Dopamine D1 Receptor Actions in Layers V–VI Rat Prefrontal Cortex Neurons *In Vitro*: Modulation of Dendritic–Somatic Signal Integration

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The ionic mechanisms by which dopamine (DA) regulates the excitability of layers V–VI prefrontal cortex (PFC) output neurons (including those that project to the nucleus accumbens) were investigated in rat brain slices using *in vitro* intracellular recording techniques. DA or the D1 receptor agonist SKF38393, but not the D2 agonist quinpirole, reduced the first spike latency and lowered the firing threshold of the PFC neurons in response to depolarizing current pulses. This was accomplished by enhancing the duration of a tetrodotoxin-sensitive, slowly inactivating Na⁺ current and attenuating a slowly inactivating, outwardly rectifying, dendrotoxin-sensitive K⁺ current. Furthermore, D1 receptor stimulation attenuated high-threshold Ca²⁺ spike(s) (HTS) evoked primarily from the apical dendrites of these PFC neurons.

Taken together, these data suggest that D1 receptor stimulation on layers V–VI pyramidal PFC neurons: (1) restricts the effects of inputs to the apical dendrites of these neurons by attenuating the dendritic HTS-mediated amplification of such inputs; and (2) potentiates the influence of local inputs from neighboring deep layers V–VI neurons by enhancing the slowly inactivating Na⁺ current and attenuating the slowly inactivating K⁺ current. By influencing the input/output characteristics of PFC → NAc neurons, DA may play an important role in the processes through which PFC signals are translated into action.

Key words: dopamine; D1 receptor; somadendritic; slow or persistent sodium current; slow potassium current; high-threshold calcium current; prefrontal cortex; electrophysiology

The prefrontal cortex (PFC) receives all major ascending monoaminergic projections, but the mesocortical dopaminergic input from the ventral tegmental area (VTA) has received much attention perhaps due to its likely involvement in cognitive and neuropsychiatric processes (Goldman-Rakic, 1992; Jaskiw and Weinberger, 1992). Although this dopaminergic input targets the dendritic spines and shafts of layers V–VI pyramidal neurons in the PFC, in close proximity to putative excitatory axonal terminals, it forms few postsynaptic specializations (Björklund and Lindvall, 1984; Descarries et al., 1987; van Eden et al., 1987; Goldman-Rakic et al., 1989; Berger et al., 1991; Smiley and Goldman-Rakic, 1993; Williams and Goldman-Rakic, 1993). Electrophysiological evidence shows that iontophoretic application of dopamine (DA) suppresses spontaneous firing of PFC neurons (Ferron et al., 1984; Sesack and Bunney, 1989; Godbout et al., 1991; Pirot et al., 1992), perhaps mediated indirectly via activation of GABAergic interneurons (Penit-Soria et al., 1987). DA also was shown to potentiate the excitatory responses of PFC neurons to subthreshold doses of NMDA or acetylcholine (Yang and Mogenson, 1990; Cépeda et al., 1992). However, the ionic

mechanisms by which DA modulates PFC activity directly remained undefined.

The mesocortical DA input is crucial for processes in which short-term memory is used to guide forthcoming behaviors (Brozowski et al., 1979; Goldman-Rakic, 1992; Mogenson et al., 1993). Administration of D1, but not D2, antagonists into the PFC disrupted the task performances profoundly in both primates and rodents (Goldman-Rakic, 1992; Sawaguchi and Goldman-Rakic, 1994; Smiley et al., 1994; Seamans et al., 1995b), whereas microiontophoretic application of DA or low doses of D1 antagonists enhanced the spontaneous firing rate of PFC neurons during the delay period of such tasks (Sawaguchi, 1987; Sawaguchi et al., 1990a; Williams and Goldman-Rakic, 1995). These data suggest that an optimal level of DA in the PFC is required to facilitate processing of short-term memory-related activity in the PFC.

One of the major routes by which memory-related activity in the PFC is translated into action is via the PFC glutamatergic efferents to the nucleus accumbens (NAc), where a terminal field of the mesolimbic dopaminergic input resides (Björklund and Lindvall, 1984; Gerfen, 1989; 1992; Sesack et al., 1989; Berendse et al., 1992; Mogenson et al., 1993; Gorelova et al., 1994). Because corticostriatal neurons express both D1 and D2 receptor mRNA and binding sites (Vincent et al., 1993; 1995; Gasper et al., 1995), these neurons may provide a link between the two major DA terminal fields and thus may mediate cortical DA modulation of subcortical DA transmission in the NAc (Carter and Pycck, 1980; Pycck et al., 1980; Lyness, 1987; Louilot et al., 1989; Jaskiw et al., 1990a,b, 1991; Vezina, 1991; Vezina et al., 1991; Mitchell and Gratton, 1992; Deutch, 1993; Roberts et al., 1994). An abnormal inter-relationship between DA activities in the PFC and the NAc has been proposed to mediate part of the pathophysiology of

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schizophrenia (Robbins, 1990; Davis et al., 1991; Goldman-Rakic, 1991; Grace, 1993; Weinberger, 1993). Thus, an understanding of DA mechanisms in corticostriatal neurons may offer significant insights into possible cellular basis of schizophrenic processes.

We have found recently that the firing threshold of PFC and PFC → NAc neurons is regulated by two opposing voltage-dependent currents: the slowly inactivating Na^+ and K^+ currents (see the companion paper in this issue). Because DA modulates threshold events in cortical and striatal neurons (Calabresi et al., 1987; Penit-Soria et al., 1987; Surmeier et al., 1992; Cpda et al., 1994, 1995), the present study examined the effects of DA on these two major ionic conductances in PFC neurons. In addition, because both DA receptors and high-voltage-activated Ca^{2+} channels are copresent on the spines of the extensive apical dendritic arbor of pyramidal cortical neurons (Hillman et al., 1991; Usowicz et al., 1992; Westenbroek et al., 1992; Hell et al., 1993; Smiley and Goldman-Rakic, 1993; Yuste et al., 1994), we examined whether DA modulates high-threshold Ca^{2+} spike(s) (HTS) in PFC neurons. Given the possibility of a heterogeneous distribution of Na^+ , K^+ , and Ca^{2+} channels in a single pyramidal neuron, DA may exert differential actions in the somatic and dendritic regions of PFC and PFC → NAc neurons. Preliminary data from these studies have been communicated in abstract forms (Yang and Seamans, 1994; Gorelova et al., 1995).

MATERIALS AND METHODS

The slice preparation and set up for intracellular recordings have been described in detail in the companion paper. In addition, some slices had the apical dendrites removed by making a cut at layer III before recording (discussed below).

Drug applications. All ion channel blockers such as tetrodotoxin (TTX), 4-aminopyridine (4-AP), tetraethylammonium (TEA), nifedipine, and CoCl_2 were first prepared as concentrated stock and stored as aqueous solutions at 4°C until use, when they were diluted appropriately and bath applied. The L-type Ca^{2+} channel blocker nifedipine was prepared fresh for each experiment by dissolving it into 50% ethanol and protecting it from ambient light. The final concentration of ethanol never exceeded 0.05%.

DA was prepared fresh before each application. The D1 agonist (SKF38393) and D2 agonist (quinpirole) were prepared as concentrated stock (5 mM) and stored as frozen aliquots until use when they were diluted appropriately and bath applied. When DA was bath applied, freshly prepared sodium metabisulphite (0.1%) was included as an antioxidant. Separate experiments showed that sodium metabisulphite alone did not alter the membrane potential, firing threshold, or input resistance of PFC neurons. DA and its agonists were bath applied briefly for 25–40 sec.

To prevent an indirect action of DA on GABAergic neurons (Verney et al., 1990; Benes et al., 1993; Rtaux et al., 1991), the GABA_A receptor antagonist bicuculline methyliodide (0.7–10 μM) (Sigma, St. Louis, MO) was applied before DA application in some experiments. Because a concentration of bicuculline greater than 1 μM can induce spontaneous epileptiform discharge in some PFC neurons, we coapplied the NMDA receptor antagonist 2-amino-5-phosphonvaleric acid (APV) (50 μM). All drugs were purchased from either Research Biochemical (Natick, MA) or Sigma.

Isolation of Na^+ plateau potentials, HTS, and Ba^{2+} plateau potentials

Na^+ plateau potential. The slices containing PFC neurons were perfused with ACSF containing TEA (20 mM) and 4-AP (1 mM), and the neurons were recorded intracellularly using cesium acetate-filled electrodes to block most K^+ currents. Co^{2+} was also present in the perfusate to block all Ca^{2+} currents. Whenever Co^{2+} or Ba^{2+} (see below) were used, Tris (base) replaced NaHCO_3 to avoid divalent cation precipitation. The perfusate was oxygenated for at least 1 hr, and the pH was adjusted to 7.4 before use. In experiments in which extracellular Na^+ was reduced to half, TRIS hydrochloride was used as a substitute for Na^+ .

HTS. TTX (1 μM) and TEA (20 mM) were used to block Na^+ and K^+

Figure 1. Graphical summary of the changes in the resting membrane potential after bath application of DA on different cell types in the PFC. Open symbols represent responses to DA, and filled symbols represent responses to DA in the presence of bicuculline (0.7–10 μM) and APV (50 μM). Circles indicate IB neurons; diamonds, RS neurons; squares, IM neurons; and asterisk, ROB neuron. Their electrophysiological and morphological characteristics are defined in the companion paper. Voltage responses above the dotted line indicate depolarization, and below, hyperpolarization. Open arrows point to cells that were double-labeled PFC → NAc neurons, and filled arrows point to PFC → NAc cells that were activated antidromically by NAc stimulations.

currents. Cs^+ -filled electrodes were also used in some experiments to block additional K^+ currents. HTS were triggered by depolarizing (50–100 msec) pulses from a holding potential of –50 mV. Peak amplitude and half-width of the HTS were measured from threshold (-38 ± 5 mV). In some experiments, the L-type Ca^{2+} channel blocker nifedipine (5–10 μM) was added to the perfusate.

Ba^{2+} plateau potential. PFC neurons were perfused with TTX (1 μM), TEA (20 mM), and 4-AP (1 mM). Ba^{2+} was used to replace extracellular Ca^{2+} and served as the charge carrier for Ca^{2+} currents to circumvent $[\text{Ca}^{2+}]_i$ inactivation of Ca^{2+} currents. Under these conditions, depolarizing pulses evoked long-lasting (tens of seconds to noninactivating) Ba^{2+} plateau potentials.

RESULTS

The data base was derived from 68 PFC neurons that had resting membrane potentials more negative than –65 mV and spike potentials that overshoot 0 mV. Data obtained from 22 of these neurons also were used in the companion paper.

Effects of DA and DA agonists on the passive membrane properties of PFC neurons

The effects of bath application of DA, D1, or D2 agonists were examined on the passive membrane properties of 19 electrophysiological characterized PFC neurons [2 regular spiking (RS), 2 intermediate (IM), 1 repetitive oscillatory bursting (ROB), and 14 intrinsic bursting (IB) neurons], of which 8 were identified as PFC → NAc neurons (see the companion paper). Bath applied DA (2–50 μM) induced membrane hyperpolarization (1–4 mV, $n = 4$) (Fig. 1, open circles), which was accompanied by little ($12 \pm 4\%$) or no change in input resistance as monitored by injection of hyperpolarizing pulses (0.1 nA, 70 msec, delivered at 0.25 Hz).

To examine the direct effects of DA on the passive membrane properties of single PFC neurons, APV and bicuculline were added to the perfusate. Under these conditions, DA induced no change in the membrane potential in three neurons, small depolarization (2–5 mV) in nine neurons, a hyperpolarization (2–8

Figure 2. D1 receptor stimulation reduced the first spike latency of PFC neurons evoked by intracellularly injected short depolarizing pulses. **A**, SKF38393, a D1 agonist, reduced the onset latency of the first spike in response to a 200-msec-long depolarizing pulse in an IB neuron. The increase in firing was not accompanied by a change in input resistance in this cell. **B**, SKF38393 also reduced the first spike latency of an IB PFC neuron recorded in a slice with layers I-III cut so that all apical dendrites of the deep layer PFC neuron were removed (apical dendrotomized). Note that in both the above and present cases, the threshold for firing was lowered. Furthermore, there was a 22% increase in input resistance in response to the D1 agonist in this particular PFC neuron, but this resistance change was not a consistent finding. **C**, Superimposed spike traces of another IB PFC neuron in response to current depolarizing pulses in control and in the presence of 20 μ M DA. Note that not only the first spike latency was reduced, but also the first ISI. **D**, Histograms summarizing the overall responses of all PFC cell types to DA application. In the presence of DA (20–50 μ M); the first spike latency and first ISI were reduced by ~40%, and the input resistance was decreased by ~17% (left). SKF38393 also reduced the first spike latency and first ISIs by ~40%, but the input resistance was reduced minimally (middle). In marked contrast, quinpirole only induced minimal changes in all these three parameters (right).

mV) in three neurons, and a biphasic response consisting of a depolarization followed by a hyperpolarization in an additional three neurons (Fig. 1). In general, the effects of DA were long lasting, although some reversible responses were observed ($n = 4$). The DA response desensitized quickly, because subsequent application of DA induced either a smaller change or no change in the membrane potential. The effects of DA on the passive membrane properties were too variable to allow any clear conclusions to be drawn.

Modulation of active voltage-dependent membrane conductances in PFC neurons by DA or DA agonists

Actions of dopamine on the active membrane properties at subthreshold potentials

Because DA is known to modulate the excitability of striatal and pyramidal PFC neurons in the subthreshold voltage range (Calabresi et al., 1987; Penit-Soria et al., 1987; Cpda et al., 1992), we examined the effects of DA, D1, or D2 agonists on subthreshold voltage responses of 30 PFC neurons. No differences were observed among the four cell types with regard to their responses to DA, D1, or D2 agonists. Thus, data from all cell types were "pooled" ($n = 12$ for DA; $n = 10$ for SKF38393; $n = 8$ for quinpirole). Bath application of DA or the D1 agonist SKF38393 reduced the overall first spike latency in 22 of 23 neurons tested (DA, $-39 \pm 15\%$; SKF38393, $-38 \pm 14\%$) (Fig. 2A–C). In one RS neuron, DA induced a marked enhancement of the first spike latency (159%). Both DA ($-39 \pm 13\%$) and SKF38393 ($-38 \pm 5\%$) also reduced the first interspike interval (ISI) elicited by a

depolarizing pulse. In PFC slices with apical dendrites cut (see below), SKF38393 also shortened the first spike latency and reduced the first ISI in four deep-layers V–VI neurons (Fig. 2B), suggesting that this DA D1 receptor action did not require the apical dendrites.

The changes in input resistance induced by DA or SKF38393 varied greatly with each individual neuron, but overall, there was a small reduction ($-17 \pm 10\%$) in input resistance after DA application and a negligible change ($-2 \pm 4\%$) after SKF38393 in PFC neurons with intact dendrites (Fig. 2D). In the four PFC layers V–VI neurons for which the apical dendrites have been removed, SKF38393 induced a mean increase of input resistance ($20.7 \pm 12\%$). In contrast to the DA and D1 receptor-mediated responses, bath application of quinpirole induced minimal changes in the first spike latency, first ISI, and input resistance (Fig. 2D).

When longer (>1 sec) depolarizing pulses were used to elicit multiple spikes, bath application of DA or the D1 agonist increased spike frequency (Fig. 3). In the presence of the D1 agonist, spike frequency adaptation was reduced greatly, and uniform ISIs were observed (Fig. 3).

Action of the DA D1 receptor agonist SKF38393 on the slowly inactivating Na^+ conductance

To determine how DA influences the excitability of PFC neurons, we focused on two opposing currents that normally determine the

Figure 3. D1 receptor stimulation induced repetitive firing and a removal of spike frequency adaptation in response to a 1-sec-long depolarizing pulse. *A*, A marked delay of first spike latency in response to a 1-sec-long, 50 pA intracellular current pulse (*left*). Increasing the intracellular current pulse to 150 pA induced repetitive firing with variable ISIs and progressive spike frequency adaptation in the same IB neuron (*right*). *B*, Bath application of SKF38393 (20 μ M, for 25 sec) induced repetitive firing in response to the same 50 pA intracellular current pulse (*left*). However, in response to the 150 pA current pulse, there was a marked suppression of the spike frequency adaptation, in addition to a reduction of the postspike afterhyperpolarization (*right*). *C*, Recovery, 25 min after the termination of the application of the D1 agonist (*left*). A graph (*right*) showing the ISIs of the control firing response (*open circle*) and the firing response after the application of SKF38393 (*filled circle*) during the 150 pA intracellular current pulse injection. Note the very variable ISIs and the progressive spike frequency adaptation (e.g., the last ISI is much longer than the first ISI within the same spike train evoked) (*open circle*). SKF38393 abolished the frequency adaptation, thus resulting in more uniform ISIs of $\sim$ 100 msec (*filled circles*).

firing threshold of PFC neurons (see the companion paper). The first was a TTX-sensitive slowly inactivating Na^+ current that is responsible for membrane inward rectification in the subthreshold voltage range (Stafstrom et al., 1985; Sutor and Zieglgansberger, 1987; see also the companion paper), and the second was a 4-AP-sensitive slowly inactivating K^+ current that was responsible for membrane outward rectification (Hammond and Crépel, 1992) (companion paper). The effects of DA on the slowly inactivating Na^+ conductance was examined below.

To block K^+ and Ca^{2+} currents that normally mask the slowly inactivating Na^+ current, six PFC neurons were recorded with Cs^+ -filled microelectrodes and perfused in ACSF containing (in mM): [TEA] $_o$, 20, 4AP2, and Co^{2+} 2.5, and lacking Ca^{2+} (Stafstrom et al., 1985; Schwindt et al., 1988; Taylor, 1993). Under these conditions, a voltage-dependent, slowly inactivating, Na^+ -mediated plateau with overlying voltage oscillations was elicited by injection of short depolarizing pulses (0.1 nA, 50 msec). Reduction of $[\text{Na}^+]_o$ to half (63 mM) reduced the amplitude and duration of the plateau markedly, confirming that it was Na^+ mediated ($n = 3$) (Fig. 4). Membrane depolarization increased the duration of the plateau but decreased its amplitude (Fig. 5).

When held at -60 mV, spontaneous regenerative slow Na^+ -plateau potentials were recorded in four of six cells.

Bath application of SKF38393 (10–50 μ M) enhanced the duration of the slow Na^+ -plateau potential and slightly reduced ($\sim$ 10 mV) its amplitude. SKF38393 (40 μ M) also lowered the activation threshold of the plateau potential by 5 mV (Fig. 5).

Action of the DA D1 receptor agonist SKF38393 on the slowly inactivating K^+ conductance

As noted above, a slowly inactivating K^+ outwardly rectifying conductance also regulates the firing threshold of PFC neurons (see the companion paper). If maximally activated at the subthreshold voltage range, this outward rectifier prevents additional membrane depolarization and can stop neuronal firing (Fig. 6).

To isolate this outwardly rectifying potential, TTX and Co^{2+} were bath applied to block, respectively, Na^+ and Ca^{2+} currents. The slowly inactivating outward rectifier was activated by first hyperpolarizing the membrane below -65 mV for 200–1000 msec and then applying a 1–4 sec, 50 pA depolarizing pulse. The hyperpolarization was necessary to remove the inactivation of this current (Hammond and Crépel, 1992). The V-I plot of the control

Figure 4. A plateau potential and the superimposed membrane oscillations are mediated directly by the slowly inactivating, persistent Na^+ current. *A*, An isolated Na^+ plateau potential lasting for >7 sec was elicited in a RS cell by a 50 msec depolarizing current pulse (100 pA), after 10 min of perfusion by Co^{2+} , TEA, and 4-AP. A fast Na^+ spike was elicited first, followed by only a partial repolarization. Thereafter, sustained membrane oscillations superimposed on the membrane depolarization were recorded ($n = 6$). *B*, Reduction of $[\text{Na}^+]_o$ to half its normal value (from 124 mM to 62 mM) resulted in a marked reduction of the amplitude and duration of the Na^+ plateau potential. This result suggested that the plateau and the oscillation were Na^+ mediated. *C*, When the same cell was current clamped to -65 mV, the same depolarizing pulse (100 msec, 100 pA) reinstated a plateau potential of a markedly shortened duration. *D*, Switching the $[\text{Na}^+]_o$ back to 126 mM reinstated the Na^+ plateau potential. (Note: time scale in *D* is different from that in *A–C*.)

response showed a typical downward bend when the membrane was depolarized to beyond -50 mV. This slowly inactivating conductance was attenuated markedly by 4-AP (0.2–2 mM) (Fig. 8 in the companion paper) or dendrotoxin (50 nM) (Fig. 6). Blockade of this current resulted in an increase in the slope of the voltage-current plot ($n = 5$ for 4-AP; $n = 4$ for dendrotoxin).

Bath application of D1 agonist SKF38393 (40 μM), or 4-AP application (data not shown), removed this slowly inactivating outward rectification, and increased the slope of the V-I plot ($n = 5$, 2 of which were identified PFC $\rightarrow$ NAc neurons) (Fig. 6).

Action of the DA D1 and D2 receptor agonists on the dendritic high-threshold Ca^{2+} conductance

Recent ultrastructural evidence has demonstrated that DA D1/D5 receptors in the primate PFC are exclusively distributed on dendritic spines and shafts (Smiley et al., 1994). Whether a similar arrangement is present in rodents is not known. One important ionic conductance present in the dendrites of cortical neurons is the high-threshold Ca^{2+} current. The following procedures were used to determine whether DA interacts with this current in PFC neurons.

PFC neurons were impaled with Cs^+ -filled or KAc-filled microelectrodes in the presence of TTX (1 μM) and $[\text{TEA}]_o$ (20 mM). Under these conditions, the HTS was elicited from -50 mV by stepped depolarizing pulses ($n = 10$, 4 were identified PFC $\rightarrow$ NAc neurons). The mean peak amplitude of the first HTS evoked by the minimum current pulse was 46 ± 1.4 mV (from threshold) with a mean half-width of 35.8 ± 5 msec. In three ROB neurons tested, the HTS was regenerative and outlasted the duration of the current pulse. Bath application of the D1 agonist SKF38393 (10–40 μM), but not D2 agonist quinpirole (10–40 μM), markedly suppressed the regenerative HTS in ROB cells (Fig. 7*A–C*), and also reduced the amplitude and half-width of the HTS in the ROB and other PFC cell types (Fig. 7*D,E*). After SKF38393 application, the suppressed HTS amplitude could be restored partially if larger depolarizing current pulses were applied (Fig. 7*C*).

To determine whether the SKF38393 primarily modulated L-type Ca^{2+} channels that are distributed close to the soma region (Westenbroek et al., 1990; Hell et al., 1993), nifedipine, an L-type Ca^{2+} channel blocker, was added to the perfusate during HTS activation. Although nifedipine alone (5–10 μM) moderately suppressed the HTS amplitude and duration ($<8\%$ reduction) evoked at different membrane voltages, coapplication with SKF38393 markedly suppressed both the amplitude and half-width ($\sim 40\%$ reduction for both) of the HTS in all five neurons tested. This result suggested that SKF38393 mainly modulated other (presumably P and N) types of high-voltage-activated Ca^{2+} channels.

Because P and N type Ca^{2+} channels are located primarily in the apical dendrites (Hillman et al., 1991; Usowicz et al., 1992; Westenbroek et al., 1992; Mills et al., 1994), SKF38393 might have suppressed the HTS generated in that region. To test this possibility, the effects of SKF38393 were examined in seven slices in which the apical dendrites were removed by making a cut at layer III (apical dendrotomized). The HTS evoked in these slices failed to respond to SKF38393 (up to 90 μM) but were attenuated markedly by nifedipine (10 μM) (Fig. 7*G–I*).

One way in which SKF38393 may suppress the HTS in intact PFC neurons is by transiently enhancing Ca^{2+} entry through high-voltage-activated Ca^{2+} channels, thus resulting in a $[\text{Ca}^{2+}]_i$ -inactivation of Ca^{2+} channels (Hille 1984). To test this possibility, $[\text{Ca}^{2+}]_o$ was substituted with Ba^{2+} (2.4 mM). Ba^{2+} acted as a charge carrier for Ca^{2+} currents but prevented $[\text{Ca}^{2+}]_i$ -

Figure 5. DA D1 receptor stimulation increases the excitability of PFC neurons by interacting directly on a voltage-dependent slowly inactivating Na⁺ current. *A*, An isolated Na⁺ plateau potential elicited by a depolarizing pulse (100 msec, 100 pA). Note the voltage-dependent changes in the duration of the Na⁺ plateau. At -70 , the same depolarizing pulse failed to elicit the Na⁺ plateau potential. *B*, The D1 agonist SKF38393 ($40 \mu\text{M}$) prolonged the duration markedly, but not the amplitude, of the Na⁺ plateau potential at all the holding potentials tested. Unlike in the control, the Na⁺ plateau potential could be elicited at -70 mV in the presence of the D1 agonist ($n = 5$). P1 and P2 indicate the early-fast and the late-slow components of the Na⁺ plateau potential, respectively. *C*, Graphical plot indicating the increase in the duration of the slow Na⁺ plateau potential and the voltage shift in its activation after SKF38393 applications (filled circles) when compared with the control (open circles). Mean data ($\pm$ SEM) was derived from five trials from the same neuron held at different voltages. *D*, *E*, Only small changes in the peak amplitude of the early-fast (P1) and late-slow (P2) components of the Na⁺ plateau potential under the influence of SKF38393 (filled circles) when compared with control (open circles). D1 receptor stimulation may induce a shift of the activation of the slowly inactivating Na⁺ current to more negative voltage (resulting in *A* lowering of the threshold for firing), and a slowing of its inactivation (thus enhancing the duration of the slowly inactivating Na⁺ current).

inactivation of Ca²⁺ channels (Connors, 1979). In the presence of Ba²⁺, TTX, and TEA, a short depolarizing current pulse triggered a long (tens of seconds to noninactivating) plateau potential (Fig. 8*A*). This long Ba²⁺ plateau potential sometimes failed to inactivate, and the membrane remained in the plateau state until it was hyperpolarized artificially by DC current injection (data not shown). Bath application of SKF38393 (20 – $50 \mu\text{M}$) potently suppressed the activation of the Ba²⁺ plateau potential. However, once a noninactivating Ba²⁺ plateau potential was initiated, bath application of the D1 agonist failed to suppress it ($n = 3$). After exposure to SKF38393, it was not possible to reinstate the plateau potential by delivering larger current pulses or by depolarizing the cell (Fig. 8, $n = 4$). Partial recovery of the Ba²⁺-plateau potential was observed 30 min after the SKF38393 was applied.

DISCUSSION

The results from this study showed that DA D1 and D2 receptor stimulation induced inconsistent changes in the passive mem-

brane properties of PFC neurons. In contrast, D1, but not D2, receptor activation enhanced the membrane excitability in response to depolarizing current pulses in PFC output neurons, including those that project to the NAc, by augmenting the voltage-dependent slowly inactivating Na⁺ current and by suppressing the voltage-dependent slowly inactivating K⁺ current. In addition, D1 receptor stimulation also suppressed dendritic HTS that were generated primarily in the apical dendrites of the deep layers V–VI PFC neurons.

DA and passive membrane properties of PFC neurons

Bath application of DA or its agonists induced small and highly variable changes in resting membrane potential (1 – 4 mV). There was no consistent pattern of change in the passive membrane properties, even when potential indirect effects of DA on GABAergic interneurons were ruled out by bicuculline application. Although an overall decrease of R_N resulted from both DA and SKF38393 application, several PFC neurons did show a small

Figure 6. Blockade of a slowly inactivating outward rectifying current by dendrotoxin (50 nM) and SKF38393 in PFC neurons. *A*, Control membrane voltage response to a long depolarizing pulse from a holding potential of -80 mV in the presence of TTX ($1 \mu\text{M}$). Note the initial low threshold Ca^{2+} spike (LTS) and the late strong outward rectification. *B*, Bath application of dendrotoxin, a blocker of the slowly inactivating K^{+} current, attenuated the outward rectification. *C*, V-I plot of the steady-state outward rectification attributable to the slowly inactivating K^{+} current (open circles) and its response to dendrotoxin (closed circles). *D*, Membrane voltage response in another PFC neuron after intracellular injection of a series of depolarizing pulses in the presence of TTX and Co^{2+} to block Na^{+} and Ca^{2+} currents. Note the slowly inactivating outward rectifying current, which normally limits membrane depolarization beyond -50 mV. *E*, Bath application of the D1 agonist SKF38393 ($50 \mu\text{M}$) removed this outward rectification. *F*, Steady-state V-I plot showing the blockade of the outward rectification by SKF38393.

enhancement in R_N . In previous studies in which higher concentrations of DA were bath-applied, deep layers V–VI PFC neurons showed either a 10–30% increase (with $400 \mu\text{M}$ DA + reuptake blocker, Penit-Soria et al., 1987) or no change (50 – $100 \mu\text{M}$, Law-Tho et al., 1994) in input resistance. Such variable changes in these studies could have been attributable to indirect effects resulting from stimulation of DA receptors on neighboring neurons.

D1 receptor regulation of the voltage-dependent slowly inactivating Na^{+} and K^{+} currents

Two voltage-dependent currents regulate the firing threshold of PFC neurons (see the companion paper). The first is a TTX-sensitive, slowly inactivating Na^{+} current that activates within 2–4 msec at subthreshold voltages by short current pulses but takes many seconds to inactivate. In cortical neurons, this Na^{+} current is responsible for both inward rectification and subthreshold membrane oscillations (Stafstrom et al., 1985; Llinas et al., 1991; Alonso and Klink, 1993; Klink and Alonso, 1993). In the present study, by blocking Ca^{2+} and K^{+} currents, the isolated slowly

inactivating Na^{+} current induced a plateau potential with superimposed membrane oscillations. SKF38393 increased the duration of this Na^{+} plateau potential and shifted its activation threshold to a more negative voltage, perhaps by delaying inactivation. This enhancing effect on the slowly inactivating Na^{+} current by SKF38393 is opposite to that observed in striatal neurons in which DA D1 receptor activation suppressed both the fast and the slowly inactivating Na^{+} currents (Calabresi et al., 1987; Surmeier et al., 1992; Cpda et al., 1995; Schiffmann et al., 1995). Possible molecular variants of the D1/D5 receptors present in the PFC and striatum may account for the opposite responses.

TTX-sensitive Na^{+} channels are present in both the dendrites and soma of pyramidal cells as suggested by electrophysiological and Na^{+} -imaging evidence (Huguenard et al., 1989; French et al., 1990; Jaffe et al., 1992; Kim and Connors, 1993; Regehr et al., 1993; Stuart and Sakmann, 1994; Schwindt and Crill, 1995). However, the soma and axon hillock have the densest distribution of immunohistochemically identified Na^{+} channel subunits (Westenbroek et al., 1989). It is not clear whether the slowly inactivating

Figure 7. DA D1 receptor stimulation suppresses dendritic Ca^{2+} mediated HTS. *A*, In a ROB cell perfused with TTX and TEA, regenerative, voltage-dependent, dendritic HTS were excited by current pulses (50 pA steps, $V_h = -50$ mV). *B*, SKF38393 attenuated the amplitude and duration of the HTS markedly and completely suppressed regenerative firing. *C*, Application of higher amplitude current pulses still activated the HTS, but the amplitude and duration was attenuated markedly. *D*, Nonregenerative HTS were recorded by a Cs^+ -filled electrode and perfused by TTX and TEA in an IB PFC neuron. *E*, SKF38393 attenuated both the amplitude and duration of the HTS. *F*, A histogram illustrating the mean ($\pm$ SEM) percentage changes in the peak amplitude (from threshold) and half-width of the HTS from control after the bath application of the D1 agonist SKF38393 (10–40 μM). *G*, HTS (recorded with Cs^+ -filled electrode in the presence of 1 μM TTX in the perfusate) was evoked in another deep layer PFC neuron for which the apical dendrites have been severed (apical dendrotomized) when layers I–III of the brain slice were cut. *H*, The evoked HTS failed to respond to a high concentration of SKF38393 (90 μM). *I*, The same HTS was attenuated markedly by the L-type Ca^{2+} channel blocker nifedipine (10 μM), suggesting that the electrogenesis of the SKF38393-insensitive HTS in this apical dendrotomized deep layer PFC neuron was near the soma.

and fast Na^+ currents are generated by the same or different Na^+ channels. Data from single Na^+ channel recordings in acutely isolated cortical pyramidal cells favor the idea that a single class of Na^+ channels can switch to a sustained opening mode that is interspersed with short-duration transient openings. When in the

sustained opening mode, rapid inactivation of the Na^+ channel is unlikely (Moorman et al., 1990; Alzheimer et al., 1993). Our findings suggest that D1 receptor stimulation in the PFC may cause the Na^+ channels to stay in a sustained opening mode.

The second current that regulates the firing threshold of PFC

Figure 8. Direct D1 receptor suppression of dendritic HTS is *not* attributable to an enhancement of $[Ca^{2+}]_i$ inactivation of the high-threshold Ca^{2+} current that mediate the HTS. *A*, Ba^{2+} is used as the charge carrier for Ca^{2+} current. Substitution of extracellular Ca^{2+} with Ba^{2+} (in TEA and TTX) also removed $[Ca^{2+}]_i$ -inactivation of the high-threshold Ca^{2+} currents. A stepwise (20 pA steps) increment of depolarizing pulses eventually evoked an all-or-none, long-lasting (100 sec), Ba^{2+} plateau potential (*asterisk*). *B*, After SKF38393 application, similar current pulses delivered at various holding potentials no longer evoked the Ba^{2+} plateau potential. *C*, Partial recovery of the Ba^{2+} plateau potential (*asterisk*) 14 min after the application of SKF38393.

neurons is a 4-AP- and dendrotoxin-sensitive current that is responsible for membrane outward rectification in the subthreshold voltage range. Its pharmacological and biophysical properties resemble the slowly inactivating K^+ currents I_D or I_{KS} characterized previously in hippocampal and cultured striatal neurons (Storm, 1988; Foehring and Surmeier, 1993; Nisenbaum et al., 1994). A very similar K^+ current also is present in the PFC (Hammond and Crépel, 1992). This current is inactive at rest, but a longer than 1 sec membrane hyperpolarization removes its inactivation. Once I_{KS} is activated within 100–200 msec by a depolarizing pulse, it takes many seconds to inactivate. I_{KS} opposes membrane depolarization and delays firing considerably, unless the neuron is activated by long-lasting or repetitive depolarizing inputs (Hammond and Crépel, 1992; Foehring and Surmeier, 1993).

Findings from the present study and others (Kitai and Surmeier, 1993) have shown that D1 stimulation attenuates the I_{KS} . However, the present data cannot rule out the possibility that a D1 agonist may also affect a dendrotoxin-insensitive K^+ current. The reduction of I_{KS} after D1 receptor activation would leave the inwardly rectifying, slowly inactivating Na^+ current unopposed. This would enable the cell to be most responsive to depolarizing inputs and would promote repetitive firing. Little is known about the distribution of the slowly inactivating K^+ channels in single cortical pyramidal neurons, although neural computational stud-

ies suggest that such K^+ channels are likely to be present in both the soma and dendrites (Bernander et al., 1994; Midtgard, 1994). Thus, D1 receptor stimulation could enhance the influence of depolarizing inputs to various regions of layers V–VI PFC neurons by increasing the slowly inactivating Na^+ conductance while inhibiting the opposing slowly inactivating K^+ conductance.

D1 receptor-mediated suppression of the dendritic high-threshold Ca^{2+} current

Cortical neurons possess all three major types (L, P, N) of high-voltage-activated Ca^{2+} channels (Franz et al., 1986; Sayer et al., 1990; 1993; Brown et al., 1993; Ye and Akaike, 1993). Although the L-type Ca^{2+} channels are distributed primarily close to the soma (Westenbroek et al., 1990; Hell et al., 1993), the P and N channels are located mainly in the dendrites (Hillman et al., 1991; Usowicz et al., 1992; Westenbroek et al., 1992; Mills et al., 1994). In the present study, the L-type Ca^{2+} channels blocker nifedipine had a small attenuating effect on the evoked HTS in intact slices, but a major suppressive effect on the HTS evoked in slices in which the apical dendrites were cut. Moreover, D1 receptor stimulation consistently suppressed the amplitude, duration, and regeneration of dendritic HTS in intact slices, but not in slices in which the apical band of the dendrites [corresponding to a “hot zone” of highest voltage-dependent influx of $[Ca]_i$ (Yuste et al., 1994)] was removed. These results suggest that the HTS evoked in

Figure 9. A highly simplified schematic of a functional model of dopaminergic modulation of dendritic-somatic signal integration in layers V-VI pyramidal PFC neurons that project to the NAc. For details, see Discussion.

apical dendrotomized PFC neurons may have represented the SKF38393-insensitive HTS mediated by the nifedipine-sensitive L-type Ca^{2+} channels near the soma region, whereas the nifedipine-insensitive HTS that was responsive to D1 receptor modulation likely was generated by P- and N-type Ca^{2+} channels in the apical dendrites. However, it should be noted that these suggestions are inferred from intrasomatic recordings, and direct apical dendritic recordings are required (experiments in progress) to determine whether the D1 receptor modulates pharmacologically identified P- or N-type Ca^{2+} currents.

The suppressive actions of a D1 agonist on HTS observed in intact slices are consistent with a DA-mediated suppression of high-threshold Ca^{2+} currents in other vertebrate and invertebrate neurons (Paupardin-Tritsch et al., 1985; Marchetti et al., 1986; Williams et al., 1990; Surmeier et al., 1995), although in some endocrine and retinal cells, D1 receptor stimulation resulted in a potentiation of dihydropyridine-sensitive high-threshold Ca^{2+} current (Liu et al., 1992; Pfeiffer-Linn and Lasater, 1993; Wong et al., 1994). In the present study, D1 receptor-mediated suppression of the HTS was overcome partially by injection of larger depolarizing pulses, suggesting that D1 receptor stimulation induced a shift in the activation or inactivation kinetics of the high-threshold Ca^{2+} channels (Bean, 1987). Furthermore, stimulation of the D1 receptor did not induce HTS inactivation by indirectly increasing $[Ca^{2+}]_i$, because SKF38393 also suppressed the activation of the Ba^{2+} plateau potential. We suggest that stimulation of the D1 receptor directly reduced Ca^{2+} entry through dendritic high-threshold Ca^{2+} channels. Imaging of Ca^{2+} entry in a specific

region of the apical dendrite triggered by local membrane depolarization or synaptic input after D1 receptor stimulation would address this issue directly.

A model for the role of DA in the PFC

The model presented in Fig. 9 is a synthesis of the results discussed above. This model explains how DA might interact with Na^+ , K^+ , and Ca^{2+} conductances in the dendrites and soma to influence information processing by layers V-VI PFC output neurons. It is known that the dendrites of pyramidal neurons receive and process a complex array of input signals. Based on the known anatomical connections, inputs to the apical dendrites arise mainly from diverse association cortices (Jones, 1984). A and B illustrate how DA might modulate inputs to the apical dendrites in layers I-II. According to recent findings (Markram and Sakmann, 1994; Magee and Johnston, 1995), subthreshold stimulation (Sub $\rightarrow$) of the afferents to the apical dendrites that evokes a somatic EPSP but no action potential activates dendritic Na^+ channels and low-threshold Ca^{2+} channels in small local areas of the dendritic arbor. In contrast, many high-threshold Ca^{2+} channels are activated by suprathreshold synaptic inputs (Supra $\rightarrow$) that elicits spike firing in the soma (Regehr et al., 1989; Miyakawa et al., 1992; Regehr and Tank, 1992; Markram and Sakmann, 1994; Stuart and Sakmann, 1994; Spruston et al., 1995). Activation of the HTS can trigger a regenerative chain reaction that activates neighboring voltage-dependent Ca^{2+} channels, depolarizing an extended portion of the dendritic arbor (broad shaded region of the downward arrow on the apical dendrites). In addition, the

dendritic HTS may function as part of a gain-control mechanism, boosting synaptic inputs that arrive in remote active dendritic regions, thereby ensuring that the effects of the depolarizing inputs will be propagated to the soma (as indicated by the *large shaded downward-pointing arrow* in Fig. 9A) (Miller et al., 1985; Shephard et al., 1985; Bernander et al., 1994; De Schutter and Bower, 1994; Jaffe et al., 1994; Mel, 1994; Yuste et al., 1994; Magee and Johnston, 1995). Presumably, maximally activated HTS also boosts subthreshold inputs in these broad region of the apical dendritic arbor (*Sub* → within the *shaded arrow area* in Fig. 9A).

D1 receptor stimulation attenuates the activation and regeneration of HTS in the apical dendritic region (Fig. 9B). Optimal D1 receptor activation, therefore, may restrict the regions of the active dendrites functionally such that only strong suprathreshold depolarizing inputs, and subthreshold inputs that are temporally synchronized and spatially contiguous with the suprathreshold inputs, will influence somatic activity. Subthreshold inputs that are outside the sphere of depolarization by the HTS will not be amplified and, therefore, unable to influence somatic activity (Fig. 9B, *Sub* → outside the *shaded area*). In this way, DA may “focus” or “sharpen” the effects of the synaptic inputs to the dendrites. The restricted dendritic–somatic flow of signals from the remote apical dendrites to the soma in the deep layers (shown as *narrow downward dark arrow* in Fig. 9B) may be enhanced by D1 receptor mediated augmentation (*upward arrow*) of the slowly inactivating Na^+ channels and suppression (*downward arrow*) of the slowly inactivating K^+ channels, which are distributed on the dendrites and soma regions. Hence, via D1 receptor activation, DA may focus or sharpen the effects of depolarizing inputs arising primarily from different cortical association areas (*square box*).

Depolarization of regions of the dendritic tree by the HTS also may briefly relieve the voltage-dependent Mg^{2+} block of the dendritic NMDA receptor channel complex, thus allowing additional Ca^{2+} entry that can activate intracellular biochemical processes responsible for altering synaptic efficacy (Hirsch and Crpel, 1990; Regehr and Tank, 1990; Sah and Nicoll, 1991; Alford et al., 1993; Perkel et al., 1993; Ghosh and Greenberg, 1995). The actions of DA in the dendritic regions of the PFC neurons may thereby restrict Ca^{2+} -dependent events to only those dendritic regions activated directly by suprathreshold synaptic inputs (*Supra* → within the *shaded region of the arrow* in B).

As illustrated in Figure 9, C and D, the known anatomical data suggest that depolarizing inputs to the somal or basal dendritic regions of deep layers V–VI PFC neurons arise from neighboring cells in adjacent columns within the same deep lamina (Levitt et al., 1993; Kritzer and Goldman-Rakic, 1995) or from the thalamic nuclei (Jones, 1984; Kuroda et al., 1995). Optimal D1 receptor activation also may induce an overall enhancement of such inputs (*broad downward arrow* in D) via the D1 receptor mediated actions on the slowly inactivating Na^+ and K^+ channels located close to the soma. This latter action of DA would promote sustained activity within local circuits in the deep layers of the PFC. This model therefore illustrates that the actions of DA on pyramidal PFC neurons is neither “excitatory” nor “inhibitory” but depends on the foci, timing, and strength of synaptic inputs, as well as on the membrane potential range at which the PFC neuron is operating.

Functions and dysfunctions of PFC DA system

Recent studies have revealed the critical importance of PFC D1 receptor mechanisms in cognitive functions. PFC neurons may retain or use previously acquired information to guide a forth-

coming response in a delayed-response task. The firing during the delayed period of this task requires an optimal level of D1 receptor stimulation (Sawaguchi et al., 1990a, b; Goldman-Rakic, 1995b; Williams and Goldman-Rakic, 1995), and systemic administration of D1 agonists can improve significantly the performance on a PFC-mediated delayed-response task in aged monkeys and monkeys with DA depletion (Arnsten et al., 1994). Conversely, D1, but not D2, antagonists microinjected into the PFC reduce markedly the accuracy of memory-guided saccades toward a correct target location in an oculomotor delayed-response task in monkeys (Sawaguchi and Goldman-Rakic, 1994), and disrupt the performance of rats in a delayed-foraging task on an eight-arm radial maze (Seamans et al., 1995b). Based on the model presented in Fig. 9, blockade D1 receptors in PFC may “bias” PFC pyramidal output neurons to (1) respond nonspecifically to all association cortical inputs to the apical dendrites, and/or (2) be less influenced by local intralayers V–VI or thalamo-cortical inputs. As a result, neuronal circuits within the deep layers of the PFC may be unable to maintain the ongoing neural activity necessary to retain and/or use previously acquired information to organize a forthcoming response.

A current hypothesis of the etiology of schizophrenia suggests that altered DA activity in the PFC and NAc may be responsible for some of the symptomatology of schizophrenia (Robbins, 1990; Deutch, 1993; Grace, 1993). Cerebral blood flow data show hypofrontality in schizophrenics during performance of cognitive tasks that activates the PFC specifically (Weinberger et al., 1986; Berman and Weinberger, 1990; Weinberger, 1991). If it could be shown conclusively that hypoactivity in the PFC is associated with attenuated PFC DA function (Daniel et al., 1991; see also Dolan et al., 1995), then the model proposed here may be relevant in explaining certain positive symptoms of schizophrenia. If DA levels are low, there will be less “focusing” or “sharpening” of signals in the apical dendrites, and PFC output neurons will be driven nonselectively by inputs from diverse cortical association areas. This may be a potential mechanism contributing to the intrusive and disorganized patterns of thoughts that are defining features of schizophrenia. Given that attenuated PFC DA function leads to a reactive augmentation of NAc DA transmission in response to stress and other acute challenges (Carter and Pycck, 1980; Pycck et al., 1980; Leccese and Lyness, 1987; Louilot et al., 1989; Jaskiw et al., 1990a, b, 1991; Vezina et al., 1991; Mitchell and Gratton, 1992; Deutch, 1993; Roberts et al., 1994), this raises the additional possibility that such reactive enhancement of NAc DA transmission in response to stressful stimuli may be mediated directly via the PFC → NAc neurons, or indirectly by way of the PFC efferents to the VTA DA neurons (Robbins, 1990; Deutch, 1993; Grace, 1993; Murase et al., 1993; Taber et al., 1995).

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