The ability of dopamine to regulate the cognitive functions of the prefrontal cortex (PFC) involves complex modulatory actions on GABA-containing local circuit neurons in addition to pyramidal cells. However, the subclasses of cortical neurons that receive direct dopamine input are not known. We sought to determine whether dopamine terminals innervate the subclasses of local circuit neurons that contain the calcium-binding protein parvalbumin (PV), namely the wide arbor and chandelier neurons that target pyramidal cell soma and axon initial segments respectively. Sections through area 9 of five monkeys were labeled with immunoperoxidase for tyrosine hydroxylase (TH), to identify dopamine terminals, and with immunogold–silver for PV. Electron microscopic examination of the middle cortical layers (IIIb–IV) revealed that TH-positive terminals were sometimes directly apposed to PV-labeled dendrites, and approximately one-third of these contacts exhibited morphological features that are typically associated with symmetric synapses. In contrast, TH-immunolabeled terminals in the superficial layers (I–IIla) were less frequently apposed to PV-positive dendrites, and none of these contacts exhibited synapse-like morphology. These findings, in concert with previous studies of GABA- or calretinin-containing local circuit neurons, suggest that dopamine’s modulatory action in the PFC involves selective effects on only certain interneuron populations, including those that mediate potent inhibitory actions on pyramidal cells.

Introduction

The prefrontal cortex (PFC) governs the integration of temporal and spatial factors that guide cognitive behaviors, such as working memory and future planning. Patients with frontal lobe lesions exhibit deficits in these behaviors (Milner and Petrides, 1984), and individuals suffering from schizophrenia exhibit a similar symptom complex that is associated with alterations in PFC (Weinberger, 1987, 1988; Selemon et al., 1995; Glantz and Lewis, 1997). In animal studies, lesions of the PFC produce abnormal behaviors that are mimicked by selective lesion or pharmacological blockade of the cortical dopamine innervation (Brozoski et al., 1979; Simon et al., 1980; Sawaguchi and Goldman-Rakic, 1991). Furthermore, the dopamine input to the PFC may be dysfunctional in schizophrenia (Weinberger, 1987; Daniel et al., 1991; Okubo et al., 1997), and preliminary anatomical studies suggest that a decline in the density of PFC dopamine fibers may attend this illness (Akil and Lewis, 1996). These observations highlight the critical role that the mesocortical dopamine system plays in normal cognitive functions and, potentially, in the pathophysiology of schizophrenia and related disorders.

Understanding the synaptic organization of the dopamine input to the PFC will reveal potential anatomical substrates for dopamine modulation of normal cortical activity. Initially, the monoamine innervation of the cerebral cortex was considered to be diffuse and non-specific (Fuxe et al., 1968; Beaudet and Descarrries, 1978), suggesting that the actions of these neurotransmitters were not directed at particular targets. However, more recent light microscopic studies suggest that each of these systems does have a distinctive pattern of cortical innervation (Parnavelas and Papadopoulos, 1989; Lewis, 1990, 1992). For example, although mesencephalic dopamine neurons project to every region of the primate cerebral cortex, these axons preferentially innervate motor over sensory regions, and sensory association over primary sensory areas (Lewis et al., 1987; Berger et al., 1988; Lewis and Sesack, 1997). In addition, cytoarchitectonic subdivisions of association cortices exhibit substantial differences in innervation density and laminar distribution of dopamine axons in monkeys (Lewis et al., 1988; Akil and Lewis, 1993; Williams and Goldman-Rakic, 1993) and humans (Gaspar et al., 1989; Lewis, 1992; Akil and Lewis, 1994). These precise innervation patterns suggest that cortical dopamine afferents are directed at specific cellular targets.

In ultrastructural studies of monkey cortex, dopamine axons synapse on the dendritic shafts and spines of pyramidal neurons (Goldman-Rakic et al., 1989) and on the dendrites of local circuit neurons (Smiley and Goldman-Rakic, 1993) that are immunoreactive for GABA (Sesack et al., 1995b). These studies estimate that ~40% of the dopamine synapses in the superficial layers of the monkey PFC are onto GABA-containing local circuit neurons. However, a complete understanding of how dopamine influences PFC function through inputs to GABA neurons requires knowledge of which subtype(s) of these cells receive dopamine innervation. Most cortical GABA neurons express one of three calcium-binding proteins: calretinin, calbindin or parvalbumin (PV), and these markers have been used to identify specific subgroups of GABA cells (Conde et al., 1994; Gabbott and Bacon, 1996a, b) with distinctive roles in cortical circuitry (White, 1989; Jones, 1993; Lund and Lewis, 1993; Kawaguchi, 1995). For example, PV-containing local circuit neurons comprise at least two morphological subgroups, wide arbor (basket) and chandelier neurons (DeFelipe et al., 1989b; Hendry et al., 1989; Lewis and Lund, 1990; Lund and Lewis, 1993). These cells furnish inhibitory synapses to the soma and axon initial segments respectively of pyramidal cells. Thus, a dopamine input to PV-containing interneurons, as compared to other classes of local circuit neurons, would be likely to exert a more powerful indirect influence on pyramidal cell activity in the PFC.

Several published findings are consistent with the hypothesis that dopamine axons directly innervate the PV-containing subclass of local circuit neurons, particularly within layers deep III–IV in area 9 of the monkey PFC. First, the middle cortical layers of area 9, in contrast to other cortical association regions, contain a relatively high density of dopamine axons (Lewis et al., 1988; Williams and Goldman-Rakic, 1993). These middle layers also exhibit the greatest density of PV-immunoreactive neurons (Conde et al., 1994; Gabbott and Bacon, 1996a, b). Second,
during postnatal development, temporally associated changes in the density of dopamine axons, and in the number of PV-immunoreactive axon terminals of chandelier neurons, occur in the middle, but not in the superficial or deep layers of the monkey PFC (Anderson et al., 1995; Rosenberg and Lewis, 1995). Finally, dopamine D4 receptors have recently been localized to PV-immunolabeled neurons in the PFC (Mrzljak et al., 1996). Together, these findings are consistent with the idea that PV-containing neurons represent a laminar specific target for dopamine axons in the monkey PFC. In order to test this hypothesis, we used a dual-labeling immunocytochemical approach to examine ultrastructural associations between tyrosine hydroxylase (TH)-labeled axon terminals and PV-positive dendrites.

**Materials and Methods**

Four adult male cynomolgus monkeys (*Macaca fascicularis*) (animals CM154, CM160, CM177, CM186) and one adult male rhesus monkey (*Macaca mulatta*) (animal MNK5) were used for this study. The cynomolgus monkeys were fully anesthetized with ketamine hydrochloride (25 mg/kg) and sodium pentobarbital (30 mg/kg), and killed by intracardiac perfusion with 4% paraformaldehyde and 0.2% glutaraldehyde (Sesack et al., 1995b). The rhesus monkey was anesthetized and perfused with 3.75% acrolein and 2% paraformaldehyde (Aoki et al., 1993). For all animals, coronal sections through Walker’s area 9 were cut at 50 µm on a Vibratome and treated for 30 min with 1% sodium borohydride. Adjacent sections from two of the cynomolgus monkeys were used for a previous study of calretinin-immunoreactive local circuit neurons (Sesack et al., 1995a).

The detailed procedure for dual immunolabeling with peroxidase and gold–silver has been described previously (Sesack et al., 1995b). Briefly, sections were treated in blocking solution, then incubated overnight in a solution containing 0.2% bovine serum albumin, 3% normal goat serum, 0.04% Triton X-100 and both primary antibodies: 1:8000 mouse monoclonal anti-TH (G. Kapatos, Wayne State University) and 1:1000 rabbit polyclonal anti-PV (K. Baimbridge, University of British Columbia). Sections were incubated in biotinylated horse anti-mouse IgG and then avidin–biotin peroxidase complex (Vectastain Standard Kit) before being processed with diaminobenzidine and H2O2. Sections were subsequently incubated in 1 nm gold-conjugated goat anti-rabbit IgG (Amersham), and bound gold particles were enhanced by treatment with silver solution (Amersham).
immunoblot and preadsorption experiments, has been described in previous publications (Wolf et al., 1991; Condé et al., 1994; Lewis et al., 1994; Sesack et al., 1995a,b). Examination of additional control sections with normal serum substituted for primary antibodies revealed no immunostaining by light or electron microscopy. In addition, previous studies indicate that this and other TH antibodies primarily label dopamine axons in primate neocortex (Lewis et al., 1988; Gaspar et al., 1989; Akil and Lewis, 1993; Lewis and Sesack, 1997). For example, antibodies against TH, dopamine and dopamine transporter produce virtually identical patterns of immunoreactivity in the monkey cortex (Akil and Lewis, 1993; Whitehead et al., 1995; Lewis and Sesack, 1997). In addition, dual-labeling studies have shown that only a small percentage of cortical fibers immunoreactive for dopamine-β-hydroxylase, a specific marker for noradrenergic axons, are also TH-positive (Noack and Lewis, 1989; Akil and Lewis, 1993). Finally, our studies in the rat demonstrate that cortical terminals immunoreactive for TH synapse on GABA-labeled dendrites to the same extent as terminals immunoreactive for dopamine (Sesack et al., 1995b).

A few sections singly labeled for PV were mounted on slides for light microscopy (Fig. 1). The remaining sections were processed for electron microscopy by post-fixation in 2% osmium tetroxide, dehydration and plastic embedding (Sesack et al., 1995b). Ultrathin sections cut from this embedded tissue (see below) were collected on copper mesh grids, stained with uranyl acetate and lead citrate, and viewed with a Zeiss 902 transmission electron microscope.

A semi-quantitative analysis of the data was performed in three of the four cynomolgus monkeys and the one rhesus monkey. Drawings of the pial surface and other landmarks in flat-embedded sections were used to record the locations of trapezoids from which ultrathin sections were taken. Trapezoids were positioned at one of two approximate locations (see Fig. 1): (i) middle layers, including the lower portion of layer III (IIIb) and layer IV; or (ii) superficial layers, with the base just beneath the pial surface and including most of layer I, all of layer II and the superficial portion of layer III (IIia). The middle layers exhibiting the maximum immunoreactivity for PV (Condé et al., 1994) were the major focus of this study. One, two or three blocks per animal were examined from this location (eight blocks total), including 46 888–258 658 μm² tissue per animal (1 297 725 m² total). The more superficial layers corresponded to the location of sampling for previous studies of GABA-, calretinin-, and parvalbumin-immunoreactive local circuit neurons (Sesack et al., 1995a,b). These layers were examined in one or two blocks per animal (five blocks total), including 15 613–143 688 μm² of tissue per animal (263 931 m² total).

As described in our previous publications (Sesack et al., 1995a,b), attempts to avoid false-negative results included sampling only from the outer surface of plastic embedded sections and analyzing only fields containing both specific peroxidase and gold–silver immunolabeling. Thus, the semi-quantitative analysis does not include a full and representative assessment of all TH-labeled profiles in area 9, but rather focuses on TH-positive axons that are close to PV-labeled dendrites. When TH-immunoreactive terminals were observed in apposition to PV-positive dendrites, these fields were examined in two, three or four adjacent serial sections to determine whether morphological evidence consistent with synaptic specializations was present. However, both synapse-like contacts and close appositions were included in semi-quantitative comparisons (see Table 1), because the peroxidase product for TH sometimes obscured morphological detail, and it was often not possible to analyze close contacts through a complete series of adjacent sections. Only a relative quantitation of data was possible in this study, because different immunolabeling techniques with unequal sensitivity (Pickel et al., 1995) were used to examine associations that were observed infrequently. The use of stereotaxical techniques to obtain estimates of the absolute number of associations was precluded, because this approach requires random sampling and, thus, would be biased toward negative findings.

**Table 1**

<table>
<thead>
<tr>
<th>Local circuit neurons immunolabeled for</th>
<th>Parvalbumin</th>
<th>Calretinin</th>
<th>GABA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Layers analyzed</td>
<td>middle</td>
<td>superficial</td>
<td>superficial</td>
</tr>
<tr>
<td>Total area examined (μm²)</td>
<td>1 297 725</td>
<td>263 931</td>
<td>363 000</td>
</tr>
<tr>
<td>Area (μm²) containing both immunomarkers in the same 32.5 μm² field and percent of the total area examined</td>
<td>5 720</td>
<td>2 308</td>
<td>3 023</td>
</tr>
<tr>
<td>Number (%) of TH-labeled terminals forming associations with immunolabeled terminals</td>
<td>18/197 (9)</td>
<td>4/74 (5)</td>
<td>6/118 (5)</td>
</tr>
<tr>
<td>Number (%) of TH-labeled terminals forming synapse-like contacts on immunolabeled dendrites</td>
<td>7/18 (39)</td>
<td>0/4 (0)</td>
<td>0/6 (0)</td>
</tr>
</tbody>
</table>

*Area encompassed by an electron micrograph at 12000× magnification.

*Includes synapse-like contacts and close appositions not separated by astrocytic processes.

*Other TH-labeled terminals contacted unlabeled dendrites or did not form associations in the sections analyzed.

**Results**

Electron microscopic examination throughout layers I–IV of area 9 revealed that immunogold–silver labeling for PV was localized to dendrites, perikarya and axon terminals forming primarily symmetric synapses. Most PV-immunoreactive dendrites exhibited morphological features characteristic of interneurons (Freund et al., 1986; Williams et al., 1992; Smiley and Goldman-Rakic, 1993; Sesack et al., 1995a,b), including abundant synaptic input (multiple synapses in single sections; Figs 2C,E and 3), varicos shape (alternate narrowing and widening of diameter; Figs 2A,E and 3), and absence of detectable spines. These observations are consistent with previous light and electron microscopic findings that PV is localized exclusively in local circuit neurons (DéFelipe et al., 1989b; Hendry et al., 1989; Lewis and Lund, 1990; Williams et al., 1992; Lund and Lewis, 1993; Condé et al., 1994; Gabbott and Bacon, 1996a). Axon terminals containing dense immunoperoxidase product for TH were also frequently detected in these layers (Figs 2 and 3). Typically, these varicosities were closely apposed to dendritic spines or dendritic shafts and were rarely opposed to cell soma.

In the middle layers (IIIb–IV), 9% of terminals immunoreactive for TH contacted PV-labeled dendrites (Fig. 2; Table 1). In many instances, these contacts consisted of apposed plasmalemmal surfaces without obvious synaptic specializations. However, approximately one-third of these contacts exhibited...
morphological features that are commonly associated with symmetric synapses and are not typically observed at simple membrane appositions (Fig. 2). These features included parallel spacing of apposed membranes, widened cleft, intercleft filaments and, in a few cases, slight densification of the dendritic membrane. Other TH-labeled terminals either contacted...
dendrites unlabeled for PV or formed no obvious dendritic associations in single or serial section.

Compared to the middle layers, fields containing both TH- and PV-immunoreactive structures were detected more frequently in the superficial layers I–IIIa (Table 1). However, TH-positive varicosities were less frequently observed to directly contact PV-immunoreactive dendrites in the superficial layers. Furthermore, morphological evidence consistent with synaptic specializations was never detected at the few appositional contacts that were seen in layers I–IIIa (Figure 3). Thus, TH-labeled terminals may provide a laminar specific input to PV-containing local circuit neurons by targeting dendrites in the middle, but not the superficial layers. However, the small number of appositions or synapse-like contacts in layers I–IIIa precluded the statistical evaluation of these laminar differences.

Comparison of these data with our previous studies of calretinin- or GABA-positive neurons (Sesack et al., 1995a,b) suggests that the laminar specificity of contacts between TH-labeled terminals and PV-positive dendrites may additionally reflect specificity in the subclasses of local circuit neurons innervated by these axons. For example, in the superficial layers, the frequency of associations between TH-positive terminals and local circuit neurons was over three times greater for GABA-positive dendrites than for either PV- or calretinin-labeled dendrites (Table 1). In addition, 50% of the contacts with GABA-positive dendrites exhibited synaptic specializations, whereas no synapse-like contacts were observed with PV- or calretinin-labeled dendrites in the superficial layers. Finally, some of the contacts on GABA-labeled dendrites in the superficial layers exhibited asymmetric thickenings (Sesack et al., 1995b), whereas such dense thickenings were never observed at synapse-like contacts on PV-positive dendrites in the middle layers. Taken together, these differences suggest that TH-positive terminals preferentially target the dendrites of PV-containing local circuit neurons in the middle cortical layers, and a subclass of GABA neurons that contain neither PV nor calretinin in the superficial layers (Fig. 4).

Discussion
This study provides morphological evidence that dopamine terminals in the monkey PFC directly innervate the subpopulation of local circuit neurons that expresses the calcium-binding protein, PV. Taken together with our previous research, the data suggest that dopamine afferents are selective in their cortical
targets, innervating only certain subclasses of local circuit neurons. The PV-positive cells that are innervated by dopamine terminals potentially include both wide- and chandelier neurons with prominent connections to pyramidal neuron soma and axon initial segments respectively. Thus, as shown schematically in Figure 4, dopamine is likely to exert indirect effects on pyramidal neurons in the PFC via certain subclasses of GABA neurons, in addition to its more direct actions on the distal dendrites and spines of pyramidal cells. These findings have important implications for determining the cellular mechanisms for dopamine modulation of cortical activity in relation to cognition.

Methodological Considerations
The dual immunoperoxidase and immunogold–silver labeling technique used in this investigation is one of the most sensitive and accurate methods currently available for demonstrating synaptic or appositional interactions between neurochemically identified neurons (Pickel et al., 1993). However, limitations inherent to any electron microscopic immunocytochemical procedure prevent the determination of the exact extent of such associations. In the present study, an underestimation of the degree of dopamine innervation to PV-containing local circuit neurons may have resulted from: (ii) incomplete antibody penetration secondary to low detergent concentrations; (ii) use of limited rather than complete serial section analyses; and (iii) obscuring of morphological detail by dense peroxidase reaction product (see Sesack et al., 1995b for further discussion). In particular, these methodological limitations may have prevented the detection of a minor synaptic input to PV-positive dendrites in the superficial layers I–IIIa of the PFC. Nevertheless, the more frequent observation of appositional and synapse-like contacts between TH-positive terminals and PV-containing dendrites in the middle layers of adjacent sections from the same animals argues that dopamine preferentially targets the PV neurons whose dendritic arbors lie within layers IIb and IV.

While the dual immunolabeling method employed does not permit a determination of absolute innervation frequency, it does permit a relative comparison of the incidence of such contacts with our two previous studies of dopamine input to dendrites labeled for GABA or calretinin (Sesack et al., 1995a,b). With regard to the superficial layers I–IIIa, our combined results suggest that dopamine afferents target GABA local circuit neurons that contain neither PV nor calretinin. The quantitative stereological findings of Gabbott and Bacon (1996b) suggest that cells expressing calretinin, PV or calbindin account for >90% of GABA local circuit neurons in the medial PFC of monkeys. Thus, it remains to be determined whether the interneurons receiving dopamine synaptic input in layers I–IIIa contain the other major calcium-binding protein, calbindin.

Another unresolved issue is whether dopamine terminals in PFC layers IIb–IV innervate only a single class of PV-containing interneurons. At present, we are unaware of morphological features that would distinguish the dendrites of wide-arbor and chandelier cells that are the likely targets. Moreover, it is possible that some small to medium-sized PV-containing neurons may belong to other cell classes (Williams et al., 1992; Condé et al., 1994), and dopamine terminals may also innervate these neurons. Finally, dopamine afferents may target PV-positive dendrites that originate from soma lying above or below the middle layers. A study that combines immunocytochemistry with Golgi impregnation of local circuit neurons will be required to resolve these issues.

Comparison with Published Findings
Several converging lines of evidence are consistent with a selective innervation by dopamine of PV-containing dendrites in the middle layers of the primate PFC. For example, the postnatal development of axonal immunoreactivity for dopamine and PV in the monkey PFC involves parallel changes only in the middle layers (Anderson et al., 1995; Rosenberg and Lewis, 1995). Furthermore, the recent localization of dopamine D₄ receptors on PV-immunolabeled neurons in the PFC (Mrzljak et al., 1996) suggests that these neurons normally receive a dopamine signal. This suggestion is further supported by preliminary electrophysiological reports (Zheng et al., 1997; C.R. Yang, personal communication) that dopamine selectively alters the membrane properties of fast-spiking, presumed PV-containing (Kawaguchi, 1995) interneurons in the rat PFC. The present results extend these observations by suggesting that dopamine’s actions on PV-containing local circuit neurons are synaptic mediators. Nevertheless, dopamine might exert additional actions via release from non-synapsing varicosities (Smiley and Goldman-Rakic, 1993) and/or extracellular diffusion (Garris and Wightman, 1994). In this case, neurons with the greatest density of dopamine receptors may respond preferentially, regardless of whether the dopamine signal is mediated synaptically or extrasynaptically.

The middle cortical layers of area 9 contain a relatively higher density of dopamine axons than other cortical association areas, such as area 46 (Lewis et al., 1988; Williams and Goldman-Rakic, 1993). More specifically, the superficial layers receive the highest density of dopamine input (Rosenberg and Lewis, 1995), but the difference between the superficial and middle layers is smaller in area 9 than in other regions. This finding suggests that...
a particular cell population in the middle layers might be selectively targeted by dopamine afferents, although it might also indicate that such an input is restricted to area 9 and regions with a similar laminar distribution of dopamine axons. Interestingly, the quantitative study of area 46 by Smiley and Goldman-Rakic (1993) did not reveal any dopamine terminals in layers III–IV that innervated local circuit neuron dendrites identified on the basis of morphological criteria. Although this might indicate regional specificity in dopamine’s synaptic targets, it should be emphasized that we observed synapse-like contacts of TH-terinals on PV-positive dendrites only infrequently (3.6% of terminals in the vicinity of PV-labeled dendrites). Such a modest innervation could have been missed in the previous study of area 46.

Finally, it should be noted that target specificity has been reported for another cortical monoamine system. Specifically, serotonergic axons in the hippocampus and neocortex form dense pericellular arrays surrounding and synapsing on neurons that are immunoreactive for calbindin or calretinin, but not PV dense pericellular arrays surrounding and synapsing on neurons that are immunoreactive for calbindin or calretinin, but not PV.

Functional Implications

The functional significance of the dopamine innervation of PV-containing local circuit neurons remains to be elucidated, although a strong correlation exists between the expression of PV and fast, non-adapting firing patterns and high metabolic rates of certain neurons (Baimbridge et al., 1992; Kawaguchi, 1995). In the present study, abundant, presumed glutamatergic synapses were observed in the immediate vicinity of dopamine terminal contacts on PV-containing neurons (see also Williams et al., 1992). Furthermore, in other cortical regions, PV-containing cells, but not calretinin-positive neurons, consistently express the glutamate receptor NMDAR1 subunit (Huntley et al., 1994). PV-containing cortical neurons also express the GluR1 subunit of AMPA receptors (Kondo et al., 1997). Thus, dopamine’s ability to facilitate glutamatergic excitation (Cepeda et al., 1992) of local circuit neurons may underlie the dopamine-mediated increases in inhibitory postsynaptic potentials recorded in pyramidal neurons in vitro (Penit-Soria et al., 1987; Gellman and Aghajanian, 1993; Yang et al., 1997). The excitatory drive to these inhibitory interneurons may originate from local collaterals of pyramidal neurons and/or extrinsic cortical and subcortical sources (Winfield et al., 1981; White, 1989; Jones, 1993; Sesack and Miner, 1997; Carr and Sesack, 1998). Furthermore, the pyramidal neurons that are likely to be modulated by the actions of dopamine on PV-containing cells include those in layers II–III (Lewis and Lund, 1990; Williams et al., 1992; Lund and Lewis, 1993; Condé et al., 1994) whose principal axons project to callosal and associational cortices (White, 1989; DeFelipe and Farriñas, 1992).

Thus, dopamine may regulate the ability of corticocortical pyramidal cells to join functional ensembles, both via direct effects and by modulating the temporal and spatial activity patterns of the local circuit neurons that control the firing of these projection neurons. Our studies suggest that this latter action involves a selective and direct regulation of PV-containing wide arbor and/or chandelier interneurons with relatively proximal inputs to pyramidal neurons (DeFelipe et al., 1989b; DeFelipe and Farriñas, 1992; Williams et al., 1992; Lund and Lewis, 1993). This effect is not likely to involve calretinin-positive double-bouquet local circuit neurons (Sesack et al., 1995a) with vertical axon arbors and more distal sites of termination on both pyramidal and non-pyramidal cells (Somogyi and Cowey, 1981; DeFelipe et al., 1989a; DeFelipe and Farriñas, 1992; Lund and Lewis, 1993).

In this regard, it is interesting to speculate on dopamine’s role within the functional circuits that connect spatially segregated clusters of supragranular pyramidal neurons in the monkey PFC (Levitt et al., 1993; Kritzer and Goldman-Rakic, 1995; Puca et al., 1996). The coordinated and sustained firing of these pyramidal cells appears to subserve the maintenance of information ‘on-line’ (Goldman-Rakic, 1995) and may be facilitated by dopamine through modulation of glutamatergic input to dendritic spines (Sawaguchi and Goldman-Rakic, 1991; Cohen et al., 1996). At the same time, dopamine may regulate the inhibition of pyramidal neurons located in adjacent cell assemblies via activation (potentially through glutamate modulation) of the PV-containing local circuit neurons that innervate these cells. In this context, the reported alterations of dopamine fiber density, pyramidal cell spine density and GABA cell function in the PFC of schizophrenic subjects (Akbarian et al., 1995; Garey et al., 1995; Akil and Lewis, 1996; Benes et al., 1996; Glantz and Lewis, 1997) may be functionally related to each other and to the disease symptoms.

In conclusion, our findings provide the first evidence for target specificity of mesoprefrontal dopamine afferents and argue against the view that monoamines mediate diffuse and non-specific actions in the cortex. However, it must be considered that cortical dopamine may exert both selective synaptic actions that are phasic (Schultz, 1992) and non-selective extrasynaptic effects (Garris and Wightman, 1994) that are tonic, similar to the hypothesized actions of dopamine in the nigrostriatal system (Grace, 1991). In any case, the selectivity of dopamine’s cellular actions in the PFC has important implications for understanding the mechanisms by which this neurotransmitter contributes to cognitive processing, as well as to the pathophysiology and treatment of schizophrenia.

Notes

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