3.4), produce cognitive deficits qualitatively comparable to those found after fimbria-fornix lesions (e.g. Chrobak *et al.*, 1989; Chrobak and Walsh, 1991; Fisher and Hanin, 1986; Gower *et al.*, 1989). Finally, there is also some evidence that the reduction of cholinergic function due to ageing is paralleled by the emergence of cognitive deficits that resemble some of the deficits due to experimental disruption of the fimbria-fornix pathways and, under some conditions, these deficits are sensitive to cholinomimetic therapy (e.g. Brandeis *et al.*, 1990; Matsuoka *et al.*, 1992; Ohta *et al.*, 1991; Riekkinen *et al.*, 1991a, 1991b; but see Sirviö *et al.*, 1992; Yamazaki *et al.*, 1995) or intrahippocampal grafts rich in cholinergic neurons (e.g. Dunnett, 1990; Gage and Björklund, 1986a). These converging arguments, however, do not appear to be sufficient to accept that the sole disruption of the cholinergic neurons in the fimbria-fornix lesion paradigm is accounting for all aspects of the mnesic deficits associated with such a lesion. It is clear at present that in all approaches mentioned above there are drawbacks, at least in terms of the neuroanatomical or neurochemical selectivity of the methods used: (i) lesions with neurotoxins such as ibotenic, quisqualic or kainic acid, although leaving the fibres *en passage* intact, damage any kind of neuron as well as glial cells in the vicinity of the injection sites; (ii) the specificity of AF64A towards cholinergic neurons has been disputed and (e.g. Hanin, 1990; Jarrard *et al.*, 1984a;

MacDonald and Sirviö, 1993; Walsh and Opello, 1994); (iii) there is not enough experience with IgG 192-saporin to consider it as a good cholinergic neurotoxin and, in addition, it only works on the neurons expressing the low-affinity NGF receptor which is not evenly associated with all cholinergic terminals in the brain; (iv) drugs given systemically act simultaneously on several cholinergic systems and there is no possibility to conclude where in the brain the neuroanatomical substrate of the effects observed is located; (v) grafts have various other possibilities than releasing a neurotransmitter for exerting functional effects in a given denervated structure of a brain-damaged organism (e.g. Dunnett and Björklund, 1987, 1994); (vi) covering co-jointly all these drawbacks, there has been enough experimental evidence accumulated showing that many neurotransmitter systems other than the cholinergic one may have cognitive implications, whether directly or indirectly (e.g. Cassel and Jeltsch, 1995; Decker and McGaugh, 1989; Haroutunian *et al.*, 1990; Levin *et al.*, 1992; Sirviö *et al.*, 1994; Steckler and Sahgal, 1995; Wenk *et al.*, 1987). As regards the fimbria-fornix lesion paradigm, especially the noradrenergic and the serotonergic systems are concerned, both of which being able to modulate the functionality of cholinergic terminals in the hippocampus as well as the cognitive consequences of cholinergic blockade (e.g. Cassel and Jeltsch, 1995; Decker and McGaugh, 1991; Haroutunian *et al.*, 1990; Starke *et al.*, 1989 for reviews). For all these reasons, the deficits reported after fimbria-fornix lesions cannot be simply and solely ascribed to the disruption of the cholinergic component of this fibre track.

3.3.2.2. *Reactive compensations and behavioural correlates*

As summarized in Sections 3.2.2.1 and 3.2.2.2, fimbria-fornix lesions induce compensatory changes such as denervation supersensitivity and reactional sprouting. The question of whether such adaptative changes may be involved in postoperative recovery (or impairment) of behavioural function has been addressed experimentally, and, under some procedural circumstances, has been answered positively. One of the first studies aimed at such a goal was reported by Azmitia *et al.* (1978). In rats subjected to 5,7-DHT-induced unilateral lesions of the cingular bundle, these authors found a systemic injection of 5-hydroxytryptophane to elicit a rotational asymetry. By approximately 1.5 months postsurgery, this response was no longer observed, a result which the authors attributed to serotonergic reafferentation of the dorsal hippocampus by sprouted serotonergic fibres, as the initially observed rotational assymetry reappeared subsequently to a second 5,7-DHT injection. In another study, Gage *et al.* (1983c) have assessed T-maze alternation at varying postoperative delays in rats that had sustained bilateral transection of the cingular bundle. By two weeks after lesion surgery, neurochemical markers such as NA and 5-HT high affinity uptake by hippocampal synaptosomes and ChAT activity were reduced. Between 6 and 24 weeks after surgery, this reduction had been attenuated substantially, and even completely compensated for in the whole hippocampus as regards ChAT activity (see Section 3.2.2.1). In parallel, rats with such lesions were impaired in learning a food-rewarded T-maze alternation task to a degree similar to that found in rats with fimbria-fornix aspiration lesions. However, this deficit was less pronounced at 3 and 6 months after surgery, an effect which the authors imputed to the attenuation of the neurochemical deficits by cholinergic, noradrenergic and serotonergic sprouted fibres. In a book chapter, Gage and Björklund (1986b) reported that two weeks after aspiration lesions of the medial cingulate cortex and the cingular bundle, rats showed a dramatic impairment in the acquisition of a Morris water maze task. By 10 and 20 weeks after surgery, two other groups given identical lesions had recovered a level of performance close to normal. Interestingly, [^{3}H]5-HT and [^{3}H]NA uptake by hippocampal synaptosomes as well as ChAT activity, which were reduced to respectively about 25%, 50% and 70% of normal two weeks after surgery, had recovered to more than 80% of normal by 20 weeks. These results further support the assumption that reactional sprouting may foster recovery of complex cognitive functions.

Regarding the modification of receptor sensitivity, a review of the litterature clearly shows that the involvement of this adaptative phenomenon in behavioural recovery from hippocampal denervations has not been investigated to the same extent as it has been in the 6-OHDA lesion paradigm of the nigrostriatal pathways. It can however be assumed that postsurgical changes in receptor sensitivity may also play some (yet not precisely determined) role in the behavioural sparing and/or recovery which may be observed following hippocampal denervation.

As summarized in Section 3.2.2.2, fimbria-fornix lesions also induce an aberrant reactional sprouting phenomenon termed sympathetic sprouting (or ingrowth) which is able to normalize and even overcompensate some noradrenergic markers in the denervated hippocampus. There has been a series of studies aimed at investigating whether this ingrowth of peripheral noradrenergic fibres was able to influence behavioural functions altered by hippocampal denervation. The first studies to address this issue were reported by Kimble *et al.* (1979a, 1979b, 1979c, 1980) who failed to find any significant contribution of sympathetic ingrowth on the recovery of spontaneous alternation, maze learning, conditioned taste aversion and open-field activity scores after lesions of the dorsal hippocampus. Crutcher *et al.* (1983) have reported similar conclusions in rats tested in a radial-maze learning task after lesions of the MS. These findings, however, are at variance with more recent reports in which sympathetic ingrowth into the cholinergically denervated hippocampus was found to have some influence upon the postsurgical behavioural recovery. Actually, using adult male rats, Ayyagari *et al.* (1991) have shown that following lesions of the MS, sympathetic ingrowth was able to alter the retention of a passive avoidance task, to attenuate gustatory neophobia and to cause hyperactivity in an open-field test. That sympathetic sprouting may also influence maintenance behaviour was reported in an earlier study by Harrell *et al.* (1987). She and her co-workers found that after MS

selective lesions of neurochemically-defined cell populations sending fibres to the hippocampus through the fimbria-fornix, the cingular bundle and the ventral pathways. Essentially cholinergic, serotonergic and to a lesser degree noradrenergic fibres have been the focus of such approaches, both for neurochemical and behavioural studies. The present section will briefly deal with these more specific lesion paradigms and their most prominent functional effects, essentially because some of these paradigms have also been used to address the question of the neurochemical and behavioural functionality of intrahippocampal grafts.

3.4.1. *Cholinergic Denervation Paradigms*

Although there exist many tools to induce more or less durable cholinergic dysfunctions in the brain (e.g. Hörtnagl and Hanin, 1992), two technical approaches have been favoured because the compounds on which they rely are able to induce true and irreversible degeneration of cholinergic neurons. The first of these compounds is commonly termed AF64A (or ECMA for ethylcholine mustard aziridinium) and consists of a nitrogen mustard derivative of choline which is highly similar to choline and is assumed to exert its specific neurotoxic effects in two steps (Hörtnagl and Hanin, 1992). In an early step, AF64A may be taken up by the high-affinity choline transport system located at the cholinergic terminal where it starts to exert its cytotoxic action, an action which must be supposed to subsequently operate by retrograde propagation. In a later step, it lastingly blocks the high-affinity choline transport system, a mechanism that may also contribute to the degeneration of cholinergic neurons as prolonged hemicholinium-3 treatment, a specific and highly potent inhibitor of the high-affinity choline transport system, was shown

the doses used, the hippocampal tissue dissection or preparation and the neurochemical marker determined, hippocampal cholinergic markers such as, for instance, ChAT or AChE activity, high affinity uptake of [^{3}H]choline by hippocampal synaptosomes and acetylcholine tissue content are depleted to values between 50% and more than 90% of normal. Interestingly, many of the behavioural deficits exhibited by rats that sustained intraventricular or intraparenchymal injections of AF64A actually resemble those reported after more or less extensive, nut non-specific lesions of the septal region or the fimbria, the dorsal fornix and the cingular bundle (e.g. Collerton, 1986; Dunnett, 1990; Jeltsch *et al.*, 1994a, 1994b, and references in Section 3.3.2.1). These rats show increased levels of activity in both a familiar and an unfamiliar environment, impaired performance in passive and active avoidance tests, as well as severely perturbated capabilities of T-maze, radial maze and Morris water maze learning (e.g. Hanin, 1990).

Controversy upon the specificity of AF64A has emerged with the demonstration that neurotransmitter systems other than the cholinergic one are also altered, although the corresponding markers are reduced to a much lower degree than the cholinergic ones and, under appropriate dosage, most of these effects appear to be reversible and/or might be functional consequences of the cholinergic degeneration rather than a direct effect of the toxin (Hanin, 1990; Hörtnagl and Hanin, 1992). Rats sustaining i.c.v. injections of high doses of AF64A were found to exhibit transient or more lasting depleted dopamine, glutamate, NA or 5-HT levels in brain regions such as the hippocampus, the cortex or the striatum (e.g. Abe *et al.*, 1994; Hörtnagl *et al.*, 1991a; Jarrard *et al.*, 1984a). Effects on glutamate decarboxylase activity in the interpeduncular nucleus have

also been reported (Villani *et al.*, 1986). Nevertheless, with low doses of a pure compound, the effects on the cholinergic system are still present and the nonspecific functional modifications do not seem to be lasting over long postsurgical periods (e.g. Dong *et al.*, 1994; Gaál *et al.*, 1986; Hanin, 1990; Hörtnagl and Hanin, 1992; Potter *et al.*, 1986). Thus, when AF64A is injected with an appropriate dosage ($\leq$ 4-5 nM/ventricle) into adequate sites (e.g. into the lateral ventricles), it seems to reach a satisfactory degree of specificity towards cholinergic neurons and to produce dramatic and lasting cholinergic denervation of the hippocampus.

So far, drawbacks qualitatively or quantitatively similar to those of AF64A have not been reported with 192 IgG-saporin. For instance, between 3 and 28 days after injection, Waite *et al.* (1994) examined the effects of the intracerebroventricularly-administered immunotoxin on various neurochemical markers in several regions of the rat brain. At 28 days, they found ChAT activity to be reduced dramatically in the parietal and the frontal cortex (> -80%), in the olfactory bulbs (close to -100%) and in the hippocampus (close to -95%). A weaker reduction was found in the septal region (-40%) and no significant modification occurred in the striatum (but see Heckers *et al.*, 1994) and the pons. With exception of the olfactory bulbs in which 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) and dopamine levels were increased by 60%, 60% and 30%, respectively, there was no significant modification of 3-methoxy-4-hydroxyphenylglycol (MHPG), 3,4-dihydroxyphenylalanine (DOPA), dopamine, DOPAC, norepinephrine, HVA, epinephrine, 5-hydroxyindolacetic acid (5-HIAA) and 5-HT levels in the other structures where ChAT activity was reduced. Nevertheless, 192 IgG-saporin was found to have other types of unspecific effects and, surprisingly, to lack some (*a priori* obvious) behavioural consequences unless an important degree of cholinergic denervation was attained (e.g. Steckler *et al.*, 1995; Waite *et al.*, 1995; Walsh *et al.*, 1995; Walsh *et al.*, 1996). Indeed, 192 IgG-saporin may damage, in some respects dose-dependently (e.g. Wiley *et al.*, 1995), part of the cerebellar Purkinje cells (e.g. Heckers *et al.*, 1994; Wiley *et al.*, 1995) as well as some cholinergic interneurons in the striatum (Heckers *et al.*, 1994). 192 IgG-saporin may also alter noradrenergic markers in the hippocampus (Walsh *et al.*, 1996). From a behavioural point of view, it was found that an average of 80% ChAT-activity or of 60-80% HACU depletion must be achieved simultaneously in various cholinergic targets (frontal, parietal, occipital cortex, hippocampus and olfactory bulbs) to observe substantial behavioural deficits in a Morris water maze (Leanza *et al.*, 1995; Waite *et al.*, 1995; Walsh *et al.*, 1995) and a passive avoidance task (Leanza *et al.*, 1995; Waite *et al.*, 1995), whereas, in the same tasks, clear-cut deficits can be observed after partial (neurochemically nonspecific) septo-hippocampal damage producing a weaker reduction of ChAT activity in only the hippocampus. In another recent study (Berger-Sweeney *et al.*, 1994), it has been reported that rats almost completely deprived of their AChE-positive hippocampal innervation by intraseptal 192 IgG-saporin injections only showed a very modest deficit in a spatial learning task (in which a similar cholinergic denervation produced by fimbria-fornix lesions induce dramatic impairments), whereas their counterparts receiving the immunotoxin into the substantia innominata (cholinergic denervation of the cortex) were approximately as dramatically impaired in performing the task as the rats given the toxin into the cerebral ventricles (basalocortical and septohippocampal cholinergic systems destroyed conjointly). The latter finding is somewhat puzzling as one largely accepted view considers the septohippocampal cholinergic system to play a more important role in spatial memory processes than does the basalocortical system. Finally, Leanza *et al.* (1996) have found that, when injected in the brain of neonate rats, 192 IgG-saporin produced a dramatic and apparently lasting loss of cholinergic neurons in both the MS and the nucleus basalis magnocellularis. However, when tested 8 months later, the rats showed no impairment in both a water maze task and a locomotor activity test. Despite these few little problems, from the overall picture in the literature, it seems that in our present state of knowledge, most behavioural deficits found after septal or fimbria-fornix lesions are also found in rats injected with 192 IgG-saporin, at least in terms of their qualitative features.

3.4.2. *Noradrenergic Denervation Paradigms*

Noradrenergic denervations of various brain regions have usually been achieved with 6-hydroxydopamine (6-OHDA), a toxin having a high affinity for the uptake sites of catecholaminergic neurons and which, therefore, does not discriminate between dopaminergic and noradrenergic neurons without the additional utilization of drug treatments which selectively protect the dopaminergic neurons. For instance, after pretreatment with a selective dopamine uptake blocker such as GBR 12909 or amfonelic acid (see MacDonald and Sirviö, 1993), 6-OHDA induces dramatic degeneration of the noradrenergic neurons, whereas the dopaminergic neurons are relatively preserved. Selective destruction of noradrenergic neurons is also achieved with N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine, a compound better known under the appellation of DSP-4 and which, being taken up by the noradrenergic terminals, does not affect the dopaminergic neurons. Usually, 6-OHDA is injected intracerebroventricularly or into the cerebral parenchyma (e.g. Langlais *et al.*, 1993), although, in some experiments, the compound was also given systemically, particularly in neonate animals (e.g. Mohammed *et al.*, 1986; Sutherland *et al.*, 1982). DSP-4 is administered systemically (50 mg/kg is the usual dosage) and induces the most dramatic noradrenergic denervations (more than 80% depletion) in the frontal cortex, hippocampus, cerebellum and spinal cord, with moderate to negligible damage to other monoaminergic systems (i.e. dopaminergic and serotonergic). There is evidence that this neurotoxin induces degeneration of the noradrenergic neurons in the locus coeruleus (e.g. Zhang *et al.*, 1995). In the studies using DSP-4 as the depleting agent and where the effects of this neurotoxin were assessed in both the

cortex and the hippocampus, it is noteworthy that the NA depletions in both structures were generally of similar magnitude (e.g. Berridge and Dunn, 1990; but see Bennett *et al.*, 1990), and so seems also to be the case with systemically administered 6-OHDA in neonates (Mason and Iversen, 1975, 1977) or 6-OHDA infused into the dorsal noradrenergic bundle (e.g. Langlais *et al.*, 1993).

As regards the functional involvement of the central noradrenergic neurons, essentially two types of approaches have been developed, one concerned with the functions of NA in postsurgical plasticity phenomena in the CNS (e.g. Gordon *et al.*, 1988), the other one with the implication of this neurotransmitter in cognitive and other aspects of behaviour. As regards the former, it appears that NA depletions abolish both the functional sparing observed after neonatal frontal cortex damage (Sutherland *et al.*, 1982; Kolb and Sutherland, 1992) and the possibility for physically and socially enriched housing conditions to attenuate the learning and memory deficits resulting from entorhinal cortex or other types of lesions (e.g. Mohammed *et al.*, 1986; Pappas *et al.*, 1987). Lesions to central noradrenergic fibres are also able to substantially attenuate learning deficits resulting from damage of the nucleus basalis assessed in reinforced T-maze alternation task (Moran *et al.*, 1992) and in the 8-arm radial maze (Sara *et al.*, 1992). As regards the second approach, central NA depletion was found to disrupt social behaviour (Zagrodzka *et al.*, 1994), to induce transient hyperactivity (e.g. Berridge and Dunn, 1990) followed by more or less lasting hypoactivity and hypoexploration (e.g. Archer, 1982; Archer *et al.*, 1983; Bennett *et al.*, 1990; Semenova *et al.*, 1987; but see Harro *et al.*, 1995), to increase perseverence during the extinction of a running for food-reward behaviour (Mason and Iversen, 1975, 1977), to slightly decrease attention (Carli *et al.*, 1983), to slow-down the acquisition of a temporal discrimination (e.g. Ho *et al.*, 1995) as well as that of a reinforced right-turning response in a modified T-maze (Archer *et al.*, 1983), to impair spontaneous T-maze alternation (e.g. Pisa and Fibiger, 1983b), active avoidance (probably through a peripheral mechanism; e.g. Bennett *et al.*, 1990) and water maze performance assessed under stressful (i.e. cold water) conditions (Selden *et al.*, 1990). There are also several studies in which central NA depletions had no detectable effects on acquisition and retention of a delayed and a non-delayed food reinforced T-maze alternation task, on passive avoidance retention (e.g. Haroutunian *et al.*, 1990), on performing discrimination tasks involving selective attentional processes (e.g. Pisa and Fibiger, 1983a, 1983b), and on 8-arm radial maze learning (e.g. Chrobak *et al.*, 1985). Finally, another series of studies showed that central noradrenergic lesions which had no proper effect in various tasks were able to potentiate the disruptive effects on cognitive functions of muscarinic blockade or cholinergic lesions (e.g. Decker and McGaugh, 1989, 1991; Ohno *et al.*, 1993; Riekkinen *et al.*, 1990, 1992; but see Langlais *et al.*, 1993). Overall, it appears that NA depletions have never been found to induce as consistant and as dramatic cognitive alterations as those found in rats with cholinergic lesions or centrally acting muscarinic blockade. Thus, regarding the aforementioned literature, one essential role of the central noradrenergic system might be to exert a neuromodulatory action on other systems of neurotransmitters more directly involved in cognitive processes. Finally, another consistent finding in rats is that after damage to the noradrenergic afferents of the hippocampus decreases the threshold to epileptogenic manipulations such as, for instance, hippocampal kindling (see description and references in Section 5.4).

3.4.3. *Serotonergic Denervation Paradigms*

As for selective destruction of cholinergic or catecholaminergic neurons in the brain, techniques allowing to specifically damage the serotonergic neurons in the fimbria-fornix and other neuroanatomically-defined serotonergic systems are now in use for more than thirty years. These techniques rely upon the intraparenchymal or intracerebroventricular injection of two dihydroxytryptamines termed 5,6-dihydroxytryptamine (5,6-DHT) and 5,7-dihydroxytryptamine (5,7-DHT), as well as on the systemic administration of the amino acid p-chlorophenylalanine (PCPA) or the amphetamine derivative p-chloroamphetamine (PCA). More recently, another amphetamine derivative, 3,5-methylenedioxymethamphetamine (MDMA, "Ecstasy") has also been used in order to damage central serotonergic neurons (e.g. Finnegan *et al.*, 1988; MacDonald and Sirviö, 1993; Ricaurte *et al.*, 1988). The administration of PCPA or PCA requires no surgical operation, in contrast to that of 5,6-DHT or 5,7-DHT. PCPA and PCA have been used extensively before 5,6-DHT and 5,7-DHT were introduced. PCPA induces a long lasting inhibition of 5-HT synthesis and PCA, although its mechanism of action is still subject to debate (e.g. MacDonald and Sirviö, 1993), is taken up by serotonergic terminals where it produces cytotoxic effects. It is however noteworthy that with both compounds, the 5-HT depletion is reversible within weeks or months, depending on the dose used and the number of daily injections made. Other drawbacks include the fact that PCPA causes degeneration also of catecholaminergic neurons (dopaminergic, noradrenergic, adrenergic) in various regions of the brain and fails to affect all markers of serotonergic function (e.g. 5-HT uptake sites are preserved). As concerns the drawbacks of PCA, substantial 5-HT depletion can be obtained only in the mature brain and, somewhat paradoxically, its initial effect consists in increased 5-HT release. Furthermore, there exists a subpopulation of serotonergic neurons resistant to PCA; these neurons provide approximately 10%, 20% and 15% of the cortical, striatal and hippocampal serotonergic innervation, respectively (e.g. Schmidt and Kehne, 1990). 5,6-DHT and 5,7-DHT have been introduced by Baumgarten *et al.* in the early seventies (e.g. Baumgarten *et al.*, 1971, 1973; Baumgarten and Lachenmayer, 1972). These compounds are taken up by the serotonergic terminals and cause a true neuronal degeneration by acting on the neuronal cell bodies (further detail in Tabatabaie *et al.*, 1993). Their effects are only poorly compensated for over

Table 3. Summary of the Possible Relationships Between the Extent of An Experimental Hippocampal Denervation, the Acute Neurochemical and Behavioural Effects of the Lesions, the Contingency of Functional and Structural Postsurgical Compensations (See Table 2), the Chances for Neurochemical and Behavioural Recovery to Occur Over Time and the Type of Palliative Treatments to be Most Relevant (Suitable) in Each Case.

Type of variable considered	Extent of hippocampal denervation		
	Small	Intermediate	Large to maximal
Acute neurochemical effects	none to weak	moderate to large	dramatic
Acute behavioural effects	none to weak	moderate to large	dramatic
Receptor sensitivity and neurotransmitter turnover	possible	yes	yes
Homotypic and/or heterotypic sprouting	possible	yes	yes (weak*)
Neurochemical recovery	complete	from partial to complete	none to weak
Behavioural recovery	complete	at most partial	none
Possible palliative treatments to influence neurochemical or behavioural recovery	–drug treatments† –neurotrophic factors†	–drug treatments‡ –neurotrophic factors‡ –intrahippocampal grafts‡	–drug treatments§ –neurotrophic factors§ –intrahippocampal grafts§

* For the cholinergic and serotonergic afferents, more pronounced for the central noradrenergic afferents, massive for the noradrenergic afferents originating in the superior cervical ganglia.

† In order to accelerate recovery.

‡ In order to ameliorate or maximize recovery.

§ In order to induce recovery which does not occur spontaneously.

time and can therefore be considered as durable. When given to neonates, the serotonergic depletion lasts for the whole life (e.g. Breese and Cooper, 1975). The utilization of 5,6-DHT and 5,7-DHT requires some precautions as both toxins are also active on dopaminergic and noradrenergic neurons. The protection of both types of catecholaminergic neurons or at least a substantial attenuation of their destruction can be obtained by pretreatment with uptake-blocking drugs such as desmethylimipramine or nomifensine. For further detail, the reader is referred to the book chapter by MacDonald and Sirviö (1993) and the reviews by Reader (1989) or Sinhababu and Borchardt (1985). All these compounds have particular advantages which must be balanced against their respective drawbacks according to the question to be experimentally addressed. However, one consensus is that they all produce dramatic alterations of serotonergic function in the brain and that, beside the frontal and other parts of the cortex, one of the regions to be affected to the highest degree is the hippocampus.

The serotonergic systems of the brain were found to be involved in many aspects of behaviour including anxiety, appetite, arousal, attention, circadian rhythmicity, cognition, sexual motivation... (e.g. Jacobs and Azmitia, 1992; Whitaker-Azmitia and Peroutka, 1990). More in line with the topic of this review, the role of serotonergic afferents of the hippocampus has been more specifically studied in terms of their cognitive implications. In the relevant literature, it seems that there is no general agreement on whether the ascending serotonergic system has a direct involvement in cognitive function, and more particularly in those underlying learning and memory. For instance, on the one hand, Altman *et al.* (1990) found that infusions of 5,7-DHT into the fimbria-fornix and the cingulum of rats resulted in enhanced performance in a positively reinforced spatial discrimination task as compared to the performance of virtually intact rats. Also Richter-Levin and Segal (1991) found an intracerebroventricular administration of 5,7-DHT to enhance performance in rats submitted to a passive avoidance task. On the other hand, Yehuda *et al.* (1995) have reported that in a Morris water maze reference memory task, rats given 5,7-DHT into the fourth ventricle showed acquisition performance which were almost as dramatically impaired as those found in rats with AF64A-induced cholinergic lesions. Dringenberg *et al.* (1995) found rats given systemic administrations of PCPA (80% decrease of the whole brain 5-HT content) to exhibit reduced activity scores with no sensory-motor impairment.

However, in a large majority of studies using rats, central serotonergic depletions performed with 5,7-DHT, PCA or PCPA were found to have no direct effect on learning and memory abilities assessed in various cognitive tasks (e.g. Asin *et al.*, 1985; Cuadra and Molina, 1990; Jäkälä *et al.*, 1992, 1993; Nilsson *et al.*, 1988b, 1990a; Richter-Levin *et al.*, 1994; Richter-Levin and Segal, 1989; Santucci *et al.*, 1995; Vanderwolf *et al.*, 1990; Volpe *et al.*, 1992; Williams *et al.*, 1990; see also references considered in the reviews by Cassel and Jeltsch, 1995; Sirviö *et al.*, 1994; Steckler and Sahgal, 1995). This, however, should not lead to the conclusion that the ascending serotonergic fibres have absolutely no involvement in cognitive function. Actually, as reviewed recently (Cassel and Jeltsch, 1995; Sirviö *et al.*, 1994; Steckler and Sahgal, 1995; see also Levin *et al.*, 1992), manipulations such as systemic blockade of the central serotonergic neurotransmission, lesions (5,7-DHT, PCA) or functional depletions (PCPA) of central serotonergic fibres were almost always found to potentiate the cognitive alterations induced by lesions of central cholinergic nuclei (nucleus basalis magnocellularis, MS and DBB) or by centrally acting blockade of the muscarinic neurotransmission (atropine, scopolamine). Thus, as already stated for noradrenergic functions, it seems that the serotonergic system in the brain is involved in cognitive

processes more indirectly as a neuromodulator of the functional contributions of other systems such as the cholinergic one.

3.5. Conclusions

More or less extensive classical (aspiration, transection, electrolysis...) lesions of the fimbria-fornix fibre track and the overlying cingular bundle induce cholinergic, noradrenergic and serotonergic denervation of the hippocampus. Roughly, the severity of this denervation can be considered as proportional to the extent of the damage. Subsequently to the lesions, two types of reactive changes may occur. One of these changes can be detected soon after the injury. It may consist of: (i) a downregulation of presynaptic inhibitory autoreceptors (e.g. muscarinic receptors on cholinergic terminals) and, under some circumstances, heteroreceptors (e.g. 5-HT_{1B} receptors on cholinergic terminals); (ii) an upregulation of presynaptic activatory autoreceptors (e.g. nicotinic receptor on spared cholinergic terminals) or of postsynaptic receptors specific to each neurotransmitter system (e.g. muscarinic M1 receptors, noradrenergic β-receptors or serotonergic 5-HT_1 receptors); (iii) in the undamaged afferent fibres, an overall increase in neurotransmitter synthesis and an augmentation of the release potential. The other postsurgical change involves neuroanatomical reorganizations and needs a much longer time before its effects become detectable. It mainly consists in regenerative (severed axons) or collateral (intact axons) sprouting of fibres which normally innervate the hippocampal parenchyma, as well as in heterotypical nonregenerative sprouting of fibres which normally do not innervate the hippocampal parenchyma (e.g. sympathetic sprouting). With lesions more specific of a neurotransmitter system, there may be similar modifications with, however, a more or less pronounced specificity towards the neurochemical identity of the altered system, a specificity depending upon the type and severity of the undesirable side effects of the neurotoxic compound used.

All these modifications are not necessarily sufficient to compensate for the behavioural deficits induced by lesions of the fimbria-fornix and cingular pathways. It seems that beneficial effects of these changes can be observed only when a substantial part of the hippocampal afferents has been spared by the lesion procedure. Otherwise, the deficits appear to be permanent or, if attenuated over time, never completely compensated for. Looking at the literature, it is tempting to speculate that in the fimbria-fornix lesion paradigm, the chances of such compensatory neuroanatomical and functional modifications to foster behavioural recovery are inversely proportional to the extent of the lesion: the larger the latter, the smaller the former. This relationship is certainly not that simplistic in reality and far from being linear. However, from a theoretical point of view (summarized in Table 3), one might distinguish at least three "windows", each of which being both delineated by a minimal and a maximal lesion extent. In the first window, the lesion extent is small, the neurochemical and behavioural consequences are weak and the neuroanatomical and functional compensatory phenomena might be sufficient to normalize both the neurochemical and behavioural functions. It is just a matter of time. In the next window, the lesion extent is larger, the neurochemical and behavioural consequences are more pronounced, and the structural and functional compensatory phenomena may only contribute to attenuate the extent of the lesion-induced deficits. Here, partial recovery is still expectable, normalization no longer. In the last window, the lesion extent is massive, the neurochemical and behavioural consequences are dramatic, and the structural and functional changes occurring after injury, which may account only for a weak attenuation of the neurochemical deficits, are insufficient to induce significant behavioural recovery. This view is extremely reductionistic, especially because it does not include a large series of other processes that may underly recovery of function (e.g. Finger *et al.*, 1988; Finger and Stein, 1982; Marshall, 1984, 1985; Stein *et al.*, 1995) and also, because it excludes consideration of neuroanatomical reorganizations such as sympathetic sprouting which, under some conditions, may account *per se* for detrimental behavioural effects (see Section 3.3.2.2). However, this extremely caricatural view proposes three theoretically-defined frames in which the relevance of recoursing to therapeutical tools such as drugs, neurotrophic factors or grafts may be addressed and discussed. In the first window, drugs and neurotrophic factors are probably appropriate measures to accelerate the recovery processes, but intracerebral grafts, because permanent once implanted (and for many other reasons; see discussion in Cassel *et al.*, 1992a), do not appear to be pertinent palliatives. In both other windows, all these tools may be used (in the second one to potentiate neurochemical and behavioural recovery, in the third one to induce it), each being one possible focus of experimental approaches. This is precisely what intracerebral grafting techniques have most often been during the last 25 years and what will be the concern of the next part of our review in relation with fimbria-fornix lesions, their neurochemical effects in the hippocampus and their behavioural consequences.

4. NEUROCHEMICAL EFFECTS OF INTRAHIPPOCAMPAL (OR PERIHIPPOCAMPAL) GRAFTS

4.1. Introductory Remarks

The very first experimental studies in the "recent" history (see Introduction) of intracerebral grafts of neural tissue were aimed at characterizing the possibilities for such grafts to survive and develop in the mature mammalian brain. Therefore, these studies had almost exclusively recourse to approaches relying upon histological and morphological techniques. Rather quickly, various technical factors, physiological constraints or limits, and surgical procedures allowing grafts of fetal neurons to survive and become integrated into a host structure which

they contributed to reinnervate were identified and characterized (for a retrospective see, e.g. chapters 1 to 10 in Björklund and Stenevi, 1985). Thereafter, a progressively increasing number of research groups in the world started to address the question of whether well surviving grafts were also functional and, if so, which type of mechanism(s) could be considered to account for their functionality. The two first lesion paradigms to be used most extensively in such a perspective consisted of animal model(s) of PD and AD, namely 6-OHDA lesions of the nigrostriatal pathways and disruption of either the fimbria-fornix or the basalocortical pathways, respectively (for a retrospective see, e.g. chapters 34,39,40-52 in Björklund and Stenevi, 1985). In that concern and although various methodologies had become available (e.g. *in oculo*, intracavitary or intraventricular transplantation of tissue blocks, intraparenchymal cell suspension grafts or peripheral nerve implantation to bridge two disconnected brain structures), essentially intracavitary (tissue blocks placed into a lesion cavity) and intraparenchymal (minced tissue or cell suspensions placed into the brain structure to be reinnervated) transplantation techniques were used to investigate the neurochemical and behavioural effects of grafts implanted close to or within the denervated hippocampus. Occasionally, the grafts have been placed in one or the other cerebral ventricle.

The question of the functionality of such grafts has also been addressed using electrophysiological methods, but this aspect, which by itself deserves a large review, will not be taken into account herein (information can be found in, e.g. Buzsàki *et al.*, 1988; Buzsàki and Gage, 1989; Segal, 1987; Segal *et al.*, 1988; Shapiro *et al.*, 1989; Vinogradova, 1995).

In Section 3, we have seen that lesions of the fimbria-fornix/cingular bundle pathways disrupted most of the cholinergic and serotonergic hippocampal innervation, whilst the hippocampal noradrenergic and GABAergic markers were less dramatically affected. Thus, it is not a real surprise to establish that, in the literature, the majority of studies investigating the functional effects of intrahippocampal grafts have used preparations from regions of the fetal brain such as the basal forebrain (e.g. the MS and the DBB, which both are rich in cholinergic neurons and are the normal source of hippocampal cholinergic afferents) or the mesencephalic *raphe* (which is rich in serotonergic neurons and is the normal source of hippocampal serotonergic afferents). Only a few experiments used grafts rich in noradrenergic neurons. More recently, there have also been studies relying upon new approaches such as the intracerebral implantation of genetically modified cell lines in order to restore altered aspects of hippacampal organization or functionality. It is the purpose of the first part of this section to deal with the neurochemical and neuropharmacological effects of the various types of grafts placed into the denervated hippocampus and, in the second part, with the graft-induced recovery of behavioural (essentially mnesic) functions and, in case of grafts rich in noradrenergic neurons, with their effects on epileptic thresholds assessed with hippocampal kindling paradigms.

4.2. Grafts Rich in Cholinergic Neurons and Other Grafts Exerting Cholinergic Effects

4.2.1. *Blocks of Fetal Basal Forebrain Tissue Placed into a Lesion Cavity*

From a technical point of view, this procedure is rather simple and can be applied in two almost simultaneous steps (lesion and implantation, respectively) or with a delay inserted between the first and the second step. The first step consists in preparing the lesion cavity, generally with a glass pipette connected to a suction apparatus and through which the cerebral tissue to be removed is aspirated. The second step consists in dissecting and cutting off the desired region of the fetal brain, laying this region down on the bottom of the cavity and covering the graft with gelfoam. Further technical details may be found in Stenevi *et al.* (1985).

Using such a transplantation technique and, after a postsurgical delay of several months, a technique of AChE histochemistry, it has been demonstrated that grafts of fetal basal forebrain are able to provide the denervated hippocampus with a new organotypic cholinergic innervation (i.e. innervate hippocampal regions where cholinergic terminals make normally synapses in intact rats; e.g. Dunnett *et al.*, 1982; Ezerman and Kromer, 1987; Kelche *et al.*, 1988; Kromer, 1982; Leanza *et al.*, 1993b; Lewis and Cotman, 1983; Low *et al.*, 1982). From a neurochemical point of view, using an *in vivo* microdialysis technique coupled to HPLC detection of neurotransmitters present in the dialysat, grafts of basal forebrain tissue blocks were found to increase the baseline release of acetylcholine in the fimbria-fornix denervated rat hippocampus to at least normal levels (Nilsson *et al.*, 1990b). This release was stimulated (+ 210%) in a manner comparable to that found in intact rats when potassium chloride (KCl, 100 mM) was added to the perfusion fluid, and was reduced to the baseline level found in lesion-only rats by the addition of tetrodotoxin (TTX, 1 μM), a sodium channel blocker. Neither of these responses was observed in lesion-only rats. Interestingly, the release of acetylcholine could also be augmented by gentlly handling the rats (+ 60%) or by electrical stimulation of the habenula (+ 65%), but this augmentation was not as pronounced as that seen in intact rats (+ 100% and + 200%, respectively). In all cases, these results demonstrate that the grafts are under control of host afferents, part of which originate in the habenular complex. According to Leanza *et al.* (1993b), some of these afferents are from catecholaminergic neurons as the systemic treatment with apomorphine (a dopaminergic agonist; 2 mg/kg, s.c.) or amphetamine (a cetacholamine uptake inhibitor that also activates catecholamine synthesis and release; 2.5 mg/kg, s.c.) was found to increase the release of acetylcholine in the grafted rats (+ 58% and + 112%, respectively), although not to a level similar to that found in intact rats (+ 190% and + 300%, respectively).

4.2.2. *Intraparenchymal Injections of Cell Suspensions*

The principal steps in this procedure consist in dissecting out the region to be grafted as for the

implantation of the tissue blocks, collecting the dissected regions into a medium containing trypsin(0.05-0.1%) or another enzyme such as collagenase, incubating the whole at 37°C for a given period of time (20-30 min), washing the trypsin away. Using a Pasteur pipette, the tissue pieces are subsequently dissociated by repeated pipetting into a homogeneous cell suspension. Under stereotaxic control, this suspension (50,000-100,000 cells/μl) is then injected into the implantation region of the host brain through a Hamilton syringe. Generally, the amounts injected are calculated such as half the cells obtained from one septal tissue piece are implanted in each hippocampus. Further technical details may be found in Björklund and Stenevi (1985).

This technique was the one to be used most frequently in studies aimed at providing the experimentally denervated hippocampus with a new graft-derived cholinergic innervation. As was the case with the tissue blocks placed into a lesion cavity, the suspension grafts rich in cholinergic neurons were found to provide the denervated hippocampus with a new organotypic AChE-positive reinnervation (e.g. Björklund *et al.*, 1983b; Dunnett *et al.*, 1982; Nilsson *et al.*, 1988a).

Regarding the neurochemical effects of such grafts, several cholinergic (but also noncholinergic) markers were found to be partially compensated for, normalized or, in some experiments, even slightly overcompensated in the vicinity of the implantation sites. Using determination of ChAT activity as a marker for cholinergic function, Björklund *et al.* (1983a) reported the over 85% fimbria-fornix lesion-induced reduction of this marker to be compensated for completely in the dorsal hippocampus, the region in which the grafts had been injected, and only partially in the ventral hippocampus, a region in which no graft had been implanted. Interestingly, Björklund *et al.* (1983a, 1983b) also showed that: (i) this graft-induced effect occurred progressively over time, with a dramatic increment between 10 days and 1 month; (ii) the earliest effects were detectable in the close vicinity of the injection sites; (iii) even after long delays, the highest levels of ChAT activity were inevitably found in the regions where the suspensions had been injected (a significant effect was also detected in the most ventral portion of the hippocampus, but only after 6 months). The latter observation (confirmed in other studies; e.g. Cassel *et al.*, 1993b; Jeltsch *et al.*, 1994b), demonstrates that, when grafts are implanted in the dorsal half of the hippocampus, there always exists a decreasing septo-temporal gradient of the graft-induced effects on the cholinergic markers. That this graft-induced increase in ChAT activity actually reflected increased cholinergic function was confirmed in the same study by the determination of [^{14}C]acetylcholine synthesis from [^{14}C]glucose (recovery to 94% of normal; lesion effect: 60% decrease). In another series of experiments which used either aspiration of the dorsal septohippocampal pathways (fimbria-fornix/cingular bundle) or electrolytic lesions of only the fimbria and the dorsal fornix (see Fig. 4, top), we also found that, after 6–10 months, cell suspension grafts rich in cholinergic neurons had increased the ChAT activity to levels between 50% and 110% of normal after aspiration lesions and 70%–120% after electrolytic ones (ventral and dorsal hippocampus, respectively). In these studies, we also assessed the effects of other cell suspension grafts or non-cholinergic effects of grafts rich in cholinergic neurons as will be discussed in Sections 4.3 and 4.4, respectively. Evidence of graft-derived cholinergic terminals in the hippocampus was obtained in studies which used the determination of high affinity [^{3}H]choline uptake (HACU) by hippocampal synaptosomes, a specific marker of cholinergic terminals.

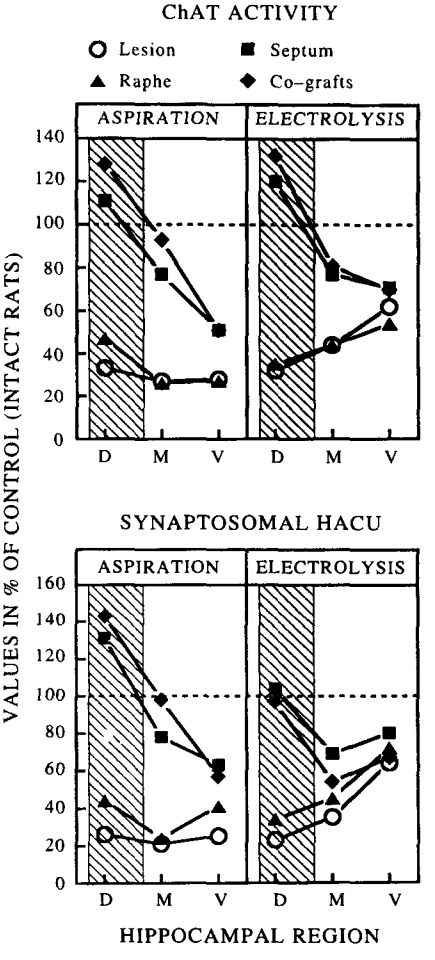

Fig. 4. ChAT activity (top) and synaptosomal high affinity uptake of [^{3}H]choline (bottom) determined between 8 and 10 months after surgery in the dorsal (D), median (M) and ventral (V) hippocampus of rats with only aspiration (left panel) or electrolytic (right panel) lesions of the fimbria-fornix pathways and of rats which, in addition to the lesions, were subjected to intrahippocampal grafting of cell suspensions prepared from the region including the medial septum and the diagonal band of Broca (septum; Section 4.2) or the mesencephalic raphe (raphe; Section 4.3) of the fetal brain, or of a mixture of both suspensions (co-grafts; Section 4.5). All values are expressed as a percentage of the average absolute values found in virtually intact rats (100%; dotted lines). The hatched bars in each panel delimit approximately the hippocampal region in which the grafts had been implanted and where histological verifications generally showed them to be located. Data are from Cassel *et al.*, 1993b (aspiration) and Jeltsch *et al.*, 1994b (electrolytic); for further details, see these two references.

For instance, Kaseda *et al.* (1989) found intrahippocampal cell suspension grafts rich in cholinergic neurons to increase the HACU to 90% and 75% of normal in the dorsal and ventral portions of the hippocampus, respectively, a marker which was reduced by 70% and 60% after aspiration lesions of the dorsal septohippocampal pathways (see also Tarricone *et al.*, 1991). In our own experiments (see Fig. 4, bottom), we also found that the synaptosomal HACU was increased by septal grafts to a supranormal level in the dorsal hippocampus after aspiration lesions of the fimbria-fornix/cingular bundle (130%; Cassel *et al.*, 1993b) and to a normal level after electrolytic lesions of only the infracallosal component of these pathways (104%; Jeltsch *et al.*, 1994b).

Using hippocampal slices from sham-operated, lesion-only and septal-grafted rats, we recently found (Cassel *et al.*, 1995) that the electrolytic fimbria-fornix lesion-induced decrease (− 65%) of electrically-evoked [^{3}H] overflow in the slices preincubated with [^{3}H]choline was restored to slightly more than normal values in the lesioned rats which had received the grafts.

Results qualitatively similar to the aforementioned ones were also obtained using other lesion paradigms including lesions of the MS (e.g. Pallage *et al.*, 1986), i.c.v. injections of AF64A (e.g. Emerich *et al.*, 1992; Ikegami *et al.*, 1991), daily ethanol intoxication for several months (e.g. Arendt *et al.*, 1989), or using aged rats exhibiting central cholinergic dysfunctions (e.g. Gage and Björklund, 1986a; Gage *et al.*, 1984b).

A few experiments based on a fimbria-fornix lesion paradigm also investigated the effects of other sources of cholinergic neurons in the fetal brain. For instance, Heuschling *et al.* (1988) reported that cortical, hippocampal, septal and striatal grafts survived best when transplanted into their respective regions of origin which had been lesioned four days before transplantation surgery. With the exception of striatal grafts which showed reasonable survival only when grafted into their region of origin, good survival was also achieved between regions that are anatomically related. Heuschling *et al.* (1988) also reported *in vitro* experiments leading to similar conclusions. Li *et al.* (1992) reported that intrahippocampal grafts of fetal striatal cells in fimbria-fornix lesioned rats are also able to increase synaptosomal HACU, although the reported effect was weaker than after the implantation of neurons from the septal region of the fetal brain (see also Clarke *et al.*, 1986, 1990; Gibbs *et al.*, 1986; Lewis and Cotman, 1983).

Regardless of the lesion paradigm or the origin of the grafted cholinergic cells, it is quite obvious that all these *in vitro* techniques do not allow to infer unequivocally, that the grafts rich in cholinergic neurons are actually working *in vivo*, nor do they inform, should the case arise, about the mechanisms which may underly an autoregulation or/and a host-derived regulation of the functional output from the grafted neurons (i.e. release of acetylcholine). Such more functional aspects have been evidenced in several recent reports. Similarly to what they found with tissue block grafts implanted into the fimbria-fornix lesion cavity, Nilsson *et al.* (1990b), using a microdialysis technique, reported that after such lesions, intrahippocampal fetal septal cell suspension grafts were able to normalize or even overcompensate the baseline release of acetylcholine. Whilst the addition of KCl (100 mM) to the perfusion fluid resulted in a 140% increase of the release, an effect which was also partly mimicked by gentle handling of the rats (+ 57%) or electrical stimulation of the habenula (+ 68%), the addition of TTX reduced the release to the level found in lesion-only rats (see also, Kalén *et al.*, 1991a, 1991b). Among other results, Nilsson and Björklund (1992) have also shown that the release of acetylcholine by grafted cholinergic neurons was increased during the second session of a swimming task (+ 50% compared to a + 90% in the intact control rats). These data do not only demonstrate that septal grafts do actually work *in vivo* (they release acetylcholine under rest conditions and respond to depolarisation), but also indicate that the grafted cholinergic neurons are regulated by host afferents. In another report by the same group (Leanza *et al.*, 1993b), it has been demonstrated that part of these afferences might be catecholaminergic. Again with a microdialysis approach, the authors showed that in fimbria-fornix lesioned rats which sustained suspension grafts rich in cholinergic neurons, a systemic treatment with apomorphine (2 mg/kg, s.c.) or amphetamine (2.5 mg/kg, s.c.) increased the release of acetylcholine by 91% and 112%, respectively (+ 190 and + 300% in intact rats). The amphetamine-induced response could be abolished by pretreatment with α-methyl-para-tyrosine, a catecholamine synthesis blocker. All these findings clearly indicate that the functional expression of grafts rich in cholinergic neurons are under a modulatory influence of the host brain.

Another mechanism by which graft-induced neurotransmitter release may be modulated involves auto- and heteroreceptors receptors located at the terminals of the axons grown from grafted neurons. We recently found that cholinergic neurons from the basal forebrain grafted into the denervated hippocampus possessed muscarinic inhibitory autoreceptors, as well as 5-HT$_{1B}$ heteroreceptors. Both types of receptors were found to exhibit almost normal functional properties (Cassel *et al.*, 1995). In hippocampal slices preincubated with [^{3}H]choline and exposed to electrical filed stimulation, the application of atropine, a muscarinic antagonist, increased the electrically-evoked release of [^{3}H] by 209% in sham-operated rats, 80% in the lesion-only ones and 117% in the grafted ones (compared to the release found in absence of drug applications). Conversely, the application of oxotremorine, a muscarinic agonist, induced a dose-dependent decrease of the evoked [^{3}H] release, as did that of CP 93129, a specific 5-HT$_{1B}$ agonist. Interestingly, in both the lesion-only and grafted rats, the sensitivity of the muscarinic and 5-HT$_{1B}$ receptors to atropine and CP 93129, respectively, was lower than in the sham-operated control rats, suggesting that these two receptor types had undergone a downregulation and/or had failed to develop normally on the terminals of the grafted neurons. This experiment also allowed us to exclude a presynaptic modulatory influence on acetylcholine release of nicotinic, 5-HT$_{1A}$, 5-HT$_2$ and 5-HT$_3$ receptors, in intact, lesion-only and grafted rats, a

finding which does not, however, preclude the possibility for such receptor subtypes to mediate a polysynaptic modulatory influence on the activity of grafted cholinergic neurons *in vivo*, perhaps in a manner similar to that reported in intact rats or guinea pigs (e.g. Consolo *et al.*, 1994; Izumi *et al.*, 1994; Wilkinson *et al.*, 1994). Although the latter possibility needs further investigation, we recently obtained preliminary data (Erb, Klein, Köppen, Löffelholz, Jeltsch and Cassel, submitted) with an intrahippocampal microdialysis approach suggesting that the graft-derived release of acetylcholine can be stimulated by systemic injection of 8-OH-DPAT, a selective 5-HT_{1A} receptor agonist. Another type of control has been suggested in the study by Kaseda *et al.* (1989) who reported that the almost normalized HACU by hippocampal synaptosomes was further increased by systemic treatment (just before sacrifice of the rats) with scopolamine (muscarinic antagonist) or picrotoxine (a GABAergic antagonist), the drug-induced increase being comparable to that found in intact rats with either drug (+ 45% and + 36%, respectively). Thus, the grafted cholinergic neurons are also able to respond to the modulatory action of a GABAergic input which might involve GABAergic neurons located outside and/or inside the grafts, as previous reports described septal grafts to also contain a subtype of GABAergic neurons positively immunostained for parvalbumin(e.g. Buzsàki *et al.*, 1992; Cassel *et al.*, 1991b). The latter observation is consistent with the close proximity of GABAergic and cholinergic neurons in the septal region of the rat brain (e.g. Kiss *et al.*, 1990).

Using hippocampal slice preparations, we failed to observe any lesion- or graft-induced effect on the carbachol evoked-formation of inositol monophosphate (Cassel *et al.*, 1991a), a product involved in the second messenger system related to muscarinic M_1, M_3 and M_5 activation. However, in other studies it was found that intrahippocampal grafts affected the lesion-induced modifications of the hippocampal muscarinic receptor density or sensitivity (see above, Section 3.2.3.1). Actually, Dawson *et al.* (1989); (see also Dawson *et al.*, 1988) reported that the fimbria-fornix lesion-induced increase of hippocampal M_1 (in region CA2) and M_2 (in regions CA2, CA3 and CA4) binding sites was counterbalanced by intrahippocampal grafts rich in cholinergic neurons at eight months after surgery, an effect which was also found by others with a technique assessing the [^{3}H]QNB binding in the hippocampus after fimbria-fornix or medial septal lesions (Segal *et al.*, 1989; Tarricone *et al.*, 1993). Using a shorter postsurgical delay, also Joyce *et al.* (1989) found that grafts rich in cholinergic neurons were able to normalize the fimbria-fornix lesion-induced increase of the number of hippocampal M1 and M2 receptors (in regions CA1, CA3 and in the dentate gyrus). Interstingly, such results were obtained with grafts of septal tissue as well as of striatal fetal tissue (the striatum also contains cholinergic neurons but these do not project to the hippocampus in intact rats). With striatal tissue, however, the reversal of the lesion effect on muscarinic receptors was observed only when the graft had provided the hippocampus with a substantial cholinergic reinnervation. Histological

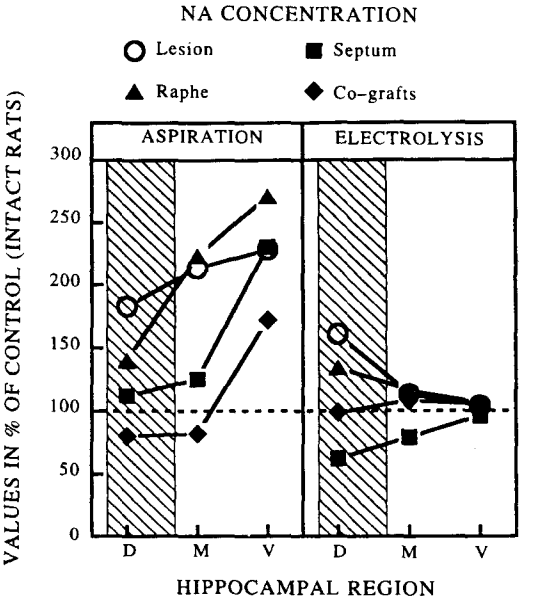

Fig. 5. Noradrenaline concentration determined between 8 and 10 months after surgery in the dorsal (D), median (M) and ventral (V) hippocampus of rats with only aspiration (left panel) or electrolytic (right panel) lesions of the fimbria-fornix pathways and of rats which, in addition to the lesions, were subjected to intrahippocampal grafting of cell suspensions prepared from the region including the medial septum and the diagonal band of Broca (septum; Section 4.2) or the mesencephalic raphe (raphe; Section 4.3) of the fetal brain, or of a mixture of both suspensions (co-grafts; Section 4.5). All values are expressed as a percentage of the average absolute values found in virtually intact rats (100%; dotted lines). The hatched bars in each panel delimit approximately the hippocampal region in which the grafts had been implanted and where histological verifications generally showed them to be located. Data are from Cassel *et al.*, 1993b (aspiration) and Jeltsch *et al.*, 1994b (electrolytic); for further details, see these two references.

evidence for a cholinergic reinnervation of the hippocampus by grafts of striatal cells (or cells from other cholinergic neurons) have been reported earlier (e.g. Gibbs *et al.*, 1986; Lewis and Cotman, 1983; but see Clarke *et al.*, 1990 and Ikegami *et al.*, 1991).

4.2.3. *Cholinergic Grafts and Sympathetic Sprouting: A Particular Case*

This paragraph deals with a neurochemical effect of grafts rich in cholinergic neurons which is particular because it does not concern markers of cholinergic function in the hippocampus, although it obviously involves the cholinergic neurones present in the grafted cells. In an article published in 1992, we (Cassel *et al.*, 1992b; see also Cassel *et al.*, 1993b) have demonstrated that grafts rich in cholinergic neurons (but not grafts rich in serotonergic ones) were able to prevent an aspiration fimbria-fornix lesion-induced increase of hippocampal NA concentration, a postsurgical modification related to the ingrowth of sympathetic fibres (see Section 3.2.2.2). Noteworthy, the values of the concentration of hippocampal NA were inversely correlated with the

HACU data. This finding was confirmed in two other experiments showing: (i) that the inhibitory effects of the grafts were maximal in the regions where the cholinergic restoration was the highest, a finding again corroborated by a negative correlation between the NA concentrations and the HACU as well as the ChAT activity values (Cassel *et al.*, 1992, 1993); (ii) that a qualitatively similar effect of the grafts could be observed after electrolytic lesions of only the infracallosal component of the septohippocampal pathways (Jeltsch *et al.*, 1994b). Part of our contributions is summarized in Fig. 5. With this article on that matter (Cassel *et al.*, 1992b), we believed we were first to report such a finding. Since that time, however, we found an article on a similar topic that was published 10 years earlier by Kromer (1982). Kromer reported that, in the denervated dentate gyrus, there was histological evidence of the co-existence of cholinergic axons originating in septal implants (intracavitary) and sympathetic fibres from the superior cervical ganglia. He finished the discussion of his results with the following sentence: "*If there is indeed competition for a common postsynaptic factor that is released after septal deafferentation, then it appears that the ingrowing septal fibres from the implant have a greater affinity for this signal since they are able both to invade the neuropil which already contains sympathetic fibres and, if the density of fibres is great enough, to cause some reduction in the number of anomalous sympathetic fibres.*" A few years earlier, Björklund and Stenevi (1977) had investigated whether grafts of superior cervical ganglia were able to provide the hippocampus with a new noradrenergic innervation and, in their discussion of the results, they speculated that "*it would seem possible that afferents coming through the fimbria -above all, probably, the cholinergic septal ones,- act to inhibit the ingrowth of the noradrenergic ganglionic fibres.*" (*Redde Caesari quae sunt Caesaris...*)

4.2.4. *Alternative Approaches*

A small, although currently growing, number of studies have investigated the neurochemical effects of grafts prepared from sources other than the basal forebrain region of the rat. Essentially, these experiments first relied upon the utilization of grafts from other brain regions rich in cholinergic neurons (e.g. the striatum, the brain stem and even the spinal cord) or from the same region dissected out from the fetal brain of other species (e.g. mouse to rat or even human to rat; e.g. Daniloff *et al.*, 1984, 1985; Nilsson *et al.*, 1988a; Wells *et al.*, 1991). Although Daniloff *et al.* (1984) have reported mouse-to-rat basal forebrain cells to result in increased ChAT activity in the denervated hippocampus, most studies have used only a histological approach to assess the graft-induced effects. Altogether, it was found that the best reinnervation (with respect to both the innervation pattern and the fibre morphology) is generally obtained with cholinergic neurons from the basal forebrain region (e.g. Clarke *et al.*, 1990; Nilsson *et al.*, 1988a), whereas preparations from the striatum, the brain stem or the spinal cord are able to survive and develop correctly, but exhibit a weak to extremely poor potential to reinnervate the host structure. Also the grafts prepared from the basal forebrain of the mouse or the human brain were found to provide the denervated rat hippocampus with a new organotypic cholinergic innervation pattern (e.g. Daniloff *et al.*, 1985; Nilsson *et al.*, 1988a), but one of the major problems in this case, as stated elsewhere, resides in the immunological compatibility between the host and the donor tissues (see e.g. Section IV in Cassel *et al.*, 1992a; Widner and Brundin, 1988 for details).

A second alternative has consisted in the intracavitary implantation of regeneration bridges, the principle of such bridges being to provide a neurotrophic and a physical support for the regrowth of axonal processes from severed cholinergic neurons of the MS and the DBB. When this goal has to be achieved, both peripheral nerve bridges or non cholinergic tissue blocks from the fetal brain have been frequently utilized as the axonal regrowth substrate (e.g. Varon *et al.*, 1991). Technical details about the procedure may be found, for instance, in David and Aguayo (1985), and the reader should be aware about the fact that most studies performed with such techniques were carried out not in the septohippocampal system, but in the visual system or in the spinal cord. In more direct relation with the scope of this review, Kromer *et al.* (1981a, 1981b) have reported that fetal hippocampal tissue strips implanted into a unilateral fimbria-fornix lesion cavity were able to allow regrowing axons from septal neurons to reach the hippocampus and to invade its most dorsal part within a few months after the implantation. Interstingly, in additon to the demonstration that these regrowing axons were at the origin of an increased AChE-positive staining in the denervated hippocampus, the authors have measured the levels of hippocampal ChAT activity. In the most septal region of the hippocampus of lesion-only rats, this activity was lastingly reduced to less than 10% of the activity found on the unlesioned side (for up to 24 postsurgical months), whereas, in the grafted rats, it had increased to 30% of control within 12 months. In another study using the same model, electrophysiological evidence was presented demonstrating that the regrown axons formed atropine-sensitive excitatory synapses in the denervated hippocampus (Segal *et al.*, 1981). Such grafts were also found to result in increased NGF levels in the septal region, but not in the hippocampus, (Messersmith *et al.*, 1991) and some of their effects (AChE-positive reinnervation of the hippocampus) could be mimicked qualitatively with intracavitary implantations of a purified Schwann cell preparation (e.g. Montero-Menei *et al.*, 1992; Neuberger *et al.*, 1992). In another study using rats with fimbria-fornix lesions, Tuszynski *et al.* (1990a, 1990b); Tuszynski and Gage, 1995) have combined the hippocampal tissue bridging technique to intracerebroventricular infusions of NGF over a 9-week period and found the tissue bridges to allow: (i) a significicant saving of ChAT-positive neurons in the MS, as the number of septal neurons expressing ChAT reached 58% of the number found on the unoperated control side in the grafted rats given NGF, 40% in the grafted rats which did not receive NGF, 44% in the nongrated

NGF-treated rats, and only 32% in the lesion-only rats; (ii) a partial AChE-positive reinnervation of the hippocampus which was not significantly augmented by the NGF treatment, although the average fibre density was 76% of normal in the NGF-treated rats with grafts, against 45% in the group of grafted rats which did not receive NGF. In another study (Springer *et al.*, 1988), mouse submaxillary glands which synthetize high levels of NGF were grafted intraventricularly to rats which had sustained a unilateral knife cut transection of the dorsal septohippocampal pathways. Two to four weeks later, Springer *et al.* (1988) found lesion-only rats to have lost 70–80% cell bodies positively stained for AChE or for the p75 NGF receptor in the medial septal region ipsilateral to the lesioned hemisphere; in the grafted rats, there was only a 25–30% cell loss.

The last but not least alternative approach was developed more recently and consists of grafting cells previously subjected to gene-transfer techniques (astrocytes, schawnn cells, pheochromocytoma cells, hepatocytes...; e.g. Doering, 1994; Fisher and Gage, 1993, 1994; Gage, 1990; Gage *et al.*, 1987; Neuwelt *et al.*, 1995). In a first step, such techniques suppose the cells to be infected by a retroviral vector containing the cDNA sequence coding for a given protein such as, for instance, nerve growth factor (NGF) or tyrosine hydroxylase, whereby these cells acquire the capacity to synthetize and release this protein both *in vitro* and from their implantation site into the host parenchyma. After transfection, the cells are grafted (as a suspension or after encapsulation in a polymer-matrix) into the hippocampus or the ventricles where they will synthetize and release the protein coded by the transgene. Although the largest number of studies have assessed the ability of intrastriatal implants of cells expressing tyrosine hydroxylase, the enzyme involved in dopamine synthesis, to attenuate the neurochemical and behavioural deficits induced by 6-OHDA lesions of the nigrostriatal pathways (e.g. Fisher and Gage, 1993; Horellou *et al.*, 1990a, 1990b; Kordower *et al.*, 1995), there have been a few experiments addressing the question of the efficiency of such an approach on some of the fimbria-fornix lesion-induced deficits, with the rationale being to supply the denervated or lesioned structure with neurotrophic factors that may promote maintenance, repair and regeneration of neurons (e.g. Blottner and Baumgarten, 1994; Varon *et al.*, 1995). It is well established that subsequently to fimbria-fornix lesions, numerous cholinergic neurons in the MS show a decreased expression of ChAT activity, and that this reduction may be prevented by intraventricular infusions of NGF (e.g. Hefti *et al.*, 1989; Will and Hefti, 1985; Williams *et al.*, 1986) or by the intraventricular implantation of a polymer matrix preloaded with NGF (e.g. Hoffman *et al.*, 1990). Rosenberg *et al.* (1988) reported that two weeks after the implantation of fibroblasts genetically modified to synthetize NGF, the unilateral fimbria-fornix lesion-induced decrease of the number of ChAT-positive neurons in the ipsilateral MS was attenuated dramatically: 92% of the neurons expressing the acetylcholine synthetizing enzyme had survived and the growth of AChE-positive terminals in the dorsal septum had been stimulated substantially. Similar results have been reported by Hoffman *et al.* (1993) who encapsulated the genetically modified fibroblasts into a polymeric matrix before implanting the latter into a cerebral ventricle: Two weeks after the implantation, the grafted rats showed slightly more than 80% of the septal cholinergic neurons to express ChAT compared to the proportion of only 25% in the lesion-only rats. Similar results could be obtained with other cell lines such as, for instance, cells derived from a mouse neuroblastoma (HT4; Whittemore *et al.*, 1991), or with a paradigm of 192 IgG-saporin-induced cholinergic lesions (Rossner *et al.*, 1996). Using a paradigm of lesions of the septohippocampal, Lucidi-Philippi *et al.* (1995) found that fibroblasts genetically modified to express brain-derived neurotrophic factor (BDNF), another neurotrophic protein allowing to rescue septal cholinergic neurons when infused into the cerebral ventricles (e.g. Knüsel *et al.*, 1992; Morse *et al.*, 1993), did not exert such a preventive effect, in contrast to the fibroblasts synthetizing NGF. Finally, Schinstine *et al.* (1995) grafted encapsulated Schwann cells genetically modified to synthetize human NGF and found such an approach to produce the saving of 80% ChAT-positive cells in the rat septum. Evidence that primary astrocytes modified to produce NGF may also stimulate the cholinergic reinnervation of the hippocampus has been reported recently (Eagle *et al.*, 1995). Unfortunately, none of these studies has assessed the neurochemical effects of such treatments in either the MS or the denervated hippocampus.

4.2.5. *Summary and Conclusions*

There is no doubt nowadays that grafts rich in cholinergic neurons, whether placed into a lesion cavity within the dorsal septohippocampal pathways or directly into the hippocampal parenchyma, are able to provide the denervated hippocampus with a cholinergic reinnervation. This reinnervation, which is more pronounced after basal forebrain tissue grafts than after grafts of cells from other cholinergic nuclei or of tissue blocks bridging the septal and hippocampal regions, increases and, sometimes, even normalizes several markers of cholinergic function in the hippocampus (ChAT and AChE activity, synaptosomal uptake of choline...). This reinnervation contributes also to attenuate, sometimes to completely reverse, part of the reactional modifications induced by the lesions (sympathetic sprouting, muscarinic receptor up- or downregulations...). All these graft-induced modifications, however, do not necessarily involve a single mechanism which, for the immature neurons, would consist in providing the hippocampal targets deprived of their cholinergic afferents with a new operational axonal input establishing synaptical contacts with cells in the host structure. As reviewed by Dunnett and Björklund (1987); see also Cassel *et al.*, 1992a), various mechanisms other than re-establishment of synaptic contacts may also account for graft-induced effects, including non-specific side effects of the transplantation surgery, diffuse paracrine "minipump-like" release of hormones, neurotransmitters or other

molecules, acute or chronic release of growth-promoting or neurotrophic factors which may stimulate the growth of intact or damaged cells in the host brain... In most studies reported so far, eventhough it is probable that all these mechanisms may have played a more or less important role in the restoration of cholinergic markers in the denervated hippocampus, we might assume that the outgrowth of cholinergic axonal processes from the grafts and not those from the host brain, whether these grafts have established new synaptic contacts or not, have accounted for a large part of the histological and neurochemical effects reported in the literature. This assumption is partly in line with the findings that grafts bridging the septal region and the hippocampus, whereby cholinergic neurons from the host may reinnervate the hippocampus, only produce modest effects on cholinergic markers in the hippocampus.

4.3. Grafts Rich in Noradrenergic Neurons

Most studies which assessed the effects of grafts rich in catecholaminergic neurons have been carried out using animal models of PD (e.g. 6-OHDA lesions of the nigrostriatal pathways) and either intrastriatal grafts of dissociated tissue from the adrenal medulla (autografts) or the substantia nigra (heterografts), or grafts of cell lines genetically modified to express tyrosine hydroxylase and secrete catecholamines (dopamine). As regards the denervated hippocampus, there have been several experiments that, in the course of the seventies, investigated the possibility for intrahippocampally grafted noradrenergic cells (from the locus coeruleus or the superior cervical ganglia) to survive and reinnervate the structure in which they were implanted. For instance, in one of their pioneering experiments, Björklund and Stenevi (1977) have shown that superior cervical ganglia grafted into a lesion cavity made at the level of the septohippocampal junction were able to survive and, along the fimbria, to develop axonal processes which enter the hippocampus where they form a new organotypic adrenergic reinnervation pattern. Similar observations were made with grafts of fetal locus coeruleus tissue (for details see, e.g. Björklund and Stenevi, 1977, 1979). As for grafts of cholinergic neurons, it seems that the survival and the integration of noradrenergic grafted neurons is favorized by an adrenergic neurotrophic factor released after noradrenergic denervation of the hippocampus (e.g. Björklund and Stenevi, 1981). Curiously, the neurochemical effects of such grafts have not been investigated as extensively as were grafts rich in either cholinergic (see previous section) or serotonergic (see Section 4.3) fetal neurons, at least when the preparations rich in noradrenergic neurons were grafted into the hippocampus. A last preliminary note concerns the preparation of the grafts: The achievement of a satisfactory survival of noradrenergic neurons grafted into the brain as a cell suspension supposes that the fragments of fetal tissues are not exposed to trypsin prior to their dissociation (e.g. Björklund *et al.*, 1986); collagenase or other proteolytic enzymes may be used instead.

4.3.1. *Grafts Rich in Noradrenergic Neurons Placed into a Lesion Cavity*

Kokaia *et al.* (1994b) have reported a study in which the neurochemical effects of grafts rich in noradrenergic neurons were examined in rats subjected to a 6-OHDA lesion of the central catecholaminergic fibres followed by an aspiration lesion cavity at the septohippocampal junction and a bilateral sympathectomy (to prevent sympathetic ingrowth elicited by lesion procedure). Using a microdialysis approach, Kokaia *et al.* (1994b) found grafts of locus coeruleus and superior cervical ganglion tissue blocks placed into the lesion cavity to partially reverse the almost complete lesion-induced abolition of spontaneous NA release in the denervated hippocampus: The baseline level reached 36% of normal in the rats with locus coeruleus grafts and only 15% in those with superior cervical ganglion grafts, both values being however significantly higher than in the lesion-only rats. Effects much higher than those reported by Kokaia *et al.* (1994b) have been described by Cenci *et al.* (1993) who used a lesion paradigm and a grafting technique identical to those used in the study of Kokaia *et al.* (1994b). Cenci *et al.* (1993) found 6-OHDA lesions to reduce the NA overflow to 3% of control values. Whereas the superior cervical ganglion grafts increased this baseline overflow to 15% of normal, the grafts of locus coeruleus tissue even overcompensated the lesion-induced deficit (180% of control value). As was the case in the intact rats, this release was enhanced in both groups of grafted rats when KCl (100 mM; eight- to ninefold increase) or desipramine (5 μM; fourfold increase) were added to the perfusion fluid. Conversely, the release of NA was dramatically reduced by addition of TTX (1 μM). Handling of the rat or forced immobilization resulted in increased release of NA, but only in the group of intact rats; in both groups of grafted rats there were only marginal effects, with, however, some of the rats being unambiguously responding to this physiologically relevant stimulations.

4.3.2. *Intraparenchymal Cell Suspension Grafts*

An early demonstration that locus coeruleus cell suspension grafts could contribute to compensate for some biochemical defects was in a paradigm of intracortical fetal cell implantations in rats subjected to diffuse catecholaminergic lesions induced by systemic postnatal administration of 6-OHDA (Semenova *et al.*, 1987). The authors found the cortical concentration of NA to be reduced by more than 85% in lesion-only rats and to be augmented to 60% of normal in the lesioned rats with grafts. Similar neurochemical effects have been reported with grafts of locus coeruleus or superior cervical ganglia cells into the 6-OHDA denervated hippocampus, but most approaches relied upon an *in vivo* microdialysis technique. In rats subjected to an i.c.v. injection of 6-OHDA and, subsequently, to the intrahippocampal implantation of fetal cell suspension rich in noradrenergic neurons, Björklund *et al.* (1986) have measured the total hippocampal noradrenaline content and estimated its turnover in the

grafted noradrenergic neurons (determination of the DOPA/NA ratio under pharmacologically-induced inhibition of dopamine decarboxylase activity). The authors found the hippocampal NA concentration to be reduced by 98% in the lesion-only rats, whereas it reached 55% of control in the grafted rats. Also, the turnover of the noradrenergic neurons was increased 10-fold in lesion-only rats and reduced to a near-normal value in the grafted ones. Using a paradigm of fimbria-fornix transection combined or not with bilateral intrahippocampal implantations of superior cervical ganglion tissue, Wang *et al.* (1994) found the hippocampal NA content to be reduced by approximately 50% in lesion-only rats and to be very close to normal (95%) in grafted ones. Using an *in vivo* microdialysis technique, Bengzon *et al.* (1991, 1993) have found suspension grafts of locus coeruleus tissue placed into the 6-OHDA cetacholamine depleted hippocampus to normalize the baseline release of NA, as well as the release observed subsequently to electrical stimulation of the hippocampus, a stimulation which remained ineffective in lesion-only rats (Bengzon *et al.*, 1991). Regarding the functional characteristics of intact hippocampal noradrenergic afferents, Kalén *et al.* (1988) have shown the baseline release of NA to be increased by about 700% after perfusion (through the dialysis probe) of the NA re-uptake inhibitor desipramine (5 μM), and by more than 2600% when 100 mM KCl were added to the perfusion fluid. Conversely, this release was decreased in presence of TTX (1 μM). In another study, these authors (Kalén *et al.*, 1989) also demonstrated that the release of NA was higher during the night (light off) than during the day (lights on) periods, and that it was transiently augmented by gentle handling of the rat or by pinching its tail. A few days after 6-OHDA lesions of the central catecholaminergic system, the baseline release of hippocampal NA was reduced by more than 99% compared to intact rats (Kalén *et al.*, 1988) and none of the aforementioned stimulating treatments were able to affect this release. When assessed between 3 to 12 months after intrahippocampal grafts of cell suspensions prepared from the locus coeruleus, the baseline release of NA had been restored to a level which did not differ from that found in intact control rats (Kalén *et al.*, 1990; 1991a; 1991b). Also, these grafted neurons responded to the infusion of desipramine (5 μM), a high concentration of KCl (100 mM) or that of TTX (1 μM) in a near normal manner. Furthermore, the increase of NA release elicited by electrical stimulation of the habenular complex under halothane anaesthesia could be mimicked in the grafted rats, but was not observed in the lesion-only ones. These results have been replicated in a later study (Kalén *et al.*, 1991a, 1991b) in which the authors also showed that the release of NA could also be stimulated by handling (in 3 out of 6 grafted rats) and forced immobilization, and that the release elicited by the electrical stimulation of the habenula was dramatically reduced, but not abolished, by a transection of the fasciculus retroflexus. In intact rats, all these manipulations were also found to affect the release of NA in a qualitatively similar manner, but the effects of forced immobilization were more pronounced than in the grafted rats and, unlike the latter, the intact rats also showed an increased release of NA when placed in a situation in which they had to swim.

4.3.3. *Summary and Conclusions*

As was the case with grafts containing cholinergic fetal neurons, noradrenergic cells grafted into the denervated hippocampus may survive and contribute to provide the hippocampus with a new noradrenergic innervation. These grafted cells may, under some conditions (see preceding section), be regulated by host afferents, although the overall picture is not as clear as it was seen for cholinergic or serotonergic neurons (see next section). As regards the graft-induced reinnervation and its neurochemical effects, the most satisfactory results seem to be achieved with grafts of locus coeruleus cells, thus from the nucleus that normally provides the hippocampus with its noradrenergic input. Alternative sources of neurons or cells to be grafted are the superior cervical ganglion, or even the adrenal medulla, but the neurochemical effects of grafts prepared from these structures are much weaker than those described with grafts of locus coeruleus cells. Finally intrahippocampal grafts of cell suspensions apparently induce more pronounced effects as compared to those observed following intracavitary grafts of tissue blocks.

4.4. Grafts Rich in Serotonergic Neurons

Intracerebral grafting of neurons dissected from central serotonergic nuclei of the fetal brain (mainly from the dorsal *raphe* nucleus) was most frequently performed with a technique of intraparenchymal injections of a cell suspension. From a neurochemical point of view, most studies published so far have concentrated on the possibility to restore serotonergic functions in the hippocampus denervated by neurotransmitter-specific lesion techniques (i.e. 5,7-DHT) or by techniques disrupting the supracallosal and/or the infracallosal component(s) of the so-called septohippocampal dorsal pathways (e.g. aspiration, knife cut, electrolysis). There are also a few experiments which performed the grafts into the intact hippocampus of the rat (e.g. Zhou *et al.*, 1987, 1988) and even the cat (Trulson *et al.*, 1986). Information concerning the electrophysiological effects of such grafts can be found, for instance, in Richter-Levin and Segal (1991) and Segal (1987).

4.4.1. *Studies on Excised Tissue Preparations (Homogenates, Synaptosomes)*

As was the case with the cholinergic grafts, it has been repeatedly demonstrated that fetal serotonergic neurons also had the capacity to survive when grafted into an adult brain, to develop and to provide a denervated host structure such as the hippocampus with a new serotonergic innervation (e.g. Anderson *et al.*, 1986; Azmitia *et al.*, 1981; Björklund *et al.*, 1976; Daszuta *et al.*, 1991a; Steinbusch *et al.*, 1987; compare also Oleskevich *et al.*, 1991 with Daszuta *et al.*, 1991a). As for fetal cholinergic neurons, the survival and development of serotonergic neurons grafted into the denervated hippocampus is probably

stimulated by a molecule having neurotrophic properties and whose hippocampal concentration is increased subsequently to denervating lesions (e.g. Azmitia, 1987; Zhou and Azmitia, 1990).

The graft-induced serotonergic reinnervation is accompanied by substantial neurochemical effects. Auerbach *et al.* (1985) found that in 5-HT depleted rats (5,7-DHT injected into the dorsal and median *raphe* nuclei), the intrahippocampal implantation of minced tissue from the fetal *raphe* area had increased the hippocampal concentration of 5-HT and 5-HIAA (lesion-induced decrease: About − 50%) to slightly supranormal levels (138% and 118% of intact, respectively), an effect which was detected already at a postoperative delay of one month. In experiments using longer post-grafting survival periods, the grafts were found to largely overcompensate the deficits induced by 5,7-DHT lesions, whether the neurotoxin was injected directly into the serotonergic nuclei or into the cerebral ventricles. For instance, Daszuta *et al.* (1988) reported that in rats given intraventricular injections of 5,7-DHT which resulted in a lasting reduction − 90%) of hippocampal 5-HT and 5-HIAA concentrations, intrahippocampal *raphe* cell suspension grafts had normalized both markers at approximately five weeks after grafting surgery. At longer delays, i.e. 7 weeks and 5 months post-grafting, the 5-HT concentration had been overcompensated to 146% and 218% of normal, respectively, whilst the concentration of 5-HIAA had reached levels of 136% and 147%. In addition to the determination of the same markers, Van Luijtelaar *et al.* (1991) assessed the accumulation of [^{3}H]5-HT by hippocampal slices and the KCl-evoked release of tritiated serotonin in rats given bilateral injections of 5,7-DHT and intrahippocampal grafts of fetal *raphe* tissue. In the hippocampal region closest to the graft injection sites, they found that 11 months after grafting, the accumulation of [^{3}H]5-HT had reached 194% of control, the release of [^{3}H]5-HT about 155%, the concentration of 5-HT and 5-HIAA 199% and 150%, respectively. All these effects were less pronounced when the distance from the graft increased in the direction of the temporal region, an observation confirming earlier findings by Steinbusch *et al.* (1987). Effects even larger than the aforementioned ones have been described in experiments by Zhou *et al.* (1987), as well as in our own experimental contributions. Using the 5,7-DHT lesioned rats, Zhou *et al.* (1987) found intrahippocampal grafts to increase the 5-HT concentration to 445% of control and the synaptosomal uptake of [^{3}H]5-HT to 355%. Our own studies on tissue content of 5-HT and 5-HIAA, as well as on synaptosomal [^{3}H]5-HT uptake in the hippocampus of rats which sustained either aspiration or electrolytic lesions of the so-called septohippocampal pathways and grafts rich in serotonergic neurons are summarized in Fig. 6.

Even when injected into the intact hippocampus, thus in a structure in which the graft survival and development do not meet ideal conditions, grafts of *raphe* cell suspensions are able to increase serotonergic markers above normal levels (e.g. Zhou *et al.*, 1987). In some reports, such grafts placed into the 5-HT depleted hippocampus were also shown to contribute to the normalization of the 5-HT turnover or even to decrease the latter below normal levels (e.g. Cassel *et al.*, 1993b; Daszuta *et al.*, 1988). In these studies, the 5-HT turnover was measured by computation of the ratio between the 5-HIAA and 5-HT tissue levels.

4.4.2. In Vivo *Approaches (microdialysis)*

Similar results have been reported with *in vivo* approaches relying upon intrahippocampal micro-

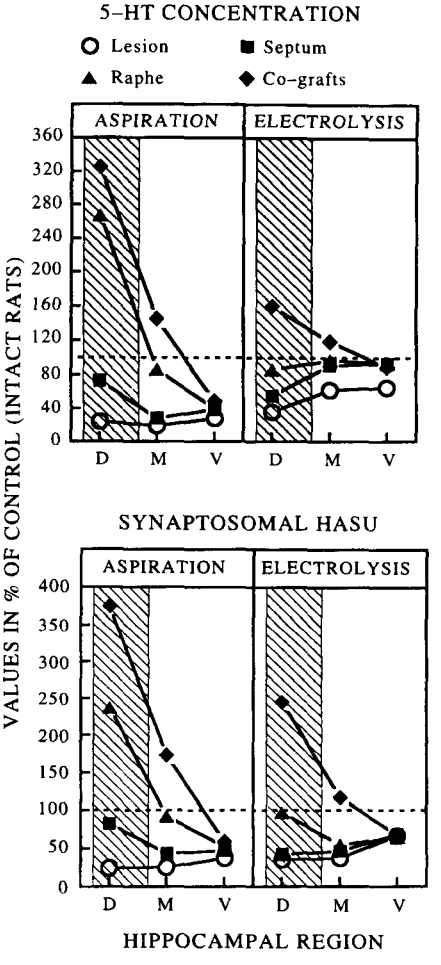

Fig. 6. Serotonin concentration (top) and synaptosomal high affinity uptake of [^{3}H]serotonin (bottom) determined between 8 and 10 months after surgery in the dorsal (D), median (M) and ventral (V) hippocampus of rats with only aspiration (left panel) or electrolytic (right panel) lesions of the fimbria-fornix pathways and of rats which, in addition to the lesions, were subjected to intrahippocampal grafting of cell suspensions prepared from the region including the medial septum and the diagonal band of Broca (septum; Section 4.2) or the mesencephalic raphe (raphe; Section 4.3) of the fetal brain, or of a mixture of both suspensions (co-grafts; Section 4.5). All values are expressed as a percentage of the average absolute values found in virtually intact rats (100%; dotted lines). The hatched bars in each panel delimit approximately the hippocampal region in which the grafts had been implanted and where histological verifications generally showed them to be located. Data are from Cassel *et al.*, 1993b (aspiration) and Jeltsch *et al.*, 1994b (electrolytic); for further details, see these two references.

dialysis techniques. For instance, Sharp and Foster (1989) found that 6 months after grafting, *raphe* grafts had increased the 5-HT baseline release to 171% of normal in the 5-HT depleted rat hippocampus, and that this effect was partly mimicked by grafts of medullary *raphe* tissue (88% of normal), a region containing serotonergic neurons that normally innervate targets in the spinal cord. Whereas the medullary *raphe* grafts contributed to normalize the KCl-evoked 5-HT release, those of mesencephalic *raphe* cells more than doubled this release as compared to that found in intact rats. With a similar technique, it was described that the release of 5-HT in the hippocampus of the freely moving intact rat was fluctuating according to both the circadian period (extrinsic modulator) and the rat's behavioural activity state (intrinsic modulator): During the night period, the intrahippocampal release of 5-HT increase was about 40% higher than that found during the light period. Also, during states of high behavioural activity, this release was approximately 45% higher than during states of resting or sleep (Kalén *et al.*, 1989). Gentle handling of the rat or pinching its tail produced a 72% and 48% increase of 5-HT release, respectively. 5,7-DHT serotonin depletion decreased the 5-HT baseline release underneath the detection limit, whilst in response to KCl- or pCA-induced stimulations, this release amounted only 5–10% of that found in intact rats (Daszuta *et al.*, 1989). In the 5,7-DHT-lesioned rat, grafts of *raphe* cells were found to increase the 5-HT tissue content to more than 300% of normal, while the baseline release was comparable to that of intact rats (Daszuta *et al.*, 1989). The addition of KCl (60 mM) to the perfusion fluid or the i.p. injection of pCA (2.5 mg/kg) raised the levels of 5-HT release to 177% and 151%, respectively, of those found in intact control rats. Under the perfusion of indalpine (1 μM), a 5-HT re-uptake blocker, the baseline release was increased by approximately 380% in the hippocampus of intact rats, as well as in the grafted hippocampus of the lesioned rats. Also, under indalpine perfusion, the addition of KCl to the medium further increased the release (4–5 fold) in the intact and grafted hippocampus, but was ineffective on the nongrafted denervated side. Conversely, perfusion of TTX reduced the indalpine steady-state release to a level close to that found in the nongrafted denervated hippocampus. Similar results were reported by Kalén *et al.* (1991a, 1991b). These results did not only clearly show that the grafted serotonergic neurons are spontaneously active (baseline release levels restored) and release 5-HT at near-normal levels, but they also strongly suggest that these neurons are under control of host brain (effects of either handling or tail-pinch) and possess autoregulatory mechanisms (levels of 5-HT release are normal despite a graft-derived hyperinnervation of the hippocampus). Although the following possibility has not been addressed so far, it could be that some of these autoregulatory mechanisms involve 5-HT_{1B} autoreceptors present at the terminals of the grafted neurons as they are on the serotonergic terminals in the hippocampus of intact rats (e.g. Bolanos-Jiménez *et al.*, 1993, 1994). Another alternative has been demonstrated by Sharp and Foster (1991): In rats previously subjected to 5-HT denervation of the hippocampus, they found the release of 5-HT from transplants of embryonic medullary or *raphe* neurons to be under an inhibitory tonic control involving 5-HT_{1A} receptors, as this release was decreased by systemic administration of 8-OH-DPAT, a selective agonist of this receptor subtype. With the exception that 5-HT_{1A} receptors are the somatodendritic autoreceptors of the serotonergic *raphe* neurons, in other brain regions such as the cortex or the hippocampus, these receptors are mainly, if not exclusively located postsynaptically (e.g. Hoyer *et al.*, 1994). Thus, in the study reported by Sharp and Foster (1991), it can reasonably be assumed that the reduced 5-HT release in response to systemic 8-OH-DPAT treatment was mediated by 5-HT_{1A} receptors located on the dendrites and the cell body of the grafted serotonergic neurons.

4.4.3. *Summary and Conclusions*

Regarding the overall layout of the present subsection, it was not possible to follow the same progression as that followed for grafts of cholinergic neurons. Some of the reasons to that are that: (i) grafts of *raphe* cell preparations have not been carried out as blocks implanted into a lesion cavity; (ii) the intracavitary implantation of a substrate allowing guidance and stimulation of host serotonergic neurons regrowth has not been attempted so far in the paradigm of fimbria-fornix/cingular bundle lesions, probably because the source-to-target distance is much larger than that separating the septum from the hippocampus, but also because the source nucleus of the serotonergic hippocampal innervation is not directly adjacent to any edge of the lesion cavity; (iii) cells genetically modified to synthetize and release neurotrophic substances acting on serotonergic neurons (although such a factor is certainly released after 5-HT depletion, its molecular characteristics have not been indentified so far) are not available; (iv) the graft-induced effects on the lesion-induced modifications of the properties of the serotonergic receptors (e.g. upregulation) have not been addressed, probably because the knowledge about which serotonergic receptors are upregulated and, if so, where in the hippocampus they are upregulated is not as clear as that concerning the functional changes of the muscarinic receptors after cholinergic denervation.

One clear conclusion, however, is that grafts of mesencephalic *raphe* tissue have an extremely high reinnervation potential which certainly accounts for the graft-induced hyperinnervation almost systematically found in the denervated hippocampus, whether following an aspiration, knife cut or electrolytic lesions of the fimbria-fornix pathways, or subsequently to intracerebral injections of the neurotoxin 5,7-DHT. There are at least two, probably complementary mechanisms which may account for this high reinnervation potential of serotonergic neurons from the fetal mesencephalic raphe. First, it has been described that, after hippocampal serotonergic denervation, a soluble and very potent neurotrophic factor is synthetized and released by hippocampal cells. This factor rather specifically stimulates the

growth of serotonergic neurons. Evidence for the fact that the increased availability of this neurotrophic factor is not the only mechanism involved in the serotonergic hyperinnervation has been provided by Zhou *et al.* (1987). These authors found that serotonergic markers can reach above normal levels when *raphe* tissue is grafted into the intact hippocampus, and thus an hippocampus in which the neurotrophic activity is probably not increase. The second mechanism has been suggested by Daszuta *et al.* (1991a, 1991b): These authors first emphasized that serotonergic terminals originating in the *raphe* nuclei are found in various brain regions other than the hippocampus, a fact suggesting that during embryogenesis, once differentiation, growth and axonal arborization are ongoing processes, *raphe* neurons must necessarily have a ("innately programmed") high innervation potential to cover all targets to be reached by their axonal terminals. In the case of an intrahippocampal implantation of fetal *raphe* cells, due to both the limited ability of graft-derived fibres to grow over long distances through the parenchyma of the recipient and an increased neurotrophic/neurotropic influence in the host target, it is conceivable that the expression of this "innate" potential remains solely confined to the host structure. The plausibility of such an explanation is reinforced by studies in which the fetal serotonergic neurons have been grafted in denervated brain structures other than the hippocampus and in which hyperinnervation patterns were also clearly observed (e.g. Daszuta *et al.*, 1991b; Wright *et al.*, 1991; but see Foster *et al.*, 1990). This hyperinnervation potential, however, does not allow grafts containing serotonergic neurons to provide the denervated hippocampus with a homogeneous density of serotonergic terminals. As for the grafts rich in cholinergic neurons, there is a reinnervation gradient which decreases proportianally to the distance from the implantation site. Finally, the remarks raised above (see 4.1.5.) on the nature and the specificity of the basal forebrain graft-induced mechanisms on cholinergic functions in the denervated hippocampus may be integrally recalled as concerns the nature and specificity of the neurochemical effects produced by grafts of serotonergic neurons.

4.5. Co-Grafting Approaches

Strictly speaking, each study using grafts of neural tissue prepared from any given region of the fetal brain basicaly uses co-grafts of different cell categories including various glial cells (microglial cells, olygodendrocytes, astrocytes) and neurons with various neurotransmitter-specific identities... Except when using genetically-modified cell populations, it is actually not possible with the usual dissection and preparation procedures to isolate or extract the neurons expressing one given neurochemical phenotype in order to graft only these neurons at the exclusion of all other ones. A cell suspension or a tissue block to be implanted into a brain structure is considered to be particularly rich in one category of neurons because it is prepared from a brain region clearly identified as including a nucleus containing, for instance, cholinergic, noradrenergic or serotonergic cell bodies, as compared to another region in which such types of cell bodies are not present. Another acceptation of the term "co-graft" refers to a grafting procedure consisting in the implantation of neuroanatomically- and/or neurochemically-defined fetal neurons concomitantly with other cell preparations (e.g. extracts of target tissue or other tissues promoting neuronal survival and fibre extension) supposed to provide the former with neurotrophic and/or neurotropic support. This topic has been reviewed in a recent article by Collier and Springer (1994).

Herein, the term co-grafts is used in a third acceptation referring to a grafting procedure of preparations in which the cells from at least two neurochemically-characterized nuclei (e.g. cholinergic and serotonergic) have been co-implanted in order to determine their functional effects as compared to those found when separate preparations from each region are implanted as "single grafts". In the denervated hippocampus, such a procedure has been used to implant cells from the septal region together with cells from the mesencephalic *raphe* after lesions of at least the cholinergic and serotonergic hippocampal afferents. In the first study published, Nilsson *et al.* (1990a) have reported histological evidence showing that such co-grafts were able to provide the denervated hippocampus with both a cholinergic and a serotonergic reinnervation pattern, as if they would simply combine the reinnervation potential of each single graft (septal cells alone or *raphe* cells alone). In a series of experiments performed in rats given more (Cassel *et al.*, 1992, 1993) or less extensive lesions (Jeltsch *et al.*, 1994b) of the so-called septohippocampal pathways, we have confirmed these data both neurochemically and neuropharmacologically: Septal grafts not only normalized or increased cholinergic markers such as HACU and ChAT activity, but also attenuated the increase of hippocampal NA concentration due to sympathetic ingrowth, whereas *raphe* grafts normalized or overcompensated serotonergic markers such as HASU and tissue levels of both 5-HT and 5-HIAA. Interestingly, the co-grafts increased, normalized or overcompensated all these markers co-jointly (see Figs 4 – 6).

4.6. Other Neurochemical Effects of Intrahippocampal Grafts

Briefly, there have been a few studies in the literature suggesting that intrahippocampal grafts of cells from various regions of the fetal brain might exert neurochemical effects other than those expected from the resources of each region in a given neurochemical category of neurons. It must be emphasized that: (i) the evidence for the plausibility of such "side" effects is indirect as it is based exclusively on morphological observations and (ii) so far, most studies simply did not address whether neurons other than cholinergic, noradrenergic or serotonergic ones in basal forebrain, locus coeruleus or *raphe* grafts, respectively, could be identified. The best example known so far concerns the presence of GABAergic neurons in basal forebrain transplants. After Cassel *et al.* (1991b), Buzsáki *et al.* (1992) have

found transplants of cell suspensions prepared from the septal region of the fetal brain to contain numerous neurons immunostained for parvalbumin, a calcium binding protein which is present in the membrane of a subpopulation of GABAergic neurons. Such morphological observations suggest that the grafts, in addition to the expression of some cholinergic function, might also contribute to modify the availability of GABA within the hippocampus, or even to modulate, through a GABAergic mechanism, some of the functional aspects of the neurons located in the grafts themselves. In a study in which we measured the hippocampal concentration of various amino acids after electrolytic fimbria-fornix lesions and intrahippocampal grafts of cell suspensions rich in cholinergic and/or serotonergic neurons (Jeltsch *et al.*, 1994c), we did not find the concentration of GABA (as well as that of many other amino acids) to be significantly modified by either type of graft. Another case concerns grafts of mesencephalic *raphe* tissue. Such grafts show a dense AChE-positive staining, although they do not provide the denervated hippocampus with more than a very poor AChE-positive fibre ingrowth (e.g. Cassel *et al.*, 1992b, 1992c; Jeltsch *et al.*, 1994a; Nilsson *et al.*, 1990a). As the dissection procedures of the fetal brain do not allow to discriminate between various types of cells within a given region, the type of neurons which might be found in basal forebrain, locus coeruleus and mesencephalic *raphe* grafts can be infered from the populations of neurons found in each of these regions in the adult rat brain. Beside cholinergic and GABAergic neurons, the septal region also contains neurons positively stained for galanin, while the diagonal band of Broca contains neurons positively stained for N-acetyl-aspartyl-glutamate. These populations of neurons give rise to approximately 20% of the septohippocampal projections. A smaller proportion of septal neurons were also found to be stained for other peptides such as substance P, somatostatine enkephalins or vasoactive intestinal polypeptide (e.g. see references in Dutar *et al.*, 1995). In the dorsal raphe, about 30% of the neurons do not stain for 5-HT (Jacobs and Azmitia, 1992). Some of these neurons are certainly GABAergic (e.g. Stamp and Semba, 1995), others stain for enkephalin (e.g. Jacobs and Azmitia, 1992). Finally, one also has to consider the neurons present in regions immediately adjacent to the one used for the preparation of the grafts (e.g.GABAergic neurons close to the locus coeruleus). Indeed, the risk that small parts of these neighbouring regions may be included during the dissection procedure can never be reduced to zero and this is an interpretation that we have proposed to account for some small cholinergic effects of grafts prepared from the mesencephalic *raphe* region in on of our previous experiments (Cassel *et al.*, 1992b, 1992c).

4.7. General Conclusions

In this general conclusion, the term reinnervation will be used indistinctly to designate histological as well as neurochemical evidence showing or suggesting that grafts are actually able to supply the denervated hippocampus with new axonal processes, regardless of whether these processes do establish functional synaptic contacts with other neurons of the host structure or fail to do so. As concerns the grafts of fetal brain tissues rich in cholinergic, noradrenergic or serotonergic neurons, a few common characteristics/properties may be recalled. First, cells or tissue blocks show the best reinnervation potential and induce the highest neurochemical recovery when they are from the normal innervation source, as compared to preparations from other sources, namely sources rich in neurons having the same neurochemical specificity as those from the normal innervation source and which do not normally project to the structure to be reinnervated. Second, whatever of these various grafts is considered, the reinnervation is always maximal in the vicinity of the grafted tissue and clearly declines when the distance from the implantation site increases. A major difference between basal forebrain, locus coeruleus and mesencephalic *raphe* preparations, is that the serotonergic neurons in the latter preparations clearly exhibit a much higher reinnervation potential than the cholinergic or noradrenergic neurons in the two former preparations. Third, in most if not all studies, it has been emphasized that, in the denervated hippocampus, the distribution pattern of the graft-derived reinnervation closely resembles the pattern found in intact control rats. Fourth, the activity of the grafted neurons is controlled and this control may involve autoregulatory and heteroregulatory mechanisms operating at the presynaptic level, as well as mechanisms operating through afferents from the host brain. However, one has to be aware that beside the aforementioned direct effects or mechanisms, grafts of tissue or cell suspensions from the fetal brain may also exert effects mediated by more indirect mechanisms, such as, for instance, the delivery of neurotransmitters by the way of a diffuse, "minipump like" or paracrine release phenomenon, or the release of growth promoting and/or neurotrophic factors that may act as agents stimulating both the regeneration of severed axons and the sprouting of undamaged fibres in the host structure. Interestingly, there is also evidence from studies combining cholinergic and serotonergic neurons within the same suspension that the technique of co-grafting cell preparations from different anatomically- or neurochemically-defined sources may allow to combine the individual neurochemical properties of each preparation grafted separately from the other one. Thus, it is quite easy to accept the idea that grafts rich in cholinergic, noradrenergic or serotonergic neurons are able to attenuate or even to normalize some of the dramatic lesion-induced depletions of cholinergic, noradrenergic and serotonergic hippocampal markers. Thus, it can be assumed that there exists a theoretical possibility for cholinergic, noradrenergic and serotonergic markers to be compensated for over time in the extensively denervated hippocampus by the implantation of a mixture of different kinds of neurons. Indeed, the grafts rich in cholinergic neurons may provide the hippocampus with a cholinergic neurite ingrowth and inhibit the aberrant reactional phenomenon of sympathetic sprouting, whilst those rich in noradrenergic and serotonergic neurons might supply the hippocampus with a new

noradrenergic and serotonergic innervation. Although empirically founded, this assumption remains highly speculative, especially when considering its applicability to human beings. The major problem in the experimenter's practice is that of an impossibility to get sufficient control over the reinnervation processes such as to make sure that the neurochemical markers are actually normalized, but not more than normalized. Nevertheless, regarding all these graft-induced neurochemical effects, the most exciting question to be addressed is that of whether neurochemical effects such as the aforementioned ones are sufficient to induce functional recovery at the level of the organism or, in other words, whether these effects allow rats with hippocampal denervations to perform normally in the behavioural tasks in which their non-grafted counterparts are disabled? This will be our concern in the next and last part of this review.

5. BEHAVIOURAL EFFECTS OF INTRAHIPPOCAMPAL GRAFTS

5.1. Grafts Rich in Cholinergic Neurons

One of the first studies to analyze the effects on cognitive function of intrahippocampal transplants containing fetal cholinergic neurons has been conducted by Low *et al.* (1982) on rats with aspirative lesions of the dorsal septohippocampal pathways and intracavitary implantations of tissue blocks from the septal region of the fetal brain. Using a standard working memory testing procedure in the 8-arm radial maze test (all arms accessible and baited), Low *et al.* (1982) found that, seven months after grafting surgery, the performance of their grafted rats was improved as compared to lesion-only controls, but only when these rats where pretreated systemically with the acetylcholinesterase inhibitor, physostigmine (0.05 mg/kg, i.p.). In lesion-only rats, this treatment did not induce a significant improvement of performance. Although this study appeared as somewhat disappointing because the detection of the graft-induced effects required additional treatment with an anticholinesterase agent, it clearly demonstrated the potential ability of grafted neurons providing the hippocampus with a new cholinergic innervation to foster recovery of cognitive function. Later on, Segal *et al.* (1989) reported similar results. Using rats with electrolytic lesions of the MS or knife cut lesions of the dorsal septohippocampal pathways, they grafted minced septal tissue into the hippocampus and tested their rats in a Morris water maze according to a procedure essentially sensitive to the disruption of spatial reference memory. Whatever lesion was considered, a beneficial effect of the grafts on water maze performance was found only when the grafted rats were tested under the influence of physostigmine (0.05 mg/kg, i.p). In another study in which we investigated the behavioural effects of fetal septal cell suspension grafts after partial damage to the medial part of fimbria or to the dorsal fornix, we found that rats with damage to the medial fimbria and intrahippocampal grafts showed improved radial maze performance, but only when systemically treated with a dose of 1.6 mg/kg d-amphetamine (Cassel *et al.*, 1988). Whereas the studies by Low *et al.* (1982) and Segal *et al.* (1989) suggest that the level of graft-induced cholinergic reinnervation of the hippocampus may be insufficient to improve cognitive function in rats with fimbria-fornix lesions, there are numerous experiments demonstrating that a sufficient reinnervation may actually contribute to re-establish a level of cholinergic function allowing beneficial behavioural effects to be observed in absence of any additional drug treatment. For instance, using rats with aspiration lesions of the dorsal septohippocampal pathways and either intracavitary grafts of septal tissue blocks, intrahippocampal cell suspension grafts or, as a control, grafts of locus coeruleus cells, a nucleus virtually devoid of cholinergic neurons, Dunnett *et al.* (1982) found that, seven months after grafting surgery, rats with both types of septal grafts recovered a close-to-normal working memory performance in a rewarded T-maze alternation task. Using the Morris water maze, Nilsson *et al.* (1987) found that fimbria-fornix lesioned rats with intrahippocampal cell suspension grafts were able to learn the location of an escape platform hidden in a quadrant of the water tank, a spatial reference memory capacity that lesion-only rats failed to exhibit. That grafts rich in cholinergic neurons may induce recovery of cognitive function after disruption of the dorsal septohippocampal pathways, particularly of spatial working and reference memory, has also been demonstrated in several other experiments that will not be summarized herein (e.g. Cassel *et al.*, 1990, 1991; Daniloff *et al.*, 1985; Hodges *et al.*, 1991a, 1991b, 1991c; Richter-Levin and Segal, 1991; Tarricone *et al.*, 1991, 1993). However, all these findings did not unquestionably demonstrate that the mechanism(s) underlying the graft-induced behavioural effects is (are) cholinergic in nature.

The first indication that this mechanism probably involves the graft-derived cholinergic reinnervation of the hippocampus comes from studies in which the degree of behavioural recovery was found to positively correlate with the graft-induced recovery of cholinergic markers (e.g. Daniloff *et al.*, 1985; Dunnett *et al.*, 1982; Tarricone *et al.*, 1991, 1993), even when the observed recovery was fostered by grafts including striatal (and thus non-septal) cholinergic neurons (e.g. Li *et al.*, 1992). A second line of evidence comes from experiments which used a lesion paradigm producing more specific damage to the cholinergic neurons in order to assess the behavioural effects of intrahippocampal grafts rich in cholinergic neurons. For instance, in a study by Emerich *et al.* (1992), cholinergic denervation of the hippocampus was produced by i.c.v. injections of AF64A and the lesion-induced spatial learning deficits assessed in radial maze task could be attenuated by intrahippocampal grafts of septal cell suspensions. Similar findings were reported by Ikegami *et al.* (1989a, 1989b); see also Ikegami *et al.*, 1991) who, in addition to a radial maze task, also assessed their AF64A lesion- and graft-induced effects in a rewarded T-maze alternation task. The grafts also improved performance in this working memory test having a lower spatial load than the

radial maze test. In an experiment by Arendt *et al.* (1989), the cholinergic lesions were produced by repeated and long lasting exposure to high doses of ethanol. These authors also found the cognitive deficits associated with the cholinergic degeneration to be attenuated by intrahippocampal (as well as intracortical) grafts rich in cholinergic neurons. As to the third series of arguments, there are a few studies which, additionally to the group of rats with grafts rich in cholinergic neurons, included a control group of rats receiving grafts virtually devoid of cholinergic neurons. In this control group, the non-cholinergic grafts were placed in exactly the same region as the grafts rich in cholinergic neurons. When observed, beneficial graft-induced effects on cognitive function always occurred in the rats bearing grafts rich in cholinergic neurons (e.g. Arendt *et al.*, 1989; Cassel *et al.*, 1991b; Dunnett *et al.*, 1982; but see Cassel *et al.*, 1990b). Finally, some studies also demonstrated that the graft-induced effects on cognitive function did not resist a treatment with an antimuscarinic agent such as atropine administered at a dose that also impaired the sham-operated rats (e.g. Hodges *et al.*, 1990, 1991b; Li *et al.*, 1992; Nilsson *et al.*, 1987; Segal *et al.*, 1989). Altogether, these observations point towards the cholinergic nature of the graft-induced effects on cognitive function.

However, if the cholinergic reinnervation of the denervated hippocampus is a *sine qua none* condition for the grafts to exert beneficial effects on spatial learning and memory, it can also be questionned whether this condition is actually sufficient. In one of our previous experiments (Cassel *et al.*, 1991b), we have compared the morphological and behavioural effects of grafts rich in cholinergic neurons prepared from the brain of fetuses aged of 16 or 14 embryonic days (ED). It was found that both types of grafts provided the hippocampus with a comparable AChE-positive reinnervation pattern and contained numerous ChAT-positive neurons, but only the grafts from ED 14 fetuses resulted in a significant attenuation of spatial memory deficits assessed in a 8-arm radial maze test (Cassel *et al.*, 1991b). Interestingly, in the ED14 septal grafts, many GABAergic neurons expressing the calcium-binding protein parvalbumin could be immunolabelled (see also Buzsàki *et al.*, 1992), whereas, in the ED16 grafts, such cells were found only exceptionally. In other experiments, we (e.g. Cassel *et al.*, 1990a, 1992c; Jeltsch *et al.*, 1994b) and other research groups (e.g. Buzsàki *et al.*, 1992; Dunnett *et al.*, 1989) observed that well surviving grafts failed to exert any significant effect on the lesion-induced behavioural deficits, in spite of the fact that the hippocampus exhibited an acceptable organotypic AChE-positive reinnervation pattern or that hippocampal cholinergic markers were increased to near-normal levels. In one of the last mentioned studies, Dunnett *et al.* (1989) have used fimbria-fornix lesioned rats given various types of septal cell suspension grafts (differing in particular by the lesion-to-grafting delays or the ages of the donor) and evaluated cognitive performance in a paradigm of operant conditionning (DRL). In their article, these authors emphasize that they were unable to establish a clear relationship between the level of behavioural recovery and the graft-derived AChE-positive reinnervation pattern of the hippocampus. Such a statement may also apply to the data of an experiment by Kelche *et al.* (1988). These authors have assessed the behavioural effects of fimbria-fornix lesions combined to intracavitary grafts of septal tissue blocks. Behavioural evaluations used a Hebb and Williams maze. During the delay from grafting to testing, approximately half their sham-operated, lesion-only and grafted rats (intracavitary implantation of septal tissue blocks) had been reared under physically- and socially-enriched housing conditions (twelve rats per large cage, many objects in each cage with the objects changed daily; for further detail, see Rosenzweig *et al.*, 1972), the other half being held according to standard maintenance conditions of laboratory rats (3 rats per cage, no objects). Kelche *et al.* (1988) reported that the grafts were actually able to reduce the lesion-induced deficits, but only when the rats had been reared under enriched housing conditions. The grafted rats reared under standard conditions performed like lesion-only rats. Upon histological verifications, it came out that despite this clear-cut difference in the performance of both groups of grafted rats, the graft-derived AChE-positive reinnervation pattern of the hippocampus did not differ between the rats reared in the enriched and those reared in the standard environments. Similar conclusions were drawn more recently from an experiment in which the behavioural effects of postsurgical training combined to intrahippocampal cell suspension grafts were assessed. Actually, Kelche *et al.* (1995) found the post-surgical training to interact positively with the grafts, but only at the level of behavioural performance. Again, the graft-induced AChE-positive reinnervation pattern did not differ between the rats which had sustained training and those which had not.

Although many of the aforementioned experiments have been regarded as supporting the hypothesis that the basal forebrain cholinergic systems critically contribute to a variety of memory processes, it seems reasonable to emphasize that the relationship between the graft-induced recovery of cholinergic markers and that of behavioural performance is probably not as simple as correlation approaches might suggest it. When septal grafts are found to exert beneficial effects on cognitive function, at least a partial graft-induced recovery of cholinergic markers in the hippocampus is verified sustematically. However, as illustrated above, the recovery of cholinergic markers in the hippocampus has no predictive value as concerns the behavioural effects of the grafts: Graft-derived cholinergic reinnervation of the hippocampus is necessary but not sufficient for beneficial effects to be observed at the level of cognitive functions. In addition, in all studies reported so far, the behavioural restoration induced by the grafts was never found to be complete, even when cholinergic markers had been restored to near-normal levels in the denervated hippocampus. Actually, whereas grafted rats are often found to perform better than do the lesion-only ones, they almost never reach the level of performance found in their virtually intact counterparts. Some of the reasons which might account for this discrepancy

between the neurochemical or histological effects of the grafts and their behavioural outcome have been enumerated recently by Tarricone *et al.* (1996). To give just a few examples, it seems that beyond the normal graft-derived AChE-positive reinnervation pattern: (i) ultrastructural characteristics of synaptic graft-host connections may be abnormal (e.g. Anderson *et al.*, 1986; Clarke, 1985; Clarke *et al.*, 1986); (ii) electrophysiological characteristics typical of hippocampal activity (i.e. theta rhythm or place cells) are not (e.g. Segal, 1987) or are only partially re-established and, in the latter case, they exhibit obvious functional abnormalities (e.g. Segal, 1987; Shapiro *et al.*, 1989); (iii) grafts may produce functional effects also by neurons other than the cholinergic ones and both the identity and the functional effects of these neurons would need extensive investigations; (iv) when a cell suspension is injected in the hippocampus, the grafting procedure itself may result in a partial disorganization of the hippocampal morphology near the injection sites, an effect which is not necessarily harmless at the level of behavioural function (e.g. Cassel *et al.*, 1993a, 1993b but see Hofferer *et al.*, 1994, 1996); (v) although there exists evidence that the grafts are under control of the host brain, due to the ectopic placement of the grafted neurons, the reconstruction of the severed neuronal network is neither complete, nor does it appear to be normal as compared to the structure of the corresponding neuroanatomical network as it is found in an intact brain (cholinergic neurons are in the septum and the DBB in normal rats and in the hippocampus in grafted rats).

In addition to the question of the completness of the graft-induced recovery, one may also raise the question of whether the graft-induced recovery is actually a genuine recovery, which means, according to O'Keefe and Nadel's theory (O'Keefe and Nadel, 1978; see also O'Keefe *et al.*, 1975) a recovery consisting in the restoration of a normal capability to built up and use a cognitive map. Such a question appears to be particularly pertinent when the results reported by Emerich *et al.* (1992) are examined carefully. These authors have used a radial-arm maze task to assess the effects of i.c.v. injections of AF64A followed by an intrahippocampal injection of a fetal cell suspension rich in cholinergic neurons. When they tested their rats according to a standard spatial working memory testing procedure with all arms accessible and baited and no trial interruption, the extent of the lesion-induced deficit was substantially attenuated by the grafts. However, when the authors switched to a testing procedure based on the interruption of a trial, the difference between the performance of lesion-only and grafted rats was no longer observed. This observation suggests that the grafts failed to restablish a real capacity to deal with and to memorize spatial information. To completely measure the meaning of such a result, some preliminary remarks might be helpful to the reader. In order to perform the standard version of the radial maze task, rats can use two equivalently efficient "strategies". One of these is basically egocentric and consists of clockwise or counter-clockwise repetitions of choice directions such as 45° (they enter the arm right next to the just-visited arm) or 135° and does not necessarily rely upon the use of extramaze cues. Such egocentric choice patterns are observed in both intact and fimbria-fornix-lesioned rats. Thus, when rats perform that way, it can be assumed that the spatial load of the task is minimal and that a low number of errors is not necessarily indicative for normally operating spatial working memory processes. The rats perform the task with what we term a sequential routine. the rats which have developed such a routine are able to keep it, even when access to extramaze cues is experimentally compromised (e.g. testing in red lights). The second strategy is basically allocentric. It consists of using extramaze cues in order to memorize the arms that have already been visited within a given trial and, therefore, it requires normally operating spatial working memory processes. In intact rats, both types of choice patterns can be observed (the egocentric strategy being probably more economical in terms of cognitive demand than the allocentric one), but when the experimenter switches from an uninterrupted to an interrupted testing procedure, intact rats usually performing the task with an egocentric strategy are able to switch to an allocentric one and to complete the test with a very small number of errors. If intact rats had persisted in using an egocentric strategy after the trial interruption, this persistence would have led to an increased number of errors, a theoretical issue which we never observed in practice. Conversely, fimbria-fornix lesioned rats which have developed the routine of exploring the maze according to an egocentric choice pattern are unable to operate a switch such as the one described in intact rats. In consequence, their number of errors increases dramatically after the trial interruption. Although Emerich *et al.* (1992) did not analyse the choice patterns of their rats, it can be speculated that the apparent recovery observed in their grafted rats with the uninterrupted testing procedure might be relying upon a higher frequency of egocentric choice patterns, rather than on a graft-induced recovery of a real ability to deal with spatial information. If so, and to come back to the matter of this paragragh, one must assume that the grafts have failed to foster a true functional recovery. In a recent unpublished study, we found that rats with fimbria-fornix lesions and intrahippocampal grafts of mesencephalic *raphe* cell suspensions performed an uninterrupted radial maze task much better that did the lesion-only rats. However, analysis of the rats' strategies revealed that this graft-induced effect did probably not rely on the restoration of an ability to deal with spatial cues: Grafted rats used egocentric choice strategies much more often than did their lesion-only counterparts (40% versus less than 10% of all trials, respectively).

5.2. Grafts Rich in Serotonergic Neurons

The first studies using intrahippocampal grafts rich in serotonergic neurons aimed essentially at identifying the neurochemical and electrophysiological effects as well as the morphological characteristics of such grafts. With findings suggesting that dysfunctions of serotonergic mechanisms might in one way or another influence the functional outputs of other neurotransmitter systems and also interfer with

cognitive functions (for reviews, see Cassel and Jeltsch, 1995; Sirviö *et al.*, 1994; Steckler and Sahgal, 1995), experiments assessing the cognitive effects of grafts rich in serotonergic neurons in rats subjected to hippocampal denervation have gained interest. Van Luijtelaar *et al.* (1991) have investigated some behavioural effects of i.c.v. injections of the serotonergic neurotoxin 5,7-DHT combined with intrahippocampal grafts of a mesencephalic *raphe* cell suspension. Although the lesions and the grafts produced clear-cut neurochemical effects, both the lesion-only and grafted rats failed to show any consistent behavioural modification, whether in a task assessing orientation in a social context or in a Morris water maze test assessing working and reference memory performance. These findings are in line with the view that serotonergic lesions alone produce only modest or no dysfunctions of spatial working and reference memory (see Section 3.4.3). In other studies, the effects of grafts rich in serotonergic neurons were assessed in rats that underwent double lesions (e.g. 5,7-DHT injections coupled to septal lesions) or a chronic serotonergic depletion combined to an acute muscarinic blockade. In one of their experiments, Richter-Levin and Segal (1989) have used i.c.v. injections of 5,7-DHT followed, one week later, by intrahippocampal grafts of small fragments of fetal mesencephalic raphe. Between 2 and 3 months after grafting, the rats were submitted to a Morris water maze task. Whilst lesion-only and grafted rats showed no impairment in this task, additional pretreatment with a subamnestic dose of the antimuscarinic agent atropine (20 mg/kg, i.p.) resulted in impaired performance in the lesion-only rats, but not in the grafted ones. These findings were partly consolidated in a second experiment published later on by the same authors (Richter-Levin and Segal, 1991). In another study, Richter-Levin *et al.* (1993) combined 5,7-DHT i.c.v. injections to intraseptal injections of colchicine, a neurotoxin which is able to produce partial damage to the septal cholinergic neurons when used under such conditions (e.g. Ginn and Peterson, 1991). Part of their double-lesioned rats sustained intrahippocampal grafts of fetal mesencephalic *raphe* cells. Again, it was found that 5,7-DHT lesions alone did not impair spatial working and reference memory performance in a water maze task. Also single colchicine lesions were unable to produce consistent impairments. However, when these two lesions were combined, both the working and the reference memory capabilities were perturbated. Interestingly, in rats given double lesions and grafts, performance was comparable to that found in the sham-operated controls. Similar results were obtained with 5,7-DHT injections combined to electrolytic lesions of the septal region (Richter-Levin and Segal, 1991). In a study by Nilsson *et al.* (1990a), intrahippocampal grafts of mesencephalic *raphe* cell suspensions had no effect on the water-maze learning deficits that resulted from combined 5,7-DHT i.c.v. injections and radiofrequency lesions of the MS. In one of our more recent experiments on rats with electrolytic lesions of the dorsal fornix and the fimbria (Jeltsch *et al.*, 1994b), we also found that intrahippocampal grafts rich in serotonergic neurons had no effect on the deficits that rats given electrolytic lesions of the fimbria and the dorsal fornix exhibited in a radial maze and a Morris water maze test. Identical conclusions could be drawn form an earlier experiment in which the lesions were made by an aspiration technique (Cassel *et al.*, 1992c).

5.3. Co-Grafts Rich in both Cholinergic and Serotonergic Neurons

Although most experiments investigating the behavioural effects of intrahippocampal grafts have used an opproach based on the implantation of neurons from only one neuroanatomically-defined region of the fetal brain, there are some data in the literature concerning the behavioural effects of co-grafts of mixed septal and mesencephalic *raphe* cells, the neurochemical effects of whose have been reviewed in Section 4.5. For instance, in rats given lesions of the MS and i.c.v. injections of 5,7-DHT, Nilsson *et al.* (1990a) have studied the behavioural effects of septal grafts alone (rich in cholinergic neurons), *raphe* grafts alone (rich in serotonergic neurons), and of a combination of both types of grafts. All grafts were placed as a cell suspension into the dorsal hippocampus and cognitive function was assessed in a Morris water maze according to a reference memory testing protocol. Whereas neither type of single grafts produced beneficial effects on water-maze performance, the combined grafts were found to improve water-maze performance at 10 months after grafting surgery. Using a different lesion paradigm (i.e. electrolytic lesions of the fimbria and the dorsal fornix), we also found that combined septal and *raphe* grafts placed into the denervated hippocampus of rats were able to improve (even to normalize) water-maze probe trial performance (reference memory protocol), an effect that neither of the single grafts was able to produce. Such co-grafts, however, failed to improve spatial working memory assessed in a radial maze task (Jeltsch *et al.*, 1994b), as we already found in an earlier experiment on rats with aspiration lesions of the dorsal septohippocampal pathways (Cassel *et al.*, 1992c).

5.4. Grafts Rich in Noradrenergic Neurons

The functionality of grafts rich in noradrenergic neurons at the level of the organism has been essentially investigated in the frame of a seizure model based on hippocampal kindling. Animals are considered kindled when a series of electrical stimulations through an electrode implanted in the hippocampus induce a generalized convulsive seizure. When compared to virtually intact rats, rats given 6-OHDA (e.g. Corcoran and Mason, 1980; McIntyre and Edson, 1982) or DSP-4 (Bortolotto and Cavalheiro, 1986; Carre and Harley, 1986) lesions of the central noradrenergic fibres show their first convulsive seizure after a number of electrical stimulations lower than that necessary in their intact counterparts. In rats with such lesions, kindling is facilitated. Conversely, in intact rats, a stimulation of

the locus coeruleus or an administration of pharmacological agents enhancing the noradrenergic transmission retards the development of convulsive seizures (e.g. Jimenez-Rivera *et al.*, 1987 and McIntyre and Edson, 1982, respectively). Using rats subjected to an i.c.v. injection of 6-OHDA, Barry *et al.* (1987) found that intrahippocampal grafts rich in noradrenergic neurons were able to attenuate the development of seizures, the degree to which this attenuation occurred being significantly correlated to the graft-derived noradrenergic reinnervation of the hippocampus. In another experiment (Bengzon *et al.*, 1990), i.c.v. injections of 6-OHDA were followed by bilateral intrahippocampal implantations of a fetal locus coeruleus cell suspension. Three months after transplant surgery, the grafted rats were subjected to hippocampal kindling, one half with prior idazoxan treatment (an α_2-adrenoceptor antagonist), the other half with vehicle injections. The kindling rate in both groups was compared to that found in intact rats treated with idazoxan. In previous experiments, idazoxan treatment had been shown to facilitate the development of seizures (e.g. Kokaia *et al.*, 1989), suggesting that the dampening effect of noradrenaline is mediated by a mechanism involving α_2 receptors. In both groups of idazoxan-treated rats, the seizures were found to develop faster than in the group of untreated grafted rats. This finding demonstrates that the graft-derived noradrenergic reinnervation of the denervated hippocampus acts on α_2 receptors, as does the noradrenergic hippocampal innervation in intact rats. Furthermore, it seems that this antiepileptic effect occurs at synapses established between the grafted noradrenergic neurons and the host hippocampus, as the intrahippocampal implantation of noradrenaline-releasing polymer matrices was not able to counterbalance the 6-OHDA-induced increase of the kindling rate (Kokaia *et al.*, 1994a). This interpretation is also in line with the results of another experiment in which intracavitary (fimbria-fornix) grafts of superior cervical ganglion were found to be ineffective on the 6-OHDA lesion-induced acceleration of kindling development (Kokaia *et al.*, 1994b). Although the grafts of superior cervical ganglion were able to release noradrenaline in the catecholamine depleted hippocampus, the authors interpreted the lack of influence of such grafts on the development of kindling as being possibly due to the absence of conventional synapses between the grafted neurons and the host hippocampal ones. In another experiment, Bengzon *et al.* (1993) confirmed their findings published in 1990, but also showed that grafts of locus coeruleus tissue were ineffective on the kindling rate when implanted into the hippocampus of intact rats (although the grafts induced a clear-cut hyperinnervation of the hippocampus) or into the hippocampus of 6-OHDA lesioned rats that were subjected to kindling before they received the grafts.

The influence of grafts rich in noradrenergic neurons placed into the hippocampus was also assessed using a model of epileptic seizures termed pilocarpine status epilepticus. After a systemic injection of a high dose of pilocarpine, a muscarinic agonist, sustained seizures are observed for approximately 1 day. Therefater, a "silent" period will last for several days before a new spontaneous seizure appears as the first of now a chronic state of recurrent seizures. Using this model, Bortolotto *et al.* (1990) have shown that intrahippocampal grafts of fetal locus coeruleus cells reduced the number of spontaneous seizures from approximately 11 per week to less than 1 par week, with the effect starting between 5 and 6 weeks after grafting surgery and being maximal at about 9 weeks. In the nongrafted rats, the average weekly number of seizures was constant throughout the observation period.

The effects of noradrenergic grafts on memory impairments have rarely been assessed in relation with surgical paradigms of amnesia. That noradrenergic grafts might also exert cognitive effects has been suggested in an experiment by Collier *et al.* (1988) who have compared the passive avoidance performances of 5-month-old rats with those of 24-month-old rats. Although this experiment was not based on an experimental lesion paradigm such as the ones considered in this article, it is interesting to note that Collier *et al.* (1988) reported that whereas the old rats were severely impaired in retention of a passive avoidance response (24 h delay), those with intraventricular (third ventricle) grafts of locus coeruleus-containing tissue blocks showed retention performances comparable to the performances found in the group of younger rats. This graft-induced effect could be blocked by administration of propranolol, a blocker of adrenergic receptors. Also, the grafted old rats showed reduced activity in an open field as compared with both their age-matched nongrafted counterparts and the 5-month-old rats. Furthermore, Collier and Sladek (1989) have provided some preliminary evidence that such grafts might ameliorate the spatial memory deficit that aged rats exhibit in a Morris water maze task. However, these graft-induced effects are probably not mediated by an action on hippocampal function, but rather, as stated by the authors (Collier *et al.*, 1988) by an action on structures close to the third ventricle such as, for instance, the hypothalamus. Close to the scope of this review, effects of grafts rich in noradrenergic neurons have also been assessed on some fimbria-fornix lesion-induced memory impairments. In rats with fimbria-fornix transections, Wang *et al.* (1994) have found that intrahippocampal grafts of superior cervical ganglion tissue which provided the hippocampus with a substantial noradrenergic fibre ingrowth were also able to induce improved retention performance in a passive avoidance test (24 h delay).

Altogether, it seems clear that intrahippocampal grafts rich in noradrenergic cells may attenuate the sensitivity to hippocampal kindling and, in some respects, exert beneficial effects on the cognitive disturbances induced by fimbria-fornix lesions. Whether the beneficial effects on the lesion-induced cognitive dysfunctions are direct or are rather due to an indirect mechanism involving the antiepileptogenic effects of the noradrenergic neurons remains to be addressed experimentally. Whatever may be, the possibility that graft-derived noradrenaline actually influences the behavioural outcome of fimbria-fornix lesions by inhibiting some epileptogenic effects of such lesions and thereby augment cognitive processes related to hippocampal functions might be an

alternative explanation to the findings reported by Wang *et al.* (1994) and an interesting issue of future research. It is also interesting to note that whereas grafts rich in noradrenergic neurons may hamper the susceptibility to epileptogenic manipulations in rats subjected to central noradrenergic depletion, other types of grafts may act as epileptic generators (e.g. Buzsàki *et al.*, 1988) or as factors that alter the susceptibility to epileptogenic treatments such as pentylenetetrazol injections or exposure to a sound with characteristics appropriate to induce audiogenic seizures in seizure-prone animals (e.g. Cassel *et al.*, 1987, 1991c).

5.5. Summary and Conclusions

As reviewed in this section, non-selective damage to the rostrally coursing afferents of the hippocampus induces pronounced depletions of markers of cholinergic, noradrenergic and serotonergic hippocampal innervations. Unquestionably, such lesions also produce dramatic impairments of cognitive functions and modifications in the hippocampal epileptic threshold. Using appropriate neurotoxins, it is possible to induce each of these neurochemically-characterized denervations separately, but only damage to the cholinergic component of these pathways seems able to mimick, in some respects even closely, the cognitive characteristics of the behavioural deficits found after non-selective lesions. With grafts containing the appropriate cell populations, each of these neurochemical deficits can be attenuated, compensated for or, sometimes, even overcompensated. Regarding the behavioural effects of these grafts, there exists evidence demonstrating that: (i) the cholinergic reinnervation of the hippocampus may attenuate some aspects of the lesion-induced cognitive "syndrome", particularly as concerns the spatial working and reference memory dysfunctions; (ii) the serotonergic reinnervation of the hippocampus does not induce or induces only modest or subtle effects on the deficits induced by non-specific denervation of the hippocampus; (iii) in case of lesions producing multitransmitter denervations of the hippocampus, co-grafts of cholinergic and serotonergic neurons are more efficient in fostering cognitive recovery than cholinergic grafts alone, at least as regards spatial reference memory performance; (iv) noradrenergic grafts may act by raising the epileptic threshold towards near-normal values after it had been decreased by hippocampal denervation. All these findings suggest that the morphological, electrophysiological, pharmacological and neurochemical effects that grafted neurons exert locally (i.e. within or in the vicinity of the denervated host structure) may be sufficient for lesion-induced dysfunctions to be attenuated also at the level of the whole organism. As such, intracerebral transplantation techniques are and should stay a tool of potential interest not only for neurobiologists who try to understand how the brain is working to produce function, but also for clinicians who are confronted to the tragic, and for most incurable, symptoms associated with neurodegenerative disease or brain injury in humans.

6. GENERAL DISCUSSION AND CONCLUSIONS

In this review, we focused on the neurochemical and behavioural effects associated with various lesion paradigms used to more or less extensively damage the dorsal components of the rostrally-coursing hippocampal afferents. Originating from the septal region, the locus coeruleus and the mesencephalic raphe, the majority of these afferents regroup in two dorsal pathways (cingular bundle and fimbria-fornix) which provide the hippocampus with a substantial part of its cholinergic, extrinsic GABAergic, noradrenergic and serotonergic inputs. Of course, these two pathways, often termed the dorsal septo-hippocampal pathways, also contain many hippocampal efferents as well as other types of afferents, but relative to the grafting experiments that were taken into account, the consideration of these other components was obviously beyond the scope of this article.

Non-selective damage to the fimbria-fornix and the cingular bundle results in dramatic cholinergic, noradrenergic and serotonergic denervations of the hippocampus, each of which can be quantitatively mimicked with appropriate use of neurotoxins such as AF64A or 192 IgG-saporin for cholinergic neurons, 6-OHDA or DSP-4 for noradrenergic neurons and 5,7-DHT for serotonergic neurons. From a behavioural point of view, one extremely consistent finding after such non-selective lesions is a dramatic impairment of working and reference memory capabilities, a deficit which is particularly prominent in all tasks requiring to deal with spatial information. While there is evidence that the disruption of the cholinergic innervation of the hippocampus plays a crucial role in the majority of these cognitive dysfunctions, there is some evidence suggesting that also the disruption of the serotonergic hippocampal afferents may be involved, in a way or another, in these cognitive perturbations. However, the sole serotonergic denervation of the hippocampus does not seem able to mimick the aforementioned deficits, whether qualitatively, or quantitatively, an observation suggesting that serotonergic neurons innervating the hippocampus might contribute to cognitive function by an interaction with other neurotransmitter systems (e.g. Cassel and Jeltsch, 1995; Steckler and Sahgal, 1995). As to the noradrenergic hippocampal afferents, it seems that these fibres exert some inhibitory modulation of hippocampal activity as their destruction results in a decreased threshold towards experimental manipulations known to induce convulsive seizures (e.g. kindling).

Morphological, neurochemical and pharmacological studies have shown that subsequently to denervation, various types of reactive reorganizations may occur in the hippocampus, all of which appear to push the residual parts of the hippocampal formation to compensate for the missing inputs or the denervation-induced dysfunctions. These reactional phenomena include homotypic and heterotypic sprouting, up- or downregulations of various receptor types as well as increased neurotransmitter turnover in the fibres spared by the lesions. Although

the magnitude of these modifications depends on the extent of the lesions and may become tremendous when the lesions are very large, in case of extensive denervation they seem unable to foster recovery of the disrupted behavioural functions: After aspiration or knifecut transection of the septohippocampal pathways, lesions restricted to only the fimbria and the dorsal fornix and even after more specific cholinergic denervation, whether the latter is combined or not to other experimentally-induce neurotransmitter dysfunctions, the cognitive deficits are lasting. Whereas such observations might be regarded as extremely disappointing, at least from a clinical point of view, they make all lesion paradigms in which recovery is weak or non-existent very helpful models to study the structural and functional effects of intrahippocampal grafts.

In that concern, evidence reviewed in the second part of the present article clearly shows that, under appropriate technical conditions, grafts defined according to their anatomical origin (and thus, with some neurochemical specificity) survive and can be integrated in the circuitry of the host hippocampus. These grafted neurons are also able to reinnervate the host hippocampus according to the neurochemical identity of the nuclei from wich the fetal neurons had been dissected out. Such grafts do not only provide the hippocampus with a locally functional reinnervation, they also produce effects at the level of behaviour: Grafts rich in cholinergic neurons may attenuate the cognitive deficits due to the lesions, perhaps even much better when they are co-grafted with serotonergic neurons, while grafts rich in noradrenergic neurons may compensate for the increased susceptibility to epileptogenic experimental manipulations such as hippocampal kindling. Furthermore, there is now sufficient evidence showing that grafts rich in cholinergic, noradrenergic or serotonergic neurons are functioning in the host hippocampus: These grafts are clearly able to release the neurotransmitter corresponding to the afferences which they were supposed to replace. In some respects, this release can even be considered as regulated by the means of autoregulatory mechanisms, as well as by neurons originating in either the host brain or in the grafts themselves.

However, when the denervated hippocampus is regarded an element of a larger system (the limbic system) in which the integration of a graft is analyzed from both a structural and functional point of view, it appears that there exists a major feature that does not show normal characteristics as compared with the organization of the corresponding system in the intact rat. In the intact brain, the cell bodies of the neurons projecting to the hippocampus are located outside the hippocampus, within nuclei (the MS and the DBB, the locus coeruleus and the mesencephalic raphe) where their activity is controlled or modulated by afferences arising from various other brain structures. In a grafted rat with partial, specific or extensive disruption of the fimbria-fornix/cingular bundle pathways, the graft is placed into or close to the hippocampus, thus in a location distant from that where the activity of the grafted cells is normally controlled in an intact brain. In other words, the graft is integrated into an unusual connectivity network as the entire cells (axons, cell body and dendrites) are inserted directly into the intrinsic circuitry of the hippocampus which normally receives only the axonal terminals of these cells. Thus, the denervated hippocampus bearing a graft appears as a new experimental construction with truncated neuroanatomical (and probably functional) characteristics in the brain of the recipient. This has a major consequence from a theoretical point of view. Actually, the question of whether such a new organization is functional can be addressed in two ways that are not necessarily related one another. One way concerns the local mechanisms or operations which the grafted neurons can restablish (e.g. neurochemical effects, auto- or hetero-regulatory processes) and will provide the scientist with information about whether the grafted neurons are working. The second way concerns the effects which such grafts may exert at the level of the organism (e.g. effects on learning and memory deficits or other behavioural alterations) and will provide the scientist with information about whether the locally identified operations have behavioural relevance. Whereas the causal relationship between the locally-operating effects of the grafts and their behavioural outcome is not always easy to demonstrate unquestionably (e.g. Cassel and Will, 1995), there are now converging and complementary arguments suggesting that this relationship may actually be causal. It is not our intention to affirm here that the graft-derived reinnervation of the hippocampus and the various associated functional effects are the only way by which grafts can contribute to compensate for the lesion-induced behavioural and other deficits. Other possible mechanisms may be effective as well (for reviews, see Cassel *et al.*, 1992a; Dunnett, 1994; Dunnett and Björklund, 1987; Sinden *et al.*, 1995) and some of these might even account for some unexpected graft-induced behavioural deficits (e.g. Dalrymple-Alford, 1994; Dalrymple-Alford *et al.*, 1988; Will *et al.*, 1989). However, if it is sometimes sufficient to restablish a certain level of neurotransmitter release in the denervated hippocampus for observing grafts to become behaviourally active, this observation suggests that the hippocampal cholinergic, noradrenergic and serotonergic afferents do work, at least partly, as level-setting systems that contribute to hippocampal function by secreting a given amount of neurotransmitters. As such, the grafted neurons work as an elaborate inexhaustible drug delivery system with at least three major advantages as compared to other drug delivery systems available so far (e.g. subcutaneously implanted minipumps): Grafting requires only one surgical operation, grafts may work over the entire life span of the experimental subject and, finally, this drug delivery system can be regulated. One obvious drawback, however, is that grafted neurons require a given postsurgical delay before they can be considered operational. Regarding cognitive functions in general and spatial memory in particular, the aforementioned observations might also have some theoretical fallouts in the field of hippocampal function. Actually, as the restoration of some behavioural function after hippocampal denervation

may be achieved by a local delivery of neurotransmitters such as acetylcholine and, perhaps, noradrenaline or serotonin, one may wonder whether one should not pay attention to a theoretical view that would, on the one hand, consider the hippocampus as the central station in which operations involved in various types of memory are processed and, on the other hand, that would regard the role of some of the rostrally-coursing dorsal afferents as being to provide some of the basic neurotransmitter-specific conditions for the processes going on in the hippocampus to operate adequately.

As pointed out by Ridley (1995) in a recent comment to a target article by Sinden *et al.* (1995), "*It is clearly easier to show that grafts can work than it is to explain how they work.*" If none of us would contest this statement, it is our belief that in this article we have reviewed some evidence suggesting that one of the possible ways by which neuronal grafts rich in cholinergic, noradrenergic or serotonergic neurons do work is the local release of neurotransmitters that are missing or severely depleted after lesions in the fimbria-fornix pathways.

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