Developing a Neuronal Model for the Pathophysiology of Schizophrenia Based on the Nature of Electrophysiological Actions of Dopamine in the Prefrontal Cortex

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This review covers some recent findings of the electrophysiological mechanisms through which mesocortical dopamine modulates prefrontal cortical neurons. Dopamine has been shown to modulate several ionic conductances located along the soma-dendritic axis of prefrontal cortical pyramidal neurons. These ionic currents include high-voltage-activated calcium currents and slowly inactivating Na^+ and K^+ currents. They contribute actively in processing functionally segregated inputs during synaptic integration. In addition, dopamine mainly depolarizes the fast-spiking subtype of local GABAergic interneurons that connect the pyramidal neurons. This latter action can indirectly control pyramidal cell excitability. These electrophysiological data indicate that the actions of dopamine are neither "excitatory" nor "inhibitory" in pyramidal prefrontal cortex neurons. Rather, the actions of dopamine are dependent on soma-dendritic loci, timing of the arrival of synaptic inputs, strength of synaptic inputs, as well as the membrane potential range at which the PFC neuron is operating at a given moment. Based on available electrophysiological findings, a neuronal model of the pathophysiology of schizophrenia is presented. This model proposes that episodic hypo- and hyperactivity of the PFC and the associated dysfunctional mesocortical dopamine system (and their interconnected brain regions) may coexist in the

same schizophrenic patient in the course of the illness. We hypothesize that the dysfunctional mesocortical dopamine input to the PFC may lead to abnormal modulation of ionic channels distributed in the dendritic-somatic compartments of PFC pyramidal neurons that project to the ventral tegmental area and/or nucleus accumbens. In some schizophrenics, a reduction of mesocortical dopamine to below optimal levels and/or a loss of local GABAergic inputs may result in a dysfunctional integration of extrinsic associative inputs by Ca^{2+} channel activity in the distal dendrites of PFC pyramidal neurons. This may account for the patients' distractibility caused by their inability to focus only on relevant external inputs. In contrast, in acute stress or psychotic episodes, an associated abnormal elevation of mesocortical dopamine transmission may greatly influence distal dendritic Ca^{2+} channel-mediated signal-processing mechanisms. This can enhance possible reverberative activity between adjacent interconnected pyramidal neurons via the effects of dopamine on the slowly inactivating Na^+ , K^+ , and soma-dendritic Ca^{2+} currents. The effects of high levels of PFC dopamine in this case may contribute to behavioral perseveration and stereotypy so that the patients are unable to use new external cues to modify ongoing behaviors. [Neuropsychopharmacology 21:161–194, 1999] © 1999 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.

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Schizophrenia strikes one in one hundred people worldwide, regardless of cultural or racial origins. As the illness progresses and if it remains unattended, patients are frequently trapped in psychological, social, and economic devastation (Gottesman 1991; Jablensky 1995). Currently, our incomplete understanding of the neurobiological bases of schizophrenia suggests that defects in the genetic controls of brain development in such limbic regions (including temporal lobe structures such as hippocampus and the amygdala) as well as the prefrontal cortex (PFC) lead to cell loss or deformation, cytoarchitectural disorganization, and abnormal innervation in these brain regions (Roberts and Bruton 1990; Stevens 1992; Bogerts 1993; Shapiro 1993; Akbarian et al. 1993, 1996; Ross and Pearlson 1996; Weinberger 1996; Karayiorgou and Gogos 1997; Lewis 1997; Selemon et al. 1995, 1998).

Some results from recent imaging studies of brains from living schizophrenics have suggested that there are defective functional communications between the interconnected cortical (PFC and cingulate cortex) and limbic subcortical structures (thalamus, striatum, and temporal lobe limbic structures) (see reviews of Liddle 1996; Pfefferbaum and Marsh 1995; Andreasen 1997; Heckers et al. 1998). Findings from these studies suggest that in schizophrenics, abnormal recruitment of several interconnected cortical and subcortical structures may underlie such symptom clusters as psychomotor poverty, thought disorganization, and reality distortion (Liddle et al. 1992; Liddle 1996; Fletcher 1998; Heckers et al. 1998).

As noted in Figure 1, the PFC receives converging limbic, association cortical, and mesocortical dopamine inputs. These inputs interact in the PFC and are involved functionally in high-level cognitive processes (Fuster 1995). Among the many brain regions that PFC output innervates, two important subcortical regions are emphasized in this review. These are the nucleus accumbens (where mesoaccumbens dopamine neurons terminate) and the ventral tegmental area (VTA, where the midbrain dopamine neurons reside) (Sesack et al. 1989; Groenewegen et al. 1990; Berendse et al. 1992a, 1992b; Sesack and Pickel 1992; Gorelova and Yang 1997b). Several of the interconnected limbic, cortical, and subcortical structures known to be affected in schizophrenia are targets of the ascending midbrain dopamine systems that normally provide functional modulation of neurotransmission (Björklund and Lindvall 1984; Mogenson et al. 1993).

Alteration of dopamine transmission in PFC and/or the nucleus accumbens has been hypothesized to be part of the pathophysiology of schizophrenia. Several

Principal limbic circuits that interact with the DA systems

Figure 1. Schematic drawing illustrating the neuroanatomical interrelationship between amygdala, hippocampus PFC and NAc, as well as PFC outputs to the NAc, and the A10 dopamine perikarya in the VTA. These connections provide the potential functional links by which cortical and subcortical dopamine systems may interact.

lines of evidence seem to favor this hypothesis. First, many clinically efficacious antipsychotics are potent dopamine receptor antagonists (Seeman 1992). Second, dopamine receptors (Okubo et al. 1997) or the release dynamics of dopamine terminals (Wong et al. 1997) are markedly altered in living schizophrenic brains. Third, several psychoactive substances (e.g., amphetamine, phencyclidine) abnormally augment dopamine transmission and induce psychotic symptoms indistinguishable from schizophrenia. These lines of evidence have provided the bases for the "Dopamine Hypothesis of Schizophrenia" (Davis et al. 1991; Cohen and Servan-Schreiber 1993; Carlson 1995).

Detailed electrophysiological mechanisms that underlie the dynamic actions of neurons (i.e., in the time-scale of milliseconds, seconds, to minutes) in interconnected cortical-subcortical network of neurons are currently lacking. This review focuses primarily on the nature of electrophysiological actions of dopamine in the PFC. It is hoped that an understanding of dopaminergic actions on cortical-subcortical interactions may lead to some insights into the mechanisms responsible

for the dopamine-mediated pathophysiology of schizophrenia. Based on available electrophysiological results, we attempt to provide a neuronal model to account for certain aspects of the pathophysiology of schizophrenia. Although outside the scope of this review, we acknowledge that other neurotransmitter/neuromodulator systems undoubtedly interact with the dopamine systems to contribute to the complex pathophysiology of schizophrenia. Among the neurotransmitter systems implicated are those that use glutamate (Olney and Farber 1995), serotonin (Iqbal and van Praag 1995; Kapur and Remington 1996; Busatto and Kerwin 1997; Marek and Aghajanian 1998), and noradrenaline (Joyce 1993).

Mammalian PFC and the Mesocortical Dopamine Inputs

Mammalian PFC has been defined anatomically as the cortical region with strong reciprocal innervation with the mediodorsal thalamus (MD) (Uylings and van Eden 1990; Kolb 1984; Groenewegen et al. 1990). Although this criterion remains a topic of debate among neuroanatomists, it has served as a useful starting point for defining the PFC. Using criteria suggested by Campbell and Hodos (1970) to define homology for brain regions between different species (e.g., connections, topography, positions of sulci, embryology, neuronal morphology, histochemistry, electrophysiology, and behavioral changes resulting from lesion and stimulations), Kolb (1984) cautiously proposed that the prelimbic and infralimbic regions of the rodent PFC and dorsolateral PFC in primates are functionally analogous.

The PFC receives a distinct branch of the dopamine inputs originating from the midbrain VTA. A large body of anatomical literature using rodent, primate, or human brains has described this mesocortical dopamine input to the PFC in considerable detail. The *rodent* PFC receives mesocortical dopamine input from separate populations of A9 and A10 dopaminergic neurons located in the substantia nigra and VTA, respectively (Fallon and Moore 1978; Swanson 1982; Björklund and Lindvall 1984). The rodent mesocortical dopamine innervation is mainly confined to the limbic cortices, including the prefrontal, anterior cingulate, insular, piriform, perirhinal, and entorhinal cortices (Björklund and Lindvall 1984; Berger et al. 1991).

Although the sources of mesocortical dopamine in *human* have not been fully characterized, it has been shown that the *primate* PFC and anterior cingulate cortex receive *mesocortical* dopamine inputs from the VTA (Porrino and Goldman-Rakic 1982). Hence, although the midbrain sources of dopamine neurons are quite similar in these three commonly studied species, human and nonhuman primates have a much expanded cortical innervation by dopamine neurons relative to the rodent cortex. This dopamine input provides a

much more expanded area of innervation in *primate and human* cortices, encompassing a widespread area of the sensorimotor and association cortices. In primate and human brain, a substantial amount of tyrosine hydroxylase- or dopamine-immunoreactive fibers are found in the motor, premotor, supplementary motor area, parietal, temporal, and posterior cingulate cortices (sensorimotor), in addition to prefrontal, anterior cingulate, insular, piriform, perirhinal, and entorhinal cortices (association) (Berger et al. 1988; Gaspar et al. 1989; Smiley and Goldman-Rakic 1993).

Within the individual cortical layers in the PFC, the mesocortical inputs exhibit a distinctly different pattern in rodent vs. primate and human. In the *rodent* PFC, afferents from the VTA region (A10) provide dense dopamine input to the deep layers V–VI. The significantly sparser, but extensively collateralized, dopamine innervation to the superficial layer I–III of the rodent PFC originates in the A9 medial substantia nigra and the lateral A10 regions (Descarries et al. 1987; van Eden et al. 1987; Berger et al. 1991). On the other hand, the *primate and human* PFC receive dense bilaminar dopamine inputs: one to the deep layers V–VI, and the other to the superficial layers I–II, with the middle layer III receiving comparatively sparse dopamine innervation (Gaspar et al. 1989; Berger et al. 1991; Lewis et al. 1992; Smiley et al. 1992; Williams and Goldman-Rakic 1993; Krimer et al. 1997). Thus, in all species, the deep layers V–VI receive dense dopamine innervation, but the density of dopamine innervation in the superficial layers I–III varies across species.

The most common synaptic target of the dopamine terminals in the PFC of rodent, primate, or human seems to be the dendritic spines and shafts of putative pyramidal neurons (Van Eden et al. 1987; Goldman-Rakic et al. 1989; Verney et al. 1990; Smiley et al. 1992; Smiley and Goldman-Rakic 1993; Carr and Sesack 1996). Both tyrosine hydroxylase- or dopamine-immunoreactive axonal terminals have been found to form symmetric synapses on the spines and shafts of small diameter distal dendrites derived from pyramidal neurons. Many of the postsynaptic spines innervated by dopamine terminals also receive unlabeled asymmetric (putative excitatory) terminals. Thus, a “triadic” synaptic arrangement is formed. This synaptic “triad” may form the neural substrate whereby pre- and postsynaptic dopamine modulation of the excitatory afferents to the pyramidal cell occurs (van Eden et al. 1987; Séguéla et al. 1988; Goldman-Rakic et al. 1989; Verney et al. 1990; Smiley et al. 1992; Goldman-Rakic 1992; Smiley and Goldman-Rakic 1993; Carr and Sesack 1996).

Multiple Forms of Dopamine Receptors in the PFC

Molecular biological techniques have enabled the identification and characterization of several genes that encode at least five different brain dopamine receptors.

These findings have led to a revision of the traditional classification of dopamine receptors D1 and D2 subtypes based simply on their positive (D1) or negative (D2) association with the G-protein-coupled adenylate cyclase system (Niznik and van Tol 1992; Ogawa 1995). On the bases of their primary structure, chromosomal location, mRNA size, and biochemical and pharmacological differences, a D5 receptor is now attributed to be a second member of the D1 receptor subfamily, and the D3 and D4 receptors are classified as members of the D2 receptor family (Sunahara et al. 1991; Seeman 1992; Niznik and van Tol 1992; Ogawa 1995).

To enhance the specificity in the detection of dopamine receptor subtypes, *in situ* hybridization of dopamine receptor mRNAs, or combined dopamine receptor immunocytochemistry and dopamine receptor binding autoradiography, have been used. Whether the receptor mRNAs detected represent those that will be completely translated into functional receptor proteins is unknown at present. Only studies that show some details of the distribution of mRNA for the dopamine receptor subtype and their corresponding binding sites in the frontal or prefrontal cortex are reviewed selectively below.

In *rodent* frontal or prefrontal cortices, there is a moderate level of expression of mRNA for D1 in deep layer V–VI (Mengod et al. 1991; Fremeau et al. 1991; Mansour et al. 1991; Huang et al. 1992; Gaspar et al. 1995). A comparatively lower expression of D2 receptor mRNA is distributed in superficial layers I–III (Mansour et al. 1990; Bouthenet et al. 1991) as well as in deep layer V (Gaspar et al. 1995). Findings from double-labeling studies using the retrograde axonal tracer Fluorogold combined with *in situ* hybridization of D1 and D2 receptor mRNAs, have shown further that many of the deep layer V–VI PFC neurons possessing D1 and D2 receptor mRNA are corticocortical, corticothalamic, and corticostriatal neurons (Gaspar et al. 1995). Thus, modulation of these PFC output neurons via D1 or D2 receptor activation can influence cortical and subcortical neurotransmission in rodent. In general, most of the D1 and D2 receptor mRNAs in rodent PFC are present in the deep layers V–VI, with much lighter labeling in the superficial layers (Mansour et al. 1990, 1991; Huang et al. 1992; Vincent et al. 1993, 1995).

With the current lack of selective ligands for dopamine D3, D4, and D5 receptors, brain distribution of these subtypes has been determined primarily by *in situ* hybridization of mRNA for these receptors. Dissimilar to the distribution of D1 and D2 receptor mRNA reviewed above, only very low levels of D3 (Sokoloff et al. 1990; Bouthenet et al. 1991), D4 (van Tol et al. 1991; Ariano et al. 1997), and D5 (Sunahara et al. 1991; Laurier et al. 1994) receptor mRNAs have been found in the rodent frontal cortex samples (which included the region of the PFC). However, using antisera raised against the D4 receptor protein, intense immunoreactive staining

was found in pyramidal neurons of the frontal cortex throughout deeper layers III–VI. In addition, smaller putative interneurons were also stained occasionally (Ariano et al. 1997). This mismatch of mRNA and binding sites may reflect our lack of understanding of the degree of efficiency of translation of receptor mRNA to functional dopamine receptor proteins.

In *primate* PFC, pyramidal neurons immunoreactive to D1 and D5 receptor proteins were found in superficial layers II–III and deep layers V–VI, with layer V neurons showing clearly stronger expression of D4 and D5 receptor mRNAs (Lidow et al. 1991, 1998). This pattern matches their receptor binding sites and the corresponding bilaminar mesocortical dopamine inputs (Goldman-Rakic et al. 1990; Lidow et al. 1991, 1998). Furthermore, immunoelectron microscopy of primate PFC revealed that D1 receptor immunoreactivity is localized in the dendritic spine head and neck, adjacent to an asymmetric synapse from putative excitatory afferents. Remarkably, D1 receptors are frequently found to be present extrasynaptically from nearby dopamine terminals, suggesting their role in volume transmission/neuromodulation (Smiley and Goldman-Rakic 1993).

On the other hand, D5 receptors seemed to be located predominantly on dendritic shafts (Bergson et al. 1995). Both D1 and D5 receptors have also been shown on the axonal terminals of nondopaminergic neurons that form asymmetric (D1 and D5) or symmetric (D5) synapses on to dendritic spines (Bergson et al. 1995; Smiley and Goldman-Rakic 1993). Although present technical limitations have prevented a precise demonstration of the distribution of D1 to D5 receptors along the dendrites in single pyramidal PFC neurons, the available ultrastructural data suggest that dopamine may act: (1) *postsynaptically* to modulate excitatory (glutamate-mediated) inputs and dendritic excitability; and (2) *presynaptically* to modulate the axonal terminals of nondopaminergic afferents that synapse onto dendritic spines.

In *human* PFC, although the densities of D1 and D4 receptor mRNAs are low, they are predominantly enriched in deep layers and are present in significantly greater amounts than D2, D3, and D5 receptor mRNAs (Matsumoto et al. 1996; Meador-Woodruff et al. 1989, 1996). Receptor ligand binding studies in human brain tissues showed that the density of D1 binding sites is an order of magnitude greater than D2 binding sites in frontal cortex (De Keyser et al. 1988; Camps et al. 1989; Cortés et al. 1989). D1 receptor density was found to be higher in superficial layer I–II than in deep layers V–VI (Cortés et al. 1989). As in the rodent, there is a mismatch of dopamine receptor subtype mRNAs and their corresponding binding sites in human PFC. Nevertheless, the significantly greater number of D1 receptors in human, primate, and rat PFC further suggests that D1 receptors may play a central role in modulating signal processing across mammalian species.

The distinct laminar patterns of dopamine innervation in PFC may be of functional significance. Each cortical lamina receives functionally segregated inputs originating from different cortical and limbic regions (van Eden et al. 1992; Condé et al. 1995; see Table 1 for a summary for rat PFC). For a deep layer V–VI PFC neuron with a long apical dendrite extending through several cortical layers and potentially receiving inputs from diverse sources, it is likely that dopamine differentially modulates these afferents. Mesocortical dopamine modulation of different inputs to the different dendritic compartment along the different layers may profoundly change the ultimate functional output of that neuron. In principle, this functional modulation is likely to be applicable to both primate and rodent PFC (with some expected species-specific variations). The neuronal model of dopamine modulation of PFC neurons developed below is based primarily on anatomic and electrophysiologic results regarding rodent mesocortical dopaminergic function.

PFC Output Neurons to the Dopamine Terminal Field in the NAc and to the Dopamine Perikarya in the VTA

Among many subcortical sites that PFC output neurons project to, layer V7–VI pyramidal neurons in primate

and rodent PFC have been shown anatomically to project to both NAc and VTA (Phillipson 1979; Sesack et al. 1989; Sesack and Pickel 1992; Berendse et al. 1992a, 1992b; Gorelova and Yang 1997a; Yang et al. 1997b). When recorded in freely behaving primates or rats, these deep layer V–VI neurons showed significant enhancement of firing during a typical “delayed-response” task, during which specific information must be “held” briefly to guide subsequent responses (Suzuki and Azuma 1977; Sakai and Hamada 1981; Batuev et al. 1990; Funahashi et al. 1989; Funahashi and Kubota 1994; Fuster 1995). This sustained active neuronal activity has been suggested as a cellular correlate of short-term working memory. The enhanced neural activity occurs during the period when the animal (including humans) must hold items of information, to manipulate and to associate them with other incoming information. Thus, this PFC neuronal process may provide the animal with “the ability to form internal representations of (the) external world for planning, organizing, and guiding of forthcoming response sequences based on ideas and thoughts instead of immediate external stimulations” (Goldman-Rakic 1996).

A sustained enhancement of delayed period firing and successful performance of these tasks are highly dependent on, not only an intact functional mesocortical dopaminergic input (Brozowski et al. 1979; Simon et

Table 1. Summary of Known Afferents from Diverse Brain Regions that Terminate in Different Layers of Rat PFC

Afferents	PFC Layers with Dense Termination	References
Contralateral PFC layer II and V (diffuse)	I–II	Mitchell and Cauller (1997)
Ipsilateral PFC deep layer VI (dense)		
Nucleus Basalis/ substantia innominata	I–II	
Entorhinal	II and V	Swanson and Kohler (1986)
Callosal	I–VI	Carr and Sesack (1996)
Perirhinal	II and V	van Eden et al. (1992)
Midline thalamus: paratenial, paraventricular intermediodorsal rhomboid	I and III, some V I and V–VI I, III, and superficial V sparse I and V–VI	Berendse and Groenewegen (1991)
Ventromedial thalamus	I, sparse deep	
Mediodorsal thalamus	III, synapses on apical dendrites of both layer III and V neurons and basilar dendrites of layer III cells	
Amygdala	II and V	Bacon et al. (1996)
Hippocampus (CA1 and subiculum)	I–VI, heavier deep	Carr and Sesack (1996)
Ventral tegmental area	III–VI	van Eden et al. (1987) Descarries et al. (1987)

Modified from an initial summary table which was generously supplied by Dr. Susan Sesack with permission.

al. 1980; Sawaguchi 1987; Sawaguchi et al. 1990a, 1990b; Sawaguchi and Goldman-Rakic 1994; Seamans et al. 1998), but an "optimal" level of dopamine must also be available (Williams and Goldman-Rakic 1995; Murphy et al. 1996; Watanabe et al. 1997; Zahrt et al. 1997; Seamans et al. 1998). A disruption of neural processes in the PFC has been attributed to many forms of psychopathology underlying schizophrenia (Goldman-Rakic 1991, 1994; Gold et al. 1992; Goldberg and Gold 1995). Clearly, the level of PFC dopamine is critical for modulating normal cognitive/behavioral processes. Deviation from the critical levels can severely disrupt cognitive processes and result in such mental disorders as schizophrenia. At present, how such levels of dopamine interact with PFC neural circuits is not known.

Electrophysiological Actions of Dopamine on PFC Neurons

The cellular bases of dopamine's actions in the neocortex are enigmatic. In vivo extracellular single-unit recording studies have shown that iontophoretically applied dopamine either increases or decreases *spontaneous* neuronal firing in the neocortex (Bunney and Aghajanian 1976; Reader et al. 1979; Bradshaw et al. 1985; Sesack and Bunney 1989; Bassant et al. 1990; Yang and Mogenson 1990). Spontaneous activity of rat PFC neurons in deep layer V–VI, where the densest mesocortical dopamine projection innervates were shown to be more sensitive to exogenous dopamine than neurons in the superficial layers I–III (Bunney and Aghajanian 1976). A significant portion of the spontaneous activity being suppressed either by local iontophoretic application of dopamine within the PFC, or by low-frequency (1 Hz) VTA stimulation, is likely to involve a dopamine activation of GABAergic neurons intrinsic to the PFC (Pirot et al. 1992). (These findings are reviewed in later sections in greater detail).

The modulatory interactions of dopamine with other transmitters has also been the subject of intense investigation. Dopamine applied iontophoretically or released by VTA stimulation, suppressed spontaneous, as well as presumed glutamate-mediated (Pirot et al. 1994) mediodorsal thalamic-evoked firing in the rat PFC in vivo (Bunney and Aghajanian 1976; Ferron et al. 1984; Godbout et al. 1991; Pirot et al. 1994, 1996; Sesack and Bunney 1989; Yang and Mogenson 1990). In contrast, PFC neuronal firing induced by iontophoretic application of acetylcholine or NMDA is enhanced by very low doses of iontophoretically applied dopamine (Cépeda et al. 1992a; Yang and Mogenson 1990). As detailed below, the mechanisms of direct action of dopamine on PFC neurons are rather complex, and thus, it is inappropriate to conclude that dopamine is an *inhibitory* transmitter based strictly on extracellular findings that simply

showed a suppression of spontaneous or synaptically evoked firing (Ferron et al. 1984; Sesack and Bunney 1989; Godbout et al. 1991; Pirot et al. 1992, 1994; Yang and Mogenson 1990).

Ionic Bases of Direct Dopamine Actions on Pyramidal Neurons in the PFC

Early in vivo intracellular recordings have revealed a very complex picture of dopamine actions in rat frontal cortical neurons. In etherized, artificially ventilated rats, iontophoretic application of dopamine has been shown to induce membrane depolarization of PFC neurons and concomitant suppression of all ongoing spontaneous firing in vivo. These effects were accompanied by little or no change in input resistance (Bernardi et al. 1982). In the same preparation, iontophoretic application of dopamine has been shown to raise the firing threshold induced by iontophoretically applied glutamate. Although these initial intracellular studies have provided useful information regarding the actions of dopamine on PFC neurons in vivo, they could not provide hints to the ionic mechanisms underlying the actions of dopamine.

The recent characterization of dopamine actions on pyramidal layer V–VI PFC neurons (some were retrogradely labeled to be NAC-projecting neurons) has enabled a more detailed understanding of the actions of dopamine in the PFC in vitro (Yang and Seamans 1996). A brief period (30–90 s) of bath application of dopamine or the D1/5 agonists (SKF38393 or SKF81297) to rat PFC slices has been shown to induce highly variable small changes in membrane potential and input resistance in the layer V–VI PFC neurons. In another PFC slice study, 1 to 5 minutes of application of dopamine in the presence of ascorbic acid (as antioxidant), induced a dose-dependent small membrane depolarization (0.5 to 5 mV) that cannot be blocked by D1, D2, D4, α -, and beta-adrenergic antagonists (Shi et al. 1997). Therefore, dopamine does *not* exert a consistent action on inactive PFC neurons, which displayed little or no spontaneous activity in vitro (because of the removal of their excitatory afferents from the brain slice preparation procedures).

If these PFC neurons were depolarized by intracellular injection of depolarizing current pulses (which mimicked a selective postsynaptic depolarization) or long depolarizing current ramps, a brief period of bath applications (30–90 s) of dopamine D1/5 agonists lowered the firing threshold of the first spike and reduced the first spike latency evoked by the depolarizing pulses (Penit-Soria et al. 1987; Yang and Seamans 1996; Shi et al. 1997; Gorelova and Yang, submitted) (Figure 2). These responses were similar, whether the recordings were made at room (whole cell patch-clamp recordings at 23°C) or at a more physiological temperature (intra-

cellular recordings at 34°C). The short duration application time 30–90 s implemented in these studies served to minimize rapid D1 receptor desensitization (Jarvie et al. 1993; Ng et al. 1994, 1995; Dumartin et al. 1998).

More recently, other intracellular and patch-clamp studies also detected an early transient suppression of input resistance that results in a late onset of first spike latency (responses start at ~2 min after a 5-min long dopamine or D2/3/4 agonist application with the re-

sponses lasting for ~5 min) (Geijo-Barrientos and Pastore 1995; Gullledge and Jaffe 1998). Responses from some of the same cells also show a delayed increase in neuronal excitability, as shown by a rebound earlier onset of first spike latency evoked by the same depolarizing pulse in PFC pyramidal neurons (Gullledge and Jaffe 1998). Thus, for a given depolarizing input, post-synaptic D1/5 and D2/3/4 dopamine receptor stimulation may induce time-dependent changes in ionic con-

Figure 2. Postsynaptic D1 receptor stimulation by the D1 agonists SKF81297 or SKF38393 evokes repetitive firing in PFC pyramidal neurons in response to a given depolarizing current pulse. (A)(left) intracellular injection of a short (70 ms) depolarizing current pulse evoked one spike. (right) bath-application of 10 μM SKF81297 resulted in lowering of spike threshold and repetitive firing in response to the same depolarizing current pulse; (B) If a longer (1 s) depolarizing pulse was injected intracellularly to induce repetitive firing, the presence of another D1 agonist SKF38393 transformed the isolated firing pattern to vigorous spike trains for the same given depolarizing pulse; (C) Reduction of first spike latency by dopamine (4 μM, left) and SKF81297 (4 μM, right) in response to slow depolarizing ramps in PFC pyramidal neurons. The current-clamp records are from whole-cell patch clamp recordings at 25°C and taken at ~9 min after a brief application of dopamine and its D1/5 agonist. Note that there is no change in the slope of the response, suggesting that the response is not accompanied by changes in input resistance at this time point.

ductances that alter the threshold for firing in PFC neurons. The D2/3/4 receptor may induce an early transient suppression of neuronal excitability; whereas, D1/5 receptor activation may induce a late, prolonged enhancement of neuronal excitability in response to depolarizing inputs. These findings also indicate that until there is a change in the firing activity or voltage-dependent, active membrane properties of the PFC neuron, it would be difficult to detect the modulatory actions of dopamine clearly. Thus, for a better understanding of dopaminergic modulation, the basic properties of these voltage-dependent *active* membrane currents that specifically regulate the *firing threshold* of pyramidal PFC neurons are reviewed below.

Possible Soma–Dendritic Compartmentalized Actions of Dopamine in Pyramidal PFC Neurons

Control of Firing Threshold in PFC Pyramidal Cells. In cortical and hippocampal pyramidal neurons, the spike firing threshold is determined by the interaction of Na^+ current, high- and low-voltage-activated Ca^{2+} currents and outwardly rectifying K^+ currents (Connors et al. 1982; Sutor and Zieglgansberger 1987; Schwindt 1992; Magee et al. 1996). In the PFC pyramidal neurons, at least two major cationic conductances control firing threshold. Up to 30 mV positive from resting membrane potential and before initiation of an action potential, a TTX or QX-314-sensitive, slowly inactivating persistent Na^+ current (I_{NaP}) is readily activated in pyramidal PFC neurons (Geijo-Barrientos and Pastore 1995; Yang et al. 1996a; Gorelova and Yang 1997b). Within this narrow voltage range subthreshold to firing, this I_{NaP} is also responsible for mediating the subthreshold membrane oscillations in diverse types of neocortical neurons, including some types of PFC pyramidal neurons (Connors et al. 1982; Stafstrom et al. 1985; Alonso and Klink 1993; Klink and Alonso 1993; Llinas et al. 1991; Geijo-Barrientos and Pastore 1995; Yang et al. 1996a; Gorelova and Yang 1997b).

Recent electrophysiological results, including those obtained from single Na^+ channel recordings in acutely isolated cortical pyramidal cells, favor the idea that a single class of Na^+ channels can switch periodically to a sustained opening mode interspersed with short duration transient openings. When in the sustained opening mode, inactivation of the Na^+ channel is temporarily lost (Alzheimer et al. 1993; Moorman et al. 1990; Brown et al. 1994). Thus, subthreshold I_{NaP} and the transient Na^+ current responsible for spike firing are conducted via the same population of Na^+ channels, which are undergoing two kinetically different gating modes. The factors or mechanisms that govern the switching of Na^+ channels between the slow inactivating persistent mode and the transient mode in the PFC pyramidal neurons are not known.

Tetrodotoxin-sensitive Na^+ channels are present in both the dendrites and the soma of pyramidal cells, as suggested by electrophysiological and Na^+ -imaging studies (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; Crill 1996). However, the soma and the axon hillock have the densest distribution of immunohistochemically identified Na^+ channels subunits (Westenbroek et al. 1989). Functionally, activation of the Na^+ current generated near the axosomatic region of cortical pyramidal neurons by synaptic inputs (e.g., following stimulation of superficial layers I–II) can serve to “amplify” the subthreshold distal synaptic signals en route to the soma of the deep layer V–VI cortical pyramidal neuron (Schwindt and Crill 1995; Stuart and Sakmann 1995).

The depolarizing action of this I_{NaP} is strongly counteracted by a 4-aminopyridine- and dendrotoxin-sensitive, slowly inactivating K^+ conductance (Yang et al. 1996a). The K^+ current responsible for this conductance is inactive at rest and requires prior hyperpolarization to remove the inactivation fully. Hence, although this current is activated within 100 to 200 ms, it often takes many seconds to inactivate (Hammond and Crpel 1992). This voltage-dependent K^+ current resembles the slowly inactivating outward K^+ current, I_{D} or I_{KS} , which has also been characterized in hippocampal, striatal, and somatosensory cortical neurons (Schwindt et al. 1988; Storm 1988; Foehring and Surmeier 1993; Nisenbaum et al. 1996). As I_{KS} functionally counteracts excessive and sustained membrane depolarization, it could effectively raise the spike threshold and suppress repetitive spike firing.

Presently, there has been no evidence for the precise locations of this K^+ channel along the soma-dendritic compartment of a typical pyramidal neuron in the PFC. The fact that this K^+ current can be recorded in acutely dissociated neurons where most of the apical and basal dendrites are lost suggested a somatic or near-somatic origin of this current. The “see-saw” opposing interplay of the slowly inactivating Na^+ and K^+ currents in the narrow membrane voltage range between -70 to -55 mV controls the threshold voltages for spike firing in PFC neurons. Transmitter modulation of either or both of these currents can profoundly alter firing threshold and can result in the subsequent initiation or suppression of regenerative spike train outputs.

Ionic Mechanisms That Regulate Spike Firing Threshold in PFC Neurons and Their Modulation by Dopamine

PERSISTENT Na^+ CURRENT (I_{NaP}). Following the blockade of Ca^{2+} and K^+ currents (using Co^{2+} , TEA, and/or 4-aminopyridine in the perfusate, and using Cs^+ -con-

taining recording electrode), current-clamp intracellular or whole-cell patch-clamp recordings in deep layer V–VI neurons of the PFC or somatosensory cortical neurons have revealed that a brief intracellular depolarizing pulse activates a sustained Na^+ plateau potential that is accompanied by superimposed membrane oscillations. The plateau potential is mediated by a Na^+ current, because reducing Na^+ content of the perfusate markedly reduces this potential, and TTX or internal QX-314 abolishes it (Stafstrom et al. 1985; Fleidervish and Gutnick 1996; Yang et al. 1996a; Yang and Seamans 1996). D1/5 receptor stimulation (by SKF38393) augments the duration of this Na^+ plateau potential and shifts the activation threshold to a more negative voltage. This finding suggests that D1/5 receptor stimulation lowers the activation threshold and delays the inactivation of the slowly inactivating Na^+ conductance (Yang and Seamans 1996).

The effects of dopamine on a putative I_{NaP} (in the absence of any blockers for Na^+ or K^+ currents) were reported recently in striatal and PFC pyramidal neurons. In rat striatal slices using whole-cell patch-clamp recordings, dopamine reduces the peak amplitude of a putative slowly inactivating Na^+ current evoked by a slow depolarizing voltage ramp (Cépeda et al. 1995). In PFC pyramidal neurons recorded in rat brain slices using sharp electrode under single electrode voltage clamp mode, bath application of dopamine (10 μM) briefly suppresses an inward current recorded during depolarizing steps in voltage range from -50 mV to ~ -45 mV (fast Na^+ spike threshold in their experiments) (Geijo-Barrientos and Pastore 1995). It should be noted that several ionic conductances, in addition to the slow I_{NaP} , contribute to the generation of the inward current in this subthreshold voltage range. Inward currents include low-threshold Ca^{2+} conductance (T-current), and mixed K^+ and Na^+ conductance (so-called I_h , which was shown to be active at resting membrane potentials in cortical neurons). Outward currents include a leak, and an outwardly rectifying K^+ current can also shape the sum current during the depolarizing voltage step or ramp. Co-activation of this mixture of currents in the absence of their blockade makes it uncertain which current was suppressed or enhanced by dopamine in PFC neurons.

We recently attempted to use whole-cell patch-clamp recordings in layer V–VI PFC pyramidal neurons under voltage-clamp mode in rat PFC slices to examine the effects of dopamine on pharmacologically isolated slow inactivating Na^+ current (Gorelova and Yang 1997b). When Ca^{2+} and K^+ channels are blocked by extracellular Cd^{2+} , TEA and internal Cs^+ , D1/5 agonists (SKF38393, SKF81297, bath-applied for 60–90 s) resulted in a leftward shift of the activation of this I_{NaP} current so that the current could be activated at a more hyperpolarized potential. This effect is most prominent

10 min after the application of dopamine or the D1/5 agonists. This leads to an apparent increase of peak inward Na^+ current in voltage range from -60 mV to -45 mV, but a decrease of this current at potentials more positive than from -40 to -35 mV. In addition, there is an increase in the time-constant of inactivation of this current, suggesting that this current takes even longer to inactivate completely following D1/5 receptor stimulation (Gorelova and Yang 1997b, 1998). Thus, following D1/5 receptor stimulation, the combined effect of an earlier onset of activation of the persistent Na^+ current at a more hyperpolarized potential, and the delayed inactivation of this current may ensure that the depolarizing effects of the Na^+ current persist. Because of the extensive dendritic arbor of the PFC pyramidal neurons and the inherent space-clamp problem, it is difficult to determine whether there was an adequate voltage-clamp control of the responses of the I_{NaP} in this study. However, if the I_{NaP} responses are recorded within close vicinity of the recording pipette in the soma-basal dendritic compartment (as suggested from immunohistochemical findings of the distribution of subunits of Na^+ channels in pyramidal neurons, Westenbroek et al. 1989), adequate voltage-clamp of the I_{NaP} are likely to have occurred, then these results may provide the ionic bases via which D1/5 receptor activation lower the threshold of first spike initiation to generate the subsequent repetitive firing in response to a subthreshold depolarizing pulse (Yang and Seamans 1996).

TRANSIENT FAST Na^+ CURRENT. The effects of dopamine on the fast Na^+ current was most well studied in striatal neurons. Because the fast Na^+ currents are conducted via the same Na^+ channels that conduct the slow persistent Na^+ currents I_{NaP} , but only in different gating modes (Alzheimer et al. 1993; Moorman et al. 1990; Brown et al. 1994), we hope by reviewing some of the striatal findings, we may be able to gain some insights into the nature of dopamine modulation of Na^+ current in PFC neurons. Adequate voltage control can be obtained from voltage-clamp studies in acutely dissociated, retrogradely prelabeled striatonigral neurons, hippocampal, nucleus accumbens, and cultured striatal neurons. D1/5 receptor agonists reduce the peak amplitude of the fast Na^+ current in all these cell types (Surmeier et al. 1992; Schiffmann et al. 1995; Cantrell et al. 1997; Zhang et al. 1998). In striatonigral neurons, a kinetic shift of its voltage-dependence of the steady-state inactivation of the Na^+ current to a more negative potential is also observed (Surmeier et al. 1992). This result suggests that D1/5 receptor stimulation reduces the number of Na^+ channels available for activation. This action of dopamine, via its D1/5 receptor, may partly account for the typical dopamine suppression of intracellular depolarizing pulse-evoked spike firing at resting potential in rodent or human striatal neurons

(Calabresi et al. 1987; Cpeda et al. 1992b; Hernndez-Lpez et al. 1997).

Brain Na^+ channels are modulated via either phosphorylation by protein kinase C (PKC) and protein kinase A (PKA) (Numan et al. 1991; Smith and Goldin 1997). Activation of PKA reduced fast Na^+ current, but did not change its activation or inactivation (Schiffmann et al. 1995; Smith and Goldin 1997; Zhang et al. 1998). In PFC neurons, voltage-clamp studies of the effects of dopamine on the transient fast Na^+ current have not been reported. Nevertheless, a recent study in mouse cortical neurons shows that activation of PKC by intracellular phorbol ester results in a reduction of the I_{NaP} only at depolarized potential more positive than -40mV (Astman et al. 1998). However, this is accompanied by a delayed (peak at 4 min) shift in the activation of this current to hyperpolarized potentials more negative than -40mV ; hence, resulting in a significant increase in the I_{NaP} in this membrane voltage range (Astman et al. 1998). These changes in I_{NaP} kinetics by PKC activation are remarkably similar to that following dopamine or D1/5 agonist application in PFC neurons as mentioned above (Gorelova and Yang, submitted; Gorelova and Yang 1997b). There is some evidence for activation of PKC by dopamine and D1 agonists (McMillian et al. 1992; Kansra et al. 1995). This finding raises the question of whether dopamine may modulate I_{NaP} in PFC neurons via activation of PKC; whereas, dopamine induces changes in fast Na^+ current in striatal neurons via activation of PKA.

SLOWLY INACTIVATING K^+ CURRENT. As mentioned above, another major current that operates in the membrane voltage range just subthreshold to spike firing is a 4-aminopyridine- and dendrotoxin-sensitive slowly inactivating K^+ conductance (Storm 1988; Hammond and Crpel 1992; Nisenbaum et al. 1994, 1996). This slow outward K^+ current is responsible for membrane outward rectification in the depolarized voltage range and functionally opposes the sustained membrane depolarization mediated by the I_{NaP} current to prevent PFC neurons from reaching firing threshold (Yang et al. 1996a).

When both Na^+ and Ca^{2+} channels are blocked, D1/5 agonists remove a membrane outward rectification caused by this slowly inactivated K^+ conductance (Yang and Seamans 1996). Recently, Nisenbaum and colleagues (1998) have shown that the full D1/5 agonist SKF82958 blocks a similar slow K^+ current in striatal neuron. This agonist may exert a novel mechanism of blockade by directly interacting with the K^+ channel, rather than via activation of the G-protein/adenylate cyclase coupled D1/5 receptor.

Functionally, for a given subthreshold depolarizing EPSP that can activate both the I_{NaP} and K^+ currents, D1/5 receptor activation in PFC neurons effectively removes this slow K^+ current-mediated hyperpolarizing

“brake” on the I_{NaP} . This reduction of the slow K^+ conductance by the D1/5 receptor mechanisms can, thus, allow full expression of the depolarizing effects of the I_{NaP} (which is simultaneously modulated by dopamine). As a result of all these events, once spike threshold is attained, the ensuing repetitive firing is temporarily sustained (Kitai and Surmeier 1993; Yang and Seamans 1996).

POSSIBLE DOPAMINE MODULATION OF SYNAPTIC INTEGRATION NEAR THE PYRAMIDAL SOMA/BASAL DENDRITIC COMPARTMENT. The opposing action of the D1 receptor on the slowly inactivating K^+ and Na^+ currents can have important functional implications for how PFC neurons process incoming signals. Direct somatic and dendritic recordings during imaging of Na^+ signals have shown that both Na^+ spikes and Na^+ signals exist in the soma and the dendrites of pyramidal neurons (Huguenard et al. 1989; Jaffe et al. 1992; Kim and Connors 1993; Regehr et al. 1993; Stuart and Sakmann 1995). It is not known under what physiological conditions in vivo that the Na^+ channels in the dendrites or in the soma are preferentially in the “persistent” gating mode. Because subunits of the cloned Na^+ channel have been shown immunohistochemically to be distributed in close proximity to the soma of a pyramidal neuron (Westenbroek et al. 1989), it is likely that the I_{NaP} that is sensitive to dopamine modulation is generated near the proximal apical dendrites and soma/basal dendrites of pyramidal neurons.

The specific location of the slowly inactivating K^+ current in pyramidal PFC neurons remains unknown. In a voltage-clamp study of PFC pyramidal neuron in brain slices (Hammond and Crpel 1992), this slow K^+ current can be effectively clamped intrasomatically. Furthermore, in acutely dissociated young adult sensorimotor cortical pyramidal neurons, where most of their dendritic arbors are severely truncated, several subtypes of slowly inactivating K^+ currents were isolated (Foehring and Surmeier 1993). More recently, direct dendritic patch-clamp recordings also show the presence of a high density of the transient A-type fast K^+ current (I_A), but not the slowly inactivating K^+ current, in the apical dendrites of hippocampal CA1 pyramidal neurons (Hoffman et al. 1997). This evidence suggests that functional K^+ channels that conduct the slowly inactivating K^+ current are likely to be present close to the soma.

Via the actions on the slowly inactivated Na^+ and K^+ currents, postsynaptic D1/5 receptor stimulation should augment the postsynaptic effects of depolarizing inputs to the soma or proximal/basal dendrites of layer V–VI PFC neurons (Yang et al. 1996b). This action will result in an increase probability of the cell in reaching firing threshold. Anatomically, inputs to the soma or proximal/basal dendrites of deep layers V–VI cortical neurons are known to arise from neighboring recip-

rocallly connected cells within the same cortical region, at least in primate PFC (Levitt et al. 1993; Lewis and Anderson 1995; Kritzer and Goldman-Rakic et al. 1995; Pucak et al. 1996), and in rat somatosensory cortex (Thompson and Deuchars 1997; Markram 1997; Markram et al. 1997b). If such an organization also exists within the prelimbic rat PFC, postsynaptic D1/5 receptor activation may bias layer V–VI neurons to respond preferentially to inputs from these cells within local reciprocally connected neighboring cortical neurons; for example, similar to those present in the PFC “stripes” of primates (Lewis and Anderson 1995; Pucak et al. 1996). This reciprocal interaction may give rise to a reverberative ensemble of local neurons. Such local activity, confined within the PFC, may be operational during working memory processing, because the PFC must rely on sustained firing to “hold” information in the absence of continuous presence of previously presented sensory cues (Amit 1995; Goldman-Rakic 1995; Lewis and Anderson 1995; Yang and Seamans 1996; Durstewitz et al. (1999). Paired-cell recordings (Thompson and Deuchars 1997; Markram 1997; Markram et al. 1997b) from interacting pyramidal PFC neurons, and a study of the effects induced by dopamine are critically needed to test this hypothesis.

It should be noted that, in addition to the postsynaptic D1/5 receptor effects, recent in vitro electrophysiological studies have shown that dopamine, or a D1/5 agonist (SKF81297), can also exert presynaptic inhibitions of glutamatergic layer V–VI afferents in some layer V–VI rat PFC pyramidal neurons (Law-Tho et al. 1994; Yang et al. 1996b; Gullledge and Jaffe 1996). It is not yet known under what in vivo conditions dopamine would

activate *presynaptic* D1/5 receptors preferentially to suppress excitatory layer V–VI afferent transmission, or under what other conditions dopamine would activate *postsynaptic* D1/5 receptors to augment depolarizing inputs. It is conceivable that the *timing* of the dopamine receptor activation on these pre- and postsynaptic sites critically determines the outcome of signal transmission and computation in layer V–VI PFC neurons.

Apical Dendritic Compartment of Deep Layer Pyramidal Cortical Neurons

The apical dendrites of typical deep layer V–VI pyramidal neurons in the neocortex (including the PFC) extend 400–1,000 μm from the soma before bifurcating into finer dendritic tuft branches (Seamans et al. 1997; Yang et al. 1996a). Synaptic inputs from many other association cortical regions converge in layer I–II, where the apical tuft of the layer V–VI pyramidal neurons extends (Peters 1987; van Eden et al. 1992; Condé et al. 1995; Mitchell and Cauller 1997; Table 2). Distal synaptic signals en route to the deep layer soma of these neurons can be greatly attenuated if the dendritic membrane is functionally passive in nature (Rall et al. 1992; Cauller and Connors 1994). Moreover, recent evidence indicates that there are high densities of K^+ and mixed cationic currents (I_{H}) in the dendrites (Hoffman et al. 1997; Stuart and Spruston 1998), which produce even greater attenuation of synaptic signals than that expected for a passive dendrite.

Biophysical and neuronal computational analyses have predicted that voltage-gated ionic currents present in the apical dendrites are likely to be functionally in-

Table 2. A Summary of the Positron Emission Tomography Studies of the Interrelationships Between Resting Regional Blood Flow Data and Symptom Profiles in Living Schizophrenics (Liddle et al. 1992; Liddle 1996)

Symptom Clusters	Prefrontal Cortex	Association Cortex	Subcortical Areas
Psychomotor poverty			
↓ Initiation of speech	↓ Lateral to medial eft PFC	↓ Superior parietal association cortex	↑ Head of caudate N
↓ Expression of affect	↓ Anterior anterior cingulate		
↓ Internal generation of actions			
Thought disorganization			
Disturbances of aspects of speech production	↓ Right ventral PFC	↓ Angular gyrus	
↓ Attention	↑ Right medial PFC	↓ Parietal association cortex	
↓ Suppression of interference from irrelevant or inappropriate mental activity	↑ Anterior cingulate		
	↑ Mediodorsal thalamus		
Reality distortion			
Failure of internal monitoring resulting in delusion and hallucination		↑ Left parahippocampus (medial temporal lobe)	↑ Left ventral striatum
Deficit in the functional link between medial temporal lobe and NAc		↑ Left PFC (near Broca's)	↑ Globus pallidus
		↓ Posterior cingulate cortex	

Adopted from Liddle et al. (1992) and Liddle (1996).

volved in integrating distal synaptic signals en route to the soma and (Miller et al. 1985; Shepherd et al. 1985; Bernander et al. 1994; Cauller and Connors 1994; Mel 1994; de Shutter and Bower 1994; Midgaard 1994). On the bases of the experimental findings that focal application of Na^+ (TTX), or Ca^{2+} channel (Cd^{2+} or Ni^{2+}) blockers onto apical dendrites attenuates distally evoked synaptic potentials, inward cationic currents via Na^+ , as well as low- and high-voltage-activated Ca^{2+} channels have been implicated in “amplifying” the propagating distal synaptic signals en route to the soma (Markram and Sakmann 1994; Yuste et al. 1994; Magee and Johnston 1995b; Schwindt and Crill 1995; 1997a, 1997b; Stuart and Sakmann 1995; Lipowsky et al. 1996; Seamans et al. 1997) (Figure 3).

Dendritic high-voltage-activated Ca^{2+} spikes may subserve multiple functional roles in synaptic signal integration processes in vivo. For example, they are observed following presentation of visual stimuli (Hirsch et al. 1995), whisker stimulation (Svoboda et al. 1997), and during spontaneous occurrence of hippocampal sharp wave (resulting from complex network-initiated spike bursts) in distal dendrites of pyramidal neurons in anesthetized animals in vivo (Komondi et al. 1998). For a more detailed investigation of the electrophysiological characteristics of dendritic Ca^{2+} potentials in pyramidal neurons, such potentials are often investigated in brain slices, following blockade of the Na^+ and K^+ channels (by external TTX + TEA, or internal QX-314 + Cs^+) (Franz et al. 1986; Sayer et al. 1990, 1993; Reuveni et

Figure 3. Cd^{2+} -sensitive Ca^{2+} currents proximal to the soma of layer V PFC neurons enhance responses evoked by stimulation of layers I–II; (A) camera Lucida drawing of a layer V–VI PFC neuron, with the apical dendritic tuft and distal and proximal apical dendritic stem regions demarcated; (B) (left to right) schematic diagram of a layer V–VI PFC neuron and the location of synaptic stimulation as well as the approximate positions of the Cd^{2+} and the APV-filled pressure ejection pipettes. Synaptic stimulation of layers I–II (in the presence of bath applied DNQX, $10\ \mu\text{M}$ and Bicuculline, $4\ \mu\text{M}$) evoked either a large subthreshold NMDA EPSP or a suprathreshold response at a V_m of $-56\ \text{mV}$. Note the “hump”-like potential during the late portion of the subthreshold EPSP. At a V_m of $-76\ \text{mV}$, a smaller subthreshold NMDA-EPSP was evoked. Cd^{2+} application to the proximal apical dendritic stem region ($100\text{--}200\ \mu\text{m}$ from the soma) reduced the large subthreshold EPSP and abolished synaptically evoked action potentials, while having no effect on the EPSP evoked at $-76\ \text{mV}$. This suggests that the dendritic Ca^{2+} “hump” potential mainly amplifies subthreshold EPSPs. Following partial recovery from the effects of Cd^{2+} application, focal application of APV to the same site had no effect on the evoked response. In all figures, an arrow denotes the time of synaptic stimulation; (C) Cd^{2+} application to the proximal dendrites also blocks the high-voltage-activated dendritic Ca^{2+} spike synaptically evoked by layer I–II stimulations.

al. 1993; Seamans et al. 1997). Under these conditions, multiphasic soma-dendritic high-voltage-activated Ca^{2+} potentials, activated from -50 mV, have been recorded from soma and in different regions of the apical dendrites of pyramidal PFC or somatosensory cortical neurons directly (Amitai et al. 1993; Kim and Connors 1993; Seamans et al. 1997; Schiller et al. 1997) (Figure 4).

Combined pharmacological, electrophysiological, and Ca^{2+} imaging studies have shown that high- and low-voltage-activated Ca^{2+} channels distribute widely, but heterogeneously, throughout the soma and the apical dendrites of pyramidal neurons (Brown et al. 1993; Kim and Connors 1993; Mills et al. 1994; Yuste et al. 1994; Markram et al. 1995; Schiller et al. 1995; Miura et al. 1997). These soma-dendritic Ca^{2+} channels include T-, L-, P/Q, and N-types (Hillman et al. 1991; Ye and Akaike 1993; Markram and Sakmann 1994; Magee and Johnston 1995a, 1995b; Kavalali et al. 1997a). L-type channel immunoreactivity is distributed primarily in the soma/basal dendrite/proximal apical dendrite compartment; whereas, N-type channel immunoreactivity is distributed throughout the apical dendrites of pyramidal neurons (Westenbroek et al. 1990, 1992; Hell et al. 1993). In addition to functional amplification of subthreshold synaptic signals en route to the soma, these dendritic Ca^{2+} channels provide a support mechanism for local regeneration of dendritic spikes necessary for somatic burst firing, the induction of Hebbian forms of synaptic plasticity (Friedman and Gutnick 1989; Yuste and Tank 1996; Johnston et al. 1996; Magee et al. 1998), and intracellular Ca^{2+} signaling (Berridge 1998).

Direct dendritic recordings in the *distal dendritic tufts*, where fine dendritic branches bifurcate from the main apical dendritic stem of deep layer V–VI pyramidal PFC neurons, have shown that evoked dendritic Ca^{2+} -mediated potentials are rare (Seamans et al. 1997). When present in the apical tuft, Ca^{2+} potentials are initiated at very high threshold. In contrast, *dendritic stem regions proximal to the soma*, somatic, and dendritic stem recordings have shown that a Cd^{2+} - or nimodipine- (L-type Ca^{2+} channel antagonist) sensitive “hump” potential can be elicited by local depolarizing pulse injections or stimulations of synaptic inputs to the distal dendritic tuft in layer I–II (Seamans et al. 1997). Because this Ca^{2+} “hump” potential is activated below Na^+ spike threshold, the “hump” potential may functionally boost the amplitude and duration of subthreshold distal EPSPs en route to the soma (Seamans et al. 1997). When stronger orthodromic synaptic inputs or local depolarizing current pulses are delivered, the evoked “hump” potentials in PFC pyramidal neurons trigger large amplitude, multiphasic and/or regenerative high-voltage-activated Ca^{2+} spikes along the apical stem, soma, or the basal dendrites (Seamans et al. 1997, Figure 4). These spikes may be involved in burst genera-

tion or internal Ca^{2+} signaling mechanisms. They may also help to amplify the propagation of Na^+ spikes back into the apical dendrites (Durstewitz and Seamans submitted).

Activation of dendritic high-voltage-activated Ca^{2+} channels is mediated by complex mechanisms (Figure 5). Sodium spike transients are generally required for triggering dendritic Ca^{2+} channel activation (Chen et al. 1997; Colbert and Johnston 1996; Komondi et al. 1998; Markram et al. 1995; Schiller et al. 1995; Stuart and Sakmann 1994). In most cases, Na^+ spikes are initiated in the axon and backpropagate into the apical dendrite (Stuart and Sakmann 1994; Stuart et al. 1997; Colbert and Johnston 1996), where they have been shown to activate dendritic high-voltage-activated Ca^{2+} channels both in vitro and in vivo (Buzsáki and Kandel 1998; Markram et al. 1995; Schiller et al. 1995; Spruston et al. 1995; Stuart and Sakmann 1994; Svoboda et al. 1997). Notably, when the timing of the arrival of the fast retrograde Na^+ spikes temporally coincides with the afferent synaptic inputs, this Na^+ spike-induced dendritic Ca^{2+} influx is supralinear (i.e., greater than the linear sum of the effects of a backpropagated spike plus a synaptic input alone), and enduring changes in synaptic efficacy and strength of the previously weak afferent are induced (Markram et al. 1997a; Magee and Johnston 1997).

Under other conditions, Na^+ spikes may also be initiated locally in the dendrites to trigger local dendritic Ca^{2+} potentials. Conditions that induce local dendritic Na^+ spikes include strong orthodromic depolarizing synaptic inputs, or focal iontophoresis of glutamate to induce tonic dendritic depolarization (Regehr et al. 1993; Regehr and Tank 1990, 1992; Stuart and Sakmann 1994; Stuart et al. 1997; Schwindt and Crill 1995, 1998). To dissociate the contribution of the soma vs. dendrite Na^+ spike initiation, some studies have attempted to “inactivate” Na^+ spike-generating mechanisms near the axosomatic regions by: (1) making a physical cut to separate the soma from the apical dendrite; (2) applying focal TTX application in the soma region; or (3) voltage clamping the soma to a very hyperpolarized potential (Regehr et al. 1993; Masukawa and Prince 1984; Schwindt and Crill 1997a). Although there are inherent problems with each approach, it nevertheless seems that Na^+ spikes can be initiated locally in the dendrites and that the large voltage changes produced by such spikes likely provide an effective means of activation for dendritic Ca^{2+} potentials.

In summary, dynamic two-way signal traffic along the apical dendrites of cortical pyramidal neurons is likely to occur. Thus, strong orthodromic depolarizing synaptic inputs can activate dendritic Na^+ spikes, which trigger dendritic high-voltage-activated Ca^{2+} potentials to “amplify” locally the propagation of synaptic signals en route to the soma, thus providing a local

Figure 4. Apical dendritic recordings from pyramidal PFC neurons showing distinct firing patterns in response to injection of depolarizing current pulses; (left): camera lucida drawing of a biocytin-stained PFC pyramidal neuron. Square boxes show the dendritic regions where patch clamp recordings were made; (right): (A) recordings made in dendritic tuft branches over 600 μm from the soma. Evoked spike firing was limited to single spike or a doublet; (B) apical dendritic stem recording showing repetitive firing in response to current pulses; (C) dendritic stem recording following blockade of Na⁺ and K⁺ currents by TTX and TEA. Intradendritic current injection evoked a "hump" potential and large high-voltage-activated regenerative Ca²⁺ plateau of >100ms duration.

mechanism for regenerative spike firing, and to trigger spike bursts. When Na⁺ spikes are initiated in the axosomatic regions, they can backpropagate to the apical dendrites. These backpropagating Na⁺ spikes can induce a large influx of Ca²⁺ into the apical dendrite, which, when closely paired with the arrival of afferent synaptic inputs, can induce long-term Hebbian/associative forms of synaptic plasticity (Markram et al. 1997a; Magee and Johnston 1997). Conceivably, neuromodulation of dendritic Na⁺, or Ca²⁺ (as well as K⁺), channel activities in the apical dendrites by transmitters or neuromodulators will profoundly alter the dynamic two-way trafficking of signals along the dendrites of cortical neurons (Chen and Lambert 1997; Kavalali et al. 1997a; Jones and Elmslie 1997) (Figure 5).

Dopamine Modulation of Dendritic High-Voltage-Activated Ca²⁺ Spike Potentials

Dopamine has been shown to modulate high-voltage-activated Ca²⁺ currents in several types of vertebrate and invertebrate neurons in vitro (Paupardin-Tritsch et al. 1985; Marchetti et al. 1986; Williams et al. 1990; Surmeier et al. 1995; Hernández-López et al. 1997). In rat PFC pyramidal layer V–VI neurons, following blockade of Na⁺ and K⁺ channels, multiphasic high-voltage-activated Ca²⁺ potentials evoked by intracellular depolarizing pulses consist of "hump," spikes (>50 ms) and plateau (>100 ms) (Seamans et al. 1997). Such multiphasic dendritic Ca²⁺ potentials may reflect multiple somadendritic sites of electrogenesis (Reuveni et al. 1993) (Figure 4C).

Under current-clamp conditions, direct D1/5 receptor stimulation (by SKF38393, SKF 81297 or A77656) induced three forms of modulation. First, in some PFC pyramidal neurons, a dihydropyridine-sensitive dendritic Ca^{2+} -“hump” potential is augmented by D1/5 receptor activation (Yang et al. 1998), suggesting that dopamine may augment the L-type Ca^{2+} current mediated “hump” potential. Second, in other pyramidal neurons, the amplitude of high-voltage-activated Ca^{2+} spikes evoked by intracellular injections of current pulses were suppressed. Similar suppression of the Ca^{2+} spike amplitude can also be observed following applications of N-type Ca^{2+} channel antagonist ω -conotoxin GVIA (Yang et al. 1996b, 1998). Third, in some other PFC pyramidal neurons, the repolarizing shoulder of the dendritic high-voltage-activated Ca^{2+} plateau (>100 ms duration), as well as the depolarizing afterpotential that follows the Ca^{2+} spike (Haj-Dahmane and Andrade 1997) were significantly broadened by D1/5 agonists. This latter action of the D1/5 agonist changed the Ca^{2+} spike to a Ca^{2+} plateau potential (Yang et al. 1998). Subsequent application of the L-type Ca^{2+} channel antagonist nimodipine markedly suppressed this augmentation of the duration of the Ca^{2+} plateau, suggesting that D1/5 receptor stimulation augmented this L-type Ca^{2+} channel-mediated Ca^{2+} potential.

The suppression of the amplitude of the N-type Ca^{2+} current by dopamine or its D1/5 agonist has been shown in striatal and sympathetic neurons (Surmeier et al. 1995; Formenti et al. 1998). On the other hand, the enhancement of a L-type Ca^{2+} conductance following D1/5 receptor activation is consistent with the results from several recent studies in striatal (Galarraga et al. 1997; Hernández-López et al. 1997) and retinal horizontal cells (Pfeiffer-Linn and Lasater 1996). In hippocampal neurons and bovine chromaffin cells, single channel recordings have shown that cAMP analog, or dopamine and its D1/5 agonist, increase the availability of L-type channels. This process is attributed to a recruitment of previously “silent” L-type Ca^{2+} channels so that there is a reopening of these channels, particularly during repolarization from a moderate depolarization (Artalejo et al. 1990; Kavalali et al. 1997b). In current-clamp dendritic recordings, this mechanism may be responsible for the enhancement of the duration of high-voltage-activated dendritic Ca^{2+} spikes by D1/5 receptor activation (Yang et al. 1998).

Although a voltage-clamp analysis of the isolated Ca^{2+} currents modulated by dopamine is necessary to characterize these effects, such an analysis is very difficult. This is because many of the Ca^{2+} potentials are generated in multiple compartments in a single neuron, and they are often inadequately clamped under whole-cell recording mode recorded in the soma or in the dendrites. Nevertheless, current-clamp data suggest that D1/5 receptor stimulation can modulate the amplitude

(N-type channel mediated), as well as the duration (L-type channel mediated), of dendritic Ca^{2+} potentials (Yang et al. 1998).

Functional Roles of Dopamine Modulation of Dendritic Ca^{2+} Potentials in Synaptic Integration of Pyramidal PFC Neurons

Synaptic activation of dendrites can lead to depolarization of regions of the dendritic tree, which then activate local dendritic high-voltage-activated Ca^{2+} channels to mediate the “hump” potential, Ca^{2+} spikes, and plateau potentials. The depolarizing Ca^{2+} “hump” potential (together with the I_{Nap} activated at the subthreshold voltage range) can also serve to relieve the voltage-dependent Mg^{2+} block of the dendritic NMDA receptor channel complex, thus allowing additional Ca^{2+} entry. Elevation of $[\text{Ca}^{2+}]_i$ has been shown to activate diverse intracellular biochemical processes responsible for altering synaptic efficacy (Hirsch and Crépel 1990, 1991, 1992a, 1992b; Regehr and Tank 1990; Sah and Nicoll 1991; Alford et al. 1993; Perkel et al. 1993; Ghosh and Greenberg 1995).

Dendritic high-voltage-activated Ca^{2+} spikes and plateau potentials are likely to participate in multiple functions that are important for burst firing mechanisms, sustaining repetitive firing, and enduring forms of changes in synaptic plasticity (Figure 5). *Moderate* attenuating effects on the amplitude of the dendritic Ca^{2+} spikes following D1/5 receptor activation may “focus” or “sharpen” the effects of suprathreshold inputs arising primarily from different cortical association areas. *Strong* suppressive actions of dopamine on the N-type channel mediated dendritic Ca^{2+} spikes may functionally *uncouple* the major input zones (in the apical dendritic arbors in layers I–II) from the soma-basal dendritic compartments of layer V–VI pyramidal PFC neuron (Yang and Seamans 1996). This latter action may help to explain in part why dopamine has often been attributed as having an “inhibitory” or “suppressive” effect on spontaneous firing or activities evoked by specific inputs in the PFC.

The actions of dopamine on N-type high-voltage-activated Ca^{2+} spike potentials may also spatially restrict Ca^{2+} -dependent events in the dendrites. If this reduction was sufficiently strong, only very strong suprathreshold synaptic inputs might activate local N-type channels. This reduction of dendritic Ca^{2+} influx should result in a reduced Ca^{2+} influx in various dendritic regions. Because it has been hypothesized that lower $[\text{Ca}^{2+}]_i$ may be a prerequisite for long-term depression (LTD) to occur (Bear and Malenka 1994; Lisman 1994), the dopamine modulation of the high-voltage-activated Ca^{2+} channels in PFC neurons may favor and facilitate LTD over LTP induction (Law-Tho et al. 1994; Otani et al. 1998). $[\text{Ca}^{2+}]_i$ -dependent LTP or LTD

Figure 5. A schematic summarizing the physiological roles of high threshold Ca^{2+} "hump" and spike potentials and their interactions with dopamine.

frequently lasts from tens of minutes to hours and, thus, is less likely to directly contribute to the short-term working memory mechanisms typically processed by the PFC (Goldman-Rakic et al. 1990). However, such long-term changes in synaptic weights could set up the local network to be more responsive to certain types of inputs or to be more or less likely to be recurrently active during a working memory task. Whether short-term (lasting for seconds or minutes only) synaptic changes in PFC neurons contribute to short-term working memory mechanisms has not been explored adequately.

On the other hand, the augmentation of the duration of L-type Ca^{2+} channel-mediated Ca^{2+} plateau by dopamine may complement the dopamine-mediated augmentation of the effects of the I_{NaP} and cause PFC neurons to fire in sustained spike train. D1/5 receptor activation also augments the duration of L-type-mediated Ca^{2+} spikes in striatal neurons (Hernández-López et al. 1997). When striatal neurons are held at depolarized membrane potentials, the voltage-dependent modulation of the L-type Ca^{2+} spike duration by dopamine or D1/5 agonists increases the excitability of the neuron to NMDA application and to intracellular depolarizing pulse injections (Cépeda et al. 1998; Galarraga et al. 1997; Hernández-López et al. 1997). Because L-type Ca^{2+} channels and NMDA receptors enable large influx of cationic currents at depolarized potentials, the modulation of these currents by DA may allow PFC neurons to be more responsive to excitatory inputs when they are in a depolarized state. The application of the new technique of differential interference contrast-infrared videomicroscopy to visualize PFC neuronal dendrites

for patch-clamp recording (MacVicar 1984; Stuart et al. 1993; Dodt and Zieglansberger 1994; Stuart and Spruston 1995), coupled with imaging of changes in cellular Ca^{2+} fluxes, will provide important clues to enable a better understanding of the mechanisms of D1/5 receptor modulation of dendritic Ca^{2+} dynamics and their contribution to electrophysiological signal processing in PFC neurons.

Interactions Of GABAergic Interneurons with Pyramidal Neurons in the PFC

Another major transmitter system that regulates the excitability of layer V–VI PFC pyramidal neurons comprises intrinsic GABAergic interneurons. Simultaneous extracellular recordings of pyramidal/putative GABAergic interneuron cell pairs in the PFC of behaving primates performing an oculomotor saccade response task to visual stimuli have been attempted recently (Wilson et al. 1994). The study showed that the activity pattern of the two cell types oppose each other. Hence, the heightened firing of the interneurons was coupled with reduced firing of pyramidal neurons. This suggests that the GABAergic interneuron has a role in shaping the firing pattern of PFC neurons in encoding such visual responses (Wilson et al. 1994).

Combined electrophysiology and morphological analyses at the light microscopic level have shown that diverse types of GABAergic interneurons have extensive axonal arbors, with their ascending and descending axons and collaterals straddling different layers of the rat frontal cortex (Kawaguchi 1993, 1995; Kawaguchi and Kubota 1995, 1996). Judging by their anatomical

arrangements, GABAergic interneurons can exert a broad range of functional influences on PFC signal processing via their actions on different soma-dendritic compartments of the pyramidal cell (see below).

Actions of GABA Interneurons on PFC Pyramidal Neurons

GABA is known to exert its hyperpolarizing action in the perisomatic region of neurons to suppress spike generation. Recently, GABA has also been shown to exert a compartmental modulation of soma and dendrites in single hippocampal pyramidal neurons (Buhl et al. 1994; Kim et al. 1995; Miles et al. 1996). In the dendrites, GABAergic inhibitory postsynaptic potentials (IPSPs) may serve the following functions. First, They may temporarily hyperpolarize pyramidal cells to de-inactivate dendritic voltage-sensitive channels, such as low threshold T-type Ca^{2+} channels. Recent evidence suggests that activation of T-channels “amplifies” local subthreshold synaptic input to a small region of the dendrite (Callaway et al. 1995; Magee and Johnston 1995a, 1995b; de la Pena and Geijo-Barrientos 1996; Gillesen and Alzheimer 1997). Thus, this GABAergic action may “prime” local dendritic regions for subsequent depolarizing inputs. Furthermore, during active background neuronal firing, many voltage-dependent currents are inactivated in the depolarized state. These currents must be reactivated by varying periods of hyperpolarization. GABAergic hyperpolarization may serve this very important role in controlling neuronal excitability. Second, they may alter the timing of onset and kinetics of activation of the dendritic high-voltage-activated Ca^{2+} channels that can be activated by synaptic inputs or by backpropagated spikes (Callaway et al. 1995; Miles et al. 1996; Tsubokawa and Ross 1996; Miura et al. 1997). Third, they may hyperpolarize dendritic membranes and shunt strong depolarizing inputs. This hyperpolarization can promote voltage-dependent Mg^{2+} block of NMDA receptors, and, thereby, reduce the probability of those synapses undergoing changes in synaptic plasticity (Kanter et al. 1996).

All these actions of GABA on pyramidal dendrites and soma could presumably be regulated *indirectly* by dopamine via its actions on GABAergic interneurons to fine tune voltage-dependent processes in the soma-dendritic axis.

Dopamine Interaction with GABAergic Interneurons in PFC

The relationship of mesocortical dopamine inputs with local GABAergic interneurons is intriguing. Mesocortical dopamine projections terminate on dendrites, soma, and from terminals of GABAergic nonpyramidal inter-

neurons that synaptically contact pyramidal neurons in the PFC. Most of the dopamine terminals form no synaptic specialization on these cellular elements of GABAergic interneurons (van Eden et al. 1987; Séguéla et al. 1988; Goldman-Rakic et al. 1989; Verney et al. 1990; Benes et al. 1993; Smiley and Goldman-Rakic 1993; Sesack et al. 1995). Both D1 and D4 receptor immunoreactivity have recently been found in parvalbumin-containing GABAergic interneurons in monkey PFC (Mrzijek et al. 1996; Muly et al. 1997). Conceivably, dopamine may *directly* interact with the apical and the proximal dendrites of deep layer pyramidal output cells, as well as *indirectly* influence pyramidal cells via D1 or D4 receptor actions on intrinsic GABAergic interneurons. Indeed, much of the so-called “inhibitory” actions of dopamine may be mediated by way of GABAergic interneurons (Pirrot et al. 1992).

The electrophysiological mechanisms of dopamine on PFC GABAergic interneurons remain unclear at present. Bath application of dopamine at high concentrations (0.4 mM) in the presence of a dopamine uptake blocker increases bicuculline-sensitive IPSPs in pyramidal neurons sampled in layers III, V, and VI of rat PFC slices (Penit-Soria et al. 1987). This suggests that dopamine activates GABAergic interneurons synapsing onto PFC pyramidal neurons. Biochemical evidence analyzing GABA release from PFC slices indicates that nanomolar concentrations of D2/3/4 agonists (quinpirole, lisuride, and RU24926) induce a <30% increase in spontaneous release of preloaded, radiolabeled GABA; whereas, electrically evoked release is suppressed by the same agonists (Rétaux et al. 1991).

A particular subpopulation of PFC interneurons within layer V–VI express mRNA that encode for a large isoform of the enzyme for GABA synthesis, glutamic acid decarboxylase (GAD_{67}). Following electrolytic or neurotoxic (6 OHDA) lesions of the VTA DA neurons, activity-dependent expression of the mRNA is suppressed (Lidefors et al. 1989; Rétaux et al. 1994). This further suggests that specific population of PFC GABAergic interneurons is functionally regulated by dopamine.

Recently, direct actions of dopamine on PFC interneurons have been studied using patch-clamp recordings under visual guidance with differential interference contrast/infrared videomicroscopy (Yang et al. 1997a; Zhang et al. 1997). Four types of small interneurons have been characterized by Kawaguchi and co-workers (Kawaguchi 1993, 1995; Kawaguchi and Kubota 1995, 1996). They are fast-spiking, low-threshold spike, late-spiking, and regular spiking nonpyramidal neurons. In the presence of TTX, which blocks all synaptic inputs, dopamine was found to depolarize reversibly only fast-spiking interneurons (Yang et al. 1997a; Zhang et al. 1997). D1/5 receptor agonists (SKF81297, SKF38393) induced a small (1–3 mV), but prolonged, membrane

depolarization that outlasted the short period of application. The D2/3/4 agonist quinpirole failed to alter membrane potential by itself, but it induced hyperpolarization only when the neuron was already depolarized by dopamine or D1/5 agonists (Gorelova and Yang 1998). The interactions of the D1/5 and D2/3/4 receptors may shape the duration of the dopamine-induced membrane depolarization in fast-spiking GABAergic interneurons in the PFC.

Functional Roles of Dopamine–ABA Interactions in Pyramidal PFC Neurons

Synaptic GABA release induced by dopamine may also modulate signal integration in individual deep layer V–VI PFC pyramidal output neurons. In the perisomatic region of pyramidal neurons, near the axon-hillock, several potential mechanisms may exist. First, dopamine activation of GABAergic inputs lead to GABA-mediated IPSPs that may suppress spike initiation mechanisms, as supported by ultrastructural evidence (Sesack et al. 1995). This mechanism may account for the main “inhibitory” actions of dopamine on spontaneous firing in the PFC (Pirou et al. 1992, 1994). Second, dopamine activation of GABAergic interneurons that innervate the perisomatic region of pyramidal neurons may synchronize firing patterns to phase-lock activity with interneurons (Cobb et al. 1995; Whittington et al. 1995). The intrinsic subthreshold membrane oscillations of PFC pyramidal neurons, mediated by a I_{NaP} (Llinas et al. 1991; Yang et al. 1996a), may provide a supporting mechanism for synchronization when tuned to the same frequency entrained by the interneuron (Amitai 1994; Jeffreys et al. 1996; Gutfreund et al. 1995; Lampl and Yarom 1993).

It has been hypothesized that membrane oscillations can functionally synchronize the activity of a given network of neurons, thus ensuring that neuronal groups that resonate at the same frequency will fire in synchrony. A common mode of oscillation shared by cortical neurons from adjacent columns (often connected by horizontally projecting axons) could constitute a synchronizing mechanism by which the activity patterns of other multiple inputs are coordinated (Alonso and Klink 1993; Engel et al. 1992; Lampl and Yarom 1993; Singer 1993; Singer and Gray 1995; König et al. 1996; König and Engel 1995). Unfortunately, the action of dopamine on such synchronizing mechanisms has not been explored. Third, dopamine increases the frequency of spontaneous GABA-mediated IPSPs. These IPSPs can interpose between repetitive spike firing and may either decrease the over-all mean firing rate of pyramidal neuron or restructure the firing pattern without changing mean firing rate. Indeed, simultaneous multi-unit recordings from PFC or cortical neurons of monkey performing some memory tasks have shown

the coding is accomplished by a restructuring of firing patterns without changing the over-all mean firing rate (Abeles et al. 1993; Vaadia et al. 1995; de Charms and Merzenich 1996). Finally, the current electrophysiological understanding of dopamine actions suggests that it is *neither* “excitatory” *nor* “inhibitory” on pyramidal PFC neurons. Rather, the actions of dopamine are *dependent* on the foci, timing, and strength of synaptic inputs, as well as the membrane potential range at which PFC neurons are operating at a given moment. In other words, the actions of dopamine in the PFC are internal state dependent.

Synthesis of A Neuronal Model of Schizophrenia Based on The Electrophysiological Actions of Dopamine

Based on the available electrophysiological results regarding dopamine actions on PFC neurons, we propose a model that may account for several key aspects of schizophrenia pathophysiology. Figure 6A illustrates a highly simplified version of a basic signal computational/processing unit, which consists of a layer V–VI PFC pyramidal neuron projecting to the NAc (mesolimbic dopamine neuron terminal fields) or to the VTA (the origins of the mesocortical and mesolimbic dopamine systems) and a GABAergic interneuron (see Figure 1). The pyramidal neuron receives functionally segregated inputs in its apical dendrites and basal dendrites from diverse cortical and subcortical regions (see Table 1). The GABAergic interneuron exerts tonic hyperpolarizing action in the apical dendrites, as well as in the somatic region of the pyramidal cell (Soltesz et al. 1995; Miles et al. 1996; Kim et al. 1995). The modulatory inputs to the pyramidal dendrite by the GABAergic interneurons can, in turn, be regulated by mesocortical dopamine inputs to these interneurons.

Under Normal Conditions (Figure 6A). Dopamine activates D1/5 receptors on pyramidal dendrites to attenuate *directly* the amplitude or to augment the duration of dendritic high-voltage-activated Ca^{2+} spikes and plateau, respectively. Dopamine also modulates dendritic N-type Ca^{2+} channels *directly* or *indirectly* via the actions of dopamine on GABA interneurons. A moderate dopamine suppression of N-type Ca^{2+} channels may “sharpen” incoming depolarizing synaptic signals (from layer I–II inputs) arriving at the distal dendrite and en route to the soma. Large suppression of N-type Ca^{2+} channels may “uncouple” the dendrites, preventing distal signals from reaching the soma. Hence, the shaping of these synaptic signals may be dependent on the degree of attenuation of the dendritic N-type Ca^{2+} potential (Figure 6A).

When soma-dendritic L-type Ca^{2+} channels are modulated by dopamine, a dendritic “hump” potential is

Figure 6. A PFC neuronal model of the pathophysiology of schizophrenia (see text for details).

augmented and amplifies subthreshold synaptic inputs. Furthermore, when the duration of soma-dendritic Ca^{2+} plateau is augmented by dopamine, the Ca^{2+} plateau can now trigger spike firing and support sustained repetitive firing in response to depolarizing synaptic inputs.

On the other hand, depolarizing signals arriving from neighboring deep layer pyramidal neurons via their axonal collaterals (intralaminar inputs) (Lewis and

Anderson 1995; Pucak et al. 1996) to the somatic/basal dendritic compartment may be augmented by the postsynaptic actions of D1/5 receptors that modulate I_{NaP} and the slowly inactivating K^+ current located near these compartments. In addition, D1/5 or D4 receptors found in GABAergic interneurons (Mrzizak et al. 1996; Yang et al. 1998) may play a role in activating the GABA interneuron. GABAergic IPSPs elicited by dopa-

mine can, in turn, suppress voltage-sensitive dendritic Ca^{2+} potentials (Figure 6A).

Possible Mechanisms Underlying Thought Disorganization (Figure 6B). Systemic administration of amphetamine or apomorphine augments local cerebral blood flow in the PFC of drug-free chronic schizophrenics. In some of these cases, such treatment resulted in an improvement in cognitive task performance (Daniel et al. 1989, 1991; Dolan et al. 1995; Fletcher et al. 1996; Mattay et al. 1996). This indirect evidence suggests a dysfunctional mesocortical dopamine input to the PFC, perhaps both at the presynaptic (terminal release mechanism) and at the postsynaptic (receptor) level. Consistent with this suggestion are postmortem findings indicating a loss of functional mesocortical dopaminergic inputs to the PFC of schizophrenic brains (Akil and Lewis 1996), and a significant change in the binding kinetics of D1/5 binding sites, as shown in the positron emission tomography (PET) images of PFC from drug-naïve or drug-free schizophrenics (Okubo et al. 1997). If both of these findings are replicable, then they suggest that a loss of mesocortical dopamine input may paradoxically lead to a *reduction* (rather than a classically predictable increase) of D1/5 receptor sites in PFC. Furthermore, a loss of intrinsic GABAergic interneurons and/or a reduction of GAD mRNA in PFC of subgroups of schizophrenics has also been reported (Benes et al. 1991, 1992, 1993; Akbarian et al. 1995). Hence, a loss of dopaminergic and/or GABAergic regulation of PFC pyramidal neurons may coexist in subtypes of schizophrenia.

A combined loss of the normal GABAergic and mesocortical dopamine function in schizophrenia may have serious consequences for normal signal processing in PFC pyramidal neurons. The model in Figure 6B postulates that under this condition, limbic/association transcortical inputs will be integrated abnormally because of *nonspecific* activation of poorly modulated dendritic N-type voltage-gated Ca^{2+} channels. This may result in abnormal forms of spike burst outputs from PFC pyramidal neurons. The nonspecific activation of PFC can disrupt normal signal processing carried out in the PFC and result in distractibility, and this may account for attentional deficits in schizophrenics. This behavioral manifestation can be exhibited primarily as an inability to disregard irrelevant information, while ignoring relevant details in a given situation (Posner et al. 1988; Saykin et al. 1991; Frith 1992; Park and Holzman 1993).

A loss of mesocortical dopamine inputs may also lead to failure of modulation of synaptic signal duration that are normally amplified by soma-dendritic L-type Ca^{2+} channels (see above). Thus, when the duration of a given train of depolarizing inputs failed to be augmented by dendritic L-type Ca^{2+} channels as the

signals propagate en route to the soma, a dramatic diminishment in the duration or strength of the input signals can result. The soma may fail to integrate the temporal duration of the signal and can fail to generate correct output spike trains for the given inputs arriving at the dendrite. When combined with the nonspecific overamplification of other associative signals by dendritic N-type Ca^{2+} channels, an abnormal pattern of active firing from PFC neurons for a given train of inputs may lead to erroneous signal encoding in the PFC. This process may underlie the cellular bases of thought disorganization. This is consistent with the PET findings of an abnormal *elevation* of regional cerebral blood flow in the right medial PFC, right anterior cingulate cortex, and the medial dorsal thalamus in schizophrenic patients suffering from *thought disorganization* (Liddle et al. 1992; Ebmeier et al. 1993) (see next section).

With a reduction or absence of dopaminergic and GABAergic dendritic modulation, the abnormal signaling in PFC output neurons can be transmitted to the NAc and VTA. In turn, an abnormal rise in NAc dopamine may result. This is consistent with some recent *in vivo* evidence that show that following 6 OHDA depletion of PFC dopamine, basal dopamine in the NAc remains unchanged, but dopamine release in the NAc is significantly potentiated by tail-pinch stress (King et al. 1997), foot-shock stress (Deutch et al. 1990), as well as by behaviorally reinforcing stimuli, such as palatable food or sex-related olfactory cues (Mitchell and Gratton 1992). These data suggest that following PFC DA depletion, a given external challenge (as a given normal sensory input) can result in a *reactive* increase of NAc dopamine (Grace 1993; Deutch 1993).

Blockade of GABA_A receptors by bicuculline infusion locally in the PFC also leads to a large increase of dopamine in the NAc (Karreman and Moghaddam 1996). Local infusion of ionotropic glutamate receptor antagonists into the VTA, but not into the striatum, blocked this PFC bicuculline-induced increase in NAc dopamine level. These data place a special emphasis on the PFC→VTA pathway in mediating PFC regulation of subcortical dopamine levels (Murasue et al. 1993; Taber et al. 1995). Conceivably, thought disorganization in schizophrenia may be the result of an absence of dopaminergic and GABAergic modulation of dendritic Ca^{2+} channels in the pyramidal neurons, resulting in a generation of “untuned” signals from the PFC neurons. Because these signals are transmitted via the PFC→VTA and PFC→NAc pathways, a *reactive* increase in NAc dopamine could contribute to the genesis of the associated psychotic symptoms.

Possible Mechanisms Underlying Behavioral Perseveration or Stereotypy (Figure 6C). In schizophrenics with intact mesocortical dopamine input and interneuron activity, psychotic episodes or severe stress may be

accompanied by hyperactivity of the mesocortical dopamine input. This can result in abnormally high levels of extracellular dopamine in the PFC, as shown in laboratory animals under acute stress (Abercrombie et al. 1989; Deutch and Roth 1990; Jedema and Moghaddam 1994; Murphy et al. 1996). Under this condition, dopamine may activate the intrinsic GABAergic interneuronal network in the PFC (Benes 1997). The hyperpolarizing actions of dopamine-activated GABAergic inputs could, in turn, inactivate all voltage-dependent currents in the apical dendrite region of pyramidal neurons, including the Ca^{2+} and Na^{+} currents that are functionally responsible for “amplifying” synaptic signals en route to the deep layer soma of the layer V–VI pyramidal neurons (Seamans et al. 1997; Stuart and Sakmann 1995; Schwindt and Crill 1995).

Near the somatic/basal or proximal dendritic compartments of the pyramidal PFC neuron, the postsynaptic effects of D1/5 receptor activation on the I_{NaP} and the slowly inactivating K^{+} currents may enhance excitability of pyramidal neurons in response to depolarizing inputs, perhaps from neighboring neurons via axonal collateral connections (Levitt et al. 1993; Kritzer and Goldman-Rakic 1995; Lewis and Anderson 1995; Pucak et al. 1996). This can be further augmented by actions of dopamine on L-type Ca^{2+} channel activity in the soma-dendritic regions. If these excitatory signals are conducted via horizontally projecting axon collaterals of the pyramidal neurons to the neighboring reciprocally connected neurons, sustained repetitive firing may result. The abnormal PFC firing transmitted via its axon collaterals to adjacent pyramidal neurons may establish a local internal reverberative ensemble among these neurons (Amit 1995; Vaadia et al. 1995).

In contrast, incoming transcortical signals from layer I–II can be shunted by a high level of dopamine acting: (1) directly on dendritic N-type Ca^{2+} channels to “uncouple” dendritic signal transmission; and (2) indirectly by dopamine activation of GABAergic interneurons innervating the apical dendrites (Figure 6C). When combined with the above reverberative activities between neighboring neurons, this may be the potential mechanism for behavioral perseveration or stereotypy. This may provide a neuronal explanation for the inability of schizophrenics to use external signals (incoming transcortical inputs) to modify ongoing behaviors. Such mechanisms would be expected to disrupt cellular processes underlying working memory (Park and Holzman 1992; Goldman-Rakic 1991, 1994; Weinberger 1991).

At first glance, the above two mechanisms (Possible Mechanisms Underlying Thought Disorganization/Behavioral Perseveration, or Stereotypy) seem to contradict some of the brain-imaging data obtained from schizophrenics. Results from many of these imaging studies suggest that PFC regional hypoperfusion are mainly observed in chronic schizophrenics exhibiting psycho-

motor poverty (with negative symptoms and a prolonged duration of illness). Hypoperfusion was found both at rest and when challenged by cognitive tasks that specifically test the functions of the PFC (e.g., Wisconsin Card Sorting Test), regardless of whether patients were drug-naïve or medicated (Ingvar and Franzen 1974; Franzen and Ingvar 1975; Berman et al. 1986; Weinberger et al. 1986; Mathew et al. 1988; Andreasen et al. 1992; Buchsbaum et al. 1992; Liddle et al. 1992; Wolkin et al. 1992). However, in several subgroups of schizophrenics with acute psychosis (including some who were unmedicated), investigators have detected increased PFC activity at rest, with no failure of activating PFC in cognitive tasks, such as verbal fluency and executive tasks (Chua and McKenna 1995; Ebmeier et al. 1993; Heckers et al. 1998). Such patients showed a greater activation, and a lack of inactivation, of PFC cerebral blood flow (Liddle et al. 1992; Ebmeier et al. 1993, Table 2). Thus, hypoactivation of the PFC cannot be generalized to all categories of schizophrenia (Weinberger and Berman 1996; Fletcher 1998). A more likely scenario would be that *episodic* PFC hyperactivity and hypoactivity coexist in schizophrenic patients during the course of the illness.

A New Perspective for a Pharmacotherapy for Schizophrenia

Several typical and atypical antipsychotic drugs (all dopamine receptor antagonists) have been shown to inhibit high-voltage-activated Ca^{2+} currents in cultured neurons and neuronal cell-lines, independent of dopamine receptor blockade (Gould et al. 1983; Quirion et al. 1985; Galazzi et al. 1986; Ogata et al. 1989; Fletcher et al. 1994; Sah and Bean 1994; Ito et al. 1996). In particular, atypical antipsychotics of the diphenylbutylpiperidine type (e.g., pimozide, fluspirilene, clopimozide) or its derivatives have been shown to be most effective in blocking brain L-type Ca^{2+} channels (Gould et al. 1983; Quirion et al. 1985; Galazzi et al. 1986). It is likely that the relief of psychotic symptoms by systemically administered typical antipsychotics is partly a result of PFC neuronal “tuning” via blockade of dendritic Ca^{2+} channels, as well as a reduction of the abnormally elevated dopaminergic transmission via blockade of dopamine D2 receptor in the NAc. If so, compounds that have the combined ability to simultaneously *stimulate* D1/5 receptors (to “tune” dendritic inputs) in the PFC (where D1/5 receptors predominate) and to *block* D2 receptors in the NAc (to reduce the effects of overactivation of the mesolimbic dopamine system) may constitute a possible “magic bullet” for treating thought disorganization in schizophrenia. In addition, restoring GABAergic functions in the PFC may constitute an additional pharmacotherapeutic strategy. The use of new anticonvulsant GABAergic agonists (e.g., Felbamate) or

their derivatives may be considered as an adjunct medication (McCabe et al. 1993; Rho et al. 1994).

As predicted in the model shown in Figure 6C, a dopamine enhancement of the effects of slow Na^+ , K^+ and L-type Ca^{2+} channels in the soma/basal dendritic compartment of pyramidal PFC neurons may increase the excitability of pyramidal neurons. In response to local deep layer V–VI glutamatergic synaptic inputs, local circuit reverberation between adjacent glutamatergic pyramidal neurons may result. This may be expressed as behavioral perseveration or stereotypy. Conceivably, agents that reduce abnormal presynaptic glutamate release between interacting adjacent pyramidal PFC neurons are likely to reduce behavioral perseveration or stereotypy. Group II metabotropic glutamate receptor agonist (e.g., LY354740), which can block presynaptic glutamate release, has been used recently to attenuate abnormal elevation of PFC glutamate release and the resulting behavioral stereotypy following chronic treatment of the psychostimulant phencyclidine (Moghadam and Adams 1998).

Finally, it should be noted that this review does not mean to assert that such a complex disorder as schizophrenia is attributable to defects in only the mesocortical and mesolimbic dopamine systems. The recent success in using atypical antipsychotic drugs that have a "rich" pharmacology (e.g., risperidone and olanzapine) to provide effective treatment for both positive and negative symptoms in schizophrenia without the extrapyramidal side effects has revolutionized our understanding of the pathophysiology of schizophrenia. These clinical findings have clearly suggested that interaction of multiple defective receptor systems are involved in the complex pathophysiology of schizophrenia. Based on the high affinities of these atypical antipsychotics with several serotonin receptor subtypes, in addition to their ability to elevate PFC dopamine (Bymaster et al. 1996; Kapur and Remington 1996), it seems that a more detailed understanding of how dopamine and serotonin receptors interact in the PFC will likely yield further insights into the pathophysiology of schizophrenia (Kapur and Remington 1996). The model described above suggests that a shift in our perspective on treatment of psychosis may be needed. Such a shift may enable us to change our approach from that of a general blockade of NAc dopamine transmission to a "tuning" process upstream to correct defective signal processing in the PFC of schizophrenia.

CONCLUSION

Available electrophysiological results regarding dopamine and GABA actions on PFC neurons have permitted synthesis of a novel neuronal model of schizophrenia pathophysiology. Distractable behavior associated with

schizophrenia may be caused by a combined dysfunction of dopamine and GABA modulation of dendritic functions in pyramidal neurons in the PFC. In turn, this may result in dysregulated dendritic signaling in response to extrinsic transcortical associative inputs in PFC output neurons (Figure 6B). On the other hand, abnormal elevation of PFC dopamine under conditions of acute stress may uncouple extrinsic inputs, while concomitantly enhancing internal reverberative activity among adjacent pyramidal neurons. This pathophysiological condition may account for behavioral perseveration and the inability of schizophrenics to use external signals to modify ongoing behavior (Figure 6C).

Current evidence suggests that schizophrenia is likely to be a neurodevelopmental disorder (Weinberger 1996; Karayiorgou and Gogos 1997; Lewis 1997). Progress in the field of developmental neurogenetics holds promise for potential new insights that may lead to gene therapy once specific genetic defects are identified. At present, we must be realistic about our efforts to treat schizophrenia. Current therapeutic strategies only aim at symptom control during the long course of development of the disease. The model above may serve to move basic research in the pathophysiology of schizophrenia beyond academic interests. This is because the insights gained may eventually enable us to design novel antipsychotic drugs that can specifically "tune" dysregulated signal processing in the PFC of schizophrenics.

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