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Review

Modulation of cholinergic functions by serotonin and possible implications in memory: General data and focus on 5-HT_{1A} receptors of the medial septum

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ABSTRACT

Cholinergic systems were linked to cognitive processes like attention and memory. Other neurotransmitter systems having minor influence on cognitive functions – as shown by the weakness of the effects of their selective lesions – modulate cholinergic functions. The serotonergic system is such a system. Conjoined functional changes in cholinergic and serotonergic systems may have marked cognitive consequences [Cassel JC, Jeltsch H. Serotoninergic modulation of cholinergic function in the central nervous system: cognitive implications. Neuroscience 1995;69(1):1–41; Steckler T, Sahgal A. The role of serotoninergic–cholinergic interactions in the mediation of cognitive behaviour. Behav Brain Res 1995;67:165–99].

A crucial issue in that concern is the identification of the neuroanatomical and neuropharmacological substrates where functional effects of serotonergic/cholinergic interactions originate. Approaches relying on lesions and intracerebral cell grafting, on systemic drug-cocktail injections, or even on intracerebral drug infusions represent the main avenues on which our knowledge about the role of serotonergic/cholinergic interactions has progressed.

The present review will visit some of these avenues and discuss their contribution to what is currently known on the potential or established implication(s) into memory functions of serotonergic/cholinergic interactions. It will then focus on a brain region and a neuropharmacological substrate that have been poorly studied as regards serotonergic modulation of memory functions, namely the medial septum and its 5-HT_{1A} receptors. Based on recent findings of our laboratory, we suggest that these receptors, located on both cholinergic and GABAergic septal neurons, take part in a mechanism that controls encoding, to some extent consolidation, but not retrieval, of hippocampal-dependent memories. This control, however, does not occur by the way of an exclusive action of serotonin on cholinergic neurons.

Contents

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1. Introduction

At a very general level, cognitive functions can be defined as an animal's capability to collect, encode, treat, store and use any kind of knowledge about its environment. Such functions are organized into a series of distributed, structurally and functionally interconnected anatomically defined modules. Schematically, one such module can be defined according to both its general structure (i.e., the different constitutive brain regions and the connectivity network enabling intra- and inter-regional information exchange) and its functional implications (i.e., the "mental" and behavioural outputs it contributes to generate). Thus, each component of this module (for instance, a particular nucleus) comprises its own neurons and its intrinsic neuronal network, but also is both the source of projection fibres sent to other components and the target of neurochemically defined afferent fibres originating in other structures of the brain. These fibres, whether efferent or afferent, can be defined at different levels of analysis, e.g., according to the type of pathway(s) to which they belong or to their neurochemical identity (e.g., cholinergic, noradrenergic, serotonergic, etc.).

Some regions of the mammalian brain receive both a serotonergic and a cholinergic innervation (e.g., the hippocampus, the cortical mantle), or comprise cholinergic nuclei that receive an extrinsic serotonergic innervation (e.g., basal forebrain nuclei, such as the septum). Providing an exhaustive neuroanatomical survey of the various serotonergic and cholinergic nuclei or targets, of the distribution of their interconnections or terminal fields, and of the various receptor sites found therein lies beyond the scope of the present review. On these matters, the reader is referred to previous publications dealing with serotonergic and cholinergic neuroanatomy, neuropharmacology and neurophysiology in the brain [3,24,27,74,111,132,142].

It can be briefly reminded, however, that the brain regions receiving both a serotonergic and a cholinergic innervation, whether extrinsic and/or intrinsic, encompass, among other structures, the striatum, the cortex and the hippocampus. These three regions are recognized to play a crucial role in various forms of cognitive processes, perhaps more particularly in memory functions, be it in terms of declarative-like or non-declarative-like ones.

Several studies have shown that an interaction between serotonergic and cholinergic processes in one or the other of these regions may result in physiological modifications that the manipulation of only one of these systems is unable to mimick, either qualitatively or quantitatively. The majority of the arguments demonstrating that an interaction between cholinergic and serotonergic processes have a functional relevance were obtained with neuro- and psychopharmacological approaches. For example, it was shown that, in the rat hippocampus, the release of acetylcholine by terminals originating in the medial septum and the diagonal band of Broca may be inhibited by a local activation of 5-HT_{1B} [20,21,37,96,118,123] and probably also 5-HT_3 receptors [60]. Under the condition of a systemic activation, this release can be facilitated *via* the activation of 5-HT_{1A} as well as 5-HT_3 receptors, or inhibited *via* the activation of 5-HT_{1B} (5-HT_{1D} in the guinea-pig) and 5-HT_4 receptors [19,43,73,104]. There is also evidence that a serotonergic denervation of the hippocampus is able to facilitate the evoked release of acetylcholine in hippocampal slices [18]. In the cortex, the release of acetylcholine may be locally controlled by 5-HT_{1B} and 5-HT_3 inhibitory receptors [42,123], whereas systemic activation of 5-HT_{1A} and 5-HT_4 receptors induces facilitatory effects [5]. Finally, in the striatum, local inhibition of the cholinergic tonus may be mediated by 5-HT_1 and/or 5-HT_2 receptors [61] and, under the condition of systemic activation, by 5-HT_{1A} receptors [6].

All these receptor sites are potential neuropharmacological targets by which serotonin (5-hydroxytryptamine or 5-HT) may influence cholinergic processes and affect cognitive function, including learning and memory [for the detail, see 36 or 131].

In the present review, we will consider serotonergic–cholinergic interactions and their relevance to memory functions. In a first part, we will glance at very general approaches relying upon more or less selective lesion techniques, combined or not to intracerebral transplantations of neurochemically defined populations of fetal neurons (i.e., cholinergic and/or serotonergic). These approaches have contributed to stimulate the interest in a possible role for cholinergic–serotonergic interactions in memory functions. In a second part, we will focus on systemic drug administration approaches by presenting data showing the effects induced by systemic treatment with serotonergic compounds on cholinergic grafts, as well as after cholinergic lesions or receptor blockade. These pharmacological approaches have the advantage, among some others, of enabling an investigation of the contribution of different subtypes of receptors. Our main focus, there, will be the 5-HT_{1A} receptor. This receptor is negatively coupled to adenylyl cyclase and to a direct activation of inwardly rectifying potassium conductance, thus contributing to membrane hyperpolarization and reducing the probability of cell firing when activated [70,71]. Finally, based on findings of our and other laboratories, of which some are very recent [84], others yet unpublished, the last part of this review will concentrate on the possible contribution of 5-HT_{1A} receptors of the medial septum to spatial memory encoding and consolidation. We will then discuss the extent to which this contribution may operate *via* an action mediated by septohippocampal cholinergic neurons.

2. Lesion and cell grafting approaches

For many years, experiments in behavioural neurobiology have used lesion techniques that selectively damaged well delineated regions of the brain (nuclei and/or pathways) in order to assess the behavioural correlates of such damage. While very useful in studying and establishing possible structure–function relationships, such approaches were of limited utility as to the understanding of the neuropharmacological regulations involved in the modulation of region- or system-specific functions. The investigation of such modulation(s) required pharmacological approaches and/or lesion techniques that were selective, before anything else for particular neurotransmitter systems. Approaches based on neurochemical selectivity of lesions have become possible only with the emergence of a series of compounds with neurotoxic properties oriented towards neurochemically defined populations of neurons.

2.1. Serotonergic and cholinergic neurotoxins

For example, 5,6-dihydroxytryptamine (5,6-DHT) and 5,7-dihydroxytryptamine (5,7-DHT), two substances that were able to

selectively damage the serotonergic neurons (under the condition of a protection of noradrenergic neurons by pre-treatment with a norepinephrine reuptake blocker such as desipramine) were introduced in the early seventies [7–9]. Subsequently, 5,7-DHT, which proved to be more useful than 5,6-DHT, has been used to damage serotonergic neurons in the rodent brain and to investigate the functional correlates of the lesion at various levels of analysis, including memory [79,91]. Briefly, the mechanism by which this neurotoxin produces selective serotonergic damage relies upon auto-oxidation and other enzymatic-mediated oxidation reactions of 5,7-DHT, after its rapid uptake into serotonergic neurons. The reaction products of these oxidations, and especially 5-hydroxytryptamine-4,7-dione, are toxic for the neurons in which they occur [133,145].

Concerning the cholinergic selectivity of neuronal lesions, AF64A (ethylcholine aziridinium) was probably one of the first compounds to open some promising perspectives. This aziridinium moiety-containing molecule (aziridinium is cytotoxic) is an analog of choline and has a strong affinity for the high affinity choline transporter, which it may inhibit reversibly or not, depending on its concentration [64]. It is noteworthy that the specificity of AF64A has been questioned [55,65,66,93]. Nevertheless, it seems that under conditions of appropriate dosage and preparation methods, the toxic effects of AF64A might reach a satisfactory degree of cholinergic specificity and can be the cause of memory dysfunctions [55]. Another compound, named 192 IgG-saporin, has become available in the early nineties [143]. It is an immunotoxin that appears to be more specific for cholinergic neurons, at least in the basal forebrain of the rat. This toxin is constituted by a monoclonal antibody that recognizes the $p75^{NGF}$ receptor, and which is coupled to the ribosomal toxin saporin [15,23,68,98,108,143]. Saporin is extracted from the plant *Saponaria officinalis*. There exists a recent murine equivalent of it [16], which permits to induce lesions that are quite comparable in extent and selectivity to those obtained in rats with 192 IgG-saporin [106].

The behavioural effects of this immunotoxin seem, however, to depend on its way of administration. When infused into the cerebral ventricles, it reaches virtually all basal forebrain cholinergic targets bearing $p75^{NGF}$ receptor and also other $p75^{NGF}$ receptor-bearing neurons such as motoneurons [12] as well as Purkinje cells in the cerebellum [140]. Under such conditions, deficits have been observed in several tasks taxing working or reference memory (Morris water-maze, radial maze, passive avoidance, operant delayed matching-to-position task) and in a relatively replicable way [e.g., 85,86,90]. Conversely, when injected intraparenchymally, either into the septal region or the nucleus basalis magnocellularis, the cholinergic damage observed was confined to the structure in which 192 IgG-saporin had eventually been injected, and memory deficits were generally weak or inexistent, unless the doses of 192 IgG-saporin were large and could have induced additional non-cholinergic damage (e.g., to septal GABAergic neurons, probably as a consequence of toxins resulting from the degeneration of cholinergic neurons [77]). It is noteworthy, however, that intrabasalis injections of the immunotoxin produced weak to severe deficits of attentional functions, for example in the five-choice serial reaction time task, although having no effect on memory functions, as found in the radial and the Morris water mazes [58,67,89,97,122]. This clear-cut shift between the memory effects that were expectable from the so-called cholinergic hypothesis of geriatric memory dysfunctions and those that were actually observed has contributed to challenge the cholinergic hypothesis of memory functions [e.g., 6]. This issue has been commented and discussed in various recent reviews [e.g., 102,114].

2.2. Combined cholinergic and serotonergic lesions

To the best of our knowledge, we have been the first ones to use 192 IgG-saporin lesions in combination with another type of neurochemically selective damage, namely 5,7-DHT-induced serotonin depletion. In general, lesion experiments based on intracerebroventricular injections of 192 IgG-saporin and 5,7-DHT clearly suggest that the cognitive effects of a cholinergic denervation of both the hippocampus (septal lesions) and the neocortex (nucleus basalis lesions) can be exacerbated by concomitant and widespread serotonin depletion. Indeed, we found that 5,7-DHT, used in combination with 192 IgG-saporin, induced working-memory deficits in the water-maze and in the radial maze, which neither toxin produced when it was injected alone. In that way, a study assessing behavioural (locomotor activity, forced T-maze alternation, beam walking, Morris water-maze and radial-maze) and neurochemical effects of intracerebroventricular injections of both the cholinergic toxin 192 IgG-saporin and the serotonergic toxin 5,7-DHT in Long-Evans rats, showed that cholinergic lesions, which reduced the concentration of acetylcholine by about 40% in the hippocampus but had no effect in the striatum, induced only severe motor deficits. Serotonergic lesions, which reduced the concentration of serotonin by 80% in the hippocampus and the striatum, produced diurnal and nocturnal hyperactivity but no other behavioural effect. Finally, rats with combined lesions were more active than those with only serotonergic lesions, showed motor dysfunctions similar to those found in rats with cholinergic lesions alone, and exhibited impaired performance in the T-maze alternation test, the water-maze working memory test and the radial-maze [90]. A consistent finding in these series of lesion experiments was that serotonin depletion alone did not produce detrimental effects in these tasks, whether assessing spatial or non-spatial working memory, or even reference-memory [e.g., 57,88,90; but see 146]. However, another study conducted in our group showed that serotonin depletion confined to the hippocampus – by injections of 5,7-DHT directly into the cingular bundle and the fimbria–fornix – could attenuate some of the behavioural deficits produced by a large dose of 192 IgG-saporin, which, this time, was injected directly into the medial septum and the diagonal band of Broca [88]. In this experiment, rats with single or combined damage were tested for locomotor activity, spontaneous T-maze alternation, sensorimotor, water maze and radial maze performance. The data showed that the cholinergic lesions, which decreased the hippocampal concentration of acetylcholine by about 65% [see also 39], induced nocturnal hyperlocomotion, reduced T-maze alternation, impaired both reference-memory in the water maze and working-memory in the radial maze, but had no effect on sensorimotor performance and working-memory in the water maze. Again, 5,7-DHT lesions, which decreased the concentration of hippocampal serotonin by about 55%, failed to induce any behavioural deficit. Nevertheless, in the group of rats given combined lesions, all deficits produced by the cholinergic lesions were observed; surprisingly, however, the nocturnal hyperactivity and the working-memory deficits in the radial maze were significantly attenuated. Interestingly, we could also establish that following serotonergic denervation of the hippocampus (by 5,7-DHT lesions), the electrically evoked release of acetylcholine was facilitated in hippocampal slices. Even more interesting was the observation that this facilitation was counterbalanced by intrahippocampal grafts rich in serotonergic neurons [18]. These results suggest that the reduction of the serotonergic tone in the hippocampus may compensate for some dysfunctions subsequent to a loss of cholinergic hippocampal inputs.

This observation is in close concordance with psychopharmacological data showing that spatial memory deficits observed in a two-platform spatial discrimination task, and which was

induced by intrahippocampal infusions of scopolamine, an antimuscarinic drug, could be reversed or attenuated by the activation of somato-dendritic 5-HT_{1A} receptors in the raphe; the activation was achieved by microinfusions of 8-OH-DPAT (8-hydroxy-2-(di-*n*-propyl-amino)-tetralin), a mixed 5-HT_{1A}/5-HT_7 agonist. Such microinfusions reduce the serotonergic tonus in the target areas of the ascending serotonergic pathways [28,30; see also below]. Similar observations were made when hippocampal 5-HT_{1A} receptors were blocked by intrahippocampal injections of WAY 100635, a selective 5-HT_{1A} antagonist in scopolamine-treated rats, as was also the case after systemic injections of this 5-HT_{1A} receptor antagonist [29,33; in these studies, scopolamine was infused bilaterally into the CA1 region of the dorsal hippocampus, 10 min before each training session]. Thus, it seems that the negative effects on cognitive functions of muscarinic blockade can be counterbalanced by a systemic blockade of post-synaptic 5-HT_{1A} receptors or by an activation of the somato-dendritic 5-HT_{1A} receptors in the raphe nuclei.

Serotonin could either inhibit (*via* presynaptic mechanisms involving heteroreceptors) or facilitate (*via* polysynaptic loops starting postsynaptically) the release of acetylcholine. Such mechanisms are present in both the hippocampus and the cortex, although they do not necessarily involve the same subtypes of pre- or postsynaptic receptors. Whatever be these mechanisms, almost all lesion experiments involving cholinergic and serotonergic damage in the limbic system converge towards the conclusion that there may be a serotonergic modulation of cholinergic function, and that this modulation could take part in spatial reference and working memory, as well as in non-spatial memory. Whether serotonin depletion attenuates or exacerbates memory deficits associated with 192 IgG-saporin lesions seems, however, to depend on which brain structures are affected and how the toxins have been delivered to target nuclei (intracerebroventricularly *vs*. intraparenchymally).

2.3. Co-grafting fetal cell suspensions rich in cholinergic and serotonergic neurons

As regards the septohippocampal system, the implication of cholinergic–serotonergic interactions in cognitive functions is further supported by studies using techniques that consisted in co-grafting neuroanatomically and/or neurochemically defined populations of neurons into denervated structures of the brain, in general without any particular neurochemical selectivity. Actually, following massive hippocampal denervation (by e.g., transection or aspiration of the fimbria–fornix and cingular bundle pathways), fetal cell suspension grafts providing new cholinergic (grafts prepared from the region of the fetal brain including the medial septum and the diagonal band of Broca) and serotonergic (grafts prepared from the mesencephalic raphe) innervations to the hippocampus induced some cognitive recovery that none of the single graft providing the hippocampus with only one or the other of these innervations was able to foster. There are several articles based on such a grafting approach [4,76,107], which clearly suggest that a serotonergic/cholinergic interaction may have cognitive relevance, as was already the case for the aforementioned combinations of selective lesion approaches. For instance, in rats given radiofrequency (and thus unselective) lesions of the medial septum combined with intracerebroventricular injections of 5,7-DHT, Nilsson and his collaborators were the first ones to study the behavioural effects of septal grafts alone (rich in cholinergic neurons), raphe grafts alone (rich in serotonergic neurons), or a combination of both types of grafts, which they termed "co-grafts" [107]. Single and co-grafts were placed into the hippocampus and reference memory was assessed in a Morris water maze. Whereas neither type of single graft produced beneficial effects on water-maze performance, whether assessed 2 or 10 months after grafting, the combined grafts, which also failed to produce effects at the early delay, had improved memory performance at the longest one.

Similar observations were made following electrolytic [76] or aspiration – and thus largely unselective – lesions of the fimbria, the dorsal fornix and the overlying cingular bundle [4]. Under other experimental conditions (i.e., serotonergic lesions combined to partial cholinergic lesions in the septal region), it appeared that even the sole serotonergic reinnervation of the hippocampus was sufficient to promote significant recovery of spatial reference as well as working memory performance in a water-maze task [119]. However, while all these data support an implication of both serotonergic and cholinergic processes in cognitive function, and perhaps may fit with the idea of a serotonergic modulation of some cognitive abilities in which cholinergic mechanisms were proposed to have a significant role, they have little or limited value as for the understanding of the pharmacological substrates involved in these modulatory interactions (where in the brain, which systems, on which receptors?). Furthermore, they could be considered contradictory to the aforementioned data showing that a reduced serotonergic tonus may have beneficial effects on memory. It should be kept in mind, however, that the co-grafting approach has been carried out in rats subjected to massive hippocampal denervations and that the determinant factor of behavioural recovery in such case might have been the restoration of serotonergic–cholinergic interactions, and perhaps even more that of a certain balance in the cooperation between both transmitter systems.

3. Systemic drug administration combined to other approaches

Approaches that have much better contributed and still contribute to the understanding of the neuropharmacological substrates of cognitively relevant cholinergic–serotonergic interactions are of the pharmacological type and rely upon receptor-targeted drug administrations. If they lack neuroanatomical selectivity when the drugs are given systemically, they have the advantage of both enabling an investigation of the contribution of various receptor subtypes and being easily combinable to other technical approaches. Although there have been several studies that investigated the effects on learning and memory of a variety of compounds acting on 5-HT receptors in intact rodents [e.g., 94,104], this third section will only focus on two of such combinations: that of serotonergic ligand administrations with grafts of cholinergic neurons, and that of serotonergic ligand administrations with cholinergic lesions or drugs blocking cholinergic receptors.

3.1. Modulation of cholinergic graft-induced effects by systemic treatment with serotonergic drugs

Concerning this point, we can start by mentioning one study assessing the effects of septal grafts on acetylcholine release from rat hippocampus following selective 192 IgG-saporin lesion [69]. In this study, the cholinergic inputs to the rat hippocampus were lesioned by intraseptal injections of 192 IgG-saporin. After 15 days post-surgical rest, fetal septal cells were grafted into the hippocampus and, 13 months later, hippocampal acetylcholine release was studied using an *in vivo* microdialysis technique. The lesions reduced basal acetylcholine release to 20% of normal, but this release was enhanced, although not totally compensated for by the graft (71%). As it is well known that serotonergic pathways project from raphe nuclei to cortical and limbic regions, and that the hippocampal cholinergic functions are modulated by serotonergic afferents [43], we investigated whether evidence could

be brought to light showing that the graft-derived acetylcholine release underwent a serotonergic modulation. To this end, we studied the effects of citalopram (100 μM), a specific serotonin uptake inhibitor, and of the mixed 5-HT_{1A}/5-HT_7 receptor agonist 8-OH-DPAT (0.5 mg/kg; s.c.) on the hippocampal acetylcholine release in sham-operated, lesion-only, and grafted rats. The retrodialysis of citalopram enhanced the hippocampal acetylcholine release in the grafted hippocampus to the same extent as it did in the sham-operated controls. These observations showed that when hippocampal serotonergic nerve terminals released more serotonin, there was an enhanced release of acetylcholine from the grafted tissue [56]. Most probably this effect was indirect and may have implicated extrahippocampal serotonin-dependent regulations (see below). The systemic administration of 8-OH-DPAT also enhanced acetylcholine release from the grafted tissue, showing that the implantation of septal grafts rich in cholinergic neurons into the massively denervated hippocampus normalized some neuropharmacological aspects of cholinergic–serotonergic interactions. It is improbable, however, that 8-OH-DPAT acted directly on 5-HT_{1A} receptors located on cholinergic neurons, since these receptors, when activated, should theoretically have an inhibitory influence on neuronal excitability. In addition, in rats subjected to intrahippocampal grafts rich in cholinergic neurons after extensive fimbria–fornix lesions, using a slice superfusion approach, we could not demonstrate that the application of 8-OH-DPAT to graft-bearing slices actually influenced the electrically evoked release of acetylcholine [37].

3.2. Effects of serotonergic drugs after cholinergic lesions or receptor blockade

The concurrent manipulations of both systems with drugs selective for given receptor subtypes allows to setup a better characterization of the pharmacological substrates underlying the cholinergic/serotonergic interactions. Briefly, and just to illustrate this issue, the activation of 5-HT_{1A} or 5-HT_{1B} receptors, as well as the inhibition of 5-HT_2 receptors (the administration route of the ligands being intraperitoneal or directly intraseptal) exacerbated a memory deficit (e.g., assessed in spontaneous alternation, passive avoidance and water maze tasks) produced by central muscarinic blockade or by cholinergic lesions in rats [87,109,120,121]. Conversely, a systemic blockade of 5-HT_3 receptors was found to attenuate the cognitive deficits induced by central cholinergic disruption in a passive-avoidance or a Morris water-maze task [25,41,44,116,117]. *In vitro* findings showed that an application of serotonin or of serotonergic agonists or antagonists to stimulated slices from given brain regions may alter the evoked release of acetylcholine. However, if one excepts the case of superfusion experiments or experiments carried out on synaptosomes, these findings do not necessarily demonstrate that the serotonergic modulation is directly occurring on the cholinergic terminals by means of an action on serotonergic heteroreceptors. *In vivo*, the problem gets even more complicated as the serotonergic influence on cholinergic function, especially when drug treatments are administered systemically, may involve complex polysynaptic loops, several brain regions at once and various neurotransmitter systems. Thus, although a change in the serotonergic input may result in a modification of the cholinergic output, the number of intermediate events and their neurochemical identity remain largely unknown. Here, selective lesion techniques may be more useful tools to explore the structural organization and the functional substrates of such loops. Finally, at the most integrated level of organization, namely that of the organism, the degree of complexity in regulation mechanisms reaches its maximum. At this level, the functional consequences of an interaction do not necessarily suppose two neurotransmitter systems to cooperate or to interact directly (for example, serotonin being necessarily activating heteroreceptors located on the cholinergic terminal or elsewhere on the neuron). The consequences of such an interaction may also be determined by the cooperation between various functions that work in parallel, and which can be themselves analyzed as resulting from interactions involving a variety of transmitter systems in the brain. Actually, that serotonin may modulate cognitive functions by a more or less direct influence on cholinergic mechanisms is a concept that has a proper heuristic value. This value, however, is equivalent to that of considering that serotonin produces a functional change at the level of the organism (for example, on attentional processes or arousal), which would allow enhanced efficiency of the cholinergic contribution to another kind of function in the organism (for example, learning).

Whatever may be, all aforementioned studies, which in no case should be considered as being listed in an exhaustive way herein, point towards an important role for cholinergic–serotonergic interactions in cognitive functions. Among the serotonergic receptors involved in the regulation of such interactions, the 5-HT_{1A} ones are far from being those having the weakest interest. For instance, their blockade was shown to exert very strong beneficial effects in various models of memory impairments, including cholinergic dysfunctions [125] and, as such, appear as one of the interesting targets to tackle the cognitive symptomatology accompanying a neurodegenerative disease such as Alzheimer's disease [26,100,124]. As said in Section 1, these receptors are widely distributed in the brain, and the question of their role has been addressed in structures such as the hippocampus, cortex or striatum, whether from a neuropharmacological or behavioural perspective [34,54,100]. The septum is one of the brain structures in which a relatively large number of 5-HT_{1A} receptors are also found. Surprisingly, it has received little attention as regards the implication of this subtype of serotonergic receptors in memory functions.

4. Intracerebral drug infusion approaches: focus on 5-HT_{1A} receptors of the medial septum

Considering the limits of lesion and psychopharmacological approaches relying upon systemic administrations of drugs or drug cocktails, and even of the combination of both, more powerful approaches, which use intraparenchymal and thus target-restricted drug administration techniques, have been developed. In experimental animals, such approaches can be carried out relatively easily in order to characterize the functional consequences of local drug infusions. It is noteworthy that also transgenic mice lacking 5-HT_{1A} receptors appear as extremely useful tools to study the involvement of serotonin-mediated modulations of various types of functions, whether at a neuropharmacological or a behavioural level [e.g., 83,134]. These tools, however, will not be considered herein, as they most often if not systematically lack on neuroanatomical selectivity.

Many studies using approaches relying upon intraparenchymal drug infusions were conducted in order to characterize the cognitive effects of an action on the 5-HT_{1A} receptors of the dorsal hippocampus or the raphe nucleus [e.g., 30–32,49,50,53,128–130]. For instance, Egarisha and coworkers [53] showed that the microinjection of 8-OH-DPAT into the dorsal hippocampus produced an impairment of spatial memory. Moreover, this impairment was completely reversed by systemic administrations of 5-HT_{1A} receptor antagonists [53]. Generally, all the data described in the literature clearly point to an 8-OH-DPAT-induced impairment of spatial memory when the drug is injected into the hippocampus. Using the same kind of approaches, two other studies showed that

there could be a hippocampal asymmetry as to the behavioural responses to the 5-HT_{1A} receptor agonist 8-OH-DPAT [13,14]. In that way, the first study was conducted in order to examine the behavioural responses to unilateral and bilateral injections of 8-OH-DPAT into the hippocampal CA1 area of male Wistar rats. It was found that 8-OH-DPAT increased locomotor activity, which was most pronounced with injections into the left hippocampus. When injected into the right hippocampus, however, the agonist also impaired learning and memory, and produced anxiety [13]. More recently, the modulation of learning and memory after left or right intrahippocampal microinjections of 8-OH-DPAT and of the 5-HT_{1A} receptor antagonist NAN190 were more precisely characterized [14]. Microinjections of 8-OH-DPAT into the right or left CA1 region produced a significant decrease in the number of avoidances in a shuttle box, this effect being more pronounced when 8-OH-DPAT was injected into the right hippocampus as compared to the left one. Microinjections of NAN190 into the right or left CA1 hippocampal area produced a significant increase in the number of avoidances in a shuttle box, right microinjections of NAN190 increasing the number of avoidances more markedly than the left ones. These stronger memory-modulating effects after injection of 8-OH-DPAT or NAN190 into the right CA1 hippocampal area suggest a rightward bias in the rat. Concerning intra-raphe nuclei administrations of 8-OH-DPAT, several studies were conducted [e.g., 30,49,128,129]. Carli and her coworkers [30] showed that the stimulation of 5-HT_{1A} receptors in the raphe by 8-OH-DPAT reversed the deficit caused by intrahippocampal scopolamine. Concerning anxiety behaviours, a wealth of evidence supports the involvement of certain serotonergic raphe neurons in these functions. In order to evaluate the role of these neurons in the regulation of inhibitory avoidance, which had been related to generalized anxiety, Dos Santos and his coworkers [49] submitted rats to the elevated T-maze test after intra-raphe administration of different drugs changing the activity of serotonergic neurons. Intra-raphe injections of 8-OH-DPAT and WAY 100635 affected inhibitory avoidance. While the former inhibited the acquisition of this behaviour, the latter facilitated it. These data showed that the serotonergic neurons of the raphe nuclei may play an important role in anxiety processing, with possible implications in pathologies such as generalized anxiety disorders.

Several tasks in which 5-HT_{1A} receptor-mediated effects were evidenced depend upon hippocampal functions. Surprisingly enough, the septal region, which is one of the essential nuclei connected with the hippocampus, has received limited attention regarding the possibility for its 5-HT afferents to modulate its implications in hippocampal functions. Actually, this structure is involved in memory [138], contains neurons that provide the hippocampus with the major part of its cholinergic innervation [51], and is the target of a serotonergic innervation originating in the raphe nuclei [1,105]. Furthermore, it shows a high density of 5-HT_{1A} binding sites [38,115]. Some of these sites are located on cholinergic neurons, others on GABAergic ones [81,92]. All these elements make this region a potential neuroanatomical substrate for direct or indirect 5-HT_{1A}-mediated interactions between cholinergic and serotonergic systems.

Nevertheless, little is known about the implication of these septal receptors in behaviour and cognitive processes. Concerning the effects of the mixed 5-$HT_{1A/7}$ agonist, 8-OH-DPAT, it was principally reported that its intraseptal injection increases maternal aggressive behaviour [45], influences anxiety [46,99,103], and induces antidepressant-like effects [47,95,127]. On the other hand, when infused into the lateral septum, 8-OH-DPAT impairs the retention of a passive avoidance [87]. However, a possible involvement of septal 5-HT_{1A} receptors in spatial memory is as to yet poorly documented.

4.1. Acquisition of a reference-memory task in the water maze under activation of septal 5-HT_{1A} receptors

In 2000, Bertrand et al. [17] published the results of a first experiment that assessed the effects of an 8-OH-DPAT-induced stimulation of these receptors on the acquisition of a standard version of the Morris water-maze task. In this task, Long-Evans rats had to use spatial information to acquire declarative-like knowledge about the location of an escape platform that was always hidden at the same place, right underneath the water surface. Thus, over successive acquisition trials, experimental animals had to construct a task-specific representation requiring encoding and progressive consolidation of a memory, which they had to retrieve upon request on subsequent trials or during the probe trial. Ten minutes before each training session the rats were microinjected with artificial cerebrospinal fluid, or with 0.5 or 4.0 μg of 8-OH-DPAT. Intraseptal microinjections of 8-OH-DPAT impaired, but did not completely prevent, acquisition of the reference memory task in the water maze, suggesting that an activation of the 5-HT_{1A} receptors of the medial septum may alter spatial memory formation.

With the protocol used in this study, it was not possible, however, to know if memory formation (encoding, consolidation) rather than retrieval was affected by 8-OH-DPAT. Indeed, as 8-OH-DPAT was infused right before each daily acquisition session, the drug could have interfered with encoding as well as with post-trial information consolidation processes, or even with the retrieval of information that might have undergone normal consolidation.

4.2. Spatial working-memory in a water-maze and septal 5-HT_{1A} receptors

In an attempt to extend these results and to further the role of septal 5-HT_{1A} receptors on cognitive processes, we conducted another series of studies, the first of which being using a protocol that placed emphasis on spatial working memory. Working memory supposes information to be held in a memory buffer for a short period of time, in general for as long as it is pertinent in a given short-lasting situation. In this study, 8-OH-DPAT (0.5 or 4.0 μg) was also directly infused into the medial septum [75]. One set of rats was tested with a hidden platform, the other one with a visible one. The location of the platforms was changed every day and all rats were given two consecutive trials. The intraseptal infusion of 4.0 μg of 8-OH-DPAT significantly impaired performance: the rats exhibited longer distances to reach the hidden platform on trials 1 and 2, but there was an overall amelioration between both trials. In the rats infused with 0.5 μg, there were similar overall alterations, but they did not reach significance. Such effects were not observed when the rats were tested with a visible platform.

A closer examination of the drug-induced impairment raised at least two questions: did this impairment reflect a genuine deficit of spatial memory? Did it correspond to a more general deficit of learning abilities? During the first of each pair of daily trials, when a rat does not know yet where the platform is located, one optimal strategy relies on the exploration of all possible places in the pool until the platform is found. Within each of these first trials, however, it is possible that rats can remember former locations of the platform which they may visit in priority in order to maximise the yield of their searching displacements. This seemed to be the case in our control rats. In fact, during their first trial, control rats spent a longer time on the place where the platform was located on the previous day as compared to chance (within subjects comparison) or to 8-OH-DPAT-treated rats (between subjects comparison). Such behaviour is probably not based on working memory as the delay separating two successive sessions was of 24 h. It also strongly suggests that the control rats, not the 8-OH-DPAT-treated ones, were

able to remember the platform location from 1 day to the next one. Given that 8-OH-DPAT rats exhibited a capacity to remember the location of the platform on the second trial, it may be postulated that the activation of septal 5-HT_{1A} receptors had in fact compromised some aspects of information consolidation. Alternatively, it is also possible that 8-OH-DPAT has interfered with a retrieval process. In any case, these observations pointed to a possible effect of the activation of 5-HT_{1A} receptors of the medial septum on formation of a lasting memory rather than on working memory.

4.3. Are 5-HT_{1A} receptors of the medial septum a target of serotonin-mediated mechanisms underlying encoding and consolidation processes?

Data in the literature suggest that systematically administered 8-OH-DPAT impairs acquisition and retention in a passive avoidance test, as well as in other tests [35,101,120]. Interestingly, when injected into the septal region, it was shown that 8-OH-DPAT impaired passive avoidance consolidation [87], suggesting that, in our last mentioned study [75], the forgetting of the place where the platform was located on the previous day may be the result of an interference with a consolidation process rather than with the capability of retrieving learned information.

As previously stated, some of the cholinergic neurons of the medial septum projecting to the hippocampus receive serotonergic inputs from the raphe [105] and express 5-HT_{1A} receptors [81]. Therefore, regarding the critical role of the septohippocampal cholinergic system in memory processes [11,90,144] as well as the aforementioned importance of serotonergic–cholinergic interactions in memory function, it could be hypothesized that the impairments observed were related to a reduced cholinergic tone in the hippocampus. However, it is noteworthy that even large cholinergic lesions in the medial septum and the diagonal band of Broca do not induce dramatic effects on memory in the water maze [88]. Thus, alternative hypotheses may be proposed. For instance, it was suggested that serotonergic fibres originating in the raphe nuclei and innervating the medial septum may exert an inhibitory influence on the rhythmical firing of septal neurons [2], which, over the past, has not only been considered as one of the "pacemakers" for the hippocampal theta rhythm [136], but was also linked to mnesic processes, especially to encoding and consolidation [110,137]. Therefore, although the type of serotonergic receptors involved in the serotonin-mediated inhibition of medial septal neurons firing is unknown, it is possible that intraseptal injections of 8-OH-DPAT interacted with the rhythmical firing of these neurons, leading to desynchronization of hippocampal activity, and thus to memory disturbance or to a more general disorganization of behaviour in the water maze. Electrophysiological approaches should contribute to further investigate the latter possibility. In conclusion, we noticed that the stimulation of 5-HT_{1A} receptors in the septal region of rats by local injections of 8-OH-DPAT induced a complex pattern of deficits in a water-maze task. Based on the characteristics of the observed deficits, we raised the possibility that the 8-OH-DPAT-induced impairment, rather than being only the result of a true alteration of working memory, in fact reflected a more global cognitive deficiency in which alteration of memory capacities were mixed with attention dysfunctions and alterations of search strategies.

4.4. 5-HT_{1A} receptors in the medial septum and encoding/consolidation of reference memory in the water-maze

More recently, we continued the characterization of the role of 5-HT_{1A} receptors of the medial septum, particularly by trying to find out if the drug was altering encoding, consolidation or retrieval of spatial information. Based on a series of experiments conducted in our laboratory, for which we went back to a testing protocol taxing reference memory, we could show that the activation of septal 5-HT_{1A} receptors altered spatial memory encoding, interfered with consolidation in a particular way (see below), but did not affect retrieval of the platform location in a water-maze task [84]. As for the other studies depicted previously, this experiment was conducted in Long-Evans male rats. The testing protocol (3 consecutive days of acquisition, 4 consecutive trials per day, and a 24-h delayed probe trial) was first validated by showing that (i) rats were actually able to acquire the location of the hidden platform and to retrieve it in the delayed probe trial and (ii) reversible lidocaine-induced inactivation of the septal region disrupted acquisition and retrieval of the task. Different series of rats were then infused with 8-OH-DPAT at the dose of 4.0 μg, which was the most efficient one among the two doses used in our previous experiments [17,75]. To test for possible interactions with encoding and/or consolidation, some rats were infused right before each acquisition session. To test for possible interactions with consolidation, other rats were infused with 8-OH-DPAT immediately or at variable intervals (1–6 h) after each acquisition session. Finally, to test for possible interactions with retrieval, the performance of a last set of rats was evaluated once the task was acquired over drug-free sessions, but the infusion was made right before the delayed probe trial. We also assessed whether the 8-OH-DPAT-induced effects were resistant to the blockade of 5-HT_{1A} (using WAY 100635) or 5-HT_7 receptors (using SB 269970). SB 269970 was used because 8-OH-DPAT also binds to 5-HT_7 receptors, which are present in the septal region of rodents [22,63]. Complementary experiments were conducted to exclude the possibility that the effects of 8-OH-DPAT on water-maze performance were biased by motivational, sensorimotor, locomotor or anxiety-related side effects [84].

It was found that 8-OH-DPAT infusions disabled learning of the location of a hidden platform, and this effect was counterbalanced by systemic or intraseptal pre-treatment with the selective 5-HT_{1A} receptor antagonist WAY 100635. It is noteworthy that the effects of the 5-HT_7 antagonist did not prevent the 8-OH-DPAT-induced deficits in a significant way. When the platform was visible, 8-OH-DPAT did not disrupt performance, suggesting no interference of motivation, sensorial or motor coordination biases with cognitive capabilities. When 8-OH-DPAT was infused immediately, or 1, 4 or 6 h after each series of acquisition trials, performance in the delayed probe trial was comparable to that of controls, indicating unaltered consolidation. It is noteworthy, however, that when the infusions occurred 2 h after each acquisition session, the rats failed to search for the platform at the appropriate place during the subsequent probe trial. Finally, when 8-OH-DPAT was infused right before a probe trial after drug-free acquisition, performance was comparable to that of controls, suggesting no interference of 8-OH-DPAT with retrieval processes. Given that, in addition to the visible platform data (rats swam to the platform, regardless of treatment), 8-OH-DPAT infusions altered neither activity levels in the home cage, nor anxiety-related behaviour in an elevated plus-maze, these findings can be interpreted in relation with dynamics of learning and memory processes, rather than with non-cognitive biases. Therefore, the aforementioned results indicate that 5-HT_{1A} receptors-driven mechanisms in the septal region play an important role in the regulation of hippocampus-dependent information encoding and, within a given post-acquisition time window, participate in consolidation.

4.5. What kind of septal neurons participate in the 8-OH-DPAT-induced effects on encoding/consolidation?

As stated above, in the septal region, 5-HT_{1A} receptors are located on both cholinergic [e.g., 81,92] and GABAergic neurons

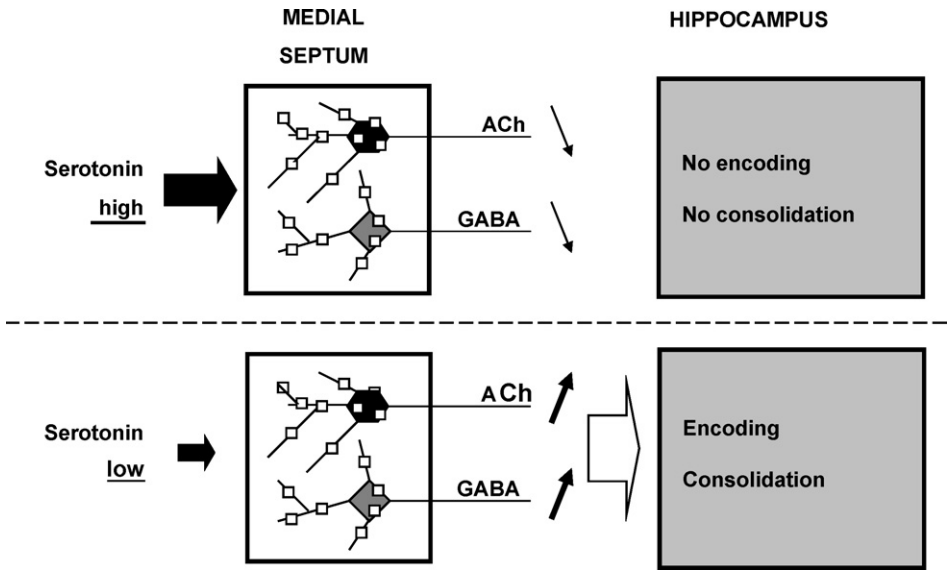

Fig. 1. Schematic illustration of our hypothesis on the role of septal 5-HT_{1A} receptors (white squares) in the encoding and consolidation of hippocampal-dependent information during acquisition. When the serotonergic tonus in the septum is high (top), 5-HT_{1A} undergo strong activation, whereby the activation of cholinergic and GABAergic neurons is reduced and both encoding and consolidation may be more difficult. When the serotonergic tonus in the septum is low (bottom), 5-HT_{1A} receptors undergo weak activation, whereby the activation of cholinergic and GABAergic neurons is facilitated and both encoding and consolidation may more easy. This hypothesis is clearly requiring further investigations, but it is compatible with findings showing that lesions of both GABAergic and cholinergic neurons in the medial septum do only weaken an important encoding- or consolidation-related activity in the hippocampus, namely theta activity, but also alter memory functions [e.g., 10,15,40,48,82,108,109,142].

[92]. As each of these neurons may contribute to, and even to some extent cooperate in, hippocampal-dependent learning and memory processes [e.g., 52,89,102,112], the next step of our approach consisted in testing whether our 8-OH-DPAT-induced effects could be attributed to an action of the drug on septal cholinergic neurons. Here, our reasoning was by elimination. In fact, we had two questions: can extensive cholinergic lesions in the septal region mimic the effects of 8-OH-DPAT? If not – which was expectable given the literature on the effects of cholinergic lesions confined to this region; see above – do such lesions alter the effects of 8-OH-DPAT? The cholinergic lesions were produced by intraseptal infusions of 192 IgG-saporin using the infusion devices to be used for the subsequent 8-OH-DPAT infusions. Thus, the lesions targeted the medial septum. As such lesions generally require about 10 days to reach their maximal extent [141], we started to train our rats after an 11-day post-surgical recovery time. Part of them, which served as controls, were infused with a PBS solution before each acquisition trial, the other ones being subjected to 8-OH-DPAT infusions instead (4 μg). This yet unpublished study by Koenig et al. yielded several interesting results. First, we confirmed that pre-acquisition infusions of 8-OH-DPAT prevented learning and subsequent recall of the task. Second, selective cholinergic lesions in the medial septum did not mimic the effects induced by 8-OH-DPAT in sham-operated rats; despite the lesions, the rats given PBS infusions acquired the task, and their retrieval performance was comparable to that of unlesioned controls. Third, the effects of pre-acquisition 8-OH-DPAT infusions on learning capabilities were comparable in control and lesioned rats, whether they had been previously familiarized or not with the learning test. Although part of the cholinergic neurons located in the medial septum bear 5-HT_{1A} receptors, the present results demonstrate that these are probably not the most important ones to be involved in the 8-OH-DPAT-induced impairments of water-maze learning. Because most if not almost all GABAergic neurons in the medial septum possess 5-HT_{1A} receptors, it is possible that a concomitant 8-OH-DPAT-induced hyperpolarization of cholinergic and GABAergic neurons, or hyperpolarization of only GABAergic ones under the condition of cholinergic damage is necessary to obliterate the acquisition of a platform location in this task. For instance, when both populations of neurons are damaged, there are memory deficits which lesions of each population alone are unable to induce [113,147]. These data could indicate that processes conjointly mediated by cholinergic and GABAergic neurons of the septum, and which undergo serotonergic modulation involving 5-HT_{1A} receptors, could be necessary for normal encoding and perhaps consolidation of spatial hippocampus-dependent memories. Further studies should now focus on the role of GABAergic neurons of the septal region in the constitution of a spatial memory. Given the available experimental evidence [e.g., 10,15,40,48,82,112,113,147], one may predict that combined cholinergic and GABAergic lesions in the medial septum could result in a disruption of encoding and consolidation of spatial memories, which should be comparable to the disruption induced by infusions of 8-OH-DPAT in intact rats. This hypothesis is illustrated in Fig. 1. Another possibility to further this issue might consist in investigating the effects on memory of intrahippocampal infusions of a cholinergic agonist and/or a GABAergic ligand in rats subjected to an intraseptal infusion of 8-OH-DPAT right before the acquisition sessions of a water-maze task.

5. Conclusions

The literature contains a series of experimental arguments finding their roots in histological, electrophysiological, pharmacological and behavioural research fields, and demonstrating or suggesting that, in the mammalian brain, cholinergic function may be under serotonergic modulatory influence. Furthermore, as documented and discussed herein, this modulation may have cognitive implications. These remarks, however, call several observations. First, 5-HT_{1A} receptors are not the only ones to be involved in such modulation. Second, if there is evidence that cognitive processes involve cholinergic functions, but cannot be reduced to them in an exclusive way, these processes also cannot be fully explained by an additional consideration of serotonergic modulatory mechanisms. Third, a given function that would be sensitive to conjoint cholinergic and serotonergic manipulations is not necessarily under the direct control of a cholinergic mechanism which

would be more or less active depending on the level reached by the serotonergic tonus. It is well possible, indeed, that this function requires both neurotransmitter systems to cooperate in a parallel, complementary and perhaps even synergistic way to operate normally (which is our hypothesis as regards the cholinergic and GABAergic septohippocampal projections). Fourth, it must be emphasized that interactions involving neurotransmitter systems other than the serotonergic one have also been dealt with in cognitive neuroscience and psychopharmacology, and that there is clear evidence that the activity of cholinergic neurons is also under the modulatory influence of other neurotransmitter systems [36,72,78].

Moreover, it must be kept in mind that the cholinergic hypothesis of memory dysfunctions has been challenged recently [102,114], mainly because highly selective cholinergic lesions in the basal forebrain produce only weak effects on learning and memory capabilities. An important tool in this line of investigations has been 192 IgG-saporin [143,144]. Therefore, if cholinergic mechanisms are not central to cognitive functions (which obviously requires further investigations), the idea that the contribution of serotonin to cognition is mediated by a serotonin-operated modulation of the functional state of cholinergic neurons of the basal forebrain must also be reconsidered.

Nevertheless, to question the role of these serotonergic/cholinergic interactions may be important for different reasons. First, there are neurological disorders such as dementia of the Alzheimer type or Parkinson's disease, with alterations in both (and also other) neurotransmitter systems, and therapeutic approaches aiming at reducing the severity of the cognitive symptomatology may have to consider dysfunctions in a multiplicity of neurotransmitter systems for the development of treatment strategies that might reveal more effective in tackling the disease-related symptoms [59]. This would mean that if highly specific ligands are well adapted to study the functional contributions of particular receptors, less specific ones could be more appropriate to treat symptoms associated with neurodegenerative diseases. Along this line and as regards Alzheimer's disease, for instance, the "monotransmitter" therapies used or proposed so far may reveal too limited, and 5-HT_{1A} receptors appear to be a particularly relevant complementary target [124–126]. These receptors are also interesting for other reasons. There are drugs frequently used for the treatment of psychiatric disorders which affect not only one neurotransmitter system, but both serotonergic and cholinergic neurotransmissions. For example, many tricyclic antidepressants are known to impair cognitive performance, an effect which has been attributed to their anticholinergic properties regardless of their serotonergic effects. Therefore, it seems possible that the combination of decreased cholinergic and increased serotonergic activity does in fact contribute to amplify the cognition impairing effects of these drugs. This possibility clearly requires further exploration. Our recent findings on the role of septal 5-HT_{1A} receptors suggest that these receptors contribute to a mechanism involved in the encoding and consolidation of hippocampal-dependent knowledge, which they may contribute to impair when activated in the septal region. These findings might have some relevance to approaches relying upon the modification of serotonergic functions in the brain for treating psychiatric disorders such as e.g., depression, anxiety or post-traumatic stress. Concerning depression, for instance, selective serotonin reuptake inhibitors (SSRI) have the best safety record among the different therapeutic options [135], but there is a literature reporting on possible SSRI-related memory problems [62,80,139]. Although these memory problems could be related to various confounding factors (subject's history, age, existence of age-related cognitive dysfunctions, etc.), in addition to depression itself, the fact that the activation of 5-HT_{1A} receptors in the septal region produces adverse effects on memory functions allows us to propose (part of) a possible neuropharmacological substrate that could be involved in the cognitive dysfunctions associated with drug therapies increasing the serotonergic tonus, namely the 5-HT_{1A} receptors located in the septal region.

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