Dopaminergic Modulation of Local Network Activity in Rat Prefrontal Cortex

Susanta Bandyopadhyay and John J. Hablitz

Department of Neurobiology and Civitan International Research Center, University of Alabama, Birmingham, Alabama

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INTRODUCTION

Prefrontal cortex is responsible for representation and execution of actions. Like other parts of neocortex, prefrontal cortex contains extensively interconnected networks of pyramidal cells and interneurons. These networks are modulated via dopaminergic inputs from the midbrain ventral tegmental area (VTA) (Bjorklund and Lindvall 1984). Dopamine plays an important role in normal executive functions including working memory (Bjorklund and Lindvall 1986; Williams and Goldman-Rakic 1995). Altered dopamine function in prefrontal cortex also has been implicated in the pathogenesis of epilepsy (Starr 1996) and neuropsychiatric disorders like schizophrenia (Egan and Weinberger 1992; Weinberger 2004). Dendritic spines of pyramidal neurons in primate and rodent neocortex form synaptic triads with dopaminergic and glutamatergic axon terminals, and dopamine is believed to gate excitatory synaptic inputs to pyramidal neurons at these synaptic triads (Goldman-Rakic 1992; Williams and Goldman-Rakic 1995). Dendrites of neocortical interneurons also receive dopaminergic axon terminals (Benes et al. 1993; Sesack et al. 1995; Verney et al. 1990; Williams and Goldman-Rakic 1993). There are two families of G protein coupled dopamine receptors: D1-like (comprising D1 and D5, coupled to G_s) and D2-like (comprising D2, D3, and D4, coupled to G_i). Both families of receptors are present in pyramidal neurons and interneurons of the prefrontal cortex (Gaspar et al. 1995; Mrzljak et al. 1996; Verney et al. 1990; Vincent et al. 1993, 1995), allowing for complex dopaminergic modulation of neocortical circuits.

Dopamine has multiple and variable effects on neuronal excitability and fast synaptic transmission in the prefrontal cortex (see Seamans and Yang 2004 for review). Knowledge concerning dopamine’s effect on local neuronal networks in the prefrontal cortex is still evolving. In vivo recordings from prefrontal cortex have mostly revealed a decrease in spontaneous firing of pyramidal neurons after iontophoretic application of dopamine or VTA stimulation (Bernardi et al. 1982; Bunney and Aghajanian 1976; Ferron et al. 1984; Pirot et al. 1992; Reader et al. 1979; Sesack and Bunney 1989; Thierry et al. 1992; Yang and Mogenson 1990). In contrast, an increase in postsynaptic excitability of pyramidal neurons in the prefrontal cortex has been generally reported in vitro (Ceci et al. 1999; Gonzalez-Burgos et al. 2002; Gorelova and Yang 2000; Henze et al. 2000; Penit-Soria et al. 1987; Tseng and O’Donnell 2004; Wang and O’Donnell 2001; Yang and Seams 1996), although decreases in pyramidal neuron intrinsic excitability have also been reported (Geijo-Barrientos and Pastore 1995; Gullelde and Jaffe 1998, 2001). Moreover, dopamine can directly increase the excitability of fast-spiking interneurons in neocortex (Gonzalez-Burgos et al. 2002; Gorelova et al. 2002; Zhou and Hablitz 1999). The effects of dopamine on excitatory postsynaptic currents (EPSCs) and inhibitory postsynaptic currents (IPSCs) are variable (see Seamans and Yang 2004 for review), varying with the species, the cortical layer, and input examined. Thus dopaminergic activation in the prefrontal cortex affects the balance between excitation and inhibition in a complex way. Such modulation by dopamine can have an important role in shaping activity in local neuronal networks in the prefrontal cortex. Because of the complexity and microheterogeneity of dopamine’s effects on neuronal excitability and synaptic transmission described in the preceding text, the net effect of dopamine on local neuronal networks under conditions of normal synaptic transmission is unclear. Previously we have reported that dopamine enhanced activity in local excitatory networks in disinhibited prefrontal cortex (Bandyopadhyay et al. 2005). In the present work, we have...
investigated dopamine’s effect on local neuronal networks in the prefrontal cortex when both excitation and inhibition are intact. Our results from whole cell recording and voltage-sensitive dye imaging show that dopamine’s net effect is to increase inhibition under these conditions. Acting via D1-like receptors, dopamine restricts spatiotemporal spread of synaptic activity in local neocortical networks.

**METHODS**

**Brain slice preparation**

Experiments were carried out in brain slices from prefrontal cortex of Sprague-Dawley rats (25–30 day old). Prior approval from the UAB Institutional Animal Care and Use Committee was obtained for all experimental protocols. Rats were anesthetized with ketamine and decapitated. The brain was removed and coronal slices (300 µm thick) were cut on a Vibrotome (Pella, Redding CA) from a block of brain containing the prefrontal cortex. During slicing, the tissue was kept submerged in a solution containing (in mM) 125 NaCl, 3.5 KCl, 26 NaHCO₃, 10 d-glucose, 3 MgCl₂, and 1 CaCl₂. Slices were stored in a solution containing (in mM) 125 NaCl, 3.5 KCl, 26 NaHCO₃, 10 d-glucose, 2.5 CaCl₂, and 1.3 MgCl₂, at 37°C for 45 min, and then, at room temperature until recording. The solution was continuously bubbled with 95%O₂,5%CO₂ to maintain pH around 7.4. Individual slices were subsequently transferred to a recording chamber continuously perfused (3 ml/min) with oxygenated saline at 32°C. The anterior cingulate cortex and the shoulder or Fr2 region of the frontal cortex (Paxinos and Watson 1986) were used for electrophysiological recording and optical imaging.

**Electrophysiology**

Neurons were visualized using a Zeiss Axioskop FS (Carl Zeiss, Thornwood NY) microscope equipped with Nomarski optics, a 40× water-immersion lens and infrared illumination. Layer II/III pyramidal neurons were identified by their morphology, distance from the pial surface and their regular spiking properties. Cells were labeled with biocytin to confirm their identity. Whole cell recordings were obtained as described previously (Bandyopadhyay et al. 2005). To examine the voltage dependence of synaptic currents, cells were held at −70 mV and stepped to voltages between −90 through −40 mV in 10-mV increments for 500 ms. Synaptic currents were evoked 100 ms after step onset. For current-clamp recordings, 500-ms hyper- and depolarizing current pulses of varying amplitudes were applied and evoked synaptic potentials were recorded by applying a stimulus 250 ms after the onset of current pulse. The intracortical solution used for recording evoked synaptic responses contained (in mM) 125 K-gluconate, 10 KCl, 10 HEPES, 2 Mg-ATP, 0.2 Na-GTP, and 0.5 EGTA. pH and osmolarity were adjusted to 7.3 and 290 mosM, respectively. When filled with this intracellular solution, patch pipettes had resistances ~3 MΩ. Series resistance ranged from 10 to 20 MΩ. Recordings were terminated whenever significant increases (>20%) in series resistance occurred. A bipolar stimulating electrode (twisted pair of 25 µm Formvar-insulated nichrome wires) was used to provide square wave current pulses (100–400 µA for 50–100 µs) to evoke synaptic responses. The stimulating electrode was positioned intracortically at a distance of 150–200 µm below the recording pipette. Signals were recorded using a Warner PC 505A amplifier (Warner Instruments Corp. Hamden, CT) and were filtered at 5 kHz, digitized at 10–20 kHz via a Digidata 1200B interface (Molecular Devices, Sunnyvale, CA). Clampfit 8.0 software (Molecular Devices) was used for analysis.

**Optical imaging**

For optical imaging experiments, slices were stained with the voltage-sensitive fluorescent dye [N-(3-(triethylammonium)propyl)-4-(4-diethylaminophenyl)buta-di-ethylpyrridinium dibromide (RH 414)] (Grinvald et al. 1988) by incubating them in saline containing RH 414 (30 µM) for 45–90 min at room temperature. Each stained slice was transferred to a recording chamber on the stage of the microscope (Axiovert 135TV, Carl Zeiss) used for optical recording and excess dye was washed out for ≥30 min prior to recording. Activity was evoked in the slices once every minute using a bipolar stimulation electrode as described in the preceding text; the stimulation site and strength were the same as those used in whole cell recordings. Fluorescence signals were detected by a Neuroplex 464-element photodiode array (Red Shirt Imaging, Fairfield, CT) using a sampling rate of 1.6 kHz. Thus frames were acquired at 0.6-ms intervals. The dye was excited by light from a 100-W halogen lamp passing through a 535 ± 40 nm band-pass filter. Emitted light was focused on the photodiode array after passing through a 590-nm long-pass filter. Illumination was precisely timed using a computer-controlled shutter that minimized toxic effects of the dye. The optical signals were amplified and stored on a computer for off-line analysis using the Neuroplex software (Red Shirt Imaging). All fluorescence measurements were normalized to the resting light intensity measured for each detector. Dye bleaching was corrected using measurements taken in the absence of stimulation. All optical signals are represented as percent changes in fluorescence (∆F/⟨F⟩ where F is the fluorescence light intensity of the stained slice during illumination without evoked activity and ∆F is the fluorescence change during neuronal activity). Membrane depolarization causes a decrease in fluorescence and is plotted as an upward deflection in all figures. Pseudocolor images were generated from acquired optical signals for visualizing spatiotemporal patterns of activity. Pseudocolor scaling was fixed for all frames in a given figure. A video camera attached to a dissecting microscope was used to acquire an image of the slice and document the position of the diode array. These images were used to match optical signals to cortical laminae.

**Drug application**

All drug solutions were prepared by dissolving frozen stock solutions in the saline prior to each experiment. Dopamine was used as the endogenous agonist for dopamine receptors. Sodium metabisulfite (50 µM) was used to protect dopamine from being oxidized (Sutor and ten Bruggencate 1990). R(+)-6-chloro-7,8-dihydroxy-1-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide (SKF 81297) and R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SCH 23390) were used as a selective D1 agonist and antagonist, respectively. Quinpirole and S(-)-eticlopride hydrochloride were used as a selective D2 agonist and antagonist, respectively. All the drugs were bath applied. For experiments with the dopamine antagonists, the antagonist was present in both control and agonist-containing solutions. Dopamine, SKF 81297, and eticlopride were purchased from Sigma (St. Louis, MO), whereas SCH 23390 and quinpirole were purchased from Tocris Cookson (Ellisville, MO).

**Data analysis and statistics**

Data from imaging experiments were analyzed as described elsewhere (Bandyopadhyay et al. 2005). A region of interest (ROI) that included photodiodes showing visually detectable activity along with a surrounding area with no apparent activity was chosen in the control recording. Peak signal amplitudes (∆F/⟨F⟩) of five diodes outside the ROI were averaged to obtain the baseline noise level. Photodiodes with peak signal amplitudes above twice that of the baseline noise were then selected for analysis. The peak signal amplitudes of these same photodiodes were summed to obtain a measure termed “peak activity” under control conditions. The peak signal amplitudes of these same photodiodes were summed to get the peak activity after drug application. The distance between the two extreme diodes in the ROI
showing activity above twice the baseline noise was used as the measure for lateral spread of activity. Duration of activity was calculated by estimating the time interval between the first and the last frames of an acquisition showing significant activity. These parameters were measured under control conditions and 10 min after drug application. Statistical comparisons between values obtained before and after drug application were done using Student’s t-test (P < 0.05 was considered significant). Data are expressed as mean ± SE.

RESULTS

Alterations in intrinsic excitability of layer II/III pyramidal cells after dopamine

Under direct visualization, current-clamp recordings were obtained from layer II/III pyramidal cells. These cells were identified on the basis of distance below the pial surface, presence of a prominent ascending apical dendrite and regular spiking behavior. We have reported previously that dopamine, in the presence of CNQX, APV, and bicuculline to block synaptic transmission, had only small effects on the resting membrane potential and decreased the number of evoked action potentials in some cells (Gonzalez-Islas and Hablitz 2001; Zhou and Hablitz 1999). In the present work, under conditions of normal synaptic transmission, bath application of dopamine did not significantly affect change the number of action potentials produced by a depolarizing current pulse (7 ± 3 under control condition vs. 5 ± 2 after 30 µM dopamine, n = 5; P > 0.05). There was also no significant change in resting membrane potential (−67 ± 1 mV under control condition vs. −66 ± 2 mV after 30 µM dopamine, n = 7, P > 0.05) or input resistance (162 ± 17 MΩ under control condition vs. 153 ± 18 MΩ after 30 µM dopamine, n = 7, P > 0.05) after dopamine.

Synaptic potentials were evoked 250 ms after the onset of current pulse (Fig. 1A). Response amplitudes were measure at 5 and 15 ms after response onset to measure excitatory and inhibitory components. Figure 1B shows that dopamine did not affect responses measured at 5 ms. Responses measure at 15 ms showed a change in reversal potential and an increase in amplitude at more positive potentials, consistent with an increase in evoked IPSPs. These results suggest that dopamine decreases overall excitability by enhancing IPSPs.

Dopamine enhances the outward inhibitory component of composite postsynaptic currents

In an attempt to better distinguish early and late components of evoked synaptic currents, voltage-clamp recordings were obtained from pyramidal cells. Postsynaptic currents recorded in layer II/III pyramidal neurons (n = 5) under control conditions are shown in Fig. 2A. The pyramidal neurons were held at −70 mV, and voltage steps were applied to record postsynaptic currents at several different voltages between −90 and −40 mV. Under control conditions at −70 mV, inward currents were recorded which increased in amplitude with steps to more hyperpolarized levels. Depolarization reduced the amplitude of the inward current and revealed an outward component at −40 mV. These results indicated that stimulation was evoking an EPSC-IPSC complex. To examine this further, response amplitudes were measured 5 and 15 ms after stimulation, before and after bath application of 30 µM dopamine. As shown in the current-voltage plots in Fig. 2B, early currents were not affected by dopamine, whereas late responses at −50 and −40 mV were enhanced (25 ± 7 vs. 64 ± 9 pA after dopamine, n = 5, P < 0.05). These results suggest that under conditions of normal synaptic transmission dopamine selectively enhances inhibition.

Dopamine restricts spatiotemporal spread of activity evoked by single and train stimulation

Optical imaging with the voltage-sensitive dye RH 414 was used to study how spatiotemporal patterns of activity were modulated by dopamine under conditions of normal synaptic transmission. The hexagonal photodiode array used for this purpose covered an area of 1.8 × 1.8 mm of the slice at the magnification (×10) used. Figure 3A shows the typical position of the photodiode array (*, site of stimulation). A pseudocolor map of dye signals recorded from a prefrontal cortical slice 12 ms after a single intracortical stimulation under control conditions is shown in Fig. 3B. Activity was most prominent in upper cortical layers and extended laterally for 900 ± 83 µm (n = 9). Dye signals from three photodiodes under control conditions and in the presence of 30 µM dopamine drug are shown superimposed in Fig. 3C. A decrease in dye signals after dopamine application is clearly evident in each of the photodiodes. A series of pseudocolor maps of activity evoked by a
Single intracortical stimulation are shown in Fig. 4A, top. The interval between each map was 15 ms. It can be seen that stimulation results in activation of a small area of the slice. Activity spreads laterally to adjacent areas and persists for 60 ± 6 ms (n = 9). After application of 30 μM dopamine for 10 min, activity in response to the same stimulation was decreased (Fig. 4A, bottom). To quantify these changes, peak amplitudes, before and after dopamine application, were calculated for diodes lying on a line drawn through the region showing the highest levels of activity. These amplitudes were normalized to the highest peak amplitude and plotted as a function of distance from the diode showing the highest peak dye signal (Fig. 4B; n = 9). Peak dye signals and lateral spread of activity were decreased after dopamine application. The level of background activity is indicated by the dotted line.

During the delay period of working-memory tasks, neurons in the prefrontal cortex in vivo exhibit firing rates in the 20-Hz range (Funahashi et al. 1989; Fuster 1973; Miller et al. 1996; Sawaguchi et al. 1990a,b). Therefore we examined the effect of dopamine on activity evoked by train stimulation in this physiological range. In response to a train of five stimuli at 20 Hz, a larger area of cortex was excited and activity persisted for a longer period of time (Fig. 5A, top). In the presence of dopamine, a decrease in activity similar to that observed with single stimulation was observed (Fig. 5A, bottom). Analysis of changes as a function of the distance from the point of maximal activation (Fig. 5B) indicated that amplitudes were decreased. Dopamine decreased the spatial extent of activation. The decline occurred over a shorter distance, indicating a greater sharpening of the excitatory field.

Further analysis of data (see METHODS) was done to compare “peak activity,” duration and lateral spread of activity before and after dopamine. Dopamine significantly decreased peak activity (0.43 ± 0.07 in control vs. 0.39 ± 0.07 after dopamine, n = 9, P < 0.05), duration (60 ± 6 ms in control vs. 46 ± 6 ms after dopamine, n = 9, P < 0.05) and lateral spread of activity (900 ± 83 μm in control vs. 708 ± 81 μm after dopamine, n = 9, P < 0.05) evoked by single stimulation in the prefrontal cortex (Fig. 6A). Significant decreases in peak (0.63 ± 0.16 in control vs. 0.57 ± 0.17 after dopamine, n = 6, P < 0.05), duration (368 ± 30 ms in control vs. 295 ± 18 ms after dopamine, n = 6, P < 0.05), and lateral spread of activity (1075 ± 92 μm in control vs. 837 ± 94 μm after dopamine, n = 6, P < 0.05) after bath application of dopamine (30 μM) were also seen when activity was evoked by train stimulation (Fig. 6B)

Restriction of spatiotemporal spread of evoked activity by dopamine is D1 mediated

In the next set of experiments, involvement of D1 and D2 receptors was examined. With single stimulation, decreases in activity, similar to those seen with dopamine, were observed when the D1 receptor agonist SKF 81297 (1 μM) was applied. Peak activity (0.29 ± 0.06 in control vs. 0.25 ± 0.05 after SKF 81297, n = 5, P < 0.05), duration (48 ± 7 ms after SKF 81297, n = 5, P < 0.05), and lateral spread (975 ± 57 μm in control vs. 696 ± 56 μm after SKF 81297, n = 5, P < 0.05) of activity significantly decreased after bath application of SKF 81297 (1 μM; Fig. 6A). The D2-like agonist quinpirole did not have any effect on activity (Fig. 6A) evoked by single shock stimulation (peak: 0.38 ± 0.04 in control vs. 0.38 ± 0.05 after quinpirole, n = 5, P >
0.05; duration: 87 ± 5 ms in control vs. 83 ± 6 ms after quinpirole, n = 5, P > 0.05; lateral spread: 900 ± 47 µm in control vs. 870 ± 61 µm after quinpirole, n = 5, P > 0.05). The effect of dopamine was not blocked by the D2-like antagonist eticlopride (10 µM; Fig. 6A). When dopamine was applied in presence of eticlopride (10 µM), peak activity decreased from 0.43 ± 0.07 in control to 0.35 ± 0.06 after dopamine (n = 5, P < 0.05), duration of activity decreased from 75 ± 9 ms in control to 42 ± 6 ms after dopamine (n = 5, P < 0.05), and lateral spread of activity decreased from 1035 ± 170 µm in control to 750 ± 142 µm (n = 5, P < 0.05) after dopamine. In contrast, SCH 23390 (10 µM), the antagonist selective for D1-like receptors, blocked the inhibitory effect of dopamine on activity evoked by a single intracortical stimulus in regular ACSF. When dopamine was bath applied in presence of SCH 23390 (10 µM), no change in peak (0.39 ± 0.03 in control vs. 0.38 ± 0.02 after dopamine, n = 5, P > 0.05), duration (73 ± 3 ms in control vs. 67 ± 6 ms after dopamine, n = 5, P > 0.05), or lateral spread (900 ± 79 µm in control vs. 825 ± 47 µm after dopamine, n = 5, P > 0.05) of activity was noted (Fig. 6A).

When train stimulation was used, the D1-like agonist SKF 81297 (1 µM) also had effects similar to those observed with dopamine. It significantly decreased the peak (0.37 ± 0.08 in control vs. 0.33 ± 0.07 after SKF 81297, n = 5, P < 0.05), duration (293 ± 23 ms in control vs. 249 ± 10 ms after SKF 81297, n = 5, P < 0.05), and lateral spread (1215 ± 93 µm in control vs. 915 ± 90 µm after SKF 81297, n = 5, P < 0.05) of activity when train stimulation was used (Fig. 6B). The D2-like agonist quinpirole had no effect on activity (Fig. 6B) evoked by train stimulation (peak: 0.47 ± 0.12 in control vs. 0.46 ± 0.12 after quinpirole, n = 5, P > 0.05; duration: 277 ± 13 ms in control vs. 269 ± 15 ms after quinpirole, n = 5, P > 0.05; lateral spread: 1005 ± 38 µm in control vs. 960 ± 28 µm after quinpirole, n = 5, P > 0.05). The effect of dopamine on activity evoked by train stimulation was not blocked when dopamine was applied in presence of the D2-like antagonist eticlopride (10 µM; peak: 0.45 ± 0.05 in control vs. 0.37 ± 0.04 after dopamine, n = 5, P < 0.05; duration: 287 ± 8 ms in control vs. 238 ± 4 ms after dopamine, n = 5, P < 0.05; lateral spread: 1,215 ± 73 µm in control vs. 975 ± 53 µm after dopamine, n = 5, P < 0.05). However, the dopamine-mediated decrease in activity evoked by train stimulation was blocked when SCH 23390 (10 µM), the antagonist selective for D1-like receptors, was present in bath (Fig. 6B). There was no change in peak (0.50 ± 0.06 in control vs. 0.49 ± 0.04 after dopamine, n = 5, P > 0.05), duration (322 ± 27 ms in control vs. 317 ± 32 ms after dopamine, n = 5, P > 0.05), or lateral spread (1125 ± 63 µm in control vs. 1065 ± 80 µm after dopamine, n = 5, P > 0.05) of activity after dopamine application. This suggests that the inhibitory effect of dopamine on spatiotemporal spread of activity evoked by intracortical stimulation in prefrontal cortical slices in vitro was due to activation of D1-like receptors.

**Discussion**

In the present work, we have studied dopaminergic modulation of the spatiotemporal spread of activity in rat prefrontal cortex in vitro. These studies were conducted under conditions...
of normal synaptic transmission, i.e., with excitation and inhibition intact. Our findings with whole cell recording suggest that dopamine’s predominant effect was to increase inhibition via activation of D1 receptors. Imaging experiments demonstrated that dopamine decreased the amplitude and duration of voltage-sensitive dye signals and inhibited the lateral spread of activity in local cortical networks.

Modulation of postsynaptic currents by dopamine in the prefrontal cortex

The effects of dopamine on neuronal excitability and synaptic responses in the prefrontal cortex are complex, showing considerable heterogeneity across cortical layers and species. An increase in the excitability of GABAergic interneurons by dopamine is a consistent finding in the prefrontal cortex (Gorelova et al. 2002; Zhou and Hablitz 1999). Spontaneous IPSCs recorded from pyramidal neurons are also enhanced by dopamine (Gulledge and Jaffé 2001; Seamans et al. 2001; Zhou and Hablitz 1999), whereas pharmacologically isolated evoked IPSCs in layer II/III pyramidal cells are decreased (Gonzalez-Islas and Hablitz 2001). The enhancement of excitability of interneurons is due to a direct postsynaptic effect of dopamine (Gorelova et al. 2002; Wu and Hablitz 2005), whereas the decrease in evoked IPSCs involves a presynaptic mechanism. Dopaminergic modulation of IPSPs may be target-specific (Gao et al. 2003) and effects can be time- and concentration dependent (Seamans et al. 2001; Trantham-Davidson et al. 2004). Our present results with recordings in normal saline show that the net effect of dopamine is to increase inhibition of layer II/III pyramidal cells.

The observed increase in amplitude of the inhibitory component of evoked postsynaptic currents presumably reflects dopamine facilitation of interneuron excitability. We have shown previously that in the presence of bicuculline, dopamine facilitates recurrent excitatory activity in disinhibited prefrontal cortex (Bandyopadhyay et al. 2005). This increased activity should augment the excitatory synaptic drive onto interneurons. In addition, dopamine also directly increases excitability of interneurons (Wu and Hablitz 2005; Zhou and Hablitz 1999). Dopamine is known to suppress spontaneous firing of pyramidal neurons in vivo (Bunney and Aghajanian 1976; Sesack and Bunney 1989; Yang and Mogenson 1990), and this effect of dopamine can be blocked by the GABA_A antagonist biperidone (Penit-Soria et al. 1987; Pirot et al. 1992). VTA stimulation in vivo can excite fast-spiking interneurons and inhibit pyramidal neurons in rat prefrontal cortex (Tseng et al. 2006). The net inhibitory effect of dopamine observed in the present in vitro study is consistent with such in vivo findings.

We have shown previously that pharmacologically isolated EPSCs are facilitated by dopamine (Bandyopadhyay et al. 2005; Gonzalez-Islas and Hablitz 2001). In the present study, EPSC amplitudes were measured at a short latency to minimize contamination by IPSCs. However, intracortical stimulation evokes pharmacologically isolated IPSCs that have an early onset (3 ms) (Gonzalez-Islas and Hablitz 2001). It is therefore likely that there is temporal overlap between EPSCs and IPSCs under conditions of normal synaptic transmission. Increases in IPSCs could therefore mask any facilitation of EPSCs.

Dopamine modulation of spatiotemporal spread of activity in the prefrontal cortex

For a more complete understanding of the nature of dopamine function in the prefrontal cortex, it is necessary to understand how dopamine alters spatiotemporal patterns of activity in local neuronal networks. Optical imaging with voltage-sensitive dyes is well suited to study spatiotemporal dynamics of activity in brain slices because it has high temporal and spatial resolution (Grinvald and Hildesheim 2004; Jin et al. 2002; Wu et al. 2001; Yuste et al. 1997). It has been used to study spatiotemporal properties of activity in slices from sensory (Laaris et al. 2000; Petersen and Sakmann 2001; Wu et al. 2001) and visual (Fukuda et al. 1998; Tucker and Katz 2003a, b) cortex. The origins of voltage-sensitive dye signals in neocortex and the effects of changes in inhibition on such responses are becoming better understood. In layer II/III, dye signals correlate highly with synchrony of evoked changes in pyramidal cell membrane potential (Petersen et al. 2003). Blocking synaptic transmission by removing extracellular calcium completely blocks thalamic evoked neocortical dye signals (Laaris et al. 2000). Pyramidal cell responses are very dependent on activity in horizontal connections that are biased toward inhibition (Tucker and Katz 2003b). The time course and relative amplitudes of EPSPs and voltage-sensitive dye signals are similar (Petersen and Sakmann 2001; Petersen et al. 2003; Tucker and Katz 2003a). Weak electrical stimulation elicits small EPSPs and optical signals with a similar time...
Dopamine modulates the spatiotemporal spread of activity in disinhibited neocortical slices (Bandyopadhyay et al. 2005). In the presence of biccuculline, dopamine, via D1-like receptors, either enhanced the local spatiotemporal spread of excitation or resulted in a previously subthreshold stimulus triggering an epileptiform discharge that propagated throughout the cortical mantle. These changes were attributed to increased recurrent activation via local excitatory axon collaterals. In the present study, when inhibition was not blocked, D1-receptor activation restricted the spatiotemporal spread of activity in the prefrontal cortex. This is consistent with our present findings from whole cell recordings demonstrating dopamine-mediated increases in evoked inhibition. This increase in inhibition presumably masks the excitatory effect seen in disinhibited conditions. An inhibitory effect of dopamine under conditions of normal synaptic transmission may be an important factor in maintaining stability in local neocortical networks. This has implications for working memory function. Modeling studies predict that dopamine-mediated increases in inhibition are necessary to prevent activation of representations unrelated to the task (Durstewitz et al. 1999, 2000a,b).

**Dopamine and local network activity in the prefrontal cortex**

Prefrontal cortex contains local networks of excitatory and inhibitory neurons that have extensive recurrent connections among each other. Such local recurrent connectivity enables the prefrontal cortex to sustain persistent activity in groups of pyramidal neurons in the absence of sensory inputs, a process believed to underlie working memory function (Goldman-Rakic 1995). Extensive recurrent connections among the cortical neurons also make the neocortex susceptible to develop epileptiform activity and seizures (McCormick and Contreras 2001). Activity and excitability are strongly influenced by neuromodulators in cortical networks (McCormick et al. 1993). Dopamine levels in the prefrontal cortex increase during working memory processing (Phillips et al. 2004), and an optimal level of activation of D1-like receptors appears crucial for working memory function (Durstewitz and Seamans 2002; Durstewitz et al. 2000a,b). Facilitation of persistent firing in groups of pyramidal neurons during the delay period of a working memory task is a major feature of dopamine modulation of activity in the prefrontal cortex (Goldman-Rakic 1995). Similar task-related activity has been reported in nearby GABAergic interneurons as well (Constantinidis and Goldman-Rakic 2002; Rao et al. 1999). Inhibition of GABA_\text{A} receptors expands the receptive field of pyramidal neurons of dorsolateral prefrontal cortex, suggesting that spatial tuning of pyramidal cells by interneurons may be an important factor in shaping activity in prefrontal cortex (Rao et al. 2000). This has been shown in modeling studies as well (Tanaka 1999; Wang et al. 2004). Our results show that, when both excitation and inhibition are intact, dopamine has a net inhibitory effect on local networks in the prefrontal cortex, decreasing the lateral spread of activity. Such inhibitory effects of dopamine may be important in shaping activity and providing stability in local neuronal networks in the prefrontal cortex.

Electrophysiological studies have shown that cortical activation patterns are abnormal in schizophrenia, displaying greater variability or “noise” (Winterer and Weinberger 2004). This could result in an inability to maintain stable representations of internal or external stimuli. Dopamine, by enhancing inhibition and sharpening activation patterns, could improve prefrontal cortical functioning. These D1 mediated effects would support the recently proposed model of dopamine action in prefrontal cortex where D1 dominated states have better signal-to-noise ratios and networks are active and stable (Seamans and Yang 2004; Seamans et al. 2001).

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**References**


