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FOREBRAIN DOPAMINE RECEPTORS IN COGNITIVE, MEMORY AND LEARNING PROCESSES

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Neurons that utilize dopamine (DA) as a neurotransmitter have attracted great interest because of their involvement in the behavioral, endocrine and descending control of major brain functions. DA is known to exert its physiological effects on target neurons through D1-like (D1 and D5) and D2-like (D2, D3 and D4) receptor subtypes. To better understand the DA modulation of brain functions, the distribution and cellular localization of D1 and D2 DA receptors in the rat forebrain is reviewed, and their possible role in cognitive aspects of behavior is discussed. In general, DA receptors are differentially expressed and mostly distributed in different target fields of DA neurons. Both D1 and D2 receptor gene products are found in the cerebral cortex, basal ganglia and hippocampal formation, albeit in different cell groups or neuronal subpopulations, whereas D3 receptors are mainly located in limbic regions. In the cortex, mRNA signals are seen in all the areas and cortical layers except layer I. In the striatum, the most intense signal is found in the caudate-putamen, nucleus accumbens and olfactory tubercle where a large number of cells are strongly labeled for D1 and D2. In the globus pallidus only scattered D2 mRNA-containing cells are present. In contrast, no D1 or D2 messages can be seen in the ventral pallidum. In the basal forebrain, mRNA encoding the D1 receptor is detected in the islands of Calleja. The medial and lateral septal nuclei show a low D2 signal. In the amygdaloid nuclear complex, the strongest D1 receptor message is observed in the basomedial and basolateral nuclei. Conversely, the highest density of D2 mRNA-expressing cells is revealed in the central nucleus. Moderately labeled for D1 and D2 cells are scattered throughout the anterior and posterior subdivisions of the bed nucleus of stria terminalis, and within all subfields of the hippocampal formation and dentate granule cell layer. Differential regional and cellular distribution of DA receptors in the forebrain provides anatomical evidence for an area-specific regulation of the DAergic neurotransmission. It can be inferred that DA facilitates learning, memory and cognition processes via *activation of both the D1 and D2 receptors.* ***Biomed Rev 2005; 16: 59-75.***

Key words: basal ganglia, cerebral cortex, in situ hybridization, psychomotor behavior, rat

INTRODUCTION

Dopamine (DA) acts as a key neurotransmitter in the brain. It has been proposed that it may play an important role in the pathophysiology of a variety of psychiatric and neurological disorders. This is particularly true for schizophrenia, Alzheimer's, Huntington's and Parkinson's diseases, where

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DA involvement in the neostriatal, mesolimbic, mesocortical or nigrostriatal systems has been well acknowledged (1-5). It is thus noteworthy that DA is thought to be included in the regulation of motor, limbic and cognitive aspects of behavior. Besides, neurons that utilize DA as a neurotransmitter constitute a focus of neuroscience research because of their involvement in the behavioral flexibility, neuroendocrine and descending control of brain functions (6). This variety of DA functions is partly related to the variable distribution of DAergic fibers and terminals in most regions of the brain, and also to the multitude of receptors mediating different types of effects in response to DA (7,8). Although numerous studies over the last 30 years provide some important clues for understanding the molecular mechanisms by which DA regulates neural functions, its receptor signaling has not been fully elucidated and is still a matter of ongoing discussion.

The diverse physiological effects of DA are mediated by at least five G protein-coupled receptor subtypes encoded by different genes referred to as D1-D5 (reviewed in 9-13). On the basis of the amino acid sequences and structural and pharmacological similarities, these have been grouped into D1-like (D1 and D5) and D2-like ($D2_{short}$, $D2_{long}$, D3 and D4) subfamilies (for reviews see 14-16). Like other receptor proteins, DA receptors are located at the cell membrane, where they interact with DA, regulate specific intracellular signaling networks, and modulate the cellular functions. However, the activation of D1-class or D2-class receptors has different effects on signal transduction pathways. In particular, a differential mode of coupling to adenylate cyclase is observed: D1 receptor stimulation elevates cyclic AMP concentration while D2 receptor activation decreases it (15-18). In addition, D1 receptor activation by agonists induces stimulation of both cyclic AMP-dependent protein kinase A (PKA) and protein kinase C (PKC), while D2 receptor stimulation can activate PKC (15). Therefore, the study of DA receptors has been a primary approach in revealing the physiological roles of the DA systems. A further important step toward understanding the specific functions of various DA receptor subtypes is to delineate their corresponding post-receptor targets (19).

The anatomical distribution of the DA receptors provides an interesting basis for speculating on the functional role of their different subsets. Thus far, the principal receptor subtypes (D1 and D2) have been visualized in the rat brain using receptor autoradiography with selective ligands (20-23) and immunohistochemistry with subtype-specific antibodies (24-27). In addition, *in situ* hybridization (ISH) histochemistry, both radioactive and non-radioactive, has revealed a widespread distribution of their corresponding mRNAs in the rat brain (23,28-35). These studies demonstrate that D1-like are more abundant than D2-like receptors. However, the latter are major targets for action of antipsychotic drugs (27,36). Previous investigations have also established the presence of the two major DA receptor subtypes, the D1 and D2 receptor, in the rat forebrain, including the cerebral cortex (37) and basal ganglia (38-40), but have not provided detailed distributional patterns of dopaminoceptive neurons in all forebrain regions at the cellular level. Moreover, many of these results are conflicting.

In the past years, it became apparent that D1 and D2 receptor genes are expressed in distinct neuronal populations in the rat forebrain. Such evidence has principally come from studies on the striatum (41). On the other hand, critiques of this speculation have also been published (see 42 and refs. therein). Although a general consensus has developed about many aspects, there are still inconsistencies and controversies, usually related to which cell types express given receptors and whether a signal obtained reflects a functionally relevant receptor (43). Last of all, complex functional interactions exist between the D1- and D2-like families, some of whose mechanisms are not clearly understood yet and remain uncertain.

The goal of this review article is therefore to develop a detailed map of the D1 and D2 receptor gene expression in the adult rat forebrain using non-radioactive ISH histochemistry, a procedure which allows a highly-resolved detection of positive neurons, and thus to provide an increasing knowledge of their regional localization. Another goal of our analysis is to compare the distribution of dopaminoceptive cells with the distribution of receptor binding sites and with that of the DAergic innervation patterns previously described. Finally, we aim at answering the question of direct involvement of DA in regulating cognition, memory and learning. In this respect, it should be emphasized that research in the field of the DAergic system, a model for studying learning and memory in health and disease, was awarded the Nobel Prize in Physiology or Medicine in 2000.

ANATOMIC AND FUNCTIONAL ORGANIZATION OF THE DOPAMINERGIC SYSTEM

It is well known that DA exerts its actions through four different pathways. The nigrostriatal pathway originates in the substantia nigra pars compacta (A9) and projects to the striatum (44). It constitutes about 80% of the brain DAergic system. The mesolimbic and mesocortical DA neurons derive from the ventral tegmental area (A10). The former project to the nucleus accumbens, septal area, olfactory tubercle,

amygdaloid cortex and piriform cortices, while the latter reach the prefrontal, cingulate and entorhinal cortices (45). Conversely, the prefrontal cortex (the prelimbic area of the medial frontal cortex), which represents the second main target of ventral tegmental area dopamine neurons (37,46), receives distinct parallel DAergic inputs and its neurons project back to the cells of origin (47). Hypothalamic DAergic neurons project to the median eminence and infundibular stem, thus forming the tuberoinfundibular pathway, the functional role of which is to suppress prolactin excretion from the pituitary gland (48).

Such an organization and prominent distribution of DAergic innervation throughout anatomically segregated neuronal systems that involve the integration of motor, limbic and cognitive processes as well as the tonic mode of functioning confer on the DAergic subsystems a key role in the coordination and integration of different aspects of behavior (49). It is generally believed that their dysregulation may result in neuropsychiatric disorders. Specifically, the nigrostriatal system is related to motor functions (50), while the mesocorticolimbic DAergic system, innervating the ventral striatum, cortex and limbic areas, is a substrate for motivation and reward (for reviews see 50,51). In addition, the nucleus accumbens receiving projections from some limbic areas (hippocampus and amygdala) is thought to be related to "motivational" behavior (52,53). Recent studies implicate an important role for the prefrontal cortex in the selection and generation of behavior patterns (47). On the other hand, it is proposed that basal forebrain neurons belong to multiple systems with distinct cognitive, motivational, emotional, motor and regulatory functions (54). They can modulate the activity of neurons in the neocortex through their direct cortical projections and indirectly through their projections to the thalamus *via* the thalamocortical system. Lately, Previc (55) emphasized a putative essential contribution of cortical DA to executive function and also to language production, which critically involves working memory processes.

A few smaller DA projecting systems are currently described as well: the mesohippocampal pathway, with an essential effect on the memory systems, and the projection of some nigral neurons to the frontal cortical areas (mesofrontal pathway), which is thought to be important in reward and motivation mechanisms.

DISTRIBUTION OF DOPAMINE AND DOPAMINE RECEPTORS IN THE RAT FOREBRAIN

General considerations

Numerous studies over the last decade have shown the cellular targets of DA innervation and occurrence of DA receptors throughout the forebrain in rodents, nonhuman primates and humans, although there is not yet a steady consensus on this issue in different species. As a rule, the mRNA hybridization signal is expressed by neurons. With the exception of ependymal cells, including the choroid plexus epithelium and tanycytes, glial cells are not distinctly labeled. The discussed brain structures onward comply with the rat brain stereotaxic atlas of Paxinos and Watson (56).

By using non-radioactive ISH, we and others have demonstrated that mRNAs encoding D1 ($mRNA^{D1}$) and D2 ($mRNA^{D2}$) receptors have a widespread distribution in the adult rat forebrain (Table 1), much larger than hitherto believed (33,35,37,57-61). D1 and/or D2 receptor messages are expressed in all major forebrain areas receiving DA projections. Particularly, the strongest ISH signals are detected in the neostriatum, olfactory tubercle, and the nucleus accumbens. Furthermore, we found that both D1 and D2 receptor gene products can be detected in other DA target areas including the amygdala, albeit in different cell groups or neuronal subpopulations. Distinct D1 and D2 hybridization patterns are also evident in the bed nucleus of the stria terminalis and the septal nuclei. In addition, D1 or D2 messages have been visualized in regions where a DAergic innervation is controversial, such as some cerebral cortical areas and the hippocampal formation. The cells containing $mRNA^{D1}$ and $mRNA^{D2}$ are distributed throughout the rostrocaudal extent of the telencephalon as follows.

Cerebral cortex

The cerebral cortex is an important target of DAergic neurotransmission (31), as it can directly mediate some of the effects of DA on working memory (62-64). In monkeys and humans, DAergic terminals innervate the entire cortical areas in a rostrocaudal gradient (65), while in rodents they are restricted to the frontal lobe and particularly to the prefrontal, entorhinal and piriform cortices (66,67). Generally, mammalian cortical neurons express mRNA and protein of D1 and D5 receptors (31,68). In the human brain, the D1 expression dominates, with a low D2 expression in most neocortical regions (69). On the other hand, D4 receptor is the most abundant D2-like receptor in the rat cerebral cortex (27,70,71). However, the exact physiological action of DA on cortical cells is not yet elucidated as D1 and D2 receptor agonists have been shown to elicit both excitatory and inhibitory responses (72-74). In a previous paper we have shown that a D1 receptor gene transcript is seen in all cortical areas and layers except layer I (35). In the regions investigated, a laminar distribution of DA

Table 1. *Comparison of DA innervation with DA receptor mRNA expression in the adult rat forebrain.*

Brain region	DA innervation*	D1 mRNA	D2 mRNA
Cerebral cortex			
Neocortex	++	++	+/–
Anteromedial prefrontal cortex	++	++	+
Suprarhinal prefrontal cortex	++	++	+
Supragenual prefrontal cortex	++	+/–	–
Entorhinal cortex	+	+++	+++
Perirhinal cortex	+	++	+
Piriform cortex	+	+++	+++
Cingulate cortex	+	+	–
Retrosplenial cortex	+	+	–
Endopiriform nucleus	+	+	–
Basal ganglia and basal forebrain			
Caudate-putamen	+++	+++	++
Nucleus accumbens	+++	+++	+++
Olfactory tubercle	+++	+++	++
Islands of Calleja	++	++	+/–
Globus pallidus	+	–	+
Ventral pallidum	+	–	–
Substantia innominata	+	–	–
Magnocellular preoptic nucleus	+	+	–
Basal nucleus of Meynert	+	+	–
Diagonal band of Broca	++	–	–
Septum			
Lateral septal nucleus	++	++	+
Medial septal nucleus	–	–	+/–
Septohippocampal nucleus	–	–	–
Hippocampal formation			
Ventral hippocampus			
Subicular complex	+/–	++	–
CA1, CA2, and CA3 fields of Ammon's horn	+/–	+++	–
Dentate gyrus	+/–	++	–
Dorsal hippocampus			
Dentate granule cells	+/–	++	–
CA1-CA3 pyramidal cells	+/–	++	–
Amygdaloid nuclear complex			
Intercalated cell groups	+++	++	–
Basolateral amygdaloid nucleus	+	+++	+/–
Basomedial amygdaloid nucleus	+	+++	+/–
Cental amygdaloid nucleus	+++	+	+++
Cortical nucleus	++	++	–
Bed nucleus of stria terminalis	+++	++	–

+++, high ISH signal; ++, moderate; +, weak; +/–, very weak; –, absent

**These data are based on Ref. 66,67,77,93,95,96,98,102,110.*

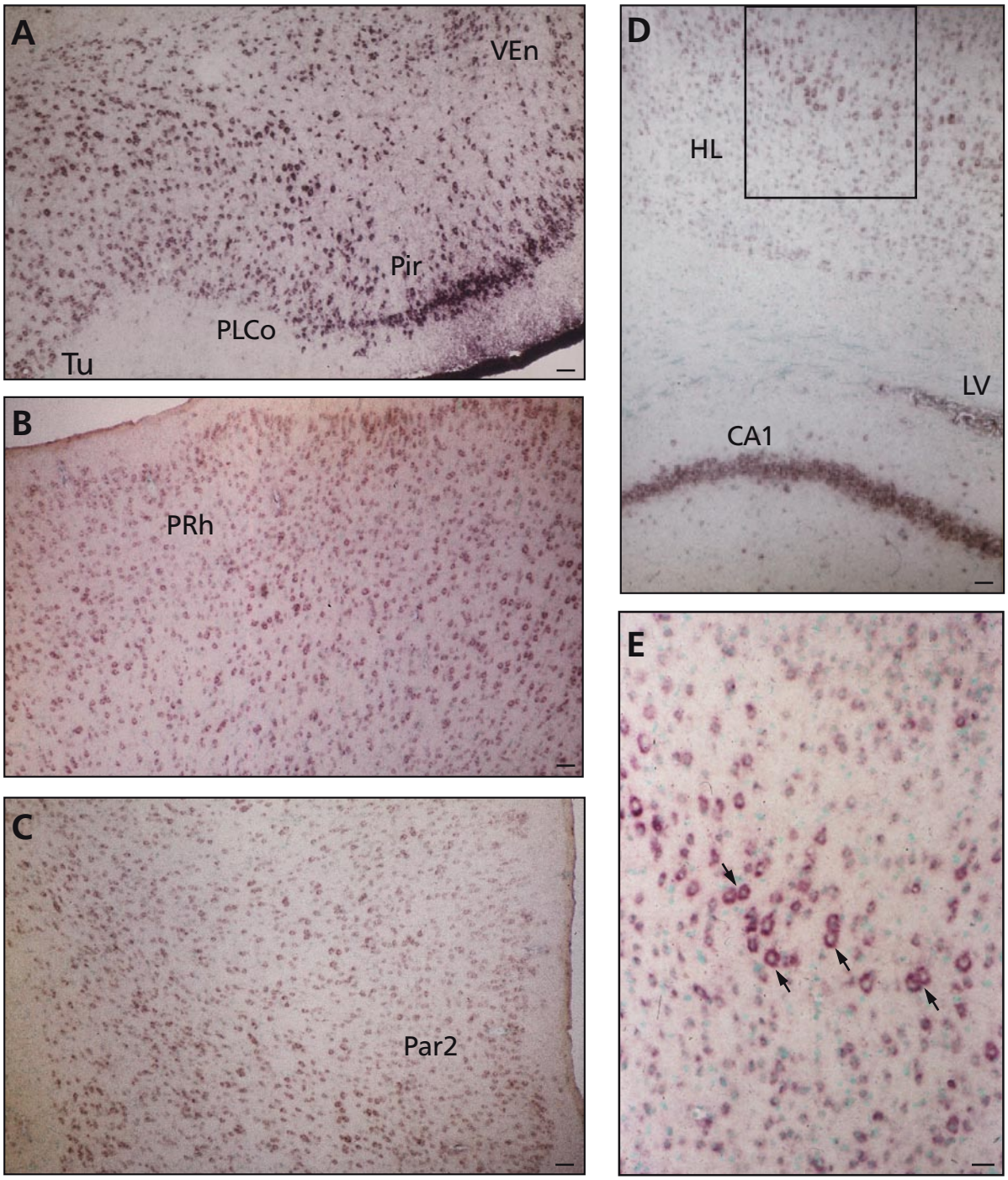


Figure 1. *Distribution and cellular localization of mRNA^{D1} and mRNA^{D2} in different regions of the rat cerebral cortex. (**A**) Piriform cortex (Pir), the olfactory tubercle (Tu) and the posteromedial cortical amygdaloid nucleus (PLCo). The most prominent signals are found in layers V and VI, and at the junction between the medial piriform cortex and cortical amygdaloid nucleus. (**B**) Perirhinal cortex (PRh). All the neurons in layers II, V and VI show an intense ISH signal. (**C**) Parietal cortex, area 2 (Par2). (**D**) Hindlimb area of the cortex (HL) and part of the hippocampus, showing high labeling of the pyramid cells of CA1. The details of neuronal labeling are shown at a higher magnification in (**E**). Note the strong hybridization signal in the cells of the pyramidal layer (arrows) and the much weaker signal in the other cortical layers. LV, lateral ventricle; VEn, ventral endopiriform nucleus. Scale bars = 170 μm in **A-D**; 30 μm in **E**.*

receptor messages is maintained, as illustrated in Fig. 1.

In the paleocortex, most $mRNA^{D1}$-expressing cells are observed in the piriform (Fig. 1A), perirhinal (Fig. 1B), entorhinal and cingulate cortex (not shown). Cells of the piriform cortex are prominently labeled, with higher levels in cortical layers II-III, V and upper layer VI. Moderate hybridization signals are obtained in the entorhinal cortex. D1 message is also expressed in other allocortical regions, such as the perirhinal cortex. Neurons are moderately labeled in layers II, V and VI, while in the middle layers the signal is weaker. Additionally, modetare-to-low levels of $mRNA^{D1}$ are observed in layers V-VI of the cingulated cortex. In the isocortex, higher signals are present in the deeper layers of the anteromedial and suprarhinal prefrontal cortex. An apparent decrease in the hybridization signal is registered in caudal direction. $mRNA^{D1}$-positive cells are also found in the endopiriform nucleus.

On the other hand, D2 receptor gene transcript distribution in the rat cortical fields is topographically more restricted. In addition, the cortical areas show a dissimilar distribution pattern of the $mRNA^{D2}$ expression. In fact, the laminar distribution pattern of the ISH signal shows bands with labeling in both the superficial and deep layers. Specifically, D2 receptor gene-expressing neurons are mainly located in the prefrontal cortex, almost exclusively in layer V. Within the paleocortical regions, entorhinal cortex (layers II-III), the most superficial cells of layer I and piriform cortex show a high density of $mRNA^{D2}$.

Regarding the neocortex, the great majority of neurons express moderate levels of $mRNA^{D1}$ (Fig. 1C-E). Furthermore, the distribution of labeled cells among the cortical layers is not even. However, we are not able to find significant regional differences in the D1 receptor gene expression along the rostocaudal axis of the cortex. In certain neocortical areas corresponding to the parietal (Fig. 1C), frontal (Fig. 1D, E), temporal and occipital cortex, most $mRNA^{D1}$-positive neurons in the deeper layers show a moderate labeling, whereas in the more superficial layers II-III they display low mRNA concentration. Conversely, the neocortical D2 receptor gene expression is extremely low to absent.

In Fig. 1E, the intracellular localization of the mRNA and the morphological features of dopaminoceptive cells in the frontal cortex are depicted at a higher magnification. As shown, most of the labeled neurons are medium-to-large-sized. The hybridization signals are located at the level of the neuronal cell bodies and confined to the cytoplasmic portion of the cells. Furthermore, the labeling is usually limited to a thin rim of cytoplasm around an unlabeled nucleus. It is also possible to distinguish that the receptor gene products appear as clusters that can correspond to the endoplasmic reticulum. In contrast, we are not able to detect any labeled neuronal processes.

Basal ganglia and basal forebrain

As shown in Fig. 2, of the telencephalic structures examined, the highest expression of both D1-like and D2-like receptor messages is detected in the basal ganglia. In fact, D1 receptors are predominantly expressed in the dorsal and ventral striatum, D2 and D4 receptor subtypes are particularly abundant in the caudate-putamen complex, whereas the D3 subtype is restricted to the olfactory tubercle and ventral striatum (27). Also, D5 gene transcripts are expressed in most of the striatal neurons (75). With respect to projection areas, the dorsal striatum (or neostriatum) is an essential element of the classical concept of "basal ganglia", and it is thought to include several loops which connect the cortex, lateral caudate-putamen, globus pallidus, subthalamic nucleus and substantia nigra. On the other hand, the ventral part has traditionally been related to the "limbic system", including loops which connect other ("limbic") cortical areas, the ventral striatum (especially the nucleus accumbens), the ventral pallidum, thalamus, and ventral tegmental area.

In the striatum, DAergic nerve terminals are present as axonal varicosities, each forming about 1000 contacts on dendrites of the spiny neurons, which represent the vast majority of the striatal neurons (76). The DAergic input contacting primarily the neck of the spine is actually in a position to modulate the input from other neuronal afferents, for example, corticostratial nerve terminals, which contact the distal part of the spine (77). The main effect of DA here is to reduce spontaneous cell firing or to decrease pharmacologically evoked activity (78,79). Previous studies in mammals (69,80) and birds (81) have found that DA acts principally through both D1 and D2 dopamine receptor subtypes, which are postsynaptically located and segregated to the direct and indirect striatal projection neurons, respectively (41,44,57,80,82). As published data confirm, the basal ganglia and basal forebrain are rich in D1 receptors. In particular, about half of the neurons throughout the striatum express D1 receptor gene (35,39). On the other hand, D2 receptors are expressed by the somata and dendrites of midbrain DA neurons in the substantia nigra and ventral tegmental area as well as by their axon terminals in their target region: the striatum and nucleus accumbens (83). There is still considerable controversy regarding whether or not D1 and D2 receptor subtypes are expressed by distinct subpopulations of medium-sized spiny neurons in the striatum, which are known to be gamma-aminobutyric acid (GABA)ergic. To date, both the D2 and D4 receptors are found in these striatal neurons

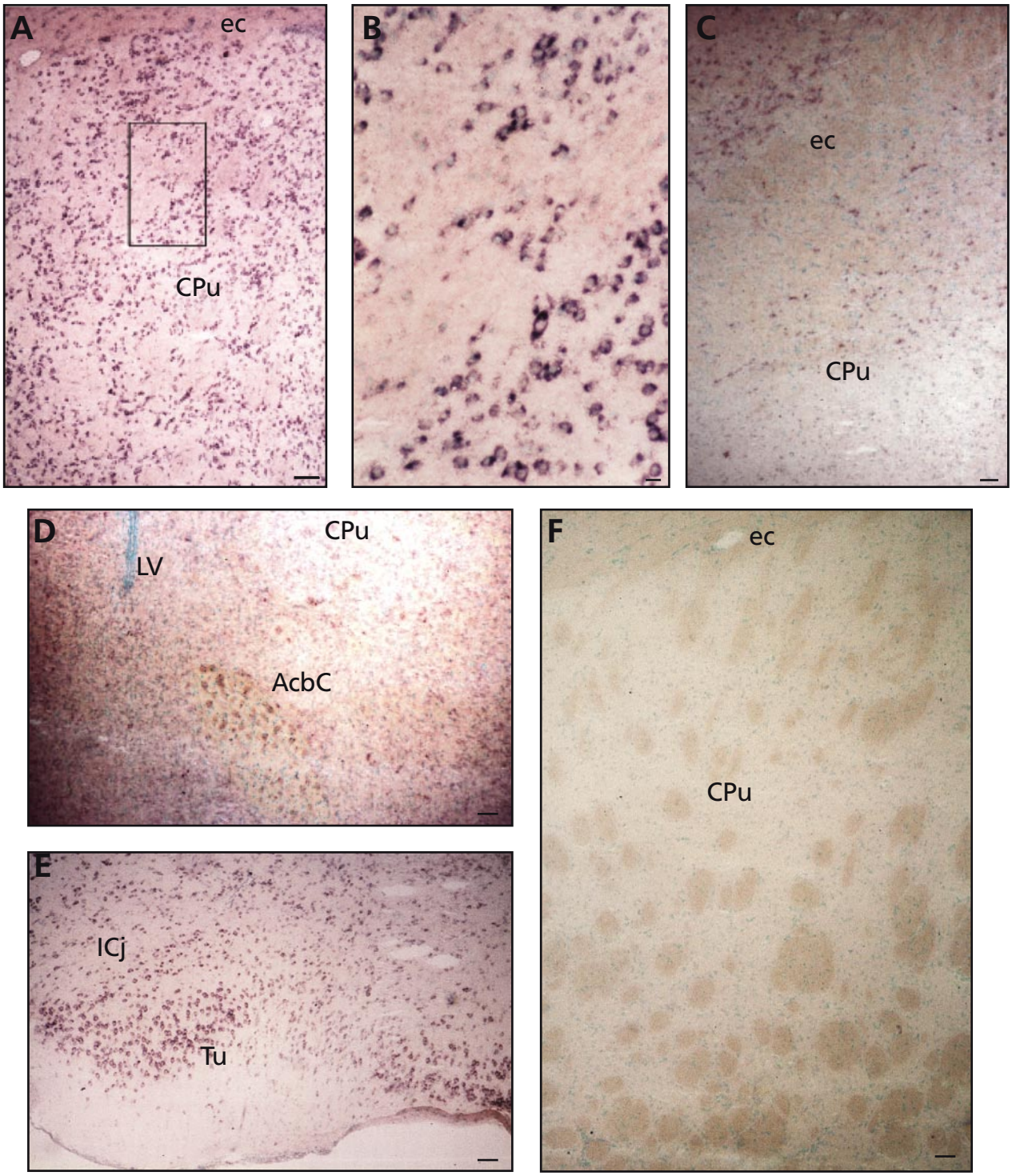


Figure 2. *Expression of DA receptor messages in the basal ganglia and basal forebrain of the rat. Localization of D1 gene transcripts in the caudate-putamen (CPu) by ISH using antisense (**A**) and sense (**F**) probes. D1 mRNA is present in most medium-sized neurons. (**B**) Higher-power view of the boxed area in (**A**). The signal is confined to the neuronal perikarya of labeled striatal neurons. (**C**) Small and a few large in size mRNA^{D2}-expressing cells are also found in the striatum. A strong ISH signal is observed in the nucleus accumbens (**D**) and olfactory tubercle (**E**) as well. AcbC, accumbens nucleus, core; ec, external capsule; ICj, island of Calleja; Tu, olfactory tubercle; LV, lateral ventricle. Scale bars = 170 μm in **A, C-F**; 30 μm in **B**.*

(27). However, Gerfen *et al* (84) and Hersch *et al* (85) report that D1 and D2 receptors are expressed by different populations of striatal neurons: D1 receptors are mainly expressed by neurons in the 'direct' pathway, while D2 receptors - by neurons in the 'indirect' pathway. Conversely, Surmeier *et al* (86) have reported that D1- and D2-class receptors co-localize in approximately 50% of all medium-sized spiny projection neurons. Still, it remains unclear whether the D4 subtype is localized in D1-positive GABAergic neurons of the 'indirect' pathway. We have shown that the most intense signal is found in the caudate-putamen, where a large number of cells are strongly labeled with D1 antisense cRNA probe (Fig. 2A, B), but only a few small neurons are labeled with D2 cRNA probe (Fig. 2C). The $mRNA^{D1}$-containing cells appear to be usually of medium size and morphologically homogenous. A strong signal is also obtained from neurons in the nucleus accumbens and olfactory tubercle (Fig 2D and E, respectively). The D3 receptor gene is selectively expressed in the ventral striatal area (32) where neurons are shown to co-express D3 receptors with D1 or D2 receptors (87). In other striatal efferent neurons, D4 and D5 receptors are also possibly co-expressed (88). Unlike a more homogenous distributional pattern throughout the extent of the caudate-putamen, the highest expression of $mRNA^{D1}$ is detected within the rostral pole, mainly in the shell, and extends into the core of the nucleus accumbens (Fig. 2D). The labeled cells are similar in morphology to cells in the caudate-putamen. Ventrally in the olfactory tubercle, D1 receptor-labeled cells are scattered throughout the nucleus (Fig. 2E). In this area, a fraction of neurons (15%) may express both D1 and D2 genes (82), thus suggesting that the olfactory tubercle could be regulated by DA differently from the dorsal striatum.

In the caudate-putamen and nucleus accumbens, the D2 receptor gene is mainly expressed by a population of small enkephalinergic neurons (89). Besides, a few large striatal neurons, identified as cholinergic, contain $mRNA^{D2}$ and thus are under the direct influence of DA (89). It should be emphasized that D2 receptors are expressed in both the shell and core of the nucleus accumbens (90). On the other hand, only scattered $mRNA^{D2}$-containing cells are present in the globus pallidus. The lack of D1 signal in this region implicates that pallidal neurons do not mediate D1 responses. In fact, it has been reported that dopamine D2 receptor activation hyperpolarizes medium spiny striatopallidal neurons and inhibits GABA release (60,91).

The classically defined nuclei that belong to the basal forebrain include, in a rostral to caudal order, the medial septum, the nuclei of the vertical and horizontal limbs of the diagonal band of Broca, the ventral pallidum, the magnocellular preoptic area, the substantia innominata, and the magnocellular basal nucleus (92). The basal forebrain system is a source of multiple, neurochemically heterogeneous ascending and descending pathways with distinct cognitive and regulatory functions. Through direct and indirect projections via the reticular thalamic nucleus, basal forebrain neurons can influence the activity of neurons in the neocortex and hippocampal formation and, thus, learning and memory (54). In the basal forebrain region, we have determined that $mRNA^{D1}$ is detected in the islands of Calleja. The medial and lateral septal nuclei show a low $mRNA^{D2}$ signal. In other subcortical limbic regions such as the bed nucleus of the stria terminalis, moderately labeled for D1 and D2 cells are scattered throughout the anterior and posterior subdivisions of this nucleus. In contrast, no D1 or D2 messages can be seen in the ventral pallidum, which is thought to be a ventral extension of the globus pallidus.

Previous findings indicate that the basolateral amygdala and the nucleus accumbens interact in influencing memory consolidation. Interestingly, DA receptor messages are heterogeneously distributed throughout numerous component nuclei in the amygdaloid nuclear complex. For example, the strongest D1 receptor message is observed in the basal nuclear group as most of the neurons in the basomedial and basolateral nuclei show an intense signal. In addition, moderately labeled cell bodies are seen in the intercalated nuclei as well as in the cortex-amygdala transitional zone. Weak labeling is also apparent in the central nucleus. Conversely, the highest density of $mRNA^{D2}$-expressing cells is revealed in the central nucleus. Other amygdala nuclei show very low expressional levels with weak signals and no detectable signal is evident in the periamygdaloid cortex.

Hippocampal formation

DAergic terminals exist also in the hippocampus (93). Hybridization with antisense probes reveals an intense labeling within all subfields of the hippocampal formation (Fig. 3), whereas no signal is obtained in adjacent sections with the sense probes.

Of particular interest in this regard are data showing that $mRNA^{D1}$ is similarly abundant in the three fields of *cornu Ammonis* (CA) and in the granule cell layer of the dentate gyrus in both regio superior and inferior, although most of the labeled perikarya are concentrated in the more ventral aspects of the hippocampus. The most intense hybridization signal is seen in the principal cell layers. In CA, virtually all pyramidal cells from CA1 to CA3 are prominently labeled for D1 receptor (Fig. 3A), with the highest expression in CA2 (Fig.

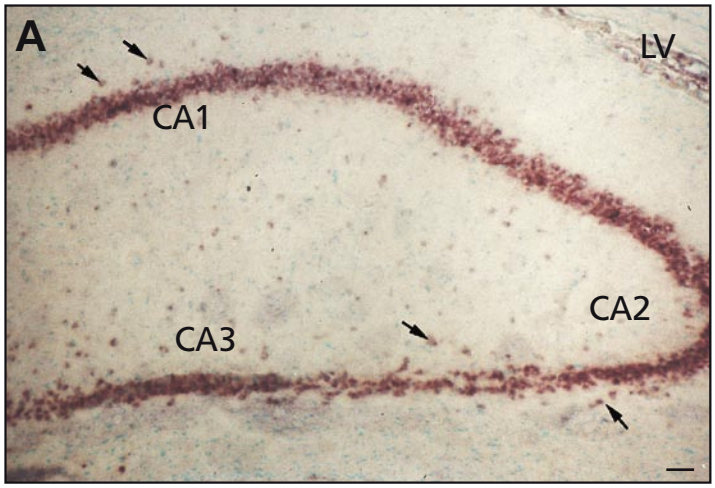
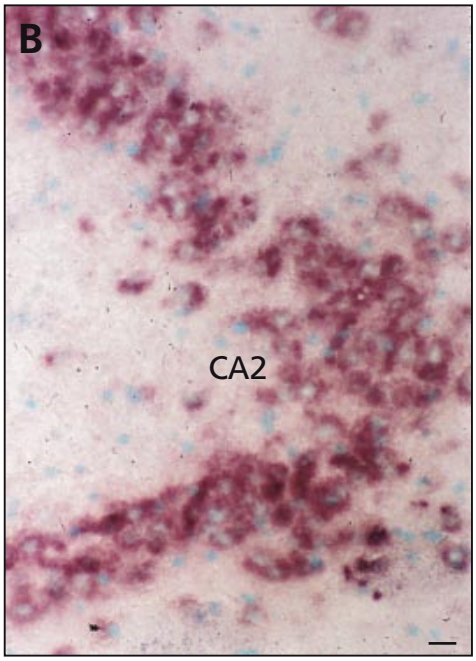
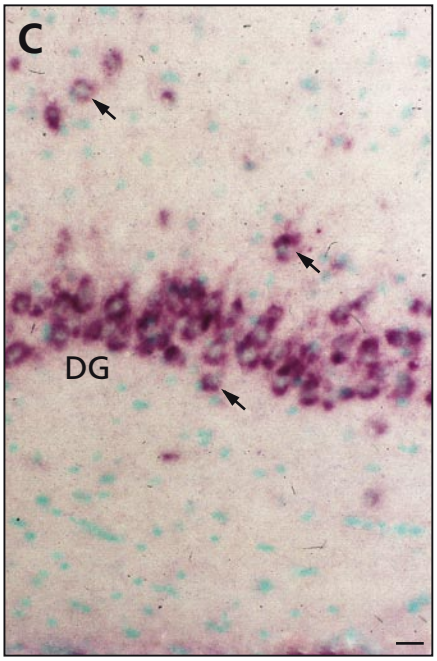
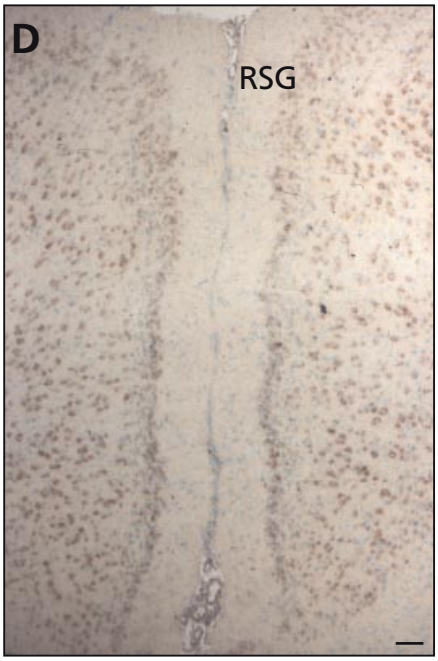


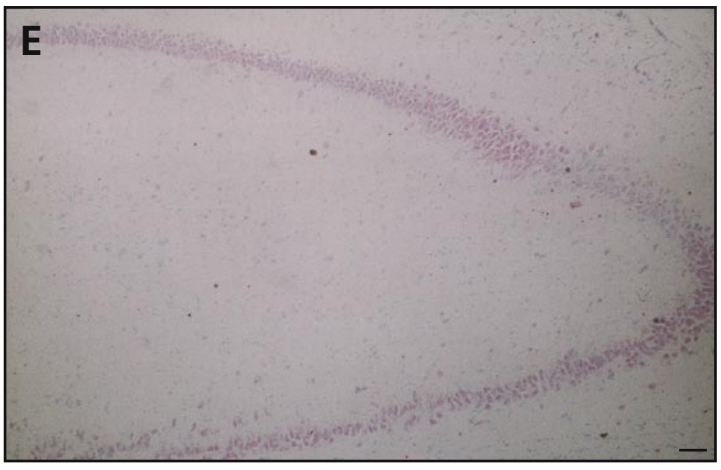
Figure 3. *Different D1 receptor gene expression patterns in the hippocampus.*

*(**A**) Overview of the hippocampus demonstrating the prominent labeling of all pyramidal cells in CA1-3. Some labeled neurons are also observed in both the stratum oriens and radiatum (arrows).*









*(**B**) Higher magnification of the CA2 field.*
*(**C**) Cells in the molecular and granular layers (arrows) of the dentate gyrus (DG) are $mRNA^{D1}$-positive.*
*(**D**)Fainter labeling is seen in the caudal dorsal hippocampus.*
*(**E**) Methyl green-Pyronin Y staining of the hippocampus showing the presence of RNA in the tissue.*

LV, lateral ventricle; RSG, retrosplenial granular cortex.

*Bars = 170 μm in **A, D, E**, 30 μm in **B** and 100 μm in **C**.*

3B). However, in the stratum radiatum occasional $mRNA^{D1}$-positive neurons are also found. Sparse cells are visible in the stratum lacunosum-moleculare as well. The granule cells in the dentate gyrus are strongly labeled, particularly in the rostral part of the dorsal hippocampus (Fig. 3C), while the granule cell layer glia is not distinctly labeled. Interneurons in the hilar region also display a strong signal. In the ventral hippocampus and in the caudal part of the dorsal hippocampus, only faint $mRNA^{D1}$ expression is observed in the subiculum proper, para- and pre- subiculum (Fig. 3D).

The rat hippocampal formation, including its subicular region, shows no positive D2 hybridization signal. In the human hippocampus, however, major cell populations express D2 message (69), the D4 subtype being the predominant D2-like receptor, particularly in the CA1 region (27).

MATCHING DISTRIBUTION OF DOPAMINE AND DOPAMINE RECEPTORS IN RAT FOREBRAIN

Perhaps the most interesting aspect of this review article deals with the issue of matching binding sites for specific ligands with those of receptor subtype expression, and matching distribution of receptors with those of their projection fields (94). In general, there is a large overlap in the expression of the receptor subtypes in the main forebrain territories innervated by the DAergic neurons (Table 1). As it can be seen, the regional and laminar distributional patterns of $mRNA^{D1}$ and $mRNA^{D2}$ in the rat forebrain are in qualitatively good agreement with the DA innervation and with the receptor binding site distribution. In rodents, the DAergic terminals are present in layers I and VI and restricted to the frontal lobe and particularly to the prefrontal, entorhinal and piriform cortices (66,67,95,96). Our previous (35) and present data show that these regions are also characterized by high expression of D1 receptors, and provide evidence that this DA receptor subtype mediates the action of DA in all DAergic projection fields. The overall distribution of $mRNA^{D1}$ herein is largely consistent with that reported using D1 receptor autoradiography (20,22,23,31,97). In fact, in most regions of the adult rat brain the correspondence between the D1 receptor binding and mRNA overlaps. In certain forebrain regions, however, there are partial or complete mismatches. For example, D1 receptor binding sites have been identified with no $mRNA^{D1}$ observed or *vice versa*. One good example of such discordance is the hippocampal formation. Indeed, D1 receptor binding is found in moderate-to-low levels within the hippocampus, predominantly in the molecular cell layer (23,31,97). We have also obtained evidence in the rat for a $mRNA^{D1}$ expression mainly within the pyramidal cell layer from CA1 to CA3 and in the dentate granule cell layer, consistent with previous data using immunohistochemical approach (25). Provided that the D1 message is translated into functional receptors, the most logical explanation for this discrepancy is that neurons in these layers are likely to synthesize D1 receptor in their cell bodies and transport them to the molecular layer of the dentate gyrus. On the contrary, Mansour *et al* (31) suggest an extra-hippocampal source of $mRNA^{D1}$ as a possible explanation of this lack of mRNA/protein correspondence. In accordance with this view, only few if any DA afferents originating from the A9-A10 area reach the hippocampal formation (93,98).

Similarly, D2 receptor messages are also found both in major DA projection fields and in traditional regions associated with DA-containing cell bodies, suggesting both postsynaptic and presynaptic autoreceptor localization (26,28,29,33). There is also a good anatomical correlation between the overall distribution of $mRNA^{D2}$ and that revealed by earlier autoradiographic studies (20,21,23) in the striatum, especially in the caudate-putamen and nucleus accumbens. D2 mRNA transcripts are, however, absent in some cortical areas and in the hippocampus, where D2 receptor binding has been repeatedly shown. Another possible explanation for these conflicting mismatches is provided by the so-called volume transmission theory (99). According to it, DA receptors are not necessarily confined to synapses but may be activated at far distances by the transmitter which diffuses away from synaptic clefts *via* the extracellular fluid. In any case, the degree of overlap implies a regional variation which may result in a regional heterogeneity in DA receptor functions.

DOPAMINE: A COMMON REGULATOR OF COGNITIVE, MEMORY AND LEARNING ASPECTS OF BEHAVIOR

It has been generally acknowledged that the projection fields of DAergic terminals determine the functional significance of DA neurons and may reflect their variability. Indeed, numerous behavioral studies have indicated that DA has a multifaceted modulating effect on memory and other prefrontal cortical cognitive functions. Thus, the identification of forebrain dopaminoceptive neurons as output pyramidal neurons or local circuit interneurons is important for understanding the physiological effects of DA in the cortex. Interaction of DA with its neuronal receptors in cortical circuits plays a major role in the regulation of excitability of pyramidal neurons by direct and indirect mechanisms (100). Further, subcortical structures, with their abundant DAergic innervation, may be of great importance for the cognitive functions.

Until not long ago, the cellular action of DA was largely thought to be mediated *via* the activation of the D1 and D2

subtypes of membrane receptors (reviewed in 101). From a functional point of view, the behavioral aspects of DA signaling have been attributed to interactions with D2 or D3 receptors, the latter being most abundant in DAergic areas known to be associated with cognitive and emotional functions (32). Nowadays, it is assumed that the direct transmission of information to the cortical neurons is mediated by dopamine D1 receptors (62) located postsynaptically (102). Further, the inactivation of the D1 receptor has been shown to induce different behavioral alterations mainly concerning the limbic system. Hence, current knowledge of the localization of DA receptors indicates that the D1 and D2 receptors are present in efferent cortical populations at both synaptic and extrasynaptic sites where they are implicated in modulating a variety of important neuronal processes including those involved in excitotoxicity and plasticity (reviewed in 103). The selectivity of this location may have important functional consequences. For example, our own work has demonstrated that D1 and D2 receptors play a significant role in integrative aspects of behavior involved in learning, memory and cognition, albeit D1 and D2 receptor-bearing neurons might subserve different functional modalities in cognition. It is worth noting that both D1-like and D2-like receptor subtypes are present in excitatory cortico-striatal and cortico-cortical projection neurons which generally contain excitatory amino acids, while only the D1 isotype has been found in cortico-thalamic projection neurons (37). A recent study in rats and humans showed that in cortical neurons D4 receptor protein is associated with both pyramidal and nonpyramidal cells, whereas D2 and D3 receptors are mostly present in nonpyramidal interneurons (27). In addition, some inhibitory GABAergic interneurons in the deep cortical layers V-VI of the medial prefrontal cortex express D1 and D2 receptor genes (60). This suggests that mesocortical DAergic inputs may directly modulate subpopulations of GABAergic interneurons and that their role in the functional organization of the prefrontal cortex involves synaptic inputs to both pyramidal and local circuits neurons. Further, DA facilitates glutamatergic transmission in rat prefrontal neurons (46). Taken together, these data further support the contention that DA may indeed have a complex action on cellular excitability in corical neurons, i.e. intitial suppression through D1 and D2 receptors and subsequent enhancement through D1 receptors (104). These observations also emphasize that the localization of DA receptor subtypes in different categories of pyramidal neurons that project to the striatum and cortex as well as in various inhibitory interneurons is indicative of the influence of DA on a vast repertoire of cortical circuits in the rat cerebral cortex.

Although the presence of a prefrontal cortex in rodents in still questioned, it is generally accepted that this area is involved in different aspects of executive control (47). Through its complex role in cognition, memory and emotion, the mammalian prefrontal cortex is thought to contribute to the organization of adaptive behavioral actions. It is also of interest to note that the prefrontal cortex is involved in stimulus-reinforcement associative learning as well (105). The medial prefrontal cortex is implicated in many cognitive functions, including working memory, temporal organization of behavior, and adaptation of behavioral strategies (105,106). In both rats and primates, the circuits that involve the prefrontal cortical areas are characterized by amygdaloid inputs. As a matter of fact, there is evidence that the medial prefrontal cortex and other regions such as the amygdala and nucleus accumbens are part of a distributed corticostriatal network mediating certain aspects of learning and expression of various motivated behaviors (107-109). The components of this network receive DAergic afferents from the ventral tegmental area (110,111). As a result, DA plays important roles in the function of the primate prefrontal cortex (62,63,106). On the other hand, the dorsolateral prefrontal cortex and posterior parietal cortices project mainly to adjacent, longitudinal domains of the anterior striatum, although there is also evidence for limited convergence of prefrontal and parietal cortical input within the striatum, particularly in the anteriormost part of the head of the caudate nucleus (112). These pathways are thought to constitute an anatomical circuit mediating spatial memory (113).

Previous work has demonstrated that in addition to a general involvement of D1 receptors, there is also a critical level of D1 receptor activation required for optimal performance of a task (63). Thus, there is evidence suggesting that activation of dopamine D1 receptors in several discrete yet interacting brain regions is involved in both the acquisition of conditioned associations and the probable mediation of the ability of conditioned stimuli to control behavior (114).

Extensive research has provided evidence that D2 receptors may play an important role in modulating synaptic plasticity and thus in cognitive and emotional processes performed by prefrontal circuits. In addition, recent studies indicate that the two isoforms of the D2 receptor may serve different synaptic functions: $D2_{long}$ receptors may act mostly as postsynaptic receptors while $D2_{short}$ receptors - as presynaptic autoreceptors (27,115). This hypothesis will undoubtedly contribute to the development of specific antagonists and agonists for presynaptic *versus* postsynaptic D2 receptors which may be useful for the improvement of pharmacological treatment of

neuropsychiatric and movement disorders (116).

The basal ganglia are usually considered to be involved in the automatic selection of previously learned procedures contributing to behavioral adaptation. The nigrostriatal DA pathway is classically described as a crucial substrate related to motor activities and also known to express both D1 and D2 receptors. We have obtained evidence in the rat that the striatum is in a position to integrate information arising from the different associative cortical areas for motor planning. Paillard (117) emphasized the central position of the striatum in the integrative processes of behavior, particularly the evaluation of the context of behavior. In addition, it has been demonstrated that DA-related processing at the level of basal ganglia play a critical role in timing mechanisms (118-120).

The expression of both D1 and D2 receptor gene transcripts in the basal ganglia suggests that DA plays an important role in the control of psychomotor behavior through different receptor subtypes. More significantly, the widespread distribution of $mRNA^{D1}$ throughout cortical, limbic, hypothalamic and thalamic regions (25,35) implies that in addition to such a role, D1 receptors may participate in the cognitive, affective and neuroendocrine effects of DAergic neurotransmission, and may be very important in mediating functions associated with memory, learning and cognitive processing.

Alternatively, the D2 receptors in the brain have been implicated in a variety of neurological and psychiatric conditions, including Parkinson disease and schizophrenia. Regarding the cognitive aspects of behavior, however, dysfunctions of mesocorticolimbic DAergic neurons may contribute to schizophrenia in patients who can also show opposite changes in DA activity at cortical level (for a recent review see 121). Because DA depletion in the medial prefrontal cortex also reduces other forms of hyperactivity (122), it may be considered that the prefrontal DA cortical system is part of the neuronal network involved in behavioral inhibition, which may be deficient in schizophrenic patients. In this respect, if schizophrenia in general could be related to a local alteration in cortical DAergic transmission, it is inferred that alterations in DA signaling could affect information processing. Moreover, aberrant levels of $mRNA^{D1}$ in subregions of the frontal cortex may be involved in the altered functional activity of schizophrenia and affective disorders (69). Certainly, a decrease in D1 receptor density has been shown in the frontal cortex of schizophrenic patients to be correlated with the severity of negative cognitive signs, whereas no change has been seen in the striatum of these patients (123). Conversely, activation of the D2 receptor in the frontal cortex with specific DA agonist has recently been shown to increase cognitive performance in humans (124).

As noted above, DA has also been implicated in the cognitive process of working memory (63). Working memory processes, which are also central for language understanding and comprehension and probably for intelligence and reasoning, are closely related to DAergic activity in the prefrontal cortex (62). Besides, experimental investigations with primates, using electrodes inserted into the cortex have shown that working memory is associated with activation of neurons in the prefrontal dorsolateral cortex (125). As indicated by pharmacological studies, inactivating the D1 receptor gene produces spatial learning deficits (126) which can be related to the involvement of the D1 receptors in working memory processes in the prefrontal cortex (62) and to the presence of such receptors in hippocampus (127). The above cited studies suggests that D1 antagonists can selectively potentiate the 'memory fields' of prefrontal neurons which subserve working memory. Similarly, our findings make it likely that cognitive processes regulated *via* these regions involve D1 signaling.

On the other hand, psychopharmacological research demonstrated that dopamine D2 agonists stimulate performance during the spatial working memory tasks whereas D2 antagonists exhibit opposite effects. Hence, the D2 receptor agonist bromocriptine has a stimulating effect on cognitive function, namely visuospatial memory. Moreover, the antagonist sulpiride induced cognitive dysfunction in healthy subjects similar to the pattern seen in Parkinson's disease, i.e. deficient spatial working memory, planning and attention shift disturbance (128). Thus, the current view supports that D2 receptor is likely to be a major type of DA receptors responsible for the modulation of D1/D2 equilibrium and so indirectly influences performance of working memory tasks (129).

CONCLUSION

It has become evident that DAergic neurons play a key role in controlling cognition, memory and learning. Importantly, it seems also reasonable to assume that the DAergic neurons are not integral parts of the neuronal networks involved in the execution of these functions but rather regulate such behavioral processes, as they do for motor and limbic aspects of behavior. Furthermore, changes in brain activity resulting in impairment or exacerbation of central DAergic transmission could probably result in pathologic effects on behavior, such as Alzheimer's disease or schizophrenia, and functional interaction of the two DA receptor subtypes may explain such clinical observations (reviewed in 130). Last but not least, gaining knowledge on forebrain DA receptors would provide new insights into the development of effective pharmacotherapy of cognitive dysfunction associated with several psychiatric disorders.

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REFERENCES

1. Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, Seitelberger F. Brain dopamine and the syndromes of Parkinson and Huntington: clinical, morphological and neurochemical correlations. *J Neurol Sci* 1973; 20: 415-455.
2. Swerdlow NR, Koob GF. Dopamine, schizophrenia, mania and depression: toward a unified hypothesis of cortico-striato-pallido-thalamic function. *Behav Brain Sci* 1987; 10: 197-245.
3. Gibb WR, Mountjoy CQ, Mann DM, Lees AJ. The substantia nigra and ventral tegmental area in Alzheimer's disease and Down's syndrome. *J Neurol Neurosurg Psychiatry* 1989; 52: 193-200.
4. Albanese A. Extrapyramidal system, motor ganglia and movement disorders. *Rev Neurosci* 1990; 2: 145-163.
5. Davis KL, Kahn RS, Ko G, Davidson M. Dopamine in schizophrenia: A review and reconceptualization. *Am J Psychiatry* 1991; 148: 1474-1486.
6. Fremeau RT, Duncan GE, Fornaretto M-G, Dearry A, Gingrich JA, Breese GR, *et al*. Localization of D_1 dopamine receptor mRNA in brain supports a role in cognitive, affective, and neuroendocrine aspects of dopaminergic neurotransmission. *Proc Natl Acad Sci USA* 1991; 88: 3772-3776.
7. Sokoloff P, Schwartz J-C. Novel dopamine receptors half a decade later. *Trends Pharmacol Sci* 1995; 16: 270-275.
8. Jaber M, Robinson SW, Missale C, Caron MG. Dopamine receptors and brain function. *Neuropharmacology* 1996; 35: 1503-1519.
9. Bunzow JR, Van Tol HHM, Grandy DK, Albert P, Salon J, *et al*. Cloning and expression of a rat D2 dopamine receptor cDNA. *Nature* 1988; 336: 783-787.
10. Zhou Q-Y, Grandy DK, Thambl L, Kushner JA, Van Tol HHM, Cone R, *et al*. Cloning and expression of human and rat D_1 dopamine receptors. *Nature* 1990; 347: 76-80.
11. Sibley DR, Monsma FJ. Molecular biology of dopamine receptors. *Trends Pharmacol Sci* 1992; 13: 61-69.
12. Civelli O, Bunzow JR, Grandy DK. Molecular diversity of the dopamine receptors. *Annu Rev Pharmacol Toxicol* 1993; 32: 281-307.
13. O'Dowd BF, Seeman P, George SR. Dopamine receptors. In: Peroutka SJ, editor. *Handbook of Receptors and Channels. G protein-coupled Receptors*. CRC Press, New York, 1994; 95-123.
14. O'Dowd BF. Structures of dopamine receptors. *J Neurochem* 1993; 60: 804-816.
15. Seeman P, Van Tol HHM. Dopamine receptor pharmacology. *Trends Pharmacol Sci* 1994; 15: 264-270.
16. Vallone D, Picetti R, Borrelli E. Structure and function of dopamine receptors. *Neurosci Biobehav Rev* 2000; 24: 125-132.
17. Stoof JC, Kebabian JW. Two dopamine receptors: biochemistry, physiology and pharmacology. *Life Sci* 1984; 35: 2281-2296.
18. Monsma FJ Jr, Mahan LC, McVittie LD, Gerfen CR, Sibley DR. Molecular cloning and expression of a D_1 dopamine receptor linked to adenylyl cyclase activation. *Proc Natl Acad Sci USA* 1990; 87: 6723-6727.
19. Hiroi N, Martín AB, Grande C, Alberti I, Rivera A, Moratalla R. Molecular dissection of dopamine receptor signaling. *J Chem Neuroanat* 2002; 23: 237-242.
20. Boyson SJ, McGonigle P, Molinoff PB. Quantitative autoradiographic localization of the D_1 and D_2 subtypes of dopamine receptors in rat brain. *J Neurosci* 1986; 6: 3177-3188.
21. Bouthenet M-L, Martres M-P, Sales N, Schwartz J-C. A detailed mapping of dopamine D-2 receptors in rat central nervous system by autoradiography with [^{125}I]iodosulpride. *Neuroscience* 1987; 20: 117-155.
22. Dawson TM, Barone P, Sidhu A, Wamsley JK, Chase TN. The D_1 dopamine receptor in the rat brain: quantitative autoradiographic localization using an iodinated ligand. *Neuroscience* 1988; 26: 83-100.
23. Mansour A, Meador-Woodruff JH, Bunzow JR, Civelli O, Akil H, Watson SJ. Localization of dopamine D_2 receptor mRNA and D_1 and D_2 receptor binding in the rat brain and pituitary: an in situ hybridization-receptor autoradiographic analysis. *J Neurosci* 1990; 10: 2587-2600.
24. Brock JW, Farooqui S, Ross K, Prasad C. Localization of dopamine D2 receptor protein in rat brain using polyclonal antibody. *Brain Res* 1992; 578: 244-250.
25. Huang Q, Zhou D, Chase K, Gusella JF, Aronin N, DiFiglia M. Immunohistochemical localization of the D_1

dopamine receptor in rat brain reveals its axonal transport, pre- and postsynaptic localization, and prevalence in the basal ganglia, limbic system, and thalamic reticular nucleus. *Proc Natl Acad Sci USA* 1992; 89: 11988-11992.

26. Levey AI, Hersch SM, Rye DB, Sunahara RK, Niznik HB, Kitt CA, *et al*. Localization of D_1 and D_2 dopamine receptors in brain with subtype-specific antibodies. *Proc Natl Acad Sci USA* 1993; 90: 8861-8865.
27. Khan ZU, Gutiérrez A, Martín R, Peñafiel A, Rivera A, de la Calle A. Differential regional and cellular distribution of dopamine D2-like receptors: an immunocyto-chemical study of subtype-specific antibodies in rat and human brain. *J Comp Neurol* 1998; 402: 353-371.
28. Meador-Woodruff JH, Mansour A, Bunzow JR, Van Tol HHM, Watson SJ, Civelli O. Distribution of D_2 dopamine receptor mRNA in rat brain. *Proc Natl Acad Sci USA* 1989; 86: 7625-7628.
29. Mengod G, Martinez-Mir MI, Vilaró MT, Palacios JM. Localization of the mRNA for the dopamine D_2 receptor in the rat brain by in situ hybridization histochemistry. *Proc Natl Acad Sci USA* 1989; 86: 8560-8564.
30. Mengod G, Vilaró MT, Niznik HB, Sunahara RK, Seeman P, O'Dowd BF, *et al*. Visualization of a dopamine D_1 receptor mRNA in human and rat brain. *Mol Brain Res* 1991; 10: 185-191.
31. Mansour A, Meador-Woodruff JH, Zhou Q, Civelli O, Akil H, Watson SJ. A comparison of D_1 receptor binding and mRNA in rat brain using receptor autoradiographic and in situ hybridization techniques. *Neuroscience* 1992; 46: 959-971.
32. Bouthenet M-L, Souil E, Martres M-P, Sokoloff P, Giros B, Schwartz J-C. Localization of dopamine D_3 receptor mRNA in the rat brain using in situ hybridization histochemistry: comparison with dopamine D_2 receptor mRNA. *Brain Res* 1991; 564: 203-219.
33. Weiner DM, Levey AI, Sunahara RK, Niznik, HB, O'Dowd BF, Seeman P, *et al*. D_1 and D_2 dopamine receptor mRNA in rat brain. *Proc Natl Acad Sci USA* 1991; 88: 1859-1863.
34. Brouwer N, Van Dijken H, Ruiters MHJ, Van Willigen J-D, Ter Horst GJ. Localization of dopamine D_2 receptor mRNA with non-radioactive in situ hybridization histochemistry. *Neurosci Lett* 1992; 142: 223-227.
35. Lazarov NE, Schmidt U, Wanner I, Pilgrim C. Mapping of D_1 dopamine receptor mRNA by non-radioactive in situ hybridization. *Histochem Cell Biol* 1998; 109: 271-279
36. Clark D, White FJ. D1 dopamine receptor - the search for a function: a critical evaluation of the D1/D2 dopamine receptor classification and its functional implications. *Synapse* 1987; 1: 347-388.
37. Gaspar P, Bloch B, Le Moine C. D1 and D2 receptor gene expression in the rat frontal cortex: cellular localization in different classes of efferent neurons. *Eur J Neurosci* 1995; 7: 1050-1063.
38. Le Moine C, Tison F, Bloch B. D_2 dopamine receptor gene expression by cholinergic neurons in the rat striatum. *Neurosci Lett* 1990; 117: 248-252.
39. Le Moine C, Normand E, Bloch B. Phenotypical characterization of the rat striatal neurons expressing the D_1 dopamine receptor gene. *Proc Natl Acad Sci USA* 1991; 88: 4205-4209.
40. Yung KK, Bolam JP, Smith AD, Hersch SM, Ciliax BJ, Levey AI. Immunocytochemical localization of D1 and D2 dopamine receptors in the basal ganglia of the rat: Light and electron microscopy. *Neuroscience* 1995; 65: 709-730.
41. Le Moine C, Bloch B. D1 and D2 dopamine receptor gene expression in the rat striatum: sensitive cRNA probes demonstrate prominent segregation of D1 and D2 mRNAs in distinct neuronal populations of the dorsal and ventral striatum. *J Comp Neurol* 1995; 355: 418-426.
42. Surmeier DJ, Reiner A, Levine MS, Ariano MA. Are neostriatal dopamine receptors co-localized? *Trends Neurosci* 1993; 16: 299-305.
43. Huang X, Lawler CP, Lewis MM, Nichols DE, Mailman RB. D_1 dopamine receptors. *Int Rev Neurobiol* 2001; 48: 65-139.
44. Gerfen CR. The neostriatal mosaic: multiple levels of compartmental organization. *Trends Neurosci* 1992; 15: 133-139.
45. Grace AA. Cortical regulation of subcortical dopamine systems and its possible relevance to schizophrenia. *J Neural Transm* 1993; 91: 111-134.
46. Otani S, Daniel H, Roisin M-P, Crepel F. Dopaminergic modulation of long-term synaptic plasticity in rat prefrontal neurons. *Cereb Cortex* 2003; 13: 1251-1256.
47. Uylings HBM, Groenewegen HJ, Kolb B. Do rats have a frontal cortex? *Behav Brain Res* 2003; 146: 3-17.
48. Kelly MA, Rubinstein M, Asa SL, Zhang G, Saez C, Bunzow JR, *et al*. Pituitary lactotroph hyperplasia and chronic hyperprolactinemia in dopamine D2 receptor-deficient mice. *Neuron* 1997; 19: 103-113.
49. Nieoullon A. Dopamine and the regulation of cognition and attention. *Prog Neurobiol* 2002; 67: 53-83.
50. Gerfen CR. The neostriatum mosaic: compartmental organisation of mesostriatal systems. In: Carpenter MB, Jayaraman A, editors. *The Basal Ganglia II*. Plenum

Press, New York London, 1987; 65-80.
51. Fiebiger HC, Phillips AG. Reward, motivation, cognition: psychobiology of mesotelencephalic dopamine system. In: Bloom FE, editor. *Handbook of Physiology. The Nervous System, Vol IV. Intrinsic Regulatory Systems of the Brain*. American Physiological Society, Baltimore, 1986; 647-675.
52. Schwarting RKW, Huston JP. Unilateral 6-hydroxydopamine lesions of mesostriatal dopamine neurons and their physiological sequelae. *Prog Neurobiol* 1996; 49: 215-266.
53. Schwarting RKW, Huston JP. The unilateral 6-hydroxydopamine lesion model in behavioural brain research, analysis of functional deficits, recovery and treatments. *Prog Neurobiol* 1996; 50: 275-331.
54. Semba K. Multiple output pathways of the basal forebrain: organization, chemical heterogeneity, and roles in vigilance. *Behav Brain Res* 2000; 115: 117-141.
55. Previc FH. Dopamine and the origins of human intelligence. *Brain Cogn* 1999; 41: 299-350.
56. Paxinos G, Watson C. *The Rat Brain in Stereotaxic Coordinates*. Academic Press, San Diego, 1998.
57. Gerfen CR, Engber TM, Mahan LC, Susel Z, Chase TN, Monsma FJ Jr, *et al*. D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. *Science* 1990; 250: 1429-1432.
58. Lazarov N, Pilgrim C. Localization of D_1 and D_2 dopamine receptors in the rat mesencephalic trigeminal nucleus by immunocytochemistry and in situ hybridization. *Neurosci Lett* 1997; 236: 83-86.
59. Lazarov N, Schmidt U, Wanner I, Pilgrim C. Localization of D_1 dopamine receptor mRNA in the rat brain with non-radioactive in situ hybridization histochemistry. *Ann Anatomy* 1997; 179 (Suppl): 319-320.
60. Le Moine C, Gaspar P. Subpopulations of cortical GABAergic interneurons differ by their expression of D1 and D2 dopamine receptor subtypes. *Mol Brain Res* 1998; 58: 231-236
61. Lazarov N. Expression of D_1 and D_2 dopamine receptor mRNAs in the rat hindbrain. *Ann Anatomy* 2002; 184 (Suppl): 99-100.
62. Sawaguchi T, Goldman-Rakic PS. D1 dopamine receptors in prefrontal cortex: involvement in working memory. *Science* 1991; 251: 947-949.
63. Williams GV, Goldman-Rakic PS. Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. *Nature* 1995; 376: 572-575.
64. Goldman-Rakic PS. Regional and cellular fractionation of working memory. *Proc Natl Acad Sci USA* 1996; 93: 13473-13480.
65. Brown RM, Goldman PS. Catecholamines in neocortex of Rhesus monkey: regional distribution and ontogenetic development. *Brain Res* 1977; 124: 576-580.
66. Thierry AM, Blanc G, Sobel A, Stinus L, Glowinski J. Dopaminergic terminals in the rat cortex. *Science* 1973; 182: 499-501.
67. Berger B, Thierry AM, Tassin JP, Moyne MA. Dopaminergic innervation of the rat pre-frontal cortex: a fluorescence histochemical study. *Brain Res* 1976; 106: 133-145.
68. Bergson C, Mrzljak L, Smiley JF, Pappay M, Levenson R, Goldman-Rakic PS. Regional, cellular, and subcellular variations in the distribution of D1 and D5 dopamine receptors in primate brain. *J Neurosci* 1995; 15: 7821-7836.
69. Hurd YL, Suzuki M, Sedvall GC. D1 and D2 dopamine receptor mRNA expression in whole hemisphere sections of the human brain. *J Chem Neuroanat* 2001; 22: 127-137.
70. Ariano MA, Wang J, Noblett KL, Larson ER, Sibley DR. Cellular distribution of the rat D4 dopamine receptor protein in the CNS using anti-receptor antisera. *Brain Res* 1997; 752: 26–34.
71. Defagot MC, Malchodi EL, Villar MJ, Antonelli MC. Distribution of D4 dopamine receptor in rat brain with sequence specific antibodies. *Mol Brain Res* 1997; 45: 1-12.
72. Penit-Soria J, Audinat E, Crepel F. Excitation of rat prefrontal cortical neurons by dopamine: an in vivo electrophysiological study. *Brain Res* 1987; 425: 263-274.
73. Ellenbroek BA, Budde S, Cools AR. Prepulse inhibition and latent inhibition: the role of dopamine in the rat medial prefrontal cortex. *Neuroscience* 1996; 75: 535-542.
74. Yang CR, Seamans JK. Dopamine D1 receptor actions in layers V-VI rat prefrontal cortex neurons in vitro: modulation of dendritic-somatic signal integration. *J Neurosci* 1996; 16: 1922-1935.
75. Rappaport MS, Sealfon SC, Prikhozhan A, Huntley GW, Morrison JH. Heterogeneous distribution of D1, D2, and D5 receptor mRNAs in monkey striatum. *Brain Res* 1993; 616: 242-250.
76. Doucet G, Descarries L, Garcia S. Quantification of the dopamine innervation in the adult rat striatum. *Neuroscience* 1986; 19: 427-445.
77. Freund TT, Powell JF, Smith AD. Tyrosine hydroxylase-immunoreactive boutons in synaptic contact with

identified striatonigral neurons, with particular reference to dendritic spines. *Neuroscience* 1984; 13: 1189-1215.
78. Siggins GR. Electrophysiological role of dopamine in the striatum: excitatory or inhibitory? In: Lipton MA, Killam KF, editors. *Phychopharmacology: A Generation of Progress*. Raven Press, New York, 1978; 143-157.
79. Brown JR, Arbuthnott GW. The electrophysiology of dopamine (D_2) receptor: a study of the actions of dopamine on corticostriatal transmission. *Neuroscience* 1983; 10: 349-355.
80. Gerfen CR, Keefe KA, Steiner H. D1 and D2 dopamine receptor-mediated gene regulation in the striatum. In: Merchant K, editor. *Pharmacological Regulation of Gene Expression in the CNS*. CRC Press, Boca Raton, 1996; 3-24.
81. Sun Z, Reiner A. Localization of D1A and D1B receptor mRNAs in the forebrain and midbrain of the domestic chick. *J Chem Neuroanat* 2000; 19: 211-224.
82. Le Moine C, Bloch B. Anatomical and cellular analysis of dopamine receptor gene expression in striatal neurons. In: Ariano MA, Surmeier DJ, editors. *Molecular and Cellular Mechanisms of Neostriatal Function*. Springer, Berlin, 1995; 45-57.
83. Sesack SR, Aoki C, Pickel VM. Ultrastructural localization of D2 receptor-like immunoreactivity in midbrain dopamine neurons and their striatal targets. *J Neurosci* 1994; 14: 88-106.
84. Gerfen CR, Keefe KA, Gauda EB. D1 and D2 dopamine receptor function in the striatum: coactivation of D1- and D2-dopamine receptors on separate populations of neurons results in potentiated immediate early gene response in D1-containing neurons. *J Neurosci* 1995; 15: 8167-8176.
85. Hersch SM, Ciliax BJ, Gutekunst CA, Rees HD, Heilman CJ, *et al*. Electron microscopic analysis of D1 and D2 dopamine receptor proteins in the dorsal striatum and their synaptic relationships with motor corticostriatal afferents. *J Neurosci* 1995; 15: 5222-5237.
86. Surmeier DJ, Song WJ, Yan Z. Coordinated expression of dopamine receptors in neostriatal medium spiny neurons. *J Neurosci* 1996; 16: 6579-6591.
87. Le Moine C, Bloch B. Expression of the D_3 dopamine receptor in peptidergic neurons of the nucleus accumbens: comparison with the D_1 and D_2 dopamine receptor. *Neuroscience* 1996; 73: 131-143.
88. Smith Y, Kieval JZ. Anatomy of the dopamine system in the basal ganglia. *Trends Neurosci* 2000; 23: S28-S33.
89. Le Moine C, Normand E, Guitteny AF, Fouque B, Teoule R, Bloch B. Dopamine receptor gene expression by enkephalin neurons in rat forebrain. *Proc Natl Acad Sci USA* 1990; 87: 230-234.
90. Missale C, Nash SR, Robinson SW, Jaber M, Caron MG. Dopamine receptors: from structure to function. *Physiol Rev* 1998; 78: 189-225.
91. Harrison MB, Wiley RG, Wooten GF. Changes in D2 but not D1 receptor binding in the striatum following a selective lesion of striatopallidal neurons. *Brain Res* 1992; 590: 305-310.
92. Butcher LL, Semba K. Reassessing the cholinergic basal forebrain: nomenclature schemata and concepts. *Trends Neurosci* 1989; 12: 483-485.
93. Verney C, Baulac M, Berger B, Alvarez C, Vigny A, Helle KB. Morphological evidence for a dopaminergic terminal field in the hippocampal formation of young and adult rat. *Neuroscience* 1985; 14: 1039-1052.
94. Herkenham M. Mismatches between neurotransmitter and receptor localizations in brain: observations and implications. *Neuroscience* 1987; 23: 1-38.
95. Berger B, Verney C, Alvarez C, Vigny A, Helle KB. New dopaminergic terminal fields in the motor, visual (area 18b) and retrosplenial cortex in the young and adult rat. Immunocytochemical and catecholamine histochemical analyses. *Neuroscience* 1985; 15: 983-998.
96. Descarries L, Lemay B, Doucet G, Berger B. Regional and laminar density of the dopamine innervation in adult rat cerebral cortex. *Neuroscience* 1987; 21: 807-824.
97. Dawson TM, Gehlert DR, McCabe RT, Barnett A, Wamsley JK. D-1 dopamine receptors in the rat brain: a quantitative autoradiographic analysis. *J Neurosci* 1986; 6: 2352-2365.
98. Scatton B, Simon H, Le Moal M, Bischoff S. Origin of dopaminergic innervation of the rat hippocampal formation. *Neurosci Lett* 1980; 18: 125-131.
99. Fuxe K, Agnati LF. Two principal modes of electrochemical communication in the brain: volume versus wiring transmission. In: Fuxe K, Agnati LF, editors. *Volume Transmission in the Brain. Novel Mechanisms for Neural Transmission, Vol I Advances in Neuroscience*. Raven Press, New York, 1991; 1-9.
100. Goldman-Rakic PS. The cortical dopamine system: role in memory and cognition. *Adv Pharmacol* 1998; 42: 707-711.
101. Sealfon SC, Olanow CW. Dopamine receptors: from structure to behavior. *Trends Neurosci* 2000; 23: S34-S40.
102. Tassin JP, Bockaert J, Blanc G, Stinus L, Thierry AM, Lavielle S, *et al*. Topographical distribution of dopaminergic innervation and dopaminergic receptors of the anterior cerebral cortex of the rats. *Brain Res* 1978;

154: 241-251.
103. Greengard P. The neurobiology of slow synaptic transmission. *Science* 2001; 297: 1024-1030.
104. Gorelova NA, Yang CR. Dopamine D1/D5 receptor activation modulates a persistent sodium current in rat prefrontal cortical neurons in vitro. *J Neurophysiol* 2000; 84: 75–87.
105. Rolls ET. The orbitofrontal cortex and reward. *Cereb Cortex* 2000; 10: 284-294.
106. Goldman-Rakic PS. Cellular basis of working memory. *Neuron* 1995; 14: 477-485.
107. McDonald RJ, White NM. A triple dissociation of memory systems: hippocampus, amygdala, and dorsal striatum. *Behav Neurosci* 1993; 107: 3-22.
108. Goldman-Rakic PS. Toward a circuit model of working memory and the guidance of voluntary motor action. In: Houk JC, Davis JL, Beiser DG, editors. *Models of Information Processing in the Basal Ganglia*. MA: MIT, Cambridge, 1995; 131-148.
109. Kelley AE. Neural integrative activities of nucleus accumbens subregions in relation to learning and motivation. *Psychobiology* 1999; 27: 198-213.
110. Lindvall O, Bjorklund A, Divac I. Organization of catecholamine neurons projecting to the frontal cortex in the rat. *Brain Res* 1978; 142: 1-24.
111. Beckstead RM, Domesick VB, Nauta WJ. Efferent connections of the substantia nigra and ventral tegmental area in the rat. *Brain Res* 1979; 175: 191-217.
112. Selemon LD, Goldman-Rakic PS. Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkey. *J Neurosci* 1985; 5: 776-794.
113. Levy R, Friedman HR, Davachi L, Goldman-Rakic PS. Differential activation of the caudate nucleus in primates performing spatial and nonspatial working memory tasks. *J Neurosci* 1997; 17: 3870-3882.
114. Sutton MA, Beninger RJ. Psychopharmacology of conditioned reward: evidence for a rewarding signal at D1-like dopamine receptors. *Psychopharmacology* 1999; 144: 95-110.
115. Usiello A, Baik JH, Rouge-Pont F, Picetti R, Dierich A, LeMeur M, *et al*. Distinct functions of the two isoforms of dopamine D2 receptors. *Nature* 2000; 408: 199-203.
116. Schmitz Y, Benoit-Marand M, Gonon F, Sulzer D. Presynaptic regulation of dopaminergic neurotransmission. *J Neurochem* 2003; 87: 273-289.
117. Paillard J. Les niveaux sensori-moteur et cognitive du contrôle de l'action. In: Laurent M, Therme P, editors. *Recherches en Activités Physiques et Sportives*. Centre de Recherche UEREPS, 1985; 147-163.
118. Meck WH. Neuropharmacology of timing and time perception. *Cogn Brain Res* 1996; 3: 227-242.
119. Ivry RB. The representation of temporal information in perception and motor control. *Curr Opin Neurobiol* 1996; 6: 851-857.
120. Gibbon J, Malapani C, Dale C, Gallistel CR. Toward a neurobiology of temporal cognition: advances and challenges. *Curr Opin Neurobiol* 1997; 7: 170-184.
121. Seamans JK, Yang CR. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. *Prog Neurobiol* 2004; 74: 1-58.
122. Sokolowski JD, Salamone JD. Effects of dopamine depletions in the medial pre-frontal cortex on DRL performance and motor activity in the rat. *Brain Res* 1994; 642: 20-28.
123. Okudo Y, Suhara T, Susuki K, Kobayashi K, Inoue O, Terasaki O, *et al*. Decreased pre-frontal dopamine D_1 receptors in schizophrenia revealed by PET. *Nature* 1997; 385: 634-636.
124. Robbins TW. Chemical neuromodulation of frontal-executive functions in humans and other animals. *Exp Brain Res* 2000; 133: 130-138.
125. Jučaitė A. Dopaminergic modulation of cerebral activity and cognitive functions. *Medicina* 2002; 38: 357-362.
126. El-Ghundi M, Fletcher PJ, Drago J, Sibley DR, O'Dowd BF, George SR. Spatial learning deficit in dopamine D_1 receptor knockout mice. *Eur J Pharmacol* 1999; 27: 95-106.
127. Brené S, Herrera-Marschitz M, Persson H, Lindefors N. Expression of mRNAs encoding dopamine receptors in striatal regions is differentially regulated by midbrain and hippocampal neurons. *Mol Brain Res* 1994; 21: 274-282.
128. Mehta MA, Sahakian BJ, McKenna PJ, Robbins TW. Systemic sulpiride in adult young volunteers simulates the profile of cognitive deficits in Parkinson's disease. *Psychopharmacol* 1999; 146: 162-174.
129. Eliis KA, Nathan PJ. The pharmacology of working memory. *Int J Neuropsychopharmacol* 2001; 4: 299-313.
130. Bonci A, Hopf FW. The dopamine D2 receptor: new surprises from an old friend. *Neuron* 2005; 47: 335-338.