Mechanisms of Dopamine Activation of Fast-Spiking Interneurons That Exert Inhibition in Rat Prefrontal Cortex

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The prefrontal cortex (PFC) of primates and rodents receives mesocortical dopaminergic projection from the ventral tegmental area (VTA) of the midbrain (Björklund and Lindvall 1984; Lewis and Sesack 1997). Dopamine (DA) modulates PFC activity encoding working memory information necessary for the temporal organization of behavior (Goldman-Rakic 1995; Sawaguchi and Goldman-Rakic 1991, 1994; Seamans et al. 1998). The mesocortical dopaminergic fibers innervate pyramidal neurons (Goldman-Rakic et al. 1989; Verney et al. 1990) and interneurons (Benes et al. 1993; Sesack et al. 1995, 1998), which contain both D1 and D2 classes of DA receptors (Gaspar et al. 1995; Mrzljak et al. 1996; Muly et al. 1998; Smiley et al. 1994; Vincent et al. 1993, 1995). This suggests a direct DA action on pyramidal neurons and indirect effects via modulation of interneurons that innervate these pyramidal neurons (Durstewitz et al. 2000a; Muly et al. 1998; Rao et al. 1999). A functional loss of GABAergic and dopaminergic inputs to the PFC is implicated in the pathophysiology of schizophrenia (Benes 2001; Lewis et al. 1999; Yang et al. 1999).

DA and GABA interact in a complex manner in the PFC. At low levels of network activity in vivo (e.g., anesthetized preparations), DA suppresses spontaneous PFC neuronal firing (Bunney and Aghajanian 1976; Sesack and Bunney 1989; Yang and Mogenson 1990), and this is often blocked by iontophoretic application of the GABA A antagonist bicuculline (Pirot et al. 1992). At high levels of network activity (during working memory), iontophoretic application of very low concentrations of D1 antagonist increase delay-period firing activity, perhaps by attenuating a D1-mediated activation of interneurons (Williams and Goldman-Rakic 1995). This suggests that DA activates GABAergic interneuronal inputs to restrict firing of pyramidal neurons.

In vitro electrophysiological studies in layer V-VI pyramidal neurons show that DA consistently increases the frequency of spontaneous GABA A receptor-mediated inhibitory postsynaptic currents (IPSCs) (Seamans et al. 2001a), suggesting that DA may activate GABAergic interneurons as shown in layer I of rat frontal cortex (Zhou and Hablitz 1999). Furthermore, synaptically evoked GABA A-IPSCs are bidirectionally modulated by DA: a D2-mediated suppression is followed by a prolonged D1-mediated enhancement (Seamans et al. 2001a). The D2 effect is mediated by direct modulation at GABAergic synapses, whereas the D1 effects appeared to be mediated by increase excitability of interneurons. Accordingly, DA via D1,

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but not D2, receptor activation should induce an increase in the intrinsic excitability of interneurons.

The mechanisms of DA actions, and the receptor subtypes that modulate different interneuron subtypes in the PFC are still unknown. In this study, we have characterized the direct effects of DA and its actions in layers II-V FS interneurons in rat PFC. We found that DA stimulates D1/D5 receptors to depolarize and increase the excitability of these interneurons. Our voltage-clamp analyses showed that DA suppressed an inward rectifier K⁺ current and a resting leak K⁺ current to depolarize FS interneurons. DA also suppressed a slowly inactivated K⁺ current in a subgroup of FS interneurons to enhance their excitability. An abstract of this study has been reported (Gorelova and Yang 1998).

METHODS

Brain slice preparations

The experiments were performed in brain slices prepared from young (PD 18–35) male Sprague-Dawley rats. Following decapitation by a guillotine (using a plastic Decapicone rat restrainer, Braintree Scientific, FL, USA), the brain was quickly removed and placed for 1–2 min in ice-cold oxygenated (95% O₂-5% CO₂) artificial cerebrospinal fluid (ACSF) containing (in mM) 110 choline chloride, 26 NaHCO₃, 2.5 KCl, 1.25 NaH₂PO₄, 0.5 CaCl₂, 7 MgCl₂, 1.3 ascorbic acid, 2.4 Na⁺ pyruvate, and 25 glucose. The temporal lobes of the cortex from both hemispheres were trimmed away, leaving the medial prelimbic PFC of both hemispheres. The prelimbic PFC corresponds to the region outlined in the stereotaxic atlas of Paxinos and Watson (1998) (A-P = 2.2–3.5 mm anterior to the bregma; D-V = 3–5 mm from the cortical surface; M-L = 0.8–0.9 mm from the midline). Two hundred fifty to three hundred-micron-thick bilateral PFC slices, containing the medial prefrontal cortex, were then cut on a vibratome (Campden, World Precision Instruments). After cutting, the slices were placed immediately in warm (32–33°C) continuously oxygenated ACSF, containing (in mM) 124 NaCl, 26 NaHCO₃, 3 KCl, 2.4 CaCl₂, 1.3 MgCl₂, and 10 glucose for 30 min. After another hour of incubation at room temperature, a single slice was transferred to a submersion recording chamber (Warner Instruments).

Whole cell patch-clamp recordings

A Zeiss Axioskop upright microscope, equipped with Nomarski differential interference contrast optics, infrared videomaging camera (C2400–07ER, Hamamatsu) and fitted with a 3× magnifier (Impex Imaging, Toronto, Canada), was used to visualize neurons in slices using a Olympus 40× water immersion objective. PFC pyramidal neurons were recognizable by their pyramidal-shaped cell body and the presence of long apical dendrite projecting toward layer I and the pia. To increase the chance of recording from the sparsely distributed interneurons, cells without apparent apical dendrites were preferentially targeted. The morphology of the cells from which recordings were made was confirmed afterwards by staining for biocytin, which was routinely included in the patch solution. The procedures for this are described in Morphology of interneurons.

Whole cell patch-clamp pipettes were fabricated from borosilicate tubing (1.5 OD, 0.75 mm ID, Sutter Instruments) on a horizontal microelectrode puller (P-87, Sutter Instruments). The electrodes had a resistance 8–10 MΩ when filled with patch pipette solutions containing (in mM): 125 K-glucolate, 20 KCl, 10 phosphocreatine, 10 HEPES, 1 EGTA, 2 Na₂ATP, 0.3 Na₂GTP, 2 MgCl₂, and 2 mg/ml biocytin. The pH of the patch pipette solution is adjusted to pH 7.3 by KOH, and the osmolality of the solution was 285–295 mOsm.

Both voltage and current signals were amplified with an Axopatch 200B amplifier (Axon Instruments, Foster City), low-pass filtered at 10 kHz. All signals were digitized with a 12 bit A/D converter (Digidata 1200B), and stored in the computer hard-disk for off-line analysis. pClamp 7.0 software (Axon Instruments, Foster City) was used for data acquisition and analysis. Series resistance (15–25 MΩ after “break-in”) was 80% compensated and periodically tested during the experiment. To reduce the effect of capacitance, the 40X water-immersion objective of the microscope was removed from the bath in order to keep a low fluid level during recordings. Junction potential changes were minimized by using an agar bridge. No additional corrections were made for junction potential between bath and pipette solutions for current clamp experiments. In voltage clamp experiments membrane potentials were corrected for a junction potential of ~11 mV (calculated using pClamp 7.0 software). Some early current-clamp data were collected at room temperature (22°C), but identical results were obtained when later experiments were performed at 30–31°C. Perfusate was heated and maintained at the desired temperature by an in-line heater connected to a temperature feedback control unit (SH-27B and TC-324B, Warner Instruments). All voltage-clamp experiments were also conducted at 30–31°C.

Intracellular depolarizing current pulses (600 ms duration, 10–300 pA) were injected into the putative interneurons to evoke spike firing at various steady-state membrane potentials. Their intracellular current-evoked firing pattern was then used to distinguish the subtypes of GABAergic interneurons (according to the classification of Kawaguchi 1993, 1995), as well as to determine changes in neuronal excitability following application of dopamine or its agonists. Instantaneous firing rate was measured from the reciprocal of the inter-spike intervals. First spike latency was measured using the same intensity of current steps in control and during application of dopamine or its agonists when the interneuron was current-clamped (DC injection) back to its resting membrane potential. The amplitude of spike and postspike afterhyperpolarization (AHP) were measured from thresholds to the positive and negative peak, respectively. All electrophysiological data were analyzed using pClamp 7.0 software (Axon Instruments).

Drug applications

All drugs were bath-applied. Stock solutions of tetrodotoxin (TTX, Alomone Labs), SCH 23390, quinpirole (Sigma/RBI), and the D2 antagonist (–)-sulpiride were prepared in deionized water and stored as frozen aliquots at −20°C. The stock solutions of the D1-adrenergic antagonist prazosin, D4 antagonists U101958 and L-745870 (Sigma/RBI), and the full agonist for D1/5 receptors dilyhydroxytocin (TOCRIS) were prepared in DMSO and stored at −20°C. Stock solutions of DA and the D1/5 receptor agonist SKF 81297 (Sigma/RBI) were prepared fresh in deionized water for each experiment. All drugs were diluted to desired concentrations in perfusate immediately before application. To reduce oxidation of DA or the D1/5 agonist, sodium metabisulfite (0.002% final concentration in ACSF) was co-applied. Appropriate vehicle controls were performed where necessary.

Morphology of interneurons

At the end of each experiment, slices were fixed in 4% paraformaldehyde in 0.1 M phosphate buffer for 2 h at room temperature. Slices were then transferred to 0.05 M Tris buffer containing 1% Triton X-100 and stored overnight at 4°C. The endogeneous hydrogen peroxidase activity was neutralized by incubation with hydrogen peroxide in methanol (1:200). After washing with Tris-Triton, tissue was incubated with horseradish peroxidase conjugated with streptavidin for 2 h at room temperature. After washing with Tris buffer, the biocytin-horseradish peroxidase conjugated streptavidin complexed with 3’3’ diaminobensidine tetrachloride to form a dark brown product for visualization. All slices were placed in DMSO without further resectioning for microscopic examination and camera lucida.
are fast-spiking (FS; recurring patterns in response to depolarizing current pulses. They study were divided into four classes based on their evoked neurons in rat frontal cortex, nonpyramidal neurons in our examination of Kawaguchi (1993, 1995) for inter-

neurons of each interneuron (Yang et al. 1996).

RESULTS

Four electrophysiologically distinct classes of interneurons in rat mPFC

The effects of DA on interneuronal excitability were studied in 66 nonpyramidal cells from rat medial PFC. In accordance with the classification of Kawaguchi (1993, 1995) for inter-neurons in rat frontal cortex, nonpyramidal neurons in our study were divided into four classes based on their evoked firing patterns in response to depolarizing current pulses. They are fast-spiking (FS; n = 44), late-spiking (LS; n = 3), low threshold spike (LTS, n = 5), and regular spiking nonpyramidal (RSNP; n = 14) interneurons (Fig. 1). A portion of the interneurons were stained for biocytin to correlate their morphology with their electrophysiological responses. Since the electrophysiological features of FS and LS interneurons (Fig. 1, A and B) could easily be distinguished from pyramidal neurons in the cortex, all interneurons of these two types were included in the analyses. In contrast, firing of LTS and RSNP cells (Fig. 1, C and D) were not distinguishable from that of pyramidal neurons. Hence, only LTS (n = 2) and RSNP (n = 8) interneuron subtypes with confirmed morphology were included in the analyses.

We recorded from 44 nonpyramidal FS interneurons that showed the distinct electrophysiological features unique to this particular subtype of interneuron. In response to near-threshold current pulses, spike discharge from FS interneurons consisted of either one or several early spikes (with each spike having a short spike duration of <1 ms) at the very beginning of the current pulse, which was followed by a variable length quiescent period before an episode of repetitive firing occurred. With strong intracellular depolarizing current pulses, FS interneurons now fired a train of nonadaptive spikes (Figs. 1A, 2D, and 3A). In general, the FS interneurons had lower input resistance and more negative resting membrane potentials than other subtypes of interneurons (Table 1). Thirteen FS interneurons recorded from layers II-III and V were stained for biocytin. The biocytin staining showed that they are multipolar cells with beaded dendrites and elaborate local axonal arbor that resemble a typical basket cell (Fig. 2B). FS interneurons in layers II-III and V of the rat and monkey frontal cortex are comprised of two or more classes of GABAergic interneurons that are either parvalbumin-immunoreactive basket or chandelier cells (Kawaguchi and Kubota 1997; Krimer and Goldman Rakic 2001).

Besides the FS interneuron subtype, LS cells are also known to be GABAergic neurogliaform cells (Condé et al. 1994; Kawaguchi 1993, 1995). LTS and RSNP interneurons in layers II-III show a characteristic time-dependent inward rectification due to activation of a hyperpolarization-activated cationic current (Ih, Kawaguchi 1993, 1995) (Fig. 1, C and D). LTS and RSNP interneurons have bitufted dendritic arbors and represent double-bouquet cells. They are both GABAergic and immunoreactive to Ca2+-binding protein calbindin or calretinin (Condé et al., 1994; Hendry et al. 1989; Kawaguchi 1995; Somogyi 1998).

**FIG. 1.** Electrophysiological characteristics of 4 subtypes of interneurons in rat medial prefrontal cortex. **A:** fast-spiking (FS) interneuron responds with short-duration (<1 ms) spikes followed by prominent postspike afterhyperpolarizations (AHPs) upon activation by threshold depolarizing current pulses. Stronger depolarization induced fast nonadapting firing. FS interneurons show time-independent inward rectification with membrane hyperpolarization by negative current pulses. **B:** late-spiking (LS) interneurons respond with a delayed spike riding on a ramp-like depolarization in response to threshold depolarizing current pulses. Stronger depolarization induced nonadapting firing, but slower than in FS interneurons. LS interneurons also showed time-independent rectification with hyperpolarization by negative current pulses. **C:** low-threshold spike (LTS) interneurons fired 2 or 3 spikes that ride on a slow depolarizing hump (top). In response to hyperpolarizing pulses, there was an additional “rebound” spike burst that is derived from de-inactivated low-threshold Ca2+ spikes (LTS) (bottom). RSNP interneurons also show a time-dependent inward rectification with membrane hyperpolarization typically due to a hyperpolarization-activated cationic current (Ih).
DA primarily depolarized FS interneurons, moderately increased their input resistance, reduced evoked spike threshold, and increased their excitability.

Bath application of DA (10–40 μM) induced a reversible membrane depolarization (2–6 mV, 5–9 min duration, dependent on the DA concentration) in 41 of 44 (91%) (29 from layer II–III, and 15 from layer V) FS interneurons tested. Addition of TTX (1 μM) to the perfusate to block Na+ channels (Fig. 2C) and CdCl2 (200 μM; data not shown) to block synaptic transmission did not affect the DA-induced depolarization, suggesting that DA directly affected FS interneurons and this depolarization was independent of Na+ channels. Of the morphologically defined non-FS interneurons, three LS interneurons tested were also depolarized moderately by DA (1–5 mV), while none of the LTS (n = 2 tested) or RSNP (n = 8 tested) interneurons tested responded to DA. Because DA primarily depolarized FS interneurons in the PFC, all subsequent experiments sought to characterize the mechanisms of DA actions only in FS interneurons.

During the DA-induced depolarization of FS interneurons, there was an increase in neuronal excitability. Depolarizing pulses which were previously subthreshold for evoking spike generation or were capable of evoking only a few spikes at the beginning of the pulse induced a continuous train of nonadapting spikes after DA application (30–40 μM; Fig. 2D; Table 2). Stronger depolarizing pulses, which evoked a continuous train of non-accommodating spikes in control, induced more spikes during the DA-induced depolarization. When the DA-depolarized cells were current-clamped (by DC injection) back to the pre-drug control membrane potentials, the same depolarizing pulses also evoked more spikes than before DA application and the latency of the first spike was decreased by 22.6 ± 12.6% (range, 7–39%; n = 8) by DA (Fig. 3, A–E; Table 2). Furthermore, DA also reduced spike threshold by 1–5 mV (mean, 2.6 ± 1.7 mV; n = 7) in all FS interneurons tested. The DA-induced changes in the spike threshold often outlasted the duration of DA-induced depolarization.

Spike analysis revealed that DA did not significantly (P >
0.3) change spike amplitude, nor did it change the amplitude of the fast postspike AHP (Table 2) when the spike was triggered by current pulses of near threshold intensity (Fig. 3C). We then converted first-spike latency and first-inter-spike intervals into their corresponding instantaneous frequencies and plotted them as a function of the injected current intensity. During DA application the membrane potential was clamped back to its resting level by applying small negative DC current. D: graph showing converted first-spike latencies and first inter-spike intervals into instantaneous firing frequencies (=1/1st spike latency, or 1/1st inter-spike intervals) and plotted as functions of injected current intensity. The plot shows that DA induced a more robust change in the 1st inter-spike intervals and therefore the instantaneous frequencies at low intensity current steps (+). At the strongest depolarizing step used (300 pA), there was no change in the 1st inter-spike intervals with DA application. The DA-insensitive delayed rectifier may strongly prevent further increases in the instantaneous firing frequency.

E: graph showing the slow onset and prolonged time-course of the DA-induced changes in first-spike latency of spikes evoked at lowest current intensity. 

**DA D1/D5 receptors, but not D2, D4, α-adrenergic, or serotoninergic receptors, directly depolarized interneurons**

We then determined the subtypes of DA receptors that mediated the depolarizing effect of DA on interneurons. Although LS interneurons were also depolarized by DA, these cells represented only a very small population of all interneurons sampled (3 of 62 interneurons) in this study and were not investigated further. All DA receptor antagonists were applied 10 min before bath application of DA to FS interneurons. As a rule, each cell was treated only with one antagonist. The D1
receptor antagonist SCH23390 (5–10 μM) significantly reduced the depolarization induced by application of DA (10–20 μM) in 7 cells (Fig. 4A). The D2 receptor antagonist (–) sulpiride (10–20 μM) did not reduce the amplitude of the DA (30 μM)-mediated depolarization in any of the 7 cells tested (Fig. 4B).

Since D4 receptors have been shown to be present in the parvalbumin-containing interneurons in primate PFC (Mrzljak et al., 1996), the effects of two D4 receptor antagonists (U101958; Merchant et al., 1996; L-745870; Patel et al., 1997) on the DA depolarization were examined. Both D4 receptor antagonists (10 μM) had no effect on DA-induced depolarization in all six interneurons tested (Fig. 4, C and E). The graph in Fig. 5E summarizes the results of pharmacological characterization of the DA-induced membrane potential changes in PFC interneurons.

We also tested the possibility that DA may exert its depolarizing effect on interneurons through stimulation of other monoaminergic receptors, specifically adrenergic receptors and serotonergic receptors. Since it was shown that stimulation of α1 adrenoreceptors induced depolarization in frontal cortical interneurons (Kawaguchi and Shindou, 1998), we used an α1 adrenoreceptor antagonist prazosin in an attempt to block the depolarizing effect of DA on interneurons. Bath application of prazosin (10 μM) had no effect on DA-induced depolarization in 3 FS cells tested (Fig. 4 D and E). Likewise, bath-application of the non-specific 5-HT1/5-HT2 antagonist mianserin (20 μM) also failed to block DA-induced depolarization (n = 2, not shown).

The D1 receptor agonists SKF81297 (3–10 μM) or dihydrexidine (3–10 μM), but not the D2 agonist quinpirole (1–5 μM), induced depolarization in 13 of 15 FS interneurons tested. It is notable that when applied for the same brief duration (3–5 min) for both dopamine and the D1 agonists, the duration of the D1 agonist-induced depolarization was remarkably longer than the duration of the DA-induced depolarizing response (Fig. 5C). While DA-induced depolarization was completely reversible in 5–10 min in most FS interneurons, the depolarization induced by SKF 81297 (or dihydrexidine) was long-lasting and showed no recovery during the course of the experiment. This may be due to an incomplete washout of the agonist from the tissue or differences in the binding characteristics of the two agents (Fig. 5, C and D).

Like dopamine, D1 receptor agonists also increases neuronal excitability of FS interneurons in PFC

As in the case with DA, the D1 agonists also caused an increase in neuronal excitability of FS interneurons (shown as an increased number of spikes evoked by the same depolarizing current pulses with the membrane potential clamped at the same levels as the predrug control). This was accompanied by a moderate increase in input resistance and a decrease in spike threshold (Fig. 6A), but no significant change in the amplitude of the postspike AHP or of the instantaneous spike firing rate (Fig. 6B, Table 2). The reduction of first spike latency by the D1/D5 agonist slowly reached a steady-state peak response only approximately 15 min after application of SKF81297 (n = 3–7 cells; Fig. 6C).

Notably, the slow time course of the change in interneuron excitability following a D1 agonist was remarkably similar to that observed for D1 mediated increases in evoked IPSCs recorded in pyramidal neurons (Seamans et al. 2001a). Moreover, unlike DA, the D1 agonist did not relax the inward rectification with large hyperpolarization, i.e., the D1 agonist did not increase the amplitude of the hyperpolarizing voltage deflections as much as in the case of DA (compare Figs. 3A and 6A). The D2 receptor agonist quinpirole (1–10 μM) alone had no effect on either the membrane potential or the neuronal excitability in 10 of 12 FS interneurons (Fig. 5B and 6D, 6E; Table 2).

**DA modulation of inward rectifying K⁺ current**

To determine the voltage dependence of the DA-induced depolarization and its possible ionic mechanisms, we performed voltage-clamp recordings from PFC layers II-V FS interneurons. When voltage clamped at −80 mV, bath application of DA (40 μM, with no channel or transmitter receptor blockers) induced reversibly a small inward current (washout achieved in 15–20 min; n = 10/11 cells tested; Fig. 7A). The slow time course of the response to DA is remarkably similar to the DA-induced membrane depolarization in current-clamp recordings shown earlier (Fig. 2B).

To analyze the voltage dependence of the DA-induced current, perfusate containing TTX (0.5 μM) and Cd²⁺ (200 μM) was used to block the Na⁺ and Ca²⁺ channels, respectively. FS

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**Table 2. Effects of DA and D1, D2 receptors agonists on spike properties of FS interneurons**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>DA (n = 8)</th>
<th>SKF81297 (n = 6)</th>
<th>Quinpirole (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spike amplitude (nV)</td>
<td>88 ± 3.8</td>
<td>88 ± 4.1</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Spike width (ms)</td>
<td>0.54 ± 0.06</td>
<td>0.54 ± 0.05</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Spike threshold (nV)</td>
<td>−40.5 ± 4.5</td>
<td>−43.3 ± 4.4†</td>
<td>−40.9 ± 3</td>
<td>−43 ± 2.5*</td>
</tr>
<tr>
<td>AHP (mV)</td>
<td>18.2 ± 4.8</td>
<td>17.8 ± 3.4</td>
<td>18.9 ± 2.8</td>
<td>19.1 ± 2.7</td>
</tr>
<tr>
<td>First spike latency (ms)</td>
<td>20.9 ± 3.2</td>
<td>16.3 ± 1.9*</td>
<td>20.4 ± 1.9</td>
<td>15.4 ± 2†</td>
</tr>
<tr>
<td>First interspike interval (ms)</td>
<td>24.7 ± 5.7</td>
<td>21 ± 4.2*</td>
<td>24.1 ± 5.5</td>
<td>19.8 ± 4*</td>
</tr>
</tbody>
</table>

The first spike latency value taken for each cell was measured from spikes evoked by minimum depolarizing current intensity that induced one or more spikes in the control. The first inter-spike interval was measured from spikes evoked by the minimum current intensity that evoked a train of non-accommodating spikes in control. Changes in spike responses to the same current intensity pulse subsequent to drug application were then analyzed. The membrane potential was held via DC current injection at the same levels in the control and in the drug. NA, not analyzed. * P < 0.01. † P < 0.005.
interneurons were clamped at \(-80\) mV, and slow voltage ramps from \(-120\) to \(-40\) mV or from \(-110\) to \(-50\) mV were applied before and during bath application of DA. Superimposition of the whole cell ramp currents before and during DA application revealed that the DA-induced inward current exhibits a reduced slope conductance and has a smaller amplitude than the control ramp current at membrane voltages more positive than \(-90\) mV (Fig. 7B1). This suggests that the apparent “inward” current induced by DA reflects a DA suppression of an outward current(s).

To further characterize the DA-sensitive current, the ramp current obtained during DA application was electronically subtracted from the ramp current obtained during the control. The resultant DA-sensitive current (Fig. 7B2) was nonlinear (\(n = 10/11\) cells tested) and had a mean reversal potential of \(-97 \pm 8\) mV. This reversal potential of the DA-sensitive current is close to the Nernst potential for K\(^+\) ions (with the assumption that intracellular [K\(^+\)] = patch solution [K\(^+\)] for our recording conditions), thus strongly suggesting that DA reduces K\(^+\) currents in FS interneurons.

To confirm that the DA-sensitive current is a K\(^+\) current, we examined the effects of altering extracellular K\(^+\) concentration on the reversal potential of the DA-induced current. The mean reversal potential of the DA-sensitive current was \(-93 \pm 3.4\) mV (\(n = 4\)) in 3 mM [K\(^+\)]o, \(-67.5 \pm 3.5\) mV (\(n = 2\)) in 6.5 mM [K\(^+\)]o and \(-59 \pm 5\) mV (\(n = 2\)) in 8 mM [K\(^+\)]o. When the reversal potential of the DA-sensitive current was plotted as a function of the Ln [K\(^+\)]o, the slope of the regression line had a value 32.5 mV per e-fold change in [K\(^+\)]o (Fig. 7D). This value approximates the value predicted by the Nernst equation calculated at 30°C (i.e., 26.12 mV).

As shown in Fig. 8A1, the control whole cell ramp current in FS interneurons was quite nonlinear, in the voltage range from \(-110\) to \(-50\) mV. Addition of CsCl (2 mM) to the perfusate resulted in a voltage-dependent reduction of the whole cell slope conductance, yielding a linear I-V relationship in the voltage range from \(-110\) to \(-50\) mV (Fig. 8A). The resulting linearity of ramp current in Cs\(^+\) (gray color trace, Fig. 8A1) suggests that Cs\(^+\) blocked the nonlinear inward rectifying (IR) current shown in the control ramp current (black trace; Fig. 8A1). Electronic subtraction of the ramp current in Cs\(^+\) from the control current unveiled this Cs\(^+\)-sensitive nonlinear current in Fig. 8A2. This Cs\(^+\)-sensitive current exhibits the voltage-dependent profile of an inward rectifying K\(^+\) current (large inward and small outward current that has a reversal potential of \(-95\) mV). With a similar approach, the effect of DA alone on ramp current was investigated. Current subtraction unveiled a nonlinear DA-sensitive current with prominent inward rectification at potentials more negative than \(-95\) mV (Fig. 8, B1 and B2), very similar to the Cs\(^+\)-sensitive IR current. This finding suggests that DA may primarily modulate an inwardly rectifying K\(^+\) current.

### DA modulation of an additional resting leak K\(^+\) current

Besides the IR K\(^+\) current, additional K\(^+\) currents are also active near resting membrane potential and may also contribute to the DA-induced membrane depolarization in FS interneurons. One such current is the resting, leak K\(^+\) current. In four FS interneurons, we tested the effects of DA on the whole cell current in the absence and in the presence of Cs\(^+\) (after washout of control DA-induced changes in non-Cs\(^+\) perfusate in the same cells). Bath application of DA in Cs\(^+\)-containing perfusate reduced an outward current at potentials more positive than \(-90\) mV (Figs. 8C1 and 10A3). Following subtraction of the ramp currents, we compared the DA-sensitive ramp current in control (Fig. 8C2) with the DA-sensitive ramp current in the presence of Cs\(^+\) (Fig. 8C2). While the DA-sensitive ramp current in normal ACSF showed significant nonlinearity (Figs. 7B2 and 8B2), the DA-sensitive ramp current in Cs\(^+\) was linear at potentials from \(-110\) to \(-50\) mV and had a mean reversal potential of \(-93 \pm 4\) mV (\(n = 4\); Fig. 8C2).

In Fig. 8D, we superimposed the subtracted DA current (Fig. 8B2) with the DA current in Cs\(^+\) (Fig. 8C2). When...
measured at \(-50\) mV, the amplitude of DA-sensitive ramp current in control perfusate was not significantly different from that in Cs\(^+\)-containing perfusate (21.4 \(\pm\) 5.6 pA in normal ACSF vs. 22.8 \(\pm\) 2.6 pA in Cs\(^+\)-containing ACSF, \(n = 3; P > 0.5\); Fig. 8E). However, when measured at \(-110\) mV, the DA-sensitive ramp current in Cs\(^+\)-containing ACSF was significantly smaller (\(P < 0.01\)) than that in normal ACSF (\(-18.3 \pm 4.3\) pA in normal ACSF vs. \(-3.9 \pm 3.4\) pA in Cs\(^+\)-containing ACSF; Fig. 8E). Furthermore, the D1/D5 antagonist SCH23390 (6 \(\mu M\)) failed to block the Cs\(^+\)-sensitive component of the DA-induced ramp current measured at \(-100\) mV, but significantly (\(P < 0.02\)) blocked the Cs\(^+\)-insensitive DA-induced ramp current measured at \(-50\) mV (Fig. 10A3). These data suggest that in the voltage range between \(-110\) and \(-50\) mV DA reduces a Cs\(^+\)-sensitive IR K\(^+\) current and a Cs\(^+\)-insensitive voltage-independent K\(^+\) current that is likely to be the linear, resting leak K\(^+\) current. Based on these data, we suggest that the DA reduction of these two K\(^+\) currents contributed to the DA-induced membrane depolarization in FS interneurons.

**DA modulation of outwardly rectifying K\(^+\) current(s)**

One of the distinct characteristics of FS interneurons is that depolarizing current steps could only induce one or a few spikes at the very beginning of the pulse (see Fig. 1A), suggesting the presence of strong membrane outward rectification. When depolarized from rest (more positive than \(-50\) mV), at least 2 types of outwardly rectifying K\(^+\) currents—delayed rectifier and \(I_{\text{Ado}-}\)—are activated. After DA application, we found that depolarizing current pulses, which previously induced only one or a few spikes at the very beginning of the pulse, started to induce a series of nonadapting spikes (e.g., Figs. 3 and 6). If this response to DA is due to changes in a delayed rectifier, it would be detected by a change in spike width and postspike AHP amplitude. However, our spike analyses (Table 2) failed to detect any changes in spike width, amplitude and AHP following DA application. Thus it appears likely that DA did not modulate a delayed rectifier outward K\(^+\) current.

The increased spike discharge in response to depolarizing input may be the result of a DA-induced suppression of an outwardly rectifying K\(^+\) current(s). In the presence of TTX and Cd\(^{2+}\) we tested the effects of DA on whole cell outward currents in response to long (1 s) voltage steps from a holding potential of \(-100\) mV. As shown in Fig. 9A, the whole cell current showed a significant outward rectification starting at potentials more positive than \(-50\) mV. In a subset of FS interneurons (6 of 11 tested), DA (40 \(\mu M\)) reduced the voltage-dependent, outwardly rectifying K\(^+\) current(s) (Fig. 9, B and C). The blockade of the outwardly rectifying K\(^+\) current(s) can contribute significantly to a DA-induced change in FS interneuron excitability. However, additional experiments are needed to clarify what subtype(s) of outwardly rectifying K\(^+\) channels are blocked by DA.

**D1 agonists suppressed the linear voltage-independent resting leak K\(^+\) current in FS interneurons**

To further characterize the DA-sensitive current, the D1/D5 receptor agonist SKF 81297 (\(n = 8\) cells) or the D2/D4 receptor agonist quinpirole (\(n = 8\) cells) were applied to FS interneurons. In 6 of 8 FS interneurons in normal ACSF (i.e., no channel blocker included), bath application of SKF 81297 (10 \(\mu M\)) induced an “inward” current (Fig. 10A). In the presence of TTX and Cd\(^{2+}\), voltage ramp injection showed SKF81297 reduced the outward ramp current and the whole cell conductance (Fig. 10A1). The D1/D5 agonist-sensitive ramp current was linear in the voltage range between \(-110\) and \(-50\) mV (Fig. 10A2) and had a mean reversal potential of \(-99 \pm 5\) mV, corresponding to the equilibrium potential for K\(^+\) ions. In the remaining two interneurons, SKF 81297 induced a parallel shift in the current-voltage relationships, indicating that the affected currents are likely to be located at distal dendrites and escaped the voltage clamp control. The linearity of the D1 agonist-sensitive current after digital subtraction of the control from the D1 agonist ramp current suggests that the D1/D5 agonist suppressed a resting, leak current (with \(V_R = -94\) mV, corresponding to the equilibrium potential for K\(^+\)), but not the IR.

Figure 10A3 shows group data that summarize the effects of DA and the D1 agonist (SKF) on whole cell ramp currents in normal ACSF and Cs\(^+\)-containing ACSF. Part of the DA data...
from Fig. 8E was replotted here for comparison with the SKF data. Measurements were taken from the resultant ramp current (control minus drug) at two voltages: −110 and −50 mV. The DA data were from the same cells (within-cell design). There was a significant difference (P < 0.002) between DA-sensitive and SKF-sensitive ramp currents measured at −110 mV (DA: −18.3 ± 4.3 pA vs. SKF: −4.6 ± 1.3 pA), thereby suggesting that the DA-mediated reduction of the ramp current at −110 mV was not through the activation of D1 receptors. The D1/D5 receptor antagonist SCH23390 (6 μM) also failed to block the effect of DA-sensitive ramp current at −110 mV (DA + SCH: −20.8 ± 2.4 pA, DA: −18.3 ± 4.3 pA). Cs⁺ reduced the DA-sensitive current measured at −110 mV. The nonlinearity of the DA-sensitive current and its reversal potential at approximately −100 mV suggest that DA blocked a Cs⁺-sensitive, inwardly rectifying K⁺ current that contributes to the whole cell current at voltages more negative than −100 mV (see Fig. 8). Note that the addition of Cs⁺ to the external media did not affect the SKF-sensitive ramp current (SKF: −4.6 ± 1.3 pA, SKF in Cs⁺: −3.8 ± 2.6 pA). On the other hand, there were no
significant differences between the DA-sensitive and SKF-sensitive ramp currents measured at −50 mV (DA: 21.4 ± 5.6 pA, SKF: 22.6 ± 5.3 pA), suggesting that DA-sensitive ramp current at this voltage is activated through D1 receptors. The DA-sensitive ramp current at −50 mV is also sensitive to SCH23390 blockade (P < 0.02), thus further suggesting that it is D1 receptor-mediated. The linearity of the SKF-sensitive ramp current, its Cs⁺-insensitivity, and its reversal potential at approximately −100 mV strongly suggest that DA, through the activation of D1 receptors, reduced a leak K⁺ current and that contributes significantly to the DA effect on the whole cell current at −50 mV.

Bath application of quinpirole had no effect in all eight FS interneurons tested (Fig. 10, B1 and B2). Collectively, these data have enabled us to suggest that activation of D1/D5 DA receptors suppressed a voltage-independent resting leak K⁺ current in most FS interneurons. Activation of D2/D4 DA receptors did not affect either of these K⁺ current in FS interneurons. The type(s) of receptor responsible for the DA effect on IR in FS interneurons remains to be clarified.

DISCUSSION

Our results from current-clamp recordings showed that DA reversibly induced membrane depolarization and increased the neuronal excitability of mainly FS and a few LS interneurons in rat PFC slices. The increase in neuronal excitability by DA was characterized by 1) an increase in spike firing in response to the same control intracellular depolarizing current steps, 2) a lowering of threshold for spike firing, and 3) a decrease in first spike latency. DA failed to alter the duration of the spikes and the amplitude of postspike AHP. The DA-induced membrane depolarization was mimicked by D1/D5 agonists and was significantly reduced by a D1/5 antagonist, but not by D2, D4, serotonin, or α1 adrenergic antagonists. Voltage-clamp analyses showed that DA depolarized FS interneurons by suppressing outward current(s) that had reversal potentials approx-

![Image](http://jn.physiology.org/content/jn/88/6/3159/F7.large.jpg)

**FIG. 7.** DA depolarized FS interneurons by suppressing K⁺ currents. A: under voltage-clamp, bath application of DA (30 μM) in a FS interneuron induced a small inward current. Note that this FS interneuron was also bombarded with spontaneous inward synaptic currents (downward going lines). Under these recording conditions (i.e., K-glucuronate in pipette, normal ACSF, no TTX, no blockers of glutamate or GABA receptors, Vhold = −80 mV), these synaptic currents mostly represent spontaneous excitatory postsynaptic currents (EPSCs). The apparent induction of steady-state inward current by DA reflects a blockade of outward currents (see RESULTS). B1: current traces obtained during slow depolarizing voltage ramps from −120 to −40 mV under control and 5 min after DA application (in the presence of TTX and Cd²⁺). Superimposition of these 2 current traces shows that the DA-induced inward current increases with depolarization in the −120 to −40 mV voltage range and had a reversal potential at approximately −95 mV (†), which corresponds to the Nernst potential for K⁺. The DA-induced reduction of the slope of the ramp current trace reflects a reduction in the whole cell conductance, which suggests that DA suppressed an outward current. This suppression of the outward currents was described as the DA-induced inward current shown in A. B2: the DA-sensitive current was unveiled by digital subtraction of the ramp current obtained during DA application from the control ramp current (shown in B1). Note the nonlinearity of DA-sensitive current and the reversal potential of approximately −95 mV (+). C: dependence of the reversal potential of the DA-sensitive current on extracellular K⁺ concentration. A graph (black circles) shows the reversal potentials of DA-sensitive current as a function of the ln[K⁺]o, the slope of the regression line had a value 32.5 mV per e-fold change in [K⁺]o. Black squares show the estimated reversal potentials for K⁺ current calculated for our recording conditions (140 mM K⁺ in the internal solution, 30°C) using Nernst equation and it has a slope of 26.12 mV per e-fold change in [K⁺]o.
imating the K⁺ equilibrium potential. Our voltage-clamp data indicated that DA suppressed Cs⁺-sensitive IR and voltage-independent leak K⁺ conductances, and in some FS interneurons, an additional slowly inactivating K⁺ current.

**DA modulates FS interneuron selectively in rat PFC**

Our data shows that DA functionally modulated mainly FS interneurons, consistent with neuroanatomical data, which shows that most parvalbumin-containing FS interneurons receive mesocortical DA innervation (Kawaguchi 1993, 1995; Sesack et al. 1995, 1998). D1/D5 agonists induced membrane depolarization, enhanced firing evoked by depolarizing current pulses in FS interneurons (present study), and increased spontaneous and evoked IPSCs in PFC pyramidal neurons (Seamans et al. 2001a). Accordingly, the late, persistent D1 mediated increases in interneuron excitability resembles the time course of the increase in IPSC amplitude (Fig. 6; Seamans et al. 2001a). Thus the prolonged D1-mediated increase in axo-somatic excitability of FS interneurons is likely the cause of larger evoked IPSCs in pyramidal cells.

**DA modulates voltage-dependent and voltage-independent K⁺ currents in FS interneurons**

Our voltage-clamp data revealed that DA modulates at least three K⁺ currents in FS interneurons to regulate neuronal
excitability. At membrane potentials more negative than -50 mV including resting, several types of inwardly rectifying K⁺ (IRK) channels may be constitutively active (see Reimann and Ashcroft 1999; Takigawa and Alzheimer 2002; Wickman and Clapham 1995). IRK channels of Kir 2.x family are tonically active at rest and their main function is to stabilize resting membrane potential near the K⁺ equilibrium potential. Kir 3.x family channels are G-protein activated (GIRK). They mediate agonist effects on electrical activity via various G-protein-coupled receptors. In several brain structures DA, through activation of D2/D3 receptors, was shown to increase IR (via activation of GIRK channels)(Inanobe et al. 1999; Kuzhikan-ndathil et al. 1998). On the other hand it has been shown that nicotine and chlorethylclonidine can block IRK channel directly, and not through the activation of the corresponding cholinergic and α2-adrenergic receptors (Barret-Jolley et al. 1999; Wang et al. 2000). Data from our present study show that DA modulates an IR current but neither D1 nor D2 agonists mimicked the effects of DA, and this DA-sensitive IR current is not blocked by the D1 antagonist SCH23390. Although nicotine and chlorethylclonidine can block IRK channel directly (e.g., I(slow) or I(D) K⁺ currents (Erisir et al. 1999). The delayed rectifier K⁺ current (via Kv.3 class of K⁺ channels) activates at membrane potentials more positive than rest and regulates spike duration, and amplitude of the postspike AHP to contribute to the overall firing properties of FS interneurons (Chow et al. 1999; Erisir et al. 1999; McBain and Fisahn 2001; Rudy and McBain 2001). The slowly inactivating K⁺ current (I(slow) or I(D) in cortical neurons can be de-inactivated from potentials more negative than resting membrane potential and regulates subthreshold synaptic events and repetitive firing (Foehring and Surmeier 1993; Hammond and Crépel 1992; Yang and Seamans 1996). Our current-clamp data showed that DA or its D1 and D2 agonists failed to change the duration of the spike and amplitude of the postspike AHP, thus ruling out the possibility that DA modulates a delayed rectifier K⁺ current in FS interneurons. On the other hand, our findings that depolarizing current pulses, which previously induced only one or few spikes at the very beginning of the pulse, started to induce a series of nonadapting spikes after DA application may be the result of a DA-induced suppression of I(D), as shown in PFC pyramidal neurons (Yang and Seamans 1996). The increased neuronal excitability and the membrane depolarizing actions of DA ultimately lead to increase GABA release from the FS interneurons to the pyramidal cells.

FIG. 9. DA reduced an outwardly rectifying K⁺ current in FS interneurons. A: whole cell current evoked by incremental voltage steps from a holding potential of -100 mV. Note the prominent noninactivating outward rectification in whole cell current at potentials more positive than -50 mV (0.5 μM TTX and 200 μM CdCl₂ were added to ACSF to block Na⁺ and Ca²⁺ currents). B: in a subgroup of FS interneurons, DA reduced the whole cell outward current evoked by progressively increasing voltage steps from -100 mV. C: DA reduced the whole cell outward current in voltage-dependent manner, resulting in a reduction of the outward rectification. D: time course of the DA-induced reduction in the whole cell outward current. Inset: DA suppresses the amplitude of the slowly inactivating K⁺ current.
Comparing DA effects in interneurons of PFC and striatum

Goldman-Rakic, 1995) (Fig. 11).

Extracellular Cs (2 mM) reduced the DA-sensitive current measured at −110 mV. The nonlinearity of the DA-sensitive current and its reversal potential at approximately −100 mV strongly suggested that DA blocked a Cs⁺-sensitive, inwardly rectifying K⁺ current that contributes to the whole cell current at voltages more negative than −100 mV (see Fig. 8). Note that the addition of Cs⁺ to the external media did not affect the SKF-sensitive ramp current. In contrast, when measured at −50 mV, the DA-sensitive current is not significantly different from the SKF-sensitive ramp current, suggesting that the DA-sensitive ramp current at this voltage is mediated through D1/D5 receptors. The DA-sensitive ramp current at −50 mV is significantly reduced by the D1 antagonist SCH23390, further suggesting that it is D1 receptor-mediated. The SKF-sensitive current measured at −50 mV was not significantly affected by extracellular Cs⁺. The linearity of the SKF-sensitive ramp current, its Cs⁺-insensitivity, and its reversal potential at approximately −100 mV strongly suggested that at −50 mV DA primarily via D1/D5 receptors reduced a leak K⁺ current (*P < 0.002; open triangle < 0.02). B: bath application of the DA D2 receptor agonist quinpirole (4 μM) didn’t induce any current in FS interneurons. Membrane potential of the interneuron was held at −80 mV. B1 and B2: quinpirole did not induce any changes in the whole cell conductance in the voltage range from −110 to −50 mV.

However, the reduction in IPSCs in medium spiny neurons may be dose-dependent as Flores-Hernandez et al. (2000) disclosed that their “preliminary experiments using higher concentrations of the D1 dopamine receptor agonist SKF81297 (10 μM) . . . have revealed an enhancement of GABA-evoked currents in medium spiny neurons.” In contrast to the cell types and dose-dependence specificity of the D1 effects on IPSCs, the D2 receptor effects may be more restrictive. D2 agonist depresses IPSCs in striatal spiny neurons, fast-spiking interneurons, and GABAergic striato-pallidal projection neurons (Bracci et al. 2002; Centozone et al. 2002; Cooper and Stanford 2001; Delgado et al. 2000). However, no such D2-mediated depression of IPSCs was observed in layer II neurons of the PFC (Gonzales-Islas and Hablitz 2001), probably because these neurons are largely devoid of D2 receptors (Al-Tikriti et al. 1992; Bouthenet et al. 1991; Vincent et al. 1993). Thus in both PFC and striatum, D1 receptor activation increases that they innervate. This may represent a mechanism that underlies the “inhibitory” action of D1 on pyramidal cell firing (i.e., spike firing suppression) that is shown in vivo (Williams and Goldman-Rakic, 1995) (Fig. 11).

Comparing DA effects in interneurons of PFC and striatum

The present findings and those of Seamas et al. (2001a) obtained in rat PFC neurons are consistent with the findings in striatal neurons. DA via D1/D5 receptors depolarized and increased the excitability of large aspiny cholinergic neurons and fast-spiking interneurons in striatum by suppressing K⁺ currents (Aosaki et al. 1998; Bracci et al. 2002). Although D1 receptor activation increased GABA currents in striatal cholinergic interneurons, it had insignificant effects on striatal fast-spiking interneurons, but reduced IPSCs in striatal medium spiny neurons (Bracci et al. 2002; Flores-Hernandez et al. 2000; Yan and Surmeier 1997).
interneuronal excitability, and thereby increases evoked IPSCs in deep layer PFC pyramidal neurons and certain striatal interneurons. On the other hand, when D2 receptors are present, their activation depresses IPSCs in both PFC and striatum. These data are consistent with those of Harsing and Zigmond (1997), who demonstrated that D1 receptor stimulation increases while D2 receptor stimulation reduces \(^3\)H GABA release in striatum and thereby provides another example of the biphasic nature of DA action (Calabrese 2001).

**Functional implications of DA modulation of GABAergic interneurons in PFC**

Morphological heterogeneity of local circuit GABAergic neurons and the targets of their axonal arbors suggest that these interneurons can play different roles in regulating cortical circuitry. Fast-spiking parvalbumin-containing GABA basket cells innervate the soma and proximal dendrites of pyramidal cells, while the axonal cartridge synapses of the FS chandelier cells innervate the initial segment of pyramidal cell axons to provide potent, but nondiscriminatory inhibitory effect on pyramidal cell excitability (Somogyi et al. 1998; Miles et al. 1996; Tamás et al. 1997; Thomson et al. 1996). Dopamine D1 receptor activation of FS GABAergic (parvalbumin-immunoreactive) interneurons that innervate the axon hillock of pyramidal neurons can result in a suppression of spike initiation in these cells. We suggest that this powerful mechanism might account for the “inhibitory” actions of D1 receptors on firing of PFC pyramidal neurons in vivo (Williams and Goldman-Rakic, 1995).

Given that dynamic GABAergic feedforward and feedback inhibition of pyramidal neurons can regulate timing of spike coding, membrane oscillation frequencies, network synchronization, ion channel activation kinetics, dendritic signaling, and synaptic plasticity (Cobb et al. 1995; Fricker and Miles 2001; Galarreta and Hestrin 2001; Kanter and Haberly 1993; Kanter et al. 1996; Miles et al. 1996; Tamás et al. 1998; Tsubokawa and Ross 1996), a DA activation of GABAergic interneurons that innervate the perisomatic region of pyramidal neurons may influence diverse events including synchronizing firing patterns to phase-lock activity with interneurons (Cobb et al. 1995; Jeffreys et al. 1996; Kuwaguchi 2001; Whittington et al. 1995) or 2) inter-posing IPSPs between repetitive spike firing of pyramidal neurons to restructure their temporal pattern of firing without changing the mean firing rate. Indeed, simultaneous multi-unit recordings from PFC or cortical neurons of monkey performing some memory tasks have shown that the memory encoding is accomplished by a restructuring of firing patterns without changing the overall mean firing rate (Abeles et al. 1993; de Charms and Merzenich 1996; Vaadia et al. 1995).

Perhaps most important to PFC function is the joint DA and GABA regulation of circuits that mediate different aspects of...
synaptic plasticity underlying short-term working memory and long-term memory (Blond et al., 2002; Hempel et al., 2000; Laroche et al., 2000; Otani et al., 1998; Rao et al., 2000; Rossi et al., 2001). The long time course of DA actions in PFC parallels the prolonged release of DA in PFC during various behaviors, including the performance of working memory tasks (e.g., Ahn et al., 2000; Feenstra et al., 1996). The prolonged pre- and postsynaptic regulation of PFC neurons by DA suggests that DA does not provide specific information to be held transiently in working memory. Although DA may not encode specific information required for working memory, it likely provides a “processing tone” making the encoding of new information in working memory more efficient across trials (Durstewitz et al., 2000a,b).

Sufficient GABAergic tone is also required to “tune” the memory fields of PFC neurons during working memory tasks (Rao et al., 2000). In computer simulations of realistic PFC networks, low GABAergic tone (i.e., as is likely to occur via activation of D2 receptors) caused spontaneous activation of multiple unstable PFC networks not related to information about a previously presented stimulus (Durstewitz et al., 2000). With optimal GABAergic tone (i.e., as is likely to occur via activation of D1 receptors) interneurons quell activity in all but the most strongly active assemblies, resulting in a single strengthened representation in the network that is resistant to subsequent inputs. In this way, DA (first via D2 receptors) may provide a chemical environment to allow “exploration” of multiple possible scenarios within working memory networks until settling on a single solution that is reinforced via D1 effects on interneurons and on other persistent currents in pyramidal cells (Durstewitz et al., 2000; Seamans et al., 2001).

In the PFC of subgroups of schizophrenics, there may exist a reduced D1 tone (Abi-Dargham et al., 2002; Akil et al., 1999; Okubo et al., 1997), a loss of intrinsic GABAergic interneurons and their axonal terminals cartridge synapses, an alteration in GABA receptor subunits, and/or a reduction of GAD mRNA (Akbarian et al., 1995; Benes et al., 1991, 1993, 2001; Huntsman et al., 1998; Lewis et al., 1999). In addition, PFC pyramidal neurons are directly modulated by DA via D1 receptor (see Yang et al., 1999 for a review), and receive indirect DA modulation by way of DA activation of GABAergic interneurons as shown in this study. Thus, with low GABAergic and D1 tone in schizophrenia, we would predict that there would be random switching between PFC networks, possibly resulting in distractibility, attentional deficits, and disruptive working memory characteristics typically found in schizophrenia (Frith 1992; Goldman-Rakic 1994; Posner et al. 1988; Saykin et al., 1991; Yang et al. 1999). These symptoms may therefore be treated effectively by bringing PFC networks under a D1 regime: by simultaneously reducing D2 receptor tone, and increasing D1 tone, thereby indirectly heightening inhibition to fine tune PFC networks in such a way that only a limited number of network representations evoke prolonged and stable sustained firing modes required to effectively hold items in attention.

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Dopamine


