Dopamine Modulation of Membrane and Synaptic Properties of Interneurons in Rat Cerebral Cortex

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Zhou, Fu-Ming and John J. Hablitz. Dopamine modulation of membrane and synaptic properties of interneurons in rat cerebral cortex. J. Neurophysiol. 81: 967–976, 1999. Dopamine (DA) is an endogenous neuromodulator in the mammalian brain. However, it is still controversial how DA modulates excitability and input–output relations in cortical neurons. It was suggested that DA innervation of dendritic spines regulates glutamatergic inputs to pyramidal neurons, but no experiments were done to test this idea. By recording individual neurons under direct visualization we found that DA enhances inhibitory neuron excitability but decreases pyramidal cell excitability, through depolarization and hyperpolarization, respectively. Accordingly, DA also increased the frequency and amplitude of spontaneous inhibitory post-synaptic currents (sIPSCs). In the presence of TTX, DA did not affect the frequency, amplitude, or kinetics of miniature IPSCs and excitatory post-synaptic currents in inhibitory interneurons or pyramidal cells. Our results suggest that DA can directly excite cortical interneurons, but there is no detectable DA gate to regulate spontaneous GABA and glutamate release or the properties of postsynaptic GABA and glutamate receptors in neocortical neurons.

INTRODUCTION

Dopamine (DA) is believed to be an endogenous neuromodulator in the cerebral cortex and to be important for normal brain function (Bjorklund and Lindvall 1986; Williams and Goldman-Rakic 1995). Clinical and experimental studies also implicated DA in the pathogenesis of a number of psychiatric disorders, schizophrenia in particular (Creese et al. 1976; Dolan et al. 1995; Okubo et al. 1997; for review see Andreasen 1996; Egan and Weinberger 1997; Grace et al. 1997; Jaskiw and Weinberger 1992). Multiple DA receptor types are expressed in the CNS. According to their pharmacological and physiological properties, DA receptors were originally classified broadly into D1 and D2 types, which are positively and negatively coupled to adenylyl cyclase, respectively (Kebabian and Calne 1979).

Since the initial discovery of DA in rat cerebral cortex by Thierry et al. (1973), a wealth of information regarding cortical DA innervation has accumulated (for review see Berger 1992; Bjorklund and Lindvall 1986). It is now clear that rat cerebral cortex, the prefrontal cortex in particular, receives a substantial DA innervation originating from midbrain DA neurons. In monkey and human brain, DA innervation was greatly expanded, and the distribution of DA axons is more extensive (Berger 1992; Smiley et al. 1992; Williams and Goldman-Rakic 1993). Immunohistochemical studies show that both cortical inhibitory interneurons and excitatory pyramidal neurons in rat and primate cortex are targets for DA innervation (Benes et al. 1993; Sesack et al. 1995; Verney et al. 1990; Williams and Goldman-Rakic 1993). It was also suggested that pyramidal neurons and interneurons may express different DA receptor types (Mrzljaj et al. 1996; Vincent et al. 1993 1995), providing an anatomic basis for differential DA modulation of cortical neurons. Therefore dopaminergic activation may shift the balance between excitation and inhibition in neuronal circuits, which may be related to clinical and experimental observations, suggesting a potential link between DA and GABA systems (Starr 1996; Trimbble 1996).

The cellular neurophysiology of the cerebral DA system is far from being established. In vivo extracellular recordings showed that DA depressed spontaneous firing of rat prefrontal pyramidal neurons (Sesack and Bunney 1989; Thierry et al. 1992). Indirect evidence also suggests that a GABAergic mechanism may be partly responsible for the DA-induced inhibition of frontal pyramidal neurons (Penit-Soria et al. 1987; Pirot et al. 1992). However, a detailed direct characterization of DA effects on frontal GABAergic neurons is lacking.

On the basis of immunohistochemical electron microscopic studies in primate cerebral cortex (Bergson et al. 1995; Goldman-Rakic et al. 1989; Smiley and Goldman-Rakic 1993; Smiley et al. 1994), it was proposed that DA terminals, together with glutamatergic axon terminals, form so-called synaptic triads on dendritic spines of pyramidal neurons such that DA activation can gate or inhibit excitatory synaptic inputs to pyramidal neurons (Goldman-Rakic et al. 1992; Williams and Goldman-Rakic 1995). It was further suggested that these synaptic triads may be involved in the pathophysiology of schizophrenia because D1 receptors on dendritic spines may be reduced in schizophrenics (Nestler 1997; Okubo et al. 1997). However, the exact physiological function of these synaptic triads was not examined.

We therefore set out to examine the cellular effects of DA on cortical neurons and to test the triad model by making high-resolution, patch-clamp recording from visually identified cortical interneurons and pyramidal neurons. Specifically, we sought to 1) examine if DA, the endogenous neurotransmitter, can alter the excitability of cortical neurons, inhibitory neurons in particular, and 2) test if DA affects spontaneously occurring, miniature inhibitory and excitatory post-synaptic currents (mIPSCs and mEPSCs) as predicted by Goldman-Rakic model. We chose the so-called prefrontal cortex because this area receives a relatively dense DA innervation and is important for cognition, which requires proper DA functions (Dolan et al. 1995;
Layers of 

**Layer I neuron**

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<td>RMP</td>
<td>-56 mV, 60 pA</td>
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**Pyramidal neuron**

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<tr>
<td>RMP</td>
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*FIG. 1. Dopamine (DA) increases interneuron excitability but decreases pyramidal neuron excitability. Records were made in the presence of 10 μM bicuculline methiodide (Bic), 20 μM 2,3-diamino-5-phosphonovaleric acid (D-APV), and 10 μM 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX). A1–A3: in a layer I neuron, bath application of 40 μM DA induced a depolarization of ~6 mV and increased the number of spikes evoked by 60-pA depolarizing current pulses. Input resistance, monitored by a current pulse of ~40 pA, was also increased from 230 MΩ in control to 280 MΩ in DA. A4 and A5: at resting potential, spontaneous spikes were not observed. DA depolarized this layer I neuron to approximately ~50 mV. At this membrane potential, spontaneous spikes were often seen. The amplitude of spikes was truncated because of slow digitization. B1–B3: in a pyramidal neuron, bath application of 40 μM DA induced a hyperpolarization of ~3 mV and decreased the spikes evoked by injecting 60-pA depolarizing current pulses. Input resistance, monitored by a current pulse of ~60 pA, was also decreased from 270 MΩ in control to 225 MΩ in DA. In both cells, DA effects were partly reversed on wash.*

**Methods**

Experiments were conducted in brain slice preparations. The methods to prepare brain slices were described by Zhou and Hablitz (1996). Briefly, 15- to 22-day-old Sprague-Dawley rats were decapitated under ketamine anesthesia, and brains were dissected out quickly. Coronal brain slices (250- to 300-μm thick) were then cut from the anterior portion of the brain on a Vibratome. Slices were kept in a storage chamber at room temperature (~22°C) for 1 h before recording. The normal extracellular bathing solution contained (in mM) 125 NaCl, 3.5 KCl, 2.5 CaCl2, 1.3 MgCl2, 26 NaHCO3, and 10 d-glucose and was bubbled with 95% O2-5% CO2 to maintain pH at ~7.4. During actual recording KCl was raised to 4 mM to induce a small depolarization such that potential DA effects on action potential-dependent spontaneous synaptic events were more detectable.

The anterior cingulate cortex and the shoulder region or Fr2 region of the frontal cortex (Paxinos and Watson 1986) were the target of this study. These two areas make up a large portion of the prefrontal cortex (Goldman-Rakic 1993). Our results indicated that DA increased spontaneous action potential firing and enhanced spontaneous inhibitory synaptic transmission but generally decreased pyramidal neuron excitability through a small hyperpolarization. We also found that DA had no effect on the frequency or amplitude of mIPSCs and mEPSCs, indicating that DA did not modulate the spontaneous release of glutamate and GABA or the properties of postsynaptic glutamate and GABA receptors. Therefore, there was no detectable DA gate of spontaneous synaptic activity in cortical neurons under the conditions employed in this study. Instead, our results suggest that a major action of DA in the rat prefrontal cerebral cortex is to enhance interneuron excitability, possibly through nonsynaptic DA receptors.

We paid particular attention to layer I neurons because they are mostly GABAergic (Gabbott and Somogyi 1986), and layer I receives a particularly dense DA innervation (Berger 1992; Sesack et al. 1995; Smiley et al. 1992; Williams and Goldman-Rakic 1995). We paid particular attention to layer I neurons because they are mostly GABAergic (Gabbott and Somogyi 1986), and layer I receives a particularly dense DA innervation (Berger 1992; Sesack et al. 1995; Smiley et al. 1992; Williams and Goldman-Rakic 1995). Our results indicated that DA increased spontaneous action potential firing and enhanced spontaneous inhibitory synaptic transmission but generally decreased pyramidal neuron excitability through a small hyperpolarization. Therefore, there was no detectable DA gate of spontaneous synaptic activity in cortical neurons under the conditions employed in this study. Instead, our results suggest that a major action of DA in the rat prefrontal cerebral cortex is to enhance interneuron excitability, possibly through nonsynaptic DA receptors (Descarcies et al. 1991).

**Layer I neuron**

A1 Control

A2 DA

A3 Wash

30 mV 200 ms

B1 Control

B2 DA

B3 Wash

$V_{RMP} = -56 \text{ mV}, 60 \text{ pA}$

$V_{RMP} = -50 \text{ mV}, 60 \text{ pA}$

$V_{RMP} = -53 \text{ mV}, 60 \text{ pA}$

$V_{RMP} = -61 \text{ mV}, 60 \text{ pA}$

$V_{RMP} = -59 \text{ mV}, 60 \text{ pA}$

**Pyramidal neuron**

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(1989) were used. Tight seals (>2 GΩ before breaking into whole cell mode) were obtained without first cleaning the cell. Patch electrodes had an open tip resistance of 3 MΩ. Series resistance during recording varied from 6 to 15 MΩ among different neurons and was not compensated. Recordings were terminated whenever significant increases (>20%) in series resistance occurred. Recordings obtained with series resistance >10 MΩ were not optimal for kinetic analysis (Zhou and Hablitz 1997a) but were still included in analysis for pharmacological purposes as long as series resistance was stable. The intracellular solution for recording synaptic currents contained (in mM) 135 KCl or CsCl, 10 HEPES, 2 Mg-ATP, 0.2 Na-GTP, and 0.5 EGTA; pH and osmolarity were adjusted to 7.3 and 285 mosm, respectively. All voltage-clamp recordings were made at a holding potential of −70 mV. KCl- and K-isothionate–based intracellular solutions were used to record action potentials in current-clamp mode. Possible liquid junction potentials developed after going whole cell mode were not subtracted from the data presented. All recordings were made at room temperature (≈22°C).

Electrical signals were recorded with an Axopatch-200A amplifier controlled by Clampex software (Axon Instruments). Continuous recordings were made to videotape via a tape recorder (Neuro-corder, Neuro Data Instruments). Individual synaptic events (400–15,000) were captured with a threshold detector in SCAN software (provided by Dr. J. Dempster, University of Strathclyde). Neurons used for statistical analysis of DA effects were required to have synaptic events with stable frequency and amplitude during both control and DA application. Statistical comparisons of the frequency and amplitude of synaptic currents before, during, and after DA were made with the Kolmogorov-Smirnov (K-S) test with StatMost software (DataMost, Salt Lake City, UT); P < 0.01 was considered significant. Numerical values were expressed as means ± SD.

**RESULTS**

**DA depolarizes cortical interneurons**

Under direct visualization, 28 layer I neurons and 4 deeper layer fast spiking interneurons in anterior cingulate cortex and frontal cortex were recorded in current clamp. No difference between the neurons from the two brain area was found, and data were pooled. These neurons had a resting membrane potential of −56 ± 2.5 mV. At this resting potential, the apparent input resistance was 360 ± 120 MΩ. Spontaneous action potentials (spikes) were rare at rest. Injection of supra-threshold depolarizing current pulses evoked a single spike or a train of nonadaptive spikes of short duration (base duration ~2 ms) followed by a strong fast afterhyperpolarization (fAHP). In contrast, pyramidal neurons (n = 24) from the same brain areas fired long-duration (base duration ~4.5 ms) spikes that showed adaptation during long pulses followed by a weak
fAHP. These spiking properties are characteristic of cortical fast spiking interneurons and pyramidal neurons (McCormick et al. 1985; Zhou and Hablitz 1996).

Bath application of DA (30–100 μM) caused a depolarization (4 ± 2.1 mV, Fig. 1, A1–A3) in 17 of 28 layer I neurons and 2 of 4 deeper layer fast spiking interneurons. Because of this depolarization, the same amount of injected depolarizing current evoked more spikes in the presence of DA. The apparent input resistance of these depolarized neurons, monitored by a constant hyperpolarizing current pulse, was also slightly increased (by ~20%) by DA application. This apparent increase in input resistance was not directly caused by DA. When the membrane potential was maintained at resting levels with current injection (n = 3), DA caused a ~15% decrease in input resistance (see also Sutor and Hablitz 1989). Spontaneous spikes were observed in 12 of 19 depolarized neurons, although the frequency was still low (<0.5 Hz) and variable (Fig. 1, A4 and A5). However, in 5 of 28 layer I neurons, DA (30–100 μM) caused a small hyperpolarization (2 ± 0.8 mV) accompanied by a slight decrease (24 ± 6%) in input resistance. In the remaining cells application of 30–100 μM DA induced no discernible change in membrane potential. These results indicate that DA can directly increase excitability of the majority of cortical fast spiking interneurons.

DA was found to have weaker and less consistent effects on cortical pyramidal neurons. In 11 of 24 pyramidal neurons tested DA (30–100 μM) induced a small hyperpolarization of 3.5 ± 1 mV and a decrease (by ~25%) in input resistance (Fig. 1, B1–B3). In 4 of 24 pyramidal neurons, DA (30–100 μM) caused a small depolarization (2–3 mV), which was not strong enough to cause spontaneous spike firing in these cells. The rest of the pyramidal neurons showed no detectable response to DA application. These results indicate that DA may cause an overall reduction in pyramidal cell excitability.

DA enhances sIPSCs in pyramidal and layer I neurons

Previous immunohistochemical studies have shown that cortical GABAergic interneurons receive DA innervation and express DA receptors, suggesting that activation of DA system may modulate the activity of GABAergic interneurons (Sesack et al. 1995; Verney et al. 1990). Our current-clamp data presented in the previous section indicate that DA can enhance the excitability of GABAergic interneurons. Therefore we hypothesized that DA can enhance action potential-dependent GABAergic inhibitory synaptic transmission. To test this idea, we recorded spontaneous IPSCs (sIPSCs) under voltage-clamp conditions in the absence of TTX and in the presence of 20 μM D-APV and 10 μM CNQX. Voltage-clamp recordings from 17 layer I neurons and 4 pyramidal neurons showed that bath application of DA (10–100 μM) increased the frequency, calculated as the reciprocal of interevent interval, of sIPSCs by ~250 ± 85% (Figs. 2, A–D, and 3, A–C). In the presence of DA there were also more large-amplitude events, presumably because of the increased spontaneous action potentials induced by DA, such that the amplitude of averaged sIPSCs was also
increased to 155 ± 25% of the control (Figs. 2, A–C and inset of D; 3, A, B, and inset of C). The enhancement of sIPSCs was more pronounced when the percentage of action potential-dependent events in control was small. Dose-response relations were not studied because of the fact that cells needed ≥10 min wash to recover, and responses to a same dose of DA varied to a great extent among different cells. When recovery was obtained and recordings were reasonably stable, neurons (n = 4) responded to repeated DA applications (Fig. 2D). The DA effects were also persistent and showed no desensitization during 10- to 30-min applications. Averaged sIPSCs had 10–90% rise time of 0.85 ± 0.14 ms and 0.88 ± 0.15 ms, double-exponential decay with time constants of 3.8 ± 0.3 ms and 19.4 ± 3.5 ms and 3.9 ± 0.3 ms and 20 ± 3.4 ms in control and during DA application, respectively (n = 21, P > 0.6; to make the comparison meaningful, overlapping and large events were excluded) (see Zhou and Hablitz 1997a,b), indicating that DA did not affect the gating of postsynaptic GABA_A receptors. The time needed for DA to exert its effects after switching to DA-containing solution was ≤2 min, a time course similar to that needed for DA to induce a depolarization and for 0.3 μM TTX to block action potentials. These results strongly support the idea that DA increases the firing of cortical interneurons innervating both interneurons and pyramidal cells and therefore enhances action potential-dependent GABAergic inhibitory synaptic transmission.

**DA had no effect on sEPSCs in pyramidal and layer I neurons**

In vivo studies reported that DA inhibits pyramidal cell firing (Bunney and Chiado 1984; Thierry et al. 1992), whereas in vitro intracellular studies suggest that DA may increase frontal pyramidal cell excitability (Shi et al. 1997; Yang and Seemans 1996). Our current-clamp data presented previously indicated that DA may increase the overall excitability of cortical pyramidal neurons, we should see a DA-induced increase in sEPSCs. If DA has only weak and mixed effects on pyramidal neuron excitability as seen in our current-clamp recordings, we should expect that DA has only minimal effects on sEPSCs, particularly when most sEPSCs in neocortical neurons in vitro are action potential independent (Zhou and Hablitz 1997a). To test these ideas, we recorded sEPSCs from seven pyramidal neurons and eight layer I neurons. The bathing solution contained 10 μM Bic and no n-APV, CNQX, or TTX. As shown in Figs. 4 and 5, in contrast to the enhancing effects of DA on sIPSCs, bath ap-
Application of DA (10–100 μM for 10–25 min) failed to induce any significant change in the frequency or amplitude of sEPSCs in layer I neurons (P > 0.01, K-S tests; Fig. 4) and pyramidal neurons (P > 0.01, K-S tests, Fig. 5). The kinetics of these sEPSCs were also not altered. These results support the idea that DA does not increase the overall pyramidal neuron excitability.

DA had no effect on mIPSCs in pyramidal neurons and layer I neurons

GABAergic interneurons receive DA innervation (Sesack et al. 1995; Verney et al. 1990; Williams and Goldman-Rakic 1993). DA receptors were also detected on the presynaptic terminals of GABAergic axons (Bergson et al. 1995). Therefore DA could potentially modulate the release of GABA as well as the properties of postsynaptic GABA receptors. To test these two potential DA effects, we recorded mIPSCs in six pyramidal neurons and seven layer I neurons in the presence of 0.3 μM TTX to block sodium action potentials and 20 μM APV and 10 μM CNQX to block ionotropic glutamate receptors. In all pyramidal cells and layer I neurons tested, bath application of 20 or 50 μM DA for 5–15 min did not alter the frequency or amplitude of mIPSCs, as indicated by K-S tests performed in individual cells (P > 0.01, Fig. 6, A–D). The waveform of mIPSCs was also not altered by DA application.

DA did not affect mEPSCs in pyramidal neurons and layer I neurons

DA receptors were found at glutamatergic axon terminals (Bergson et al. 1995), suggesting that DA may modulate the release of glutamate vesicles. It was proposed that DA may regulate excitatory synaptic inputs to cortical neurons, based on findings that DA receptors are found on dendritic spines (Goldman-Rakic 1992). We reasoned that such a DA gate could either modulate the spontaneous glutamate vesicle release and/or the postsynaptic glutamate receptors. To test this idea experimentally, we recorded mEPSCs in 10 pyramidal neurons and 9 layer I neurons. As shown in Fig. 7, bath application of 20 or 50 μM DA for 8–20 min was unable to induce any visible change in the frequency, amplitude, or shape of mEPSCs. The frequency and amplitude of mEPSCs in the presence of DA was 97 ± 2% and 98 ± 2% of control, respectively. K-S tests also showed that distributions of mEPSC frequency and amplitude in individual cells were not different before and during DA application (P > 0.01, Fig. 7, A1–A4 and B1–B4). These results indicate that DA activation does not modulate the spontaneous glutamate vesicle release or the sensitivity of postsynaptic glutamate receptors in cortical pyramidal neurons and fast spiking interneurons.

DISCUSSION

The main finding of this study is that DA can directly excite cortical fast spiking interneurons. A DA gate to modulate the
spontaneous release of GABA and glutamate was not observed in these experiments. The amplitude and kinetic properties of GABA- and glutamate-mediated spontaneous synaptic currents in rat cortical pyramidal neurons and interneurons were also not altered.

DA enhances interneuron excitability

Our ability to make recordings routinely from cortical fast spiking interneurons enabled us to directly examine the effects of DA on these interneurons. Therefore we were able to demonstrate that DA can directly depolarize the majority of cortical interneurons in frontal and cingulate areas, increase their excitability and spontaneous spike firing, and enhance action potential-dependent spontaneous GABAergic transmission. These results provide direct evidence for the suggestion that a GABAergic component is involved in mediating the inhibitory effects of ventral tegmental DA neuron activation on prefrontal pyramidal neurons (Pirot et al. 1992). Our results are consistent with early brief reports showing that DA increased sIPSPs in rat prefrontal neurons (Penit-Soria et al. 1987) and in rat piriform cortex (Gellman and Aghajanian 1993). It is also generally consistent with immunohistochemical studies showing that cortical interneurons receive DA innervation (Krimer et al. 1997; Sesack et al. 1995; Smiley and Goldman-Rakic 1993; Verney et al. 1990). Our result that DA can induce a direct depolarization in interneurons suggests that the most likely site of DA effects is the soma and proximal dendrites. This agrees particularly well with findings that DA varicosities preferentially make contacts with the somata of rat prefrontal interneurons and pyramidal neurons (Benes et al. 1993) and that DA receptors are more concentrated in the somata in these two cell types (Vincent et al. 1993).

The endogenous neurotransmitter DA was used to maximize the probability of seeing the possible effects mediated by different DA receptors. Further studies are needed to identify the receptor subtypes responsible for the observed DA effects on cortical interneurons. Also, these studies were conducted at room temperature. Studies by Hardingham and Larkman (1998) reported temperature-dependent changes in the reliability of excitatory synaptic transmission in rat visual cortex. It remains to be determined if possible neuromodulatory actions are also temperature dependent.

DA decreases pyramidal neuron excitability

Our results show that the direct effects of DA on the cortical pyramidal neurons tested are weak and more variable. A majority of the pyramidal neurons responded to DA with a small hyperpolarization accompanied with a small decrease in input resistance, and some cells showed a small depolarization, whereas others showed no response at all. Therefore the overall effect of DA on cortical pyramidal neurons was a small decrease in excitability. This conclusion is further supported by the failure of DA to induce any change in sEPSCs. If DA can enhance the overall excitability of pyramidal neurons as reported in a number of studies.
DA does not affect spontaneous GABA and glutamate release or the sensitivity of these postsynaptic receptors

Our study showed no effect of DA application on mIPSCs and mEPSCs. Because the frequency of mIPSCs and mEPSCs is an index of the frequency of GABA and glutamate vesicles being released from the presynaptic terminals, our results suggest that there may be no functionally detectable presynaptic DA receptors in GABA and glutamate axon terminals in cerebral cortex. This is generally in agreement with immunohistochemical electron microscopic studies showing that DA receptors were not frequently detected in presynaptic axonal terminals in primate cerebral cortex (Bergson et al. 1995). Verney et al. (1990) also reported that there are no axoaxonic synapses between GABAergic terminals and DA terminals in rat frontal cortex. Our data showing that DA did not alter the amplitude or kinetics of mIPSCs and mEPSCs indicate that DA activation may not modulate the sensitivity of postsynaptic GABA and glutamate receptors in these cortical neurons, in contrast to the triad model that proposes that DA activation gates excitatory synaptic inputs (Goldman-Rakic 1992; Williams and Goldman-Rakic 1995). However, DA may affect evoked transmitter release because of effects on membrane excitability (our current study) and calcium signaling (Missale et al. 1998).

One possible reason for our failure to detect any acute effect of DA on mEPSCs and mIPSCs could be inadequate recording conditions. However, the enhancement of sIPSCs by 10 μM DA indicates that there should be sufficient amount of DA, when bath applied at 20–100 μM, reaching neurons in the...
depths of slice. Second, the fast kinetics of mIPSCs and mEPSCs recorded in this study, similar to those reported in our previous studies (Zhou and Hablitz 1997a,b), indicate adequate voltage clamp. Finally, bath application of the metabotropic glutamate receptor agonist 1S,3R-1-aminocyclopentane-1,3-dicarboxylic acid induced a reversible decrease (~50%) in the frequency of mEPSCs in these same cortical neurons under the same recording conditions used for DA experiments (Zhou and Hablitz 1997c). This indicates that changes in synaptic activity caused by activation of G-protein-coupled receptors are detectable under the current recording conditions. The relative scarcity of DA terminals and synapses in the cortex may be the major factor contributing to our failure to detect any DA effect on mIPSCs and mEPSCs. In the macaque prefrontal cortex, a recent quantitative three-dimensional analysis (Krimer et al. 1997) found that a pyramidal neuron and a GABAergic neuron receive only ~90 and 45 catecholaminergic appositions, respectively. These numbers are very small compared with the total synapses a pyramidal neuron typically receives, which are ~10,000–30,000 (Peters 1987). Other studies also indicate that non-GABA nonglutamate axon terminals, i.e., DA, serotonin, noradrenaline, and acetylcholine terminals, only constitute <1% of the total nerve terminals in the cerebral cortex (Descarries and Umbrici 1995; Micheva and Beaulieu 1996). Interestingly, in nucleus accumbens, which has a much higher DA innervation (Bjorklund and Lindvall 1986) and DA receptor density (Boyson et al. 1986) than those in cerebral cortex, it was reported that DA activation depressed the frequency of mEPSCs but not mIPSCs (Nicola and Malenka 1997). It is also possible that DA may have long-term effects on synaptic inputs at synaptic triads, which are beyond the detection of the techniques employed here.

Clinical and experimental observations suggested that there may be an intrinsic link between epilepsy, a disorder primarily associated with dysfunction of GABAergic inhibition, and schizophrenia, a disorder closely involving DA system (Starr 1996; Trimble 1996). More recent studies indicate that there may be modest abnormalities in GABAergic system in prefrontal cortex of schizophrenic patients (Akbarian et al. 1995; Benes et al. 1996). Our results show that DA activation can directly enhance cortical GABAergic outputs. Therefore we speculate that DA modulation of cortical GABAergic inhibitory systems could play a role in both epilepsy and schizophrenia.

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