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Dopamine: a potential substrate for synaptic plasticity and memory mechanisms

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Abstract

It is only recently that a number of studies on synaptic plasticity in the hippocampus and other brain areas have considered that a heterosynaptic modulatory input could be recruited as well as the coincident firing of pre- and post-synaptic neurons. So far, the strongest evidence for such a regulation has been attributed to dopaminergic (DA) systems but other modulatory pathways have also been considered to influence synaptic plasticity. This review will focus on dopamine contribution to synaptic plasticity in different brain areas (hippocampus, striatum and prefrontal cortex) with, for each region, a few lines on the distribution of DA projections and receptors. New insights into the possible mechanisms underlying these plastic changes will be considered. The contribution of various DA systems in certain forms of learning and memory will be reviewed with recent advances supporting the hypothesis of similar cellular mechanisms underlying DA regulation of synaptic plasticity and memory processes in which the cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) pathway has a potential role. To summarize, endogenous DA, which depends on the activity patterns of DA midbrain neurons in freely moving animals, appears as a key regulator in specific synaptic changes observed at certain stages of learning and memory and of synaptic plasticity.

Contents

Abbreviations: AC, adenylate cyclase; ACSF, artificial cerebral spinal fluid; AMPA, α-amino-3-hydroxy-5-methyl-isoxazoleproprionic acid; CaMKII, Ca^{2+}/calmodulin-kinase II; cAMP, cyclic adenosine monophosphate; CREB, cyclic adenosine monophosphate response element bonding protein; DA, dopamine (dopaminergic); DARPP-32, dopamine and cyclic adenosine monophosphate-regulated phosphoprotein; EPSP, excitatory post-synaptic potential; GABA, γ-amino-butyric acid; 5 HT, serotonin; LTD, long-term depression; LTP, long-term potentiation; GluR1, glutamate receptor subunit 1; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NA, norepinephrine; NMDA, *N*-methyl-D-aspartate; NR1, *N*-methyl-D-aspartate subunit 1; 6-OHDA, 6-hydroxydopamine; PKA, protein kinase A; PP1, protein phosphatase 1; Rp-cAMPS, Rp-adenosine 3′,5′-cyclic monophosphorothioate triethylamine; VTA, ventral tegmental area

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1. Introduction

The idea that an additional mechanism was necessary for the *N*-methyl-D-aspartate (NMDA) receptor-dependent long-term potentiation (LTP) to produce a long-lasting maintenance of several hours was suggested by the fact that neither *N*-methyl-D-aspartate alone or in combination with other glutamatergic agonists was able to produce a non-decremental LTP (Kauer et al., 1988). The involvement of aminergic influences on LTP was first considered when two studies concurrently demonstrated that a depletion of 5-hydroxytryptamine (5 HT) or global catecholamine could modulate LTP in the dentate gyrus of freely moving rats (Bliss et al., 1983; Krug et al., 1983). In the field of catecholamine transmitters, dopamine (DA) pathways have then been recognized to play a critical role in cognition and emotion, and the last decade has seen a large increase in the experimental evidence for a role of DA in both synaptic plasticity and memory processes. The cloning of five DA receptors and the development of more specific agonists and antagonists of the different DA receptors have helped in characterizing the action of DA on synaptic plasticity. Concomitantly, sophisticated behavioral paradigms have let us progress in elucidating the role of DA in cognition.

A large number of different paradigms have been used to examine the role of DA in synaptic plasticity in mostly three brain regions innervated by DA: the striatum including the nucleus accumbens, the hippocampus and the prefrontal cortex. Studies in the striatum have been reviewed by Lovinger and Tyler (1996), Arbuthnott et al. (2000) and Centonze et al. (2001a) and data in the hippocampus summarized by Lisman and Otmakhova (2001) in an extension of their network model of hippocampal function. The focus of this review is on the coverage of data collected over the last decade on DA and synaptic plasticity in the striatum, nucleus accumbens, hippocampus and prefrontal cortex. The first part of the review provides an overview of the modulatory effects of DA on synaptic plasticity including LTP, long-term depression (LTD) and depotentiation in these different brain regions innervated by midbrain DA systems. For each region considered, a short summary on DA innervation and DA receptor distribution has been included or appropriate review articles referenced. The description of a possible cellular mechanism of action of DA on LTP is then outlined. The second part of the review addresses the functions of hippocampal, striatal or prefrontal DA systems in different forms of memories as assessed with behavioral, pharmacological or lesion studies, and a few experiments on cellular mechanisms underlying the function of DA in memory processes are summarized. The conclusion is an attempt to compare the function of DA in the memory processes with its role in synaptic plasticity.

2. Dopamine and synaptic plasticity

Since the discovery of LTP in the hippocampus (Bliss and Lomo, 1973), synapses that undergo plastic changes have been described in various parts of the brain and particularly in brain regions that receive DA innervations. It is now well established that the strength of synaptic transmission can be modified on a long-term basis by specific patterns of activation such as high frequency trains that produce LTP, and also by the action of endogenous modulators such as DA. Using different in vitro or in vivo preparations, studies that have addressed the question of DA modulation of LTP have been performed in several brain areas mainly the hippocampus, the neocortex and the striatum. Although all these different regions receive DA projections from the ventral tegmental area (VTA), adjacent substantia nigra and/or retrorubral fields that contain the DA neurons of the A10, A9 and A8 groups, respectively, the specific origin of DA neurons and the intensity of innervation are different. On the other hand, the levels of DA receptor may be related to the levels of DA input. Five DA receptor subtypes, D1 to D5, have been cloned and characterized so far. Although pharmacological and physiological studies cannot not yet differentiate their individual roles because of the absence of specific agonists and antagonists, the distribution of these different DA receptor subtypes is beginning to emerge, and we will soon be able to identify the individual contribution of D1 versus D5 receptors in synaptic plasticity and cognitive function.

These observations led us to question the functional similarity of DA modulation in synaptic plasticity when induced in a neocortical, hippocampal or striatal region.

Table 1
Summary of the effects of DA receptor agonists and antagonists on LTP in the hippocampus, striatum and prefrontal cortex

Region	Receptor drug	Effect	References
Hippocampus (CA1 region)			
In vitro (rats)	D1 agonist	Late potentiation	Huang and Kandel (1995)
	D2 agonist	No effects	Huang and Kandel (1995)
	D1 antagonist	Blockade late LTP	Frey et al. (1991)
	D1 antagonist	Blockade early and late LTP	Otmakhova and Lisman (1996)
	D1 antagonist	Blockade late LTP	Swanson-Park et al. (1999)
In vitro (D1-knock out mice)		No late LTP	Matthies et al. (1997)
In vivo (rats)	D1 antagonist	Blockade late LTP	Swanson-Park et al. (1999)
Hippocampus (dentate gyrus)			
In vitro	D1 antagonist	No effects	Swanson-Park et al. (1999)
In vivo	D1 agonist (IP)	Blockade LTP	Yanagihashi and Ishikawa (1992)
	D1 agonist	No effects	Kusuki et al. (1997)
	D1 antagonist (IP)	No effects	Yanagihashi and Ishikawa (1992)
	D1 antagonist (IP)	Blockade LTP	Kusuki et al. (1997)
	D1 antagonist	No effects	Swanson-Park et al. (1999)
Striatum (cortico-striatal synapses)			
In vitro (rats)	D1 antagonist	Blockade LTP	Kerr and Wickens (2001)
	D2 antagonist	No effects	Kerr and Wickens (2001)
	D2 antagonist	Enhancement LTP	Centonze et al. (2001a)
In vitro (D2-knock out mice)		Enhancement LTP	Calabresi et al. (1997)
Nucleus accumbens (hippocampal-accumbens synapses)			
In vitro (rats)	Mixture D1/D2 antagonist	No effects	Pennartz et al. (1993)
In vivo (rats)	D1 antagonist (IP)	Blockade LTP	Floresco et al. (2001)
Prefrontal cortex (hippocampal-prefrontal synapses)			
In vivo (rats)	D1 agonist	Facilitation LTP	Gurden et al. (2000)
	D1 antagonist	Blockade LTP	Gurden et al. (2000)
	D2 antagonist	No effects	Gurden et al. (2000)

2.1. Pharmacological evidence for a modulatory dopamine input of different LTPs (Table 1)

2.1.1. The hippocampal formation

The hippocampal formation receives a DA input from different midbrain groups and according to Swanson (1982), approximately the same number of DA cells in A9 and A10 appear to project to the dorsal hippocampus (Ammon's horn and dentate gyrus). However, a further clarification of the organization of DA projections to the hippocampus by using anterograde and/or retrograde tracers, and tyrosine hydroxylase immunohistochemistry have indicated that the major terminal fields of A8, A9 and A10 projections include the ventral and dorsal subiculum and the adjacent CA1 field (Gasbarri et al., 1991, 1994, 1996). These studies that clearly noted a more prominent DA input to the temporal (ventral and caudal) rather than the septal (dorsal) pole of the hippocampus were in accordance with other work reporting higher levels of DA in the ventral hippocampus (Hortnagl et al., 1991) or showing morphological evidence of only a few positive axons in the hilus of the dentate gyrus and CA3 (Verney et al., 1985). At the ultrastructural level, tyrosine hydroxylase-immunoreactive terminals form symmetric synapses with dendrites and perikarya of dentate granule cells and pyramidal neurons in CA3 and CA1 (Milner and Bacon, 1989). Some of these terminals (10%) are found in close apposition to unlabeled terminals that form asymmetric synapses with dendrites and dendritic spines. The characterization of neuronal populations expressing DA receptor subtypes in the hippocampus have shown a prominent labeling of D1 receptors dorsally in granular cells of the dentate gyrus and in most cells of the subicular complex (Fremeau et al., 1991). Only a few labeled cells expressing D1 receptors were observed in the stratum oriens and radiatum of CA1–CA3 fields. However, little or no D1 receptor protein is expressed in the hippocampus and recent data have suggested that D5 receptor is the predominant D1-like receptor in these non-classical recipients of DA innervation (Levey et al., 1993; Ciliax et al., 2000). D5 immunoreactive neurons are localized in the hilus and granular cells of the dentate gyrus, in pyramidal cells of the subiculum, but also in CA1 and CA3 (Ariano et al., 1997; Ciliax et al., 2000; Khan et al., 2000). In rat, D5 receptors appear to be concentrated mostly on cell bodies rather than on dendrites of hippocampal neurons whereas in monkeys and human, the reactivity is also associated with dendrites (Khan et al., 2000; Bergson et al., 1995). For the distribution of D1 receptors at the subcellular level in the hippocampus, studies in monkeys

show a prominent labeling in pyramidal cells and dendrites (Bergson et al., 1995) but localization of these receptors has not been explored yet in the rat.

In contrast, low levels of D2 receptor mRNA and no D2 receptor protein have been detected in the hippocampus (Meador-Woodruff et al., 1989; Levey et al., 1993). Binding sites for D2 receptors are more pronounced in septal portions of the lacunosum moleculare of CA1 and stratum moleculare of the subiculum whereas no binding to D2 receptors exists in the temporal hippocampus (Goldsmith and Joyce, 1994). D3 receptor has also been detected at a low level in the hippocampus, while a high level of D4 receptor was later shown to reflect the localization of the receptor itself in the dentate gyrus, CA1, CA2 and CA3 (Defagot et al., 1997).

2.1.1.1. Dopamine receptors and LTP in the CA1 region. The first reports on the actions of DA in CA1 pyramidal cells in vitro included varied results from the elevation of spike threshold (Stanzione et al., 1984) to long-lasting modifications of excitability (Gribkoff and Ashe, 1984) and a reduction in the after hyperpolarization following a train of action potentials (Malenka and Nicoll, 1986). The question of a possible relationship between LTP and DA was then tackled by a pharmacological approach. Several studies applying D1 and D2 receptor antagonists in the same in vitro preparation provided evidence that besides glutamate through *N*-methyl-D-aspartate and non-NMDA receptors, DA receptor-mediated signals were additionally if not necessarily involved in the production of a long-lasting maintenance of LTP (Frey et al., 1990, 1991). Indeed, application of the specific D1 antagonist, SCH 23390 during tetanization can prevent the long-term maintenance of LTP, whereas application immediately after tetanization has no influence on established LTP. This was later confirmed by Huang and Kandel (1995) who also showed that agonists of the D1/D5 receptors (SKF 38393) produced a persistent increase of the excitatory post-synaptic potential (EPSP) slope, with a very slow onset synaptic potentiation starting 50–90 min after drug application and reaching a peak after 3–4 h. On the contrary, agonists of the D2 receptor did not induce potentiation. More recently, Swanson-Park et al. (1999) replicated these experiments by showing that D1/D5 receptor antagonism blocks LTP persistence in CA1 slices in the rat in vitro. The possible involvement of D1 receptor in CA1 LTP was also investigated using gene-targeted mutant mice. In D1-knock out mice, Matthies et al. (1997) found that short-term post-tetanic LTP declined over 6 h to reach control values. Together these results indicate that only the late phase of LTP in the CA1 region of the hippocampus appears to be heterosynaptically mediated. However, Otmakhova and Lisman (1996) have found that application of a D1 agonist, although not the most specific one, and a D1 antagonist during tetanization altered the early component of LTP in CA1 slices.

The difficulty of inducing LTP in vivo in area CA1 without producing epileptiform after discharges might explain why only Swanson-Park et al. (1999) investigated whether there was a DA modulation of LTP in this region in awake animals. The authors demonstrate that the D1 antagonist, SCH 23390 blocks persistence of LTP beyond 3 h, confirming the results obtained on CA1 slices in vitro.

2.1.1.2. Dopamine receptors and LTP in the dentate gyrus. Contrary to CA1, just a few studies have investigated DA modulation of LTP in the dentate gyrus, even if DA innervation is also present in a small amount but to a similar extent in this hippocampal region. Yanagihashi and Ishikawa (1992) found that LTP of the population spike in the dentate gyrus disappeared in the presence of a D1 agonist (SKF 38393) that was administered intraperitoneally, and this inhibition was dose-dependently antagonized by the D1 antagonist, SCH 23390. However, Kusuki et al. (1997) found exactly the opposite when infusing the same D1 agonist in the lateral ventricle, although LTP induction was blocked when the D1 antagonist was preinfused before tetanus. These mixed findings were later reconsidered by Swanson-Park et al. (1999) who found no effect of SCH 23390 on LTP induction on either slices or in awake animals. The D1 antagonist was injected intraperitoneally 30 min prior to high-frequency stimulation at the same dose that was shown in the same study to cause a faster decay of LTP in area CA1 over the 3 h post-tetanus recording period.

2.1.2. Dopamine receptors and LTP in the striatum

The critical importance of DA in striatal activity has also led to investigations on DA modulation of LTP in the corticostriatal pathway. The striatum receives a major glutamatergic input from the cortex and the projection neurons in the striatum are medium spiny neurons. These neurons that use GABA as neurotransmitter also receive a major DA projection from cells in the substantia nigra pars compacta and DA terminals are localized in close proximity to the corticostriatal inputs (Freund et al., 1984; Smith and Bolam, 1990). Both D1 and D2 receptors are found at high levels in the dorsal striatum, with a certain amount of overlap in medium spiny neurons although this is still a matter of debate. At the subcellular level, D1 and D2 receptor immunoreactivity is found to be mainly associated with the membrane post-synaptic to terminals forming symmetrical synapses and less commonly asymmetrical synapses (Yung et al., 1995). D1 receptors present in medium spiny GABAergic neurons are concentrated on spines and shafts of projection neurons whereas D5 receptors appear to be expressed in only a few of them making asymmetric synapses (Bergson et al., 1995; Khan et al., 2000).

A number of reports suggested that LTD was the predominant form of plasticity at corticostriatal synapses in vitro, but by removing the voltage-dependent block of the NMDA receptor channels in magnesium-free medium, it was possible to induce LTP (Walsh, 1993; Calabresi et al., 1992a,b, for review, Lovinger and Tyler, 1996; Arbuthnott et al., 2000). With this protocol, Kerr and Wickens (2001)

recently reported that this form of LTP is blocked by a D1 (SCH 23390) but not by a D2 antagonist (remoxipride). The authors discuss on an early phase of LTP that was not affected by the presence of SCH 23390, but the recording after tetanus lasting only 20 min does not allow us to define different phases in LTP. In contrast to these data, Centonze et al. (2001b) found that LTP in the cortico-striatal pathway (magnesium-free medium) was enhanced by using either a D2 receptor antagonist (sulpiride; magnesium-free medium) in striatal slices or in mice lacking D2 receptors (Calabresi et al., 1997). To clarify these discrepancies, it would be interesting to compare these results to studies which have demonstrated either in vivo or in vitro that LTP constitutes the normal form of synaptic plasticity at cortico-striatal synapses, although none of them has yet investigated the role of DA (Walsh and Dunia, 1993; Charpier and Deniau, 1997; Charpier et al., 1999; Spencer and Murphy, 2000).

2.1.3. Dopamine receptors and LTP in the nucleus accumbens

Although the ventral part of the striatum, i.e. the nucleus accumbens, receives a major DA input from the VTA, DA regulation of synaptic plasticity has not been well explored. On the basis of differences in projection patterns and neurochemistry, the nucleus accumbens is divided in two main subregions, the core and the shell. As in the striatum, the principal cells of the nucleus accumbens are medium spiny GABAergic neurons that receive excitatory inputs from a variety of brain regions. The whole nucleus accumbens receives a DA input from the VTA but also from the retrorubral mesencephalic nuclei and the substantia nigra (Oades and Halliday, 1987) and DA terminals are apposed to both symmetric as well as asymmetric synapses (Sesack and Pickel, 1992). D1 and D2 receptor immunoreactivities with DA immunoreactive terminals, as well as high levels of D3 receptors have been found in the core region (Levesque et al., 1992; Jansson et al., 1999). LTP can be induced after stimulation of the cortical afferents (Pennartz et al., 1993; Kombian and Malenka, 1994) but only one study has shown that this LTP was not affected by DA, nor by D1 or D2 receptor antagonists (Pennartz et al., 1993). The variability for getting LTP or LTD on this pathway, as mentioned by the authors, could explain the absence of a DA effect. LTP can also be induced in the nucleus accumbens by stimulating hippocampal fibers (Boeijinga et al., 1993; Mulder et al., 1997) and tetanic stimulation of the hippocampal input (fimbria), increasing DA levels in the nucleus accumbens, leads to a potentiation of firing activity of hippocampal-accumbens neurons through D1 receptor activation (Floresco et al., 2001).

2.1.4. Dopamine receptors and LTP in the prefrontal cortex

Although DA innervation in the neocortex extends to a few cortical areas, studies on synaptic plasticity and DA are concentrated on the prefrontal cortex because of its major role in cognitive function. DA terminals located mostly in deep layers (V and VI) of the prelimbic and anterior cingulate areas form synaptic contacts preferentially with distal dendrites and spines of pyramidal cells, with a preference of synapses on dendrites and soma relative to spines in rodents (Berger et al., 1991; Van Eden et al., 1987; Seguela et al., 1988; Verney et al., 1990). Synaptic triads involving the DA input to the prefrontal cortex, whereby dendritic spines of pyramidal neurons are the targets of both DA afferents and another unspecified excitatory input, have been described in the prefrontal cortex of rats, monkeys and humans (Goldman-Rakic et al., 1989; Verney et al., 1990; Smiley et al., 1992; Smiley and Goldman-Rakic, 1993). In the rat, D1 receptors are expressed at a higher level than D2 receptors in the prefrontal cortex (three- to five-fold) and are more concentrated in deep layers while D2 receptors are localized in superficial and deep layers (Gaspar et al., 1995; Lu et al., 1997). Recently, D5 receptors have also been observed predominantly in deep layers and associated with pyramidal neurons and their dendrites (Bergson et al., 1995; Ariano et al., 1997; Khan et al., 2000). At the subcellular level, the labeling of D1 and D5 receptors in the prefrontal cortex is comparable to the hippocampus although different in intensity. D1 receptors are localized directly at the spines that receive excitatory terminals from different inputs, whereas D5 receptors are expressed on dendritic shafts (Smiley et al., 1994; Bergson et al., 1995). The preferential localization of these closely related receptors suggest a selective modulation of excitatory synapses although as mentioned in the introduction, the unavailability of specific agonists and antagonists of these receptor subtypes does not allow differentiation of their individual role. D4 receptors are also present at a high level in this neocortical region but no studies have yet explored the participation of D4 receptors in synaptic plasticity and memory processes.

LTP can be induced in vivo on a direct extrinsic input to the prefrontal cortex by applying tetanic stimulation in the hippocampus, and this LTP is an NMDA receptor-dependent process (Laroche et al., 1990; Jay et al., 1995). The close proximity of hippocampal and DA terminals in the PFC targeting the same dendrites in deep layers of the prelimbic area (Carr and Sesack, 1996) suggested a DA control of hippocampal-prefrontal synaptic strength. We recently investigated the role of D1 and D2 receptors on this in vivo preparation (Gurden et al., 2000). LTP at hippocampal to prefrontal cortex synapses is significantly higher when the D1 agonist, SKF 81297, is locally infused (reverse dialysis) in the prefrontal cortex prior to tetanus. The increase in LTP amplitude is significantly larger at certain doses tested when compared to ACSF-controls, demonstrating that an optimal range of D1 receptor activation is necessary to induce sustained enhancement of prefrontal LTP. Conversely, application of the D1 receptor antagonist SCH 23390 at different doses in the prefrontal cortex dose-dependently impaired LTP at hippocampal to prefrontal cortex synapses. The D2 receptor antagonist sulpiride did not affect cortical LTP. Thus, these studies showing a clear facilitating effect of a D1 agonist on LTP induction demonstrated that D1 but

not D2 prefrontal DA receptors play an essential role on the expression of LTP at hippocampal-prefrontal synapses (Gurden et al., 2000).

2.2. Enhancement or depletion of dopamine modulates different LTPs

Based on all these data, it was suggested that DA could act as a neurotransmitter involved in different mechanisms of LTP. As a result, how DA could modulate synaptic plasticity has also been examined in these different brain regions.

In the hippocampus, a myriad of different effects has been reported in the first in vitro studies on the Shaffer collateral inputs to CA1 pyramidal cells where high doses and long exposures of DA were applied into hippocampal slices. As mentioned earlier, long-lasting modifications of excitability, depolarization and blockade of after-depolarization were described (Gribkoff and Ashe, 1984; Malenka and Nicoll, 1986; Pedarzani and Storm, 1995). However, with lower doses (1 μM or less) applied in the bath, the afterhyperpolarization was increased, the spontaneous activity and spike threshold decreased (Benardo and Prince, 1982; Stanzione et al., 1984; Pockett, 1985). The ambiguity of those results explains why the neurotransmitter DA was later replaced by specific D1 and D2 agonists. Conversely, depletion of catecholamines (reserpine) decreases the early LTP and abolishes the effect of D1/D5 antagonists in the CA1 region (Otmakhova and Lisman, 1996). A similar lesion was also shown to affect LTP in the dentate gyrus (Stanton and Sarvey, 1985). In hippocampal slices taken from 6-hydroxydopamine (6-OHDA)-treated animals, theta-burst stimulation at 100 Hz failed to induce LTP at CA1 synapses (Yang et al., 2002) and even though 6-OHDA lesion usually affects both NA and DA systems, activation of D1/D5 receptors was able to restore LTP.

In the striatum, opposite results have been found with different in vitro or in vivo preparations. EPSPs evoked by stimulating cortico-striatal fibers appear to decrease in bath-applied DA but surprisingly, a similar pharmacology was observed when these EPSPs were recorded from DA-denervated slices (Calabresi et al., 1993; Centonze et al., 1999). On the contrary, Wickens et al. (1996) describe a potentiation in the strength of synaptic transmission following pulsatile application of DA. The main difference between these in vitro studies is that the former used magnesium-free medium. Opposite results have also been found on striatal LTP in DA-denervated slices: (1) an increase in LTP expression (Dos Santos Villar and Walsh, 1999; Smith et al., 2001); (2) no LTP induced with the magnesium-free medium (Centonze et al., 1999). In addition, these results have been challenged by the recent in vivo findings which show that a shift in synaptic efficacy in the direction of a spontaneous depression was observed in the cortico-striatal pathway of DA-depleted rats (Reynolds and Wickens, 2000). Apart from the parameters used in the three studies to induce LTP, these differences probably reflect the degree of loss in DA. While a 6-OHDA lesion was used in the first two studies, Reynolds and Wickens used a pretreatment with α-methyl-*para*-tyrosine to delete the releasable DA.

In the ventral striatum (nucleus accumbens), no difference in LTP was found when comparing slices bathed in DA and controls (Pennartz et al., 1993).

In the prefrontal cortex, local infusion of DA or a DA uptake blocker (nomifensine) induces a long-lasting enhancement of the hippocampal-prefrontal cortex LTP in vivo (Jay et al., 1996). Following these findings and to better understand the critical modulatory role of endogenous DA on the hippocampal input to the prefrontal cortex, we studied the effects of either VTA stimulation (to increase endogenous DA) or electrolytic VTA lesion (to deplete endogenous DA) on the hippocampal-prefrontal synaptic plasticity. Transient stimulation of the VTA (50 Hz, 2 s) applied prior to tetanic stimulation of the hippocampus is sufficient to produce a long-lasting increase in the magnitude of LTP in the hippocampal-prefrontal cortex synapses (Gurden et al., 1999). The experimental protocol for VTA stimulation was chosen to increase the release capacity for mesocortical DA neurons (Garris et al., 1993; Garris and Wightman, 1994). These findings provided additional support demonstrating that DA has a facilitatory role in the induction of cortical LTP. We then examined the effects of an electrolytic lesion of the VTA on the induction of hippocampal-prefrontal LTP. A dramatic decrease in the magnitude of LTP was observed in VTA-lesioned rats with significant cortical DA depletion when compared to sham-operated rats. Interestingly, by pooling all the data, a significant correlation was found between the magnitude of cortical DA depletion and the disruption of hippocampal-prefrontal LTP (Gurden et al., 1999). Therefore, these results strengthened evidence of a functional role for DA in the regulation of LTP in the prefrontal cortex.

In prefrontal cortex slices, a first bath with DA facilitates LTD (see Section 2.3 on dopamine and LTD), whereas a second application of DA when coupled to high-frequency stimuli after washout of DA, induces LTP instead of LTD (Blond et al., 2002). This LTP protocol differs from the LTD protocol only in terms of the addition of a prior application of DA. The results are interpreted by the authors as a possible difference in the sensitivity of certain second messengers after a first application of DA. Thus, DA in the prefrontal cortex, can induce either LTD or LTP, at least in vitro.

2.3. Dopamine release and LTPs

Since endogenous DA appears to be involved in the expression of LTPs and LTDs, the release of DA has been measured during electrophysiological experiments when inducing LTP. Only one study on CA1 slices using [^{14}C] DA has shown that tetanization produces a significantly enhanced release of DA (Frey et al., 1990). A transient increase in the release of endogenous DA after tetanic stimulation of

cortico-striatal fibers has been found to be associated with LTD induction in the dorsal striatum (Calabresi et al., 1995; Partridge et al., 2002). We have also measured a significant but transient increase in DA release in the prefrontal cortex during tetanic stimulation of the ventral hippocampus (Gurden et al., 2000).

One possible explanation of these data could be the putative existence of heterosynaptic NMDA receptors on DA pre-synaptic terminals that could be activated both on post-synaptic pyramidal neurons and mesoprefrontal terminals in the prefrontal cortex. As a consequence, extracellular DA would increase, and through activation of post-synaptic D1 receptors powerfully modulate NMDA receptor activation, triggering LTP. This hypothesis, largely supported by other studies in the prefrontal cortex, could also work for CA1 and the striatum. A study dealing with the synaptic localization of both DA and glutamatergic receptors in the prefrontal cortex, CA1 and the striatum would help in clarifying this DA–NMDA interaction.

2.4. Dopamine and LTD

In contrast, identical studies performed in the hippocampus, striatum and neocortex have demonstrated that DA does not increase LTP expression but instead increases LTD expression.

In the CA1 region, LTD induced by low-frequency stimulation in CA1 slices appears to be modulated by both D1 and D2 receptors but in opposite directions (Chen et al., 1996). Activation of D1 receptors enhances LTD, while activation of D2 receptors blocks induction. It is worth mentioning that LTD in the hippocampal CA1 region is dependent on NMDA and γ-amino-butyric acid A (GABAA) receptors. In Chen's preparation, LTD blocked by picrotoxin can be restored by D1 agonist. From the results on DA modulation of LTP in CA1, it would appear that D1 receptors facilitate both LTP and LTD, and D2 receptors work in the other direction.

Several in vitro studies have shown that activation of DA receptors is a critical requirement for LTD to occur at cortico-striatal synapses (for review, see Centonze et al., 2001a). Antagonists of D1 and D2 receptors block the induction of LTD, and this form of synaptic plasticity is absent in mice lacking D2 receptors. LTD cannot be induced in dopamine-depleted slices but can be restored in the presence of DA. It has also been reported that LTD induced in medium spiny neurons is not affected by DA or by DA antagonists in slices of the nucleus accumbens (Thomas et al., 2000). Therefore, two different forms of LTD can be induced in the striatum that are differentially modulated by DA: LTD in the dorsal striatum is not dependent on NMDA receptor but requires activation of DA receptors while LTD in the ventral striatum involves activation of NMDA receptors but is not affected by DA.

In the prefrontal cortex, DA favors the emergence of LTD versus LTP, lowering the threshold for LTD, as observed in vitro on glutamatergic synapses (layers I–II to layer V neurons) (Law-Tho et al., 1995). Using DA antagonists, the following pharmacological analyses suggested that DA action on either D1 or D2 receptors could facilitate the induction of LTD. However, only D2 agonists could mimic the DA effect (Otani et al., 1998). These results, although opposite to ours, could be explained by a different population of afferents activated in the two studies, but also to other parameters. At hippocampal to prefrontal cortex synapses, LTD which can be reliably induced when using short trains of repeated low-frequency pairs of pulses applied in the hippocampus (Takita et al., 1999) has not been explored yet after VTA stimulation or DA drugs infusion in the prefrontal cortex.

2.5. Dopamine and depotentiation

Recently, a few studies have explored whether DA could affect another form of synaptic plasticity, depotentiation or the reversal of LTP. Even though these studies were performed in the CA1 region and the dentate gyrus using two different preparations (in vitro slices or freely moving animals) similar results were obtained. D1/D5 receptor agonists inhibited depotentiation in CA1 and the dentate gyrus, and this effect was prevented by D1/D5 antagonists (Otmakhova and Lisman, 1998; Kulla and Manahan-Vaughan, 2000). It appears surprising, however, that in the dentate gyrus DA receptors that are not critically involved in LTP could play a prominent role in the expression of depotentiation.

2.6. Dopamine and LTP: mechanisms of action

The regional discrepancies observed on the action of DA on synaptic plasticity could be explained by a difference in DA content and DA receptor subtype distribution in each region, and as a consequence a difference in the level of DA receptor activation at a given time in a specific preparation when LTP or LTD are induced. Indeed, a number of studies have tested whether bidirectional changes in synaptic efficacy depend on the history of the synapses, which would imply a different recruitment of the glutamatergic pathway, but also of other transmitter pathways directly controlling induction of LTP or LTD. Neuromodulators and particularly DA resident in the synapses could strongly influence the induction of LTP and/or LTD through specific changes in the initial levels of cAMP and Ca^{2+}, which are key regulators of LTPs in the hippocampus, striatum and prefrontal cortex (Frey et al., 1993; Jay et al., 1998; Spencer and Murphy, 2002; Gurden et al., 2000). An important convergence of action of different neurotransmitters could be provided at this level, indicating that glutamate but also other transmitters could be integrated in the induction mechanisms of these plastic events. As already pointed out by several works, DA through D1 receptors increases NMDA currents (Cepeda et al., 1998) and this synergism that occurs at the post-synaptic level appears to be mediated through

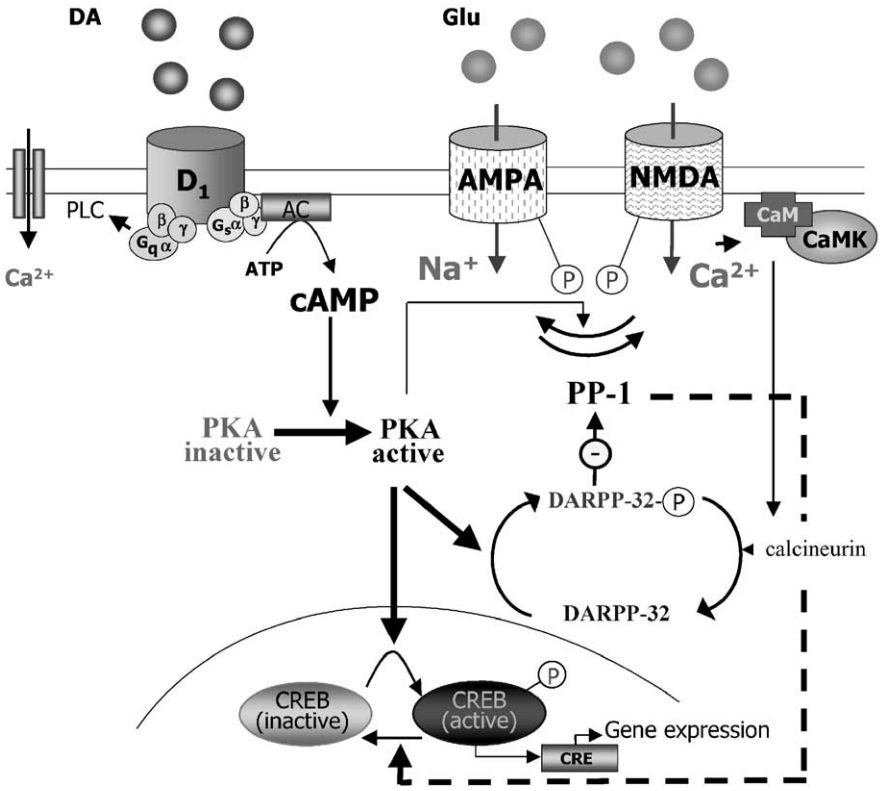

Fig. 1. Schematic representation of a major contribution of the D1/cAMP/PKA/PP1 signaling pathway in the DA regulation of LTP. The D1 receptor positively coupled to adenylate cyclase (AC) increases AC activity leading to the formation of cAMP that subsequently activates the cAMP-dependent PKA by binding to the regulatory subunits. The release of the active catalytic subunit permits phosphorylation of specific target substrates localized in different cellular compartments (cytosol, membrane, nucleus). (1) Activated PKA phosphorylates both AMPA and NMDA receptors and DARPP-32. Once phosphorylated, DARPP-32 is converted to a potent inhibitor of PP1 that will promote phosphorylation of CaMKII. (2) Concurrently, activation of NMDA receptors increases the influx of Ca^{2+} into the cell that activates through the Ca^{2+}/calmodulin complex the CaM kinases (II and IV) and also the protein phosphatase 2B (PP2B) calcineurin. Calcineurin is able to dephosphorylate DARPP-32 which then promotes dephosphorylation through a disinhibition of PP1. (3) PKA also phosphorylates CREB, switching this transcription factor from its inactive to its active state. Conversely, PP1 specifically dephosphorylates CREB. The control of PP1 through DARPP-32, a key regulator of DA transmission and NMDA receptors activity, is likely to have a significant effect on the DA regulation of LTP.

both a PKA and Ca^{2+}-dependent mechanisms (Wang and O'Donnell, 2001).

We therefore suggest a cooperative action of D1 and NMDA receptors in the mechanisms of LTP that would induce accumulation of cAMP and activation of PKA (Fig. 1). Since PKA activation can only proceed when cAMP is elevated above a threshold concentration, whether or not D1 activation participates in the induction of LTP could explain the differences in LTP mechanisms regarding the involvement of PKA in the early phase. On the other hand, a cooperative action of D2 and NMDA receptors in LTP induction would decrease the amount of cAMP, and either attenuates the implication of PKA in certain regions for LTP or favors the induction of LTD instead of LTP. PKA is one of the numerous protein kinases implicated in the triggering of LTP that modulates glutamate receptor function by phosphorylation of specific AMPA receptor subunits. It was recently shown that LTP induction increases phosphorylation of the major PKA site of the AMPA receptor GluR1 subunit, whereas LTD induction dephosphorylates this site (Lee et al., 2000). If the recruitment of these different signal-transduction pathways depends on the synaptic history, then the phosphorylation and dephosphorylation of AMPA receptors will be influenced by the amount of DA and D1 receptors present in the synapse. This hypothesis coincides with recent data indicating that PKA-mediated phosphorylation plays a pivotal role in regulating in vivo D1 receptor binding (Abe et al., 2002). Furthermore, we know that D1 receptors require DA and cAMP-regulated phosphoprotein (DARPP-32) to mediate their action. DARPP-32 activation occurs through the cascade involving cAMP/PKA, and once phosphorylated by PKA it is a potent inhibitor of the protein phosphatase 1 (PP1) (Hemmings et al., 1984). Conversely, PP1 can be activated by the calcium/calmodulin-dependent phosphatase calcineurin, activated by calcium influx through NMDA receptors. Calcineurin dephosphorylates DARPP-32 and then through inactivation of DARPP-32 blocks the inhibition of PP1. On the other hand, CaMKII, a key enzyme in LTP is a substrate for PP1 and the inhibition of PP1 seems to promote the activation of CaMKII (Blitzer et al., 1998). Thus,

the control of PP1 through DARPP-32, a key regulator of DA transmission, is likely to have a significant effect on the regulation of the synaptic strength of plasticity. In addition, DA through D1 receptors is also able to control the rate of phosphorylation/dephosphorylation of the NR1 subunit that is required for a functional NMDA receptor, and these mechanisms occur through the DA/D1/PKA/DARPP-32/PP1 pathway (Snyder et al., 1998). In contrast, D2 receptors are able to block the D1 receptor-mediated increase in NR1 phosphorylation.

The importance of the second messenger Ca^{2+} has also been questioned in the DA modulation of synaptic plasticity. A rise in post-synaptic Ca^{2+} appears necessary for triggering the D1/D5-induced effect in the hippocampus, although the source of Ca^{2+} is still unclear (Yang, 2000). It could result from voltage-gated Ca^{2+} channels and from Ca^{2+} entry through the NMDA or Ca^{2+} permeable AMPA receptor (Surmeier et al., 1995). It has also been reported recently that D1 receptor stimulation releases Ca^{2+} from intracellular stores in cultured neocortical neurons (Lezcano and Bergson, 2002) and that calcyon, a 24 kDa protein localized on cells expressing D1 receptors could confer the ability to stimulate intracellular Ca^{2+} release by potentiating a crosstalk between Gs- and Gq-coupled receptors (Lezcano et al., 2000). The initiation of a Ca^{2+}-dependent signaling cascade involves PKA and CaMKII, two critical mediators of NMDA receptor-dependent LTPs. In principle, changes in intracellular Ca^{2+} can have profound effects on cellular concentrations of cAMP if appropriate isoforms of adenylyl cyclase are present. Thus, DA receptors could integrate multiple signals to produce maximal cAMP signals that play a critical role in LTPs. PKA activity could serve as a gate for synaptic plasticity by modulating calmodulin-dependent protein kinase II (CaMKII) through the PP1, the phosphatase that primarily regulates LTP expression (Blitzer et al., 1998). Therefore, DA could play a significant role in the dynamic balance between kinase and phosphatase activities necessary to set the synaptic strength (Lisman and Zhabotinsky, 2001).

Furthermore, PKA stimulates the transcription of a number of genes by catalyzing the phosphorylation of the cAMP regulatory element binding protein (CREB), and PP1 retains the ability of CREB to stimulate transcription. Here is another step where, DA receptors could control the kinetics and duration of phosphorylation of CREB through the PKA/PP1 signaling complex. DA as a critical regulator of CRE-mediated gene expression has already been shown in striatal neurons (Konradi et al., 1996; Liu and Graybiel, 1996). Given the role of the transcription factor CREB in long-lasting forms of synaptic plasticity, these interactions could explain the strong impact of DA through D1 receptors on the duration of LTP. Understanding the transcriptional regulation of CREB and its requirement for long-term changes in synaptic plasticity will help to characterize the transcriptional response to DA.

3. Interaction of dopaminergic systems with memory processes

Different approaches from unit recording to lesion and pharmacological studies have demonstrated that DA plays a critical role in the modulation of neuronal activities that are related to different forms of learning and memory. It is beyond the scope of this review to summarize the effects of DA on all types of memory. Rather, major studies dealing with local prefrontal, hippocampal or striatal DA systems and different forms of memories will be summarized and compared to DA modulation of synaptic plasticity in each of these structures.

3.1. Hippocampal dopaminergic systems

Compared to other DA systems, the involvement of hippocampal DA systems with memory has not been investigated much. Neurotoxic lesion of mesohippocampal DA neurons following bilateral injection of 6-OHDA in the dorsal and ventral hippocampus in rats impair the retention of spatial information in the Morris water maze but not the retention of a classical inhibitory avoidance test (Gasbarri et al., 1996). Additional support comes from pharmacological manipulation of hippocampal DA receptors, which showed that intrahippocampal injection of D1 and D2 agonists improves spatial working memory in the win-shift eight-arm radial maze (Packard and White, 1991). Since most hippocampal DA systems are located in the ventral part of the hippocampus (Verney et al., 1985; Gasbarri et al., 1994), Wilkerson and Levin (1999) have measured the effects of D1 and D2 agonists and antagonists on spatial working memory when these compounds were injected locally in this region. While no significant effects of the D1 agonist and antagonists were observed, hippocampal D2 activity appears to be positively related to the performance of the animals, with an improvement in quinpirole-treated rats (D2 agonist), and an impaired choice accuracy with the D2 antagonist raclopride. More recently, an impairment in memory performance mediated by D2 receptors in the ventral hippocampus has also been observed in a more complex learning task using an aversive motivated T-maze instead of an appetitive motivated maze as in the previous studies (Umegaki et al., 2001). Together these results suggest that hippocampal DA systems interact with memory, but the mnemonic role of DA identified in the ventral part of the hippocampus still remains to be explored in the dorsal hippocampus. In view of the recent identification of the D5 receptor as the predominant D1-like receptor in the hippocampus (Ciliax et al., 2000), it would be of interest to explore the impact of hippocampal D5 and not D1 receptor subtype on memory processes. A further characterization of hippocampal DA systems with memory function should help in comparing data on DA regulation of the persistence of LTP in the dorsal CA1 region. Indeed, most of the LTPs induced in the hippocampus are recorded in the dorsal and not the ven-

tral part. As a consequence, the contribution of DA and DA receptors has only been explored in the dorsal region of the hippocampus.

3.2. Striatal dopaminergic systems

Cognitive impairment shown in advanced Parkinson's disease demonstrates the interference of DA depletion in the striatum with both motor activity and learning processes. Searching for models to study memory disabilities related to Parkinson's disease, some studies have used the DA neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) that causes a specific loss of DA and its metabolites in the dorsal striatum and in the prefrontal cortex but not in the hippocampus or the ventral striatum (nucleus accumbens). Although there are some inconsistencies in the different studies, MPTP administration in monkeys resulted in deficits in performance of variable delayed response tasks (delay matching-to-sample, delayed alternation tasks) and in a classical conditioning task (Roeltgen and Schneider, 1994; Aosaki et al., 1994). Attentional deficits, task impersistence and impairment in the cognitive component of object retrieval were also described in these animals (Schneider and Pope-Coleman, 1995). The significance of these results is that in this Parkinsonian model, most of the cognitive deficits appear to precede measurable motor deficits tasks, and a significant improvement is observed with levodopa therapy (Schneider and Pope-Coleman, 1995; Fernandez-Ruiz et al., 1999). Memories disabilities are also present in the rat model of Parkinson's disease (Da Cunha et al., 2002). These animals (MPTP-treated rats) present learning and memory deficits that affect habit learning (the cued version of the water maze task and the two-way avoidance task) and working memory (a working memory version of the water maze) but long-term spatial memory is preserved (Da Cunha et al., 2001; Miyoshi et al., 2002). Therefore, the importance of the striatum for habit learning as stressed by Packard and McGaugh (1992) appears to depend on the DA nigrostriatal pathway, supporting their later findings (Setlow and McGaugh, 2000) showing that a D2 antagonist impairs the performance of another animal model of habit learning, the cued version of the water maze. MPTP-treated rats are also impaired in spatial working memory. Whether these deficits in working memory performance are related to the depletion of DA in the nigrostriatal pathway or in the prefrontal cortex that would then alter the mesocortical and corticostriatal transmission remains to be determined. Intracerebral administration of 6-OHDA to rats has also been widely used to produce a nigrostriatal DA depletion, but this procedure is known to also cause depletion of norepinephrine (NA) and 5-HT. Therefore, the MPTP-lesioned rats appear to be more appropriate to study memory impairments related to lesion of the DA nigrostriatal pathway.

Using the MPTP model in rats, it would be worthwhile to examine if cortico-striatal synapses still develop long-term plastic changes. These experiments could clarify the diversity of results obtained on the plastic properties that corticostriatal synapses express in DA-depleted rats, but also provide key information on the implication of the nigrostriatal DA system and associated striatofrontal neuronal circuits in memory impairment associated with Parkinson's disease (Pillon et al., 1998).

3.3. Prefrontal dopaminergic systems

Converging evidence indicates that DA innervation of the prefrontal cortex plays a major role in working memory, a form of memory that allows to maintain and manipulate active representations of information that are held temporarily in mind. DA loss in the prefrontal cortex can lead to a great deficit in the performance of a working memory task in monkeys (Brozoski et al., 1979) as does lesion of the VTA in the rat (Simon et al., 1980). These neurotoxic lesions of DA neurons that were affecting DA but also NA in the prefrontal cortex were later sharpened up with combined electrophysiological and pharmacological experiments using specific antagonists. D1 receptors were thus identified as main regulators of working memory in monkeys (Sawaguchi and Goldman-Rakic, 1991). Subsequently, Williams and Goldman-Rakic (1995) and Murphy et al. (1996) found that even though DA is essential for the maintenance of internal visuospatial representations, excessive release of DA or supranormal stimulation of D1 receptors within the prefrontal cortex will impair working memory performance. The detrimental effects of DA have also been found in rats (Zahrt et al., 1997). Therefore, insufficient DA or D1 receptor stimulation, as well as excessive DA or D1 receptor stimulation impairs prefrontal cortex cognitive function, whereas normal levels of DA or D1 receptor activation have a beneficial influence. This inverted U dose–response curve for DA and D1 receptors fits well with electrophysiological studies of pyramidal cells in the prefrontal cortex of rats, where DA or D1 receptors modulate dendritic-somatic signal integration (Yang and Seamans, 1996). Our electrophysiological data are also in agreement with these dose-dependent effects: an overstimulation of D1 receptors disrupts the facilitatory effects of DA on synaptic plasticity at hippocampal to prefrontal cortex synapses (Gurden et al., 2000) and an intact mesocortical DA input to the prefrontal cortex is necessary for LTP to occur at these synapses (Gurden et al., 1999). In addition, the hippocampal input to the prefrontal cortex which is an important target of DA modulation was recently shown to be involved in working memory processes (Floresco et al., 1997) and D1 receptor modulation of those circuits appears critical for the performance of the animals in the spatial delayed task (Seamans et al., 1998). Certainly, the NMDA-based LTP at hippocampal-prefrontal cortex synapses provides a useful model for further investigation of prefrontal long-term plasticity in working memory processes and the contribution of mesoprefrontal DA neurons.

DA systems are also involved in the processing of information related to rewards (Robbins and Everitt, 1996). In the VTA and substantia nigra, DA neurons are able to track the reward prediction error and emit a signal that has the typical characteristics of a positive reinforcing signal for learning (Hollerman and Schultz, 1998; Waelti et al., 2001). Although considered as global neuromodulatory systems, DA systems are capable to deliver precisely timed information to specific targets structures to influence a number of cognitive functions. As recently suggested by Schultz (2002) (see review), the DA signal progresses by a very rapid and brief firing, through a wave of activity to the prefrontal cortex and striatum, and creates and/or "fixes" the plasticity of ongoing glutamatergic activity. The modification occurs only when the DA signal is active at about the same time as the cortical glutamatergic input.

3.4. Influence of dopamine in memory processes: cellular mechanisms

Specific intracellular signaling cascades are implicated in LTP and the scheme represented in Fig. 1 illustrates DA as a key regulator. If we assume that LTP is a candidate for cellular information storage, DA should facilitate this memory process and as reported just above, different studies illustrate this function of DA. However, only a few behavioral studies have explored the mechanisms underlying DA involvement in memory function. One study has shown that activation of the cAMP/PKA signaling pathways by DA acting at D1 receptors in the frontal cortex is necessary for working memory (Aujla and Beninger, 2001). The approach used by the authors involved the disconnection procedure reported previously (Seamans et al., 1998), where performance in working memory retrieval is impaired after coadministration of lidocaine unilaterally in the ventral hippocampus and lidocaine or a D1 antagonist in the contralateral prefrontal cortex. Replicating these experiments, Aujla and Beninger have replaced the D1 antagonist by the specific inhibitor of PKA, Rp-adenosine 3′,5′-cyclic monophosphorothioate triethylamine (Rp-cAMPS) and shown that rats were selectively impaired in the delayed task performance. Similar injection of Rp-cAMPS in the prefrontal cortex have also been shown to disrupt LTP at hippocampal to prefrontal cortex synapses (Gurden et al., 2000), a pathway directly related to the spatial delayed task used by Aujila and Beninger (Floresco et al., 1997). These two sets of experiments with behavioral and electrophysiological data provide evidence of a link between working memory retrieval and prefrontal synaptic changes with the cAMP/PKA pathway.

Pharmacological inhibition of PKA in the CA1 region of the hippocampus has been implicated in long-term memory. The late phase of memory consolidation of an inhibitory avoidance is modulated by the cAMP/PKA pathways in the hippocampus (Bernabeu et al., 1997; Vianna et al., 1999) and rats showed learning specific increase in hippocampal D1 binding 3 and 6 h after training. Genetic inhibition of PKA also disrupt hippocampal-based long-term memory (Abel et al., 1997; Bourtchouladze et al., 1998) and these behavioral deficits in spatial memory and in long-term but not short-term memory for contextual fear conditioning are paralleled by deficits in the late phase of LTP in the CA1 region.

Other experiments using infusion of the PKA inhibitor Rp-cAMPS in the nucleus accumbens have also shown the involvement of the cAMP/PKA pathway in reward-related incentive learning and in instrumental learning (Baldwin et al., 2002a), two forms of learning strongly dependent on D1 receptors (Beninger and Miller, 1998; Baldwin et al., 2002b).

Taken together, these recent advances in the molecular processes of DA-mediated learning suggest that similar mechanisms underlie DA regulation of synaptic plasticity and memory processes. The next step is to identify proteins or specific genes that may be involved in these D1/cAMP/PKA signaling pathways downstream of PKA activation.

4. Interaction of dopamine and glutamate systems on local circuits

The existing data show an heterogeneous action of DA in the different structures examined and controversies still remain on this topic. However, DA receptor activation appears to be important in expressing either LTP and/or LTD in all regions examined. To understand the cellular basis of the interactions of DA and glutamate systems during these different forms of plasticity, it will be important to learn which specific cells and which specific receptors are the targets of DA terminals and how these cells influence the intrinsic and extrinsic circuits.

It would be beyond the scope of this review to include the electrophysiological complex actions of DA at the cellular level, which have been covered by appropriate reviews in each structure examined (Yang et al., 1999; Nicola et al., 2000; Tzschentke, 2001). DA can depolarize or hyperpolarize individual targets cells (principal cells and interneurons) but in vivo and in vitro characterizations have been controversial for more than two decades. A number of studies have reported excitatory or inhibitory effects on the same cells in different structures examined while some other studies failed to see either effect. The nature of DA modulation could depend on the glutamate receptor subtype involved: as mentioned earlier, DA may enhance NMDA receptor-mediated responses and decrease non-NMDA receptor-mediated responses (Levine et al., 1996) so the action of DA might be determined by the ratio of NMDA versus non-NMDA components in the transmission. However, the picture is not so simple. Otmakhova and Lisman (1999) have shown that DA reduces both the NMDA and AMPA components of transmission in the perforant path input to CA1.

Attempts to identify the membrane currents modified by DA have shown a modulation of voltage-gated Ca^{2+}

currents and of slowly inactivating Na^+ and K^+ currents of post-synaptic neurons that can profoundly affect their firing threshold. These currents modulate the membrane potential and we know that the effects of DA depend on the history of the membrane potential. Medium spiny neurons in the striatum/nucleus accumbens and pyramidal cells in the prefrontal cortex show in vivo membrane potential shifts between a negative down state and a depolarized up state (Wilson, 1993; O'Donnell and Grace, 1995; Lewis and O'Donnell, 2000) and it was recently shown that DA modulates the stabilization of neurons in an up state (depolarization) through D1 receptors in the prefrontal cortex and a similar effect of DA was observed in the nucleus accumbens (Lewis and O'Donnell, 2000; Goto and O'Donnell, 2001). Thus, during tetanic stimulation of glutamate afferents to the neurons where LTP is induced, DA could maintain those neurons to a depolarization level and facilitate the induction of LTP. Furthermore, as suggested by the authors, these fluctuations in membrane potential states with the up state bringing the cell to fire, could have a strong impact at the behavioral level in the definition of a distributed set of neurons where DA would be the controller and its role essential for driving DA-related behaviors.

Ultrastructural studies in the different structures examined have found that DA terminals form symmetric synapses on spines and shafts of dendrites from pyramidal cells or medium spiny neurons and these spines are also innervated by a glutamatergic terminal (synaptic triad). Therefore, DA can directly modulate the excitability of dendrites at the post-synaptic level by modulating the response to activation of glutamatergic receptors located on post-synaptic neurons. The preferential localization of D1 receptors to the spines and shafts of pyramidal cells or medium spiny neurons supports post-synaptic mechanisms for a potential role of D1 receptors in synaptic plasticity and memory processes. However, in monkeys prefrontal cortex, D1 receptors are also found on GABAergic interneurons and preferentially on those subtypes of interneurons that provide an inhibitory input on pyramidal cells (Muly et al., 1998) suggesting also a presynaptic mechanism for the DA modulation of excitatory transmission. In support of these observations, Gao et al. (2003) have recently shown that interneurons that target the perisomatic domain of pyramidal cells in the cerebral cortex are inhibited by DA through a presynaptic D1-mechanism whereas interneurons targeting more distal dendrites are enhanced but not depressed by DA. From this complex interplay of DA at D1 receptors in pyramidal versus non-pyramidal cells in the prefrontal cortex, the authors have elaborated a model that explains the relationship between D1 receptor stimulation and working memory performance where a high level of DA that enhances the glutamatergic inputs to both pyramidal cells and interneurons induces a depression of pyramidal cell activity by feed forward inhibition and an impairment of working memory function (Goldman-Rakic et al., 2000). Together these data emphasize a crucial role of DA and D1 receptors in the surrounding extrinsic (afferent input) and intrinsic (local) circuitry that may have a functional significance in plasticity and memory processes.

5. Conclusion

Synaptic plasticity induced in the different regions examined (hippocampus, striatum and prefrontal cortex) does not appear to recruit the DA systems in similar manners. It is conceivable that a local regulation of these plastic events is specific to the region where the synapses are activated. Although a comparable DA modulation appears to be present in the hippocampus and the prefrontal cortex, only the consolidation of LTP in the hippocampus is dependent on D1 receptors whereas a potential permissive and facilitatory effect of DA and D1 agonists is observed at an early stage of LTP and required for the initiation of this plastic event in the prefrontal cortex.

On top of a different subcellular DA innervation and spatial distribution of D1 and D5 receptors in the two regions that could explain these discrepancies, a distinct temporal combination between the glutamate and the modulatory DA pathways might also be at the origin, for functional purposes, of the immediate versus delayed recruitment of DA systems. Indeed, DA neurons are differentially activated depending on cognitive demands. Thus, the heterosynaptic influence of the DA signal could gain its selectivity from the activity patterns that are initiated in the VTA during changes in behavioral states and that are present in the DA inputs to the post-synaptic sites in the hippocampus or the prefrontal cortex. Whether the mesohippocampal or mesocortical DA systems are involved in different memory processes would differentially alter the relative strength of the synapses in the two regions. This mode of synaptic plasticity and modulation by a DA tone demonstrates a dynamic and specific regulation of synapses that may be important for memory.

The future will define more precisely at the cellular level which specific target cells of DA terminals and which receptors influence intrinsic and extrinsic circuits and at the molecular level which proteins are specifically involved in these DA/glutamate interactions relevant to plasticity and memory processes. Increased understanding of these mechanisms may also be relevant to the pathophysiology of DA-related psychiatric disorders.

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