Dopaminergic Modulation of Long-term Synaptic Plasticity in Rat Prefrontal Neurons

In rat prefrontal cortex (the prelimbic area of medial frontal cortex), the induction of long-term depression (LTD) and long-term potentiation (LTP) of glutamatergic synapses is powerfully modulated by dopamine. The presence of dopamine in the bathing medium facilitates LTD in slice preparations, whereas in the anesthetized intact brain, dopamine released from dopaminergic axon terminals in the prefrontal cortex facilitates LTP. Dopaminergic facilitation of LTD is at least partly achieved by postsynaptic biochemical mechanisms in which enzymatic processes triggered by dopamine receptor activation cooperate with those triggered by glutamate metabotropic receptor activation. Evidence suggests that dopamine facilitates LTP also in the slice condition. In this case, dopamine receptors must be pre-stimulated (‘primed’) before the application of high-frequency stimuli in the presence of dopamine. This procedure may mimic baseline stimulation of dopamine receptors that occurs under physiological conditions.

Dopamine Modulates Glutamatergic Transmission in the Prefrontal Cortex

Dopamine plays important roles in the function of primate prefrontal cortex (PFC) (Sawaguchi and Goldman-Rakic, 1991, 1994; Goldman-Rakic, 1995; William and Goldman-Rakic, 1995) and the rodent medial frontal cortex (Glowinski et al., 1984), which is believed by many to be the functional counterpart of primate dorsal/lateral prefrontal cortex (particularly the prelimbic area of the medial frontal cortex) (Floresco et al., 1997; Zahrt et al., 1997; Birrell and Brown, 2000). In monkeys, interruption of dopaminergic transmission in dorsolateral PFC by focal D1 antagonist application impairs spatial working memory (Sawaguchi and Goldman-Rakic, 1991, 1994) and exaggerates or inhibits (depending on the dose) the delay period activity of PFC neurons during the working memory task (William and Goldman-Rakic, 1995). Dopamine neurons in substantia nigra and ventral tegmental area (VTA) show increases of firing in response to salient or appetitive stimuli (Ljungberg et al., 1992; Mirenowicz and Schultz, 1996) or to conditioned stimuli predicting reward (Schultz et al., 1993). In the latter case (Schultz et al., 1993), one of the task phases in which the dopamine neurons showed the increases is actually a delay period of a spatial task. These results therefore raise the possibility that at least in certain behavioral phases, a phasic dopamine release coincides with the activity of PFC neurons to tune neuronal transmission at these neurons. Similarly in rats, normal working memory requires optimal levels of dopamine in the prelimbic area (i.e. rat PFC) (Zahrt et al., 1997; Mizoguchi et al., 2000), and some VTA neurons and PFC deep layer neurons were shown to increase their activity at the same behavioral phases in an appetitive operant task (Kosobud et al., 1994).

Modulation of PFC glutamatergic transmission by dopamine has been studied at the cellular level. For example, it was shown that at least D1 subtype of dopamine receptors co-localize with glutamate receptors on dendritic spines and shafts of pyramidal neurons in monkey frontal layers II and V (Smiley et al., 1994; Bergson et al., 1995). Electrophysiologically, the D1 agonist was shown to reduce excitatory transmission in collateral synapses between a pair of layer V pyramidal neurons (Gao et al., 2001). Pyramidal neuron collateral transmission is believed to participate in the generation of the sustained delay period activity (Goldman-Rakic, 1995). Interestingly, collateral transmission between layer III pyramidal neurons in monkey PFC slices was unaffected by dopamine (Urban et al., 2002), while dopamine reduced excitatory transmission in the presumably projection fiber synapses on the same neurons (Urban et al., 2002). In rat PFC slices, dopamine inhibits glutamatergic transmission at layer V pyramidal neurons after stimulation of the superficial (Law-Tho et al., 1994, 1995; Otani et al., 1998, 1999) or deep layer fibers (Law-Tho et al., 1994). The deep layer afferents probably contain projection fibers from the hippocampus (Jay and Witter, 1991), which is involved in working memory (Floresco et al., 1997) and schizophrenia pathogenesis (Lipska and Weinberger, 2002). Several in vivo studies confirm that the synaptic transmission in the hippocampo-PFC monosynaptic connection is inhibited by dopamine (Jay et al., 1995b; Gurden et al., 1999; Floresco and Grace, 2003).

Lasting Neural Traces in the PFC

The above results suggest that a dopamine action in the PFC is tuning or stabilization of ongoing glutamatergic transmission to regulate online information processing. However, the other well-known cellular effect of dopamine in the PFC is its powerful modulation on the induction of long-term plasticity in glutamatergic synapses. This effect is as important, because the PFC appears to be involved not only in online processes but also in the formation of long-term memory. For example, a transient disturbance of PFC function by transcranial magnetic stimulation impairs the formation of episodic long-term memory in humans (Rossi et al., 2001, 2003). At cellular levels, the early study in monkeys (Fuster, 1973) remarked that sustained activity of PFC neurons as seen in trained animals does not occur in the animals untrained in the delayed-response paradigm. Also in monkeys, it was shown that during the progress of an associative learning, the response-related PFC activity appeared progressively earlier in a trial (Assad et al., 1998), indicating an underlying plastic process. In rats, learning in an operant discrimination task was accompanied by persistent increases or decreases in PFC neuron activity (Mulder et al., 2000). In mice, the persistence of the memory for conditioned fear and its successful extinction were nicely correlated with a lasting decrease and increase in the thalamo-PFC synaptic responses, respectively (Herry and Garcia, 2002). Based on these and other...
Pioneering Works

Pioneering in vitro studies on LTP and LTD in rat PFC (Hirsch and Crepel, 1990, 1991, 1992) showed that the application of 50 or 100 Hz tetanic stimuli to layer II afferent fibers in the presence of γ-aminobutyric acid A (GABA-A) antagonist bicuculline induce LTP or LTD of monosynaptic glutamatergic responses in the portion of layer V pyramidal neurons. Both LTP and LTD are dependent on postsynaptic Ca²⁺ increases (Hirsch and Crepel, 1992). For LTP, but not LTD, at least part of the critical Ca²⁺ enter through NMDA (N-methyl-D-aspartate) receptor-linked ion channels, because the NMDA receptor antagonist AP5 (2,3-amino-5-phosphonopentanoic acid) selectively blocks LTP and unmaskss underlying LTD (Hirsch and Crepel, 1991).

NMDA receptor-dependency of LTD was also shown by Vickery et al. (1997) in the identical preparation. In this case, they applied stimuli mimicking hippocampal theta burst (four shocks at 100 Hz, repeated 10 times in every 200 ms) and showed LTD induction in ~60% of the neurons tested. AP5 significantly reduced this LTD. It is known that in hippocampal neurons, the short burst (four shocks) ‘primes’ the stimulated dendrites so that a successive burst arriving 200 ms later optimally activates the voltage-dependent NMDA receptor-channel complex (Larson and Lynch, 1988). Thus, the 10 times repetitive applications of the burst (Vickery et al., 1997) should strongly activate NMDA receptors to induce LTP.

Anatomically, there is a monosynaptic projection from ventral CA1/subiculum to the prelimbic area in the rat (Jay and Witter, 1991). Therefore, theta-patterned discharge of hippocampal neurons may excite synaptic inputs to induce NMDA-dependent LTD under, for example, exploratory behavioral conditions (O’Keefe and Nadel, 1978). Although the effect of theta burst stimuli to the hippocamp-PFC synapses has not been tested, LTP in this connection was induced by brief 250 Hz tetanic stimuli (Laroche et al., 1995a). AP5 signif-

Dopaminergic Facilitation of Prefrontal LTD

As discussed above, application of tetanic stimuli (50 or 100 Hz) induced LTD or LTD in the layer I-II to layer V pyramidal neuron glutamatergic synapses in rat PFC slices (Hirsch and Crepel, 1990, 1991, 1992). Law-Tho et al. (1995) found that the presence of dopamine (50–100 µM) in the bathing medium during tetanic stimuli facilitates LTD and inhibits LTP. Dopamine application alone only transiently depressed the synaptic responses. Subsequent studies (Otani et al., 1998, 1999) fixed the train parameter as 50 Hz, 2 s (four times at 0.1 Hz), and showed that while the tetanic stimuli alone do not induce lasting plasticity, application of the stimuli in the presence of dopamine consistently induces LTD (Fig. 1). Dopamine acts through both D1 and D2 dopamine receptors for the induction of this LTD (Otani et al., 1998). The dopamine-facilitated LTD does not require NMDA receptors but requires postsynaptic depolarization and postsynaptic Ca²⁺ increases (Otani et al., 1998), consistent with the earlier studies (Hirsch and Crepel, 1991, 1992).

Mechanisms of Dopamine-facilitated LTD

Enhancement of Postsynaptic Excitability by Dopamine

It was shown that dopamine enhances late postsynaptic depolarization during the LTD-inducing 50 Hz stimuli while it reduces postsynaptic responses evoked by low-frequency stimuli (Otani et al., 1998; Otani and Kolomiets, 2003). Dopamine also increases the number of spikes upon depolarizing current injection (Penit-Soria et al., 1987; Yang and Seamans, 1996) through D1 receptor activation (Yang and Seamans, 1996). Underlying mechanisms of this effect may be the enhancement of tetrodotoxin-sensitive slowly-inactivating persistent Na⁺ current (I_{NAP}) and the attenuation of slowly inactivating, outwardly rectifying K⁺ current (Yang and Seamans, 1996). Dopamine action on the I_{NAP} may require protein kinase C (PKC) (Goerlova and Yang, 2000).

Despite these data, however, it is still unclear whether the enhancement of postsynaptic excitability by dopamine is necessary for LTD induction in deep layer pyramidal neurons of the PFC. First, there are contradictions in the literature. Geijo-Barrientos and Pastore (1995) found a reduction of the I_{NAP} by dopamine in layer II-VI regular spiking neurons. Gulledge and Jaffe (1998) found a reduction in the number of spikes in layer V pyramidal neurons by D2 receptors. Maurice et al. (2001) found no effect of dopamine on the I_{NAP} in acutely dissociated PFC pyramidal neurons. These results are rather consistent to dopamine effects found in striatal medium spiny neurons (Nicola et al., 2000) (see Concluding Remarks for more discussion). Secondly, more importantly, our recent analysis showed that the dopaminergic enhancement of postsynaptic depolarization during 50 Hz tetanus is blocked by NMDA antagonist AP5 (Otani and Kolomiets, 2003; see also Wang and O’Donnell, 2001), but LTD is inducible in the presence of AP5 (Otani et al., 1998). Thus, the enhancement of depolarization by dopamine during tetanus appears unnecessary for LTD, although it is possible that depolarization enhancement in local dendritic sites was not adequately monitored by somatic electrodes.

But, the NMDA-dependent enhancement of postsynaptic depolarization by dopamine may play roles in online information processing. Recent modeling studies (Durstewitz et al., 2000; Brunel and Wang, 2001) suggest that an increase in NMDA-mediated conductance by dopamine is a major factor to cause the enhancement of signal-to-noise ratio and the stabilization of sustained high-frequency collateral activity during delay period of working memory tasks.

Cooperativity between Dopamine Receptors and mGluRs

Blockade of group I or group II mGluRs during tetanus blocked dopamine-facilitated LTD (Otani et al., 1999). This result suggests that the dopamine receptors and the groups I and II mGluRs cooperate for LTD induction in the PFC. The following lines of evidence showed that this cooperativity involves postsynaptic converging activation of MAP-Ks (mitogen-activated protein kinases) (Valjent et al., 2000) (see Concluding Remarks for more discussion). Firstly, more importantly, our recent analysis showed that the dopaminergic enhancement of postsynaptic depolarization during 50 Hz tetanus is blocked by NMDA antagonist AP5 (Otani and Kolomiets, 2003; see also Wang and O’Donnell, 2001), but LTD is inducible in the presence of AP5 (Otani et al., 1998). Thus, the enhancement of depolarization by dopamine during tetanus appears unnecessary for LTD, although it is possible that depolarization enhancement in local dendritic sites was not adequately monitored by somatic electrodes.

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Fourthly, combined application of dopamine and one of these mGluR agonists synergistically or additively activated MAP-Ks (Otani et al., 1999). Although critical target(s) of the MAP-Ks for LTD induction is still unknown, a study in the hippocampus suggested a link between MAP-Ks and the modification of dendritic spine shape (Wu et al., 2001). Also in the hippocampus, MAP-Ks are necessary for the phosphorylation of CREB (cyclic AMP response element-binding protein) by PKC and protein kinase A (PKA) (Roberson et al., 1999), confirming the importance of the MAP-Ks as a mediator for long-term cellular changes (Valjent et al., 2001; Fig. 2A).

**Dopaminergic Facilitation of Prefrontal LTP**

In Vivo Studies

Gurden et al. (1999) tested the effect of VTA stimulation on LTP of the hippocampo-PFC monosynaptic projection (Jay and Witter, 1991) in anesthetized rats. First, single VTA stimulation just before a test pulse delivery to the ventral CA1/subiculum reversibly depressed the hippocampo-PFC synaptic responses, consistent with the observation made in vitro that bath-applied dopamine transiently depresses PFC synaptic responses (Law-Tho et al., 1995; Otani et al., 1998, 1999). Second, application of 50 Hz 2 sec stimuli to the VTA 2 sec before 250 Hz tetanus to the ventral CA1/subiculum enhanced LTP induced by the 250 Hz tetanus. Third, VTA lesion reduced the magnitude of LTP induced by the 250 Hz tetanus. Gurden et al. (2000) subsequently showed that the hippocampal stimulation evokes dopamine release in the PFC. In terms of the mechanism, it was shown that dopamine stimulates PKA through D1 receptors to facilitate LTP (Gurden et al., 2000). Because LTP in the PFC requires NMDA receptors (Hirsch and Crepel, 1991; Jay et al., 1995a), D1 receptors and NMDA receptors may cooperate in LTP-inducing mechanisms (see Fig. 2B). Interestingly, Baldwin et al. (2002) showed that normal acquisition of appetitive operant conditioning in the rat requires D1 receptors, NMDA receptors, and PKA in the PFC. This agreement at the cellular level supports the idea that LTP-like processes in the PFC may be

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**Figure 1.** Dopaminergic facilitation of LTD induction in rat PFC (prefrontal) neurons in vitro. (A) Layer V pyramidal neurons of the prelimbic area in coronal slices were penetrated by a sharp micro pipette, and glutamatergic synaptic responses evoked by layer I–II stimulation were recorded. Slope analysis was applied to the initial rising phase (<1 ms from onset), which is monosynaptic component (Hirsch and Crepel, 1990). (B) Application of tetanic stimuli (50 Hz, 2 s, repeated four times in every 10 s) does not itself induce long-lasting synaptic changes. (C) Bath-application of dopamine (100 µM for 10–15 min) induces a transient inhibition of synaptic responses which recovers within 30 min. (D) Combination of the tetanic stimuli and the bath-application of dopamine induces LTD. The synaptic responses taken from the baseline period (1) and 40 min after the coupling (2) are shown in the inset. Adapted from figure 1 of Otani et al. (1999) with permission.
**A. Possible LTD mechanism**

**B. Possible LTP mechanism**

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**Figure 2.** Schematic drawings showing possible postsynaptic mechanisms underlying LTD and LTP in the rat PFC neurons. (A) Possible mechanism for LTD. When dopamine receptors are in unstimulated (‘non-primed’) state, they are in normal slice conditions, dopamine receptor activation combined with identical tetanic stimuli induces LTD, not LTP. We tentatively call the hypothetical dopamine-induced LTD ‘metaplastic’ effects (Abraham and Bear, 1996). In this regard, Seamans et al. (2001) showed that D1 receptor stimulation induces enhancement of NMDA receptor-mediated transmission in PFC layer V neurons that manifests slowly (note: this slow effect should be separated from the rapid inhibition of synaptic responses, dopamine lastingly changes cellular chemistry so that a delayed dopamine receptor activation combined with identical tetanic stimuli induces LTD, not LTD (Blond et al., 2002; Fig. 3). Furthermore, unlike the first application, the second application of dopamine does not enhance postsynaptic depolarization during tetanic stimuli (Otani and Kolomiets, 2003). These results suggest the possibility that although the inhibition of glutamatergic synaptic responses by the first dopamine application is only transient (~30 min), the first dopamine lastingly changes cellular chemistry so that a delayed dopamine receptor activation combined with identical tetanic stimuli induces LTD, not LTD. We tentatively call the hypothetical lasting dopamine effects as ‘priming’ (e.g. Christie and Abraham, 1992) or ‘metaplastic’ (Abraham and Bear, 1996) effects (Fig. 2B). In this regard, Seamans et al. (2001) showed that D1 receptor stimulation induces enhancement of NMDA receptor-mediated transmission in PFC layer V neurons that manifests slowly (note: this slow effect should be separated from the rapid inhibition of NMDA transmission by dopamine, Law-Tho et al., 1994). Also, Gorelova and Yang (2000) showed that a D1 agonist lastingly decreases first spike latency in layer V neurons. These may be the dopamine-induced metaplastic effects, although it is the case, postsynaptic depolarization during tetanus in the presence of the second dopamine is expected to be larger than that in the presence of the first unstimulated. By contrast, baseline stimulation of dopamine receptors occurs in the physiological situations, since dopamine levels in the PFC are tonically maintained (Takahata and Moghaddam, 2000) and show repeated increases during behavior (Bassareo and Di Chiara, 1997).

We attempted to partially control this factor by exposing the slices to bath-applied dopamine first (10–15 min; Blond et al., 2002; Fig. 3). When the synaptic responses recovered from the transient inhibitory effect of dopamine (in ~50 min), dopamine was identically applied for the second time. This second application was coupled to 50 Hz stimuli. This protocol induced LTD, not LTD (Blond et al., 2002; Fig. 3). The second application of dopamine was necessary for LTD induction (Blond et al., 2002). Still little is known about cellular mechanisms of this LTD. However, it was noted that the transient inhibition of the synaptic responses by the second application of dopamine is always smaller than that by the first application (Blond et al., 2002; Fig. 3). Furthermore, unlike the first application, the second application of dopamine does not enhance postsynaptic depolarization during tetanic stimuli (Otani and Kolomiets, 2003). These results suggest the possibility that although the inhibition of glutamatergic synaptic responses by the first dopamine application is only transient (~30 min), the first dopamine lastingly changes cellular chemistry so that a delayed dopamine receptor activation combined with identical tetanic stimuli induces LTD, not LTD. We tentatively call the hypothetical lasting dopamine effects as ‘priming’ (e.g. Christie and Abraham, 1992) or ‘metaplastic’ (Abraham and Bear, 1996) effects (Fig. 2B). In this regard, Seamans et al. (2001) showed that D1 receptor stimulation induces enhancement of NMDA receptor-mediated transmission in PFC layer V neurons that manifests slowly (note: this slow effect should be separated from the rapid inhibition of NMDA transmission by dopamine, Law-Tho et al., 1994). Also, Gorelova and Yang (2000) showed that a D1 agonist lastingly decreases first spike latency in layer V neurons. These may be the dopamine-induced metaplastic effects, although if it is the case, postsynaptic depolarization during tetanus in the presence of the second dopamine is expected to be larger than that in the presence of the first unstimulated. By contrast, baseline stimulation of dopamine receptors occurs in the physiological situations, since dopamine levels in the PFC are tonically maintained (Takahata and Moghaddam, 2000) and show repeated increases during behavior (Bassareo and Di Chiara, 1997).
dopamine. Our recent analysis suggests the contrary (Otani and Kolomiets, 2003).

Concluding Remarks
Dopaminergic modulation of the function of PFC neurons is still not clearly understood. The reason for the difficulty to pin down clear cellular effects of dopamine appears to be the anatomical, pharmacological, and biochemical diversities of dopamine actions. For example, dopamine has been reported to reduce ongoing glutamatergic transmission in collateral synapses between layer V pyramidal neurons (Gao et al., 2000) and the projection fiber synapses on layer III pyramidal neurons (Urban et al., 2002), but not in the collateral synapses between layer III pyramidal neurons (Urban et al., 2002). Furthermore, dopamine triggers lasting ‘metaplastic’ cellular processes. Therefore, depending on the time elapsed between the beginning of dopamine application and the electrophysiological test, the result may differ dramatically. This may be a main reason for the discrepancy seen in the literature of the dopamine effects on postsynaptic excitability in rat deep layer pyramidal neurons. Thus, one group (Yang and Seams, 1996; Gorelova and Yang, 2000) found enhancing effects of dopamine on the \( b_{\text{NaP}} \) and neuronal discharge by performing the electrophysiological tests after dopamine or a D1 agonist was washed out of the bath. The other groups (Geijo-Barrientos and Pastore, 1995; Gulledge and Jaffe, 1998) showed opposite results by testing dopamine effects during 1–2 min (Geijo-Barrientos and Pastore, 1995) or 5 min (Gulledge and Jaffe, 1998) bath-application of dopamine. Importantly in this respect, Gorelova and Yang (2000) found a biphasic action of D1 agonist SKF81297 on the first spike latency (their figure 8A3): i.e. an early increase (within 5 min after a brief agonist application) and a late lasting (>20 min) decrease (see also Gulledge and Jaffe, 2001). Taken together therefore, dopamine may indeed have complex actions on cellular excitability in deep layer pyramidal neurons; i.e. initial suppression through D1 and D2 receptors (Gulledge and Jaffe, 1998; Gorelova and Yang, 2000) and subsequent enhancement through D1 receptors (Gorelova and Yang, 2000).

In conclusion, in order to accurately assess short- and long-lasting cellular effects of dopamine in the PFC, anatomical identification of stimulated axons and neurons, and a good control over the application protocol and the pattern of VTA stimulation must be taken into consideration.

Notes
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