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CHAPTER 13

Electrophysiological Pharmacology of Mesencephalic Dopaminergic Neurons

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We dedicate this chapter to the memory of Dr. Stephen J. Young, mentor, colleague and friend. For decades Steve contributed tirelessly and selflessly to the advancement of the science of countless students, colleagues and scientists around the world. His presence is sorely missed.

A. Introduction

In spite of the fact that actions of dopamine, as a neurotransmitter in its own right, were foreseen as early as the 1930s (Blaschko 1939) and explicitly postulated in the 1950s (Carlson et al. 1958), it took over a decade more to begin to explore the electrophysiological features, characteristics, and responsiveness to drugs of central dopaminergic neurons (Bunney et al. 1973b; Groves et al. 1975). In the 1960s much effort was employed attempting to map the location of catecholamine neurons in the mammalian central nervous system. The use of the histofluorescence technique (Falck et al. 1962) coupled with lesion experiments enabled anatomists to locate dopaminergic cell bodies in the mesencephalon (Anden et al. 1964; Bertler et al. 1964). Subsequent work (Dahlstrom and Fuxe 1964; Anden et al. 1965; Ungerstedt 1971) refined and extended those initial and pioneering findings and formed the basis for modern anatomical (see Sesack this volume for an updated view), biochemical, and electrophysiological investigation of central dopaminergic neurons.

Physiological studies of central dopaminergic neurons began with in vivo extracellular recordings which described the basic electrophysiological and pharmacological properties of mesencephalic dopaminergic neurons (Bunney et al. 1973a,b). From the very beginning, the unusually long duration action potential, the persistent low frequency of spontaneous discharge, including unusually low frequency burst firing and slow conduction velocity (Deniau et al. 1978; Guyenet and Aghajanian 1978), together with inhibitory responses to dopamine and dopamine agonists such as apomorphine and amphetamine (Bunney et al. 1973a,b; Groves et al. 1975) have been unanimously recognized as the extracellular, electrophysiological "fingerprint" of dopamine-containing neurons in the midbrain.

There are several compelling reasons for studying central dopaminergic systems over and above their uniqueness and intrinsically interesting properties. Chief among them is the central role that they play in mediating the effects of antipsychotic drugs, and in the neurobiology of many psychotropic drugs, drug abuse, and addiction. In this chapter we review some of the principal aspects of the neurobiology of dopaminergic neurons as they relate to the pharmacology of psychotherapeutic drugs and drugs of abuse. Electrophysiological studies of dopaminergic neurons have provided important evidence implicating these cells as components of systems of fundamental importance in normal CNS functioning as well as in various pathological conditions including degenerative disorders such as Parkinson's disease, schizophrenia, and drug addiction. Controversy and disagreement with respect to the interpretation of data is common in the scientific literature, and the literature on the neurophysiology and neuropharmacology of dopaminergic neurons is no exception. Where relevant, we will point out some of the current areas of contention and discuss them in light of recent findings.

B. Anatomical Organization

Although some dopaminergic neurons are located elsewhere in the brain (i.e., tuberoinfundibular dopaminergic neurons that regulate the release of prolactin from the anterior pituitary gland; Moore et al. 1987 and in the retina where they regulate receptive field size by altering the conductance of electrotonic synapses e.g., Teranishi et al. 1983), most of the dopaminergic neurons in the central nervous system are located in the midbrain. In the present chapter, we will focus on the dopaminergic pathways originating in the mesencephalon which have been most extensively studied and whose function has been most convincingly linked to human psycho- and neuropathology. Although the topography of their inputs and outputs differs somewhat, the mesencephalic dopaminergic neurons exist for the most part as a single continuous and contiguous group of cells, and the axon of many of these neurons collateralizes to one or more additional target structures (Fallon 1981). However, historically the midbrain dopaminergic cell groups and their projections have been functionally subdivided into three systems: the nigrostriatal, mesolimbic, and mesocortical dopaminergic systems.

Most of the cell bodies of origin of the nigrostriatal dopaminergic system are located in the substantia nigra pars compacta (A9 in the terminology of Dahlstrom and Fuxe 1964) with the remainder being located in the pars reticulata. The neurons are medium to large sized, multipolar, fusiform, or polygonal in shape and emit 3–5 large, rapidly tapering smooth dendrites. There is no local axon collateral arborization within the substantia nigra (Juraska et al. 1977; Tepper et al. 1987b). These neurons send their axons anterior and rostral to the neostriatum where they form Gray's type II symmetrical synapses, mainly on the dendrites or the necks of the dendritic spines of the striatal medium spiny projection neurons (Pickel et al. 1981; Freund et al. 1984) (See Fig. 1).

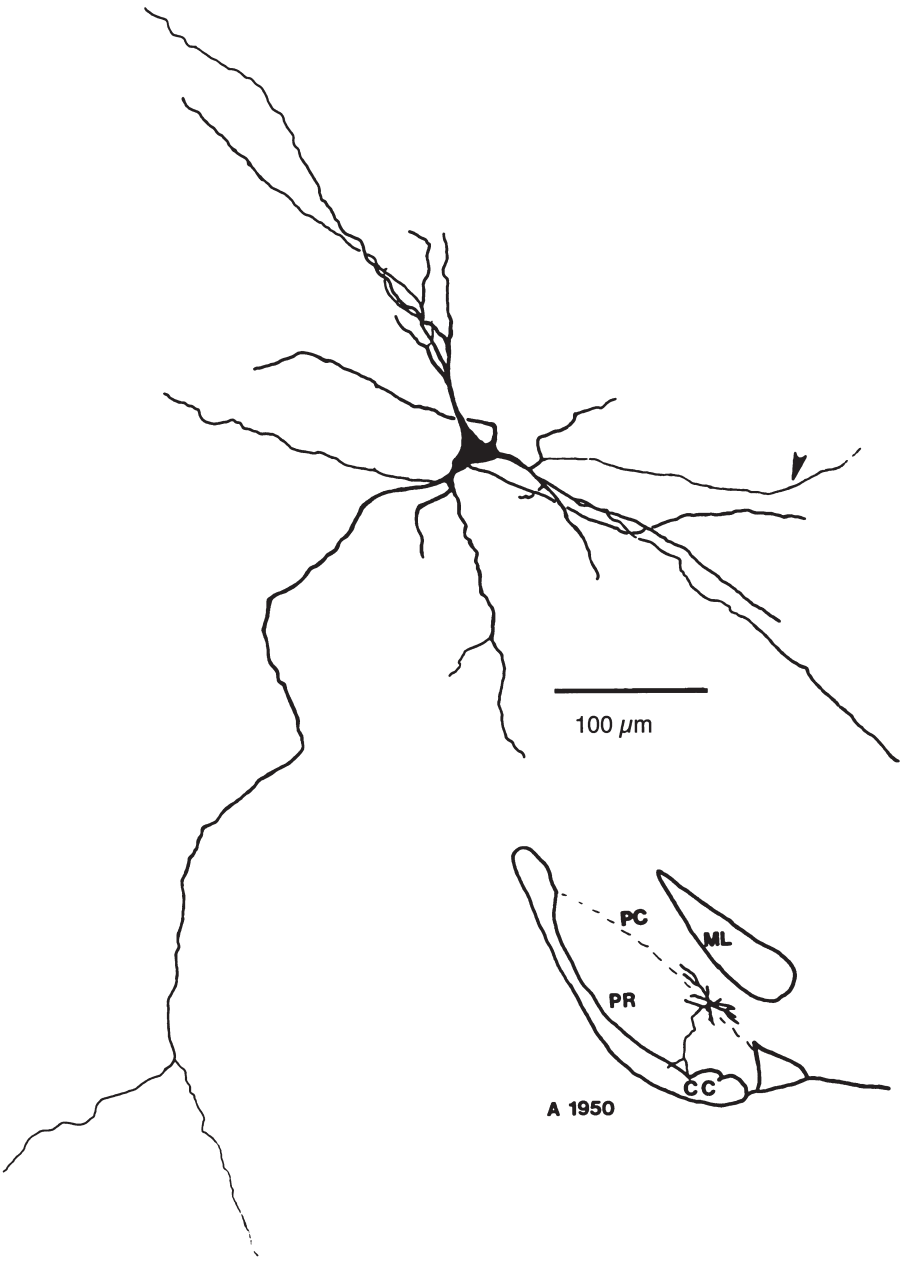


Fig. 1. Drawing tube reconstruction of an HRP-filled substantia nigra pars compacta neuron that was antidromically activated from both ipsilateral globus pallidus and neostriatum. The *inset* is drawn approximately to scale to illustrate the location of the dendritic arborization of the neuron within substantia nigra. The coordinates refer to the location of the coronal section from the atlas of Konig and Klippel (1963). The *arrow* points to the proximal portion of the axon, which emerges from a dendrite. PC, pars compacta, PR, pars reticulata, ML, medial lemniscus. (Reproduced from Tepper et al. 1987b with permission of the publishers)

Most of the cells of origin of the mesolimbic dopaminergic system are located medial to the main body of the substantia nigra pars compacta in the ventral tegmental area (A10 in the terminology of Dahlstrom and Fuxe 1964) and medial substantia nigra. These neurons project to the ventral part of the striatal complex, including the nucleus accumbens (both core and shell) and the olfactory tubercle.

The mesocortical dopaminergic projection arises from the mediodorsal, most parts of the pars compacta and ventral tegmental areas (VTAs) and innervates the prefrontal, cingulate, perirhinal, and entorhinal cortices in a loosely topographical manner (for review see Fallon and Laughlin 1995).

The most caudal, lateral, and superior extension of the midbrain dopaminergic cell group, and the smallest of the three cell groups, is termed the retrorubral field (A8 in the terminology of Dahlstrom and Fuxe 1964) and innervates largely striatal regions. For a more detailed description of the anatomical organization of mesencephalic dopaminergic neurons in rat, the reader is referred to other chapters in this volume and to the excellent review by Fallon and Laughlin (1995).

C. Basic Electrophysiological Properties

I. Extracellular Recordings

In in vivo extracellular recordings from anesthetized adult rats, midbrain dopaminergic neurons fire spontaneously at slow rates, averaging around 4 spikes per second (Bunney et al. 1973b; Deniau et al. 1978; Guyenet and Aghajanian 1978; Bunney 1979; Tepper et al. 1982). Dopaminergic neurons exhibit three distinct modes or patterns of firing. The most common pattern of activity in vivo is a random, or occasional mode of firing characterized by an initial, prolonged trough in the autocorrelation function representing a long post-firing inhibition. The next most common firing pattern is a very regular, pacemaker-like firing, characterized by very regular interspike intervals with a low coefficient of variation, and a lack of bursting. The third and least common mode of firing is bursty firing, characterized by stereotyped bursts of 2–8 action potentials in which the first intraburst interspike interval is around 60 ms, followed by progressively increasing interspike intervals and progressively decreasing spike amplitudes (Wilson et al. 1977; Grace and Bunney 1984a,b; Tepper et al. 1995). In anesthetized, unanesthetized, and freely moving rats (Freeman et al. 1985; Diana et al. 1989), dopaminergic neurons often switch between different firing modes, and these firing patterns can best be thought of as a existing along a continuum, with the pacemaker-like firing on one end and bursty firing on the other (Fig. 2). The bursty mode of firing has generated particular interest as action potentials fired in bursts have been linked to an increased overflow of dopamine in terminal areas compared to an equal number of evenly spaced action potentials (Gonon 1988) which could alter dopaminergic neurotransmission in axonal terminal fields qualitatively

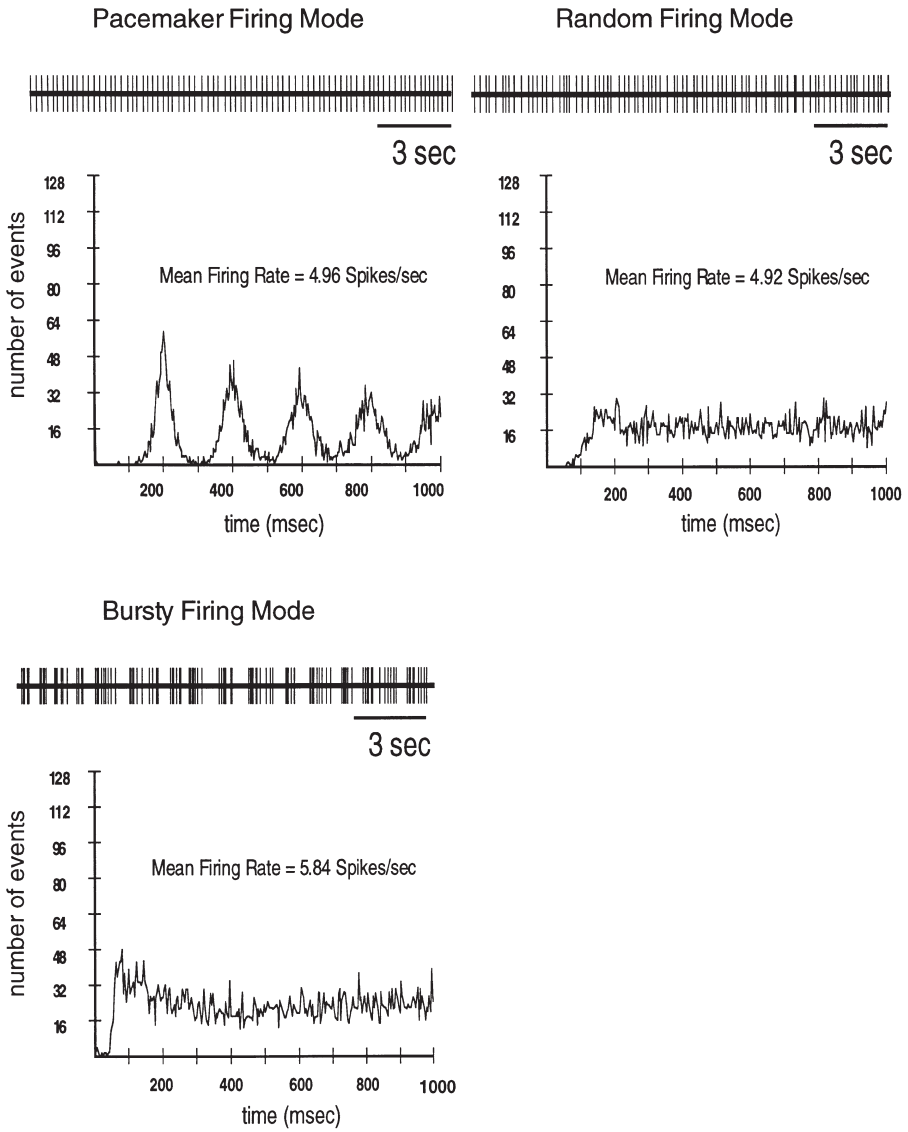


Fig. 2. Autocorrelograms of representative neurons exhibiting the three firing modes of dopaminergic neurons in vivo. Above each autocorrelogram is the first approximately 15 s of the spike train used to create the autocorrelogram. Bin width = 3 ms. (Reproduced from TEPPER et al. 1995 with permission of the publishers)

as well as quantitatively (e.g., Gonon 1997), and which may play a role in the dendritic release of dopamine (Bjorklund and Lindvall 1975; Groves et al. 1975; Cheramy et al. 1981) as well.

Anesthesia affects the expression of the three firing patterns and their responsiveness to drugs (Mereu et al. 1984b; Kelland et al. 1990a). Although all three firing patterns are expressed in unanesthetized freely moving or immobilized preparations, burst firing is more common in unanesthetized rats than under any anesthetic (Wilson et al. 1977; Freeman et al. 1985; Diana et al. 1989; Kelland et al. 1990a). Different anesthetics also differentially affect the distribution of firing patterns; burst firing is expressed least under urethane, is intermediate under chloral hydrate, and is expressed most under ketamine anesthesia with an incidence almost equal to that observed in unanesthetized preparations (Kelland et al. 1990a).

The extracellularly recorded action potential of midbrain dopaminergic neurons is of unusually long duration, almost always greater than 2 ms and sometimes as much as 5 ms depending on the level of depolarization of the neuron, and often displays a notch or inflection on the initial rising phase termed an initial segment-somatodendritic (IS-SD) break (Bunney et al. 1973b; Guyenet and Aghajanian 1978; Grace and Bunney 1983b) by analogy to a similar phenomenon in spinal motoneurons (Coombs et al. 1957; Eccles 1957).

Early studies using antidromic activation of mesencephalic dopaminergic neurons from terminal fields in striatum revealed that these neurons have very slow conduction velocities (~0.5 m/s in rat; Deniau et al. 1978; Guyenet and Aghajanian 1978) consistent with their thin (less than 1 μm) and unmyelinated nature (Tepper et al. 1987b). Most of the time (64%; Trent and Tepper 1991) the antidromic response consists of a small spike, assumed to be an initial segment (IS) spike (Coombs et al. 1957; Eccles 1957; Guyenet and Aghajanian 1978). Multiple discrete antidromic latencies are often present, presumably reflecting the highly branched nature of the terminal field, giving rise to multiple sites of initiation of the antidromic spike (Collingridge et al. 1980; Tepper et al. 1984a).

Although many of the early extracellular recording studies focused on dopaminergic neurons in substantia nigra, the majority of subsequent studies revealed that with a few exceptions, VTA neurons exhibit electrophysiological and pharmacological properties that are similar or identical to those of substantia nigra dopaminergic neurons in most ways (e.g., Bunney 1979; Wang 1981a–c; Freeman et al. 1985; Mereu et al. 1985; Freeman and Bunney 1987; Clark and Chiodo 1988).

The most commonly reported difference between A9 and A10 dopaminergic neurons has to do with the pattern and rate of spontaneous activity in vivo. Although A10 neurons exhibit the same range of firing patterns as A9 neurons, many studies report that the incidence of burst firing is greater among VTA neurons than substantia nigra pars compacta neurons (Grenhoff et al. 1986, 1988; Charlety et al. 1991). Interestingly, it does not appear as if the

characteristics of the burst firing are different; most of the burst parameters are the same among A9 and A10 neurons, but the proportion of A10 neurons firing in the bursty mode is greater (Chiodo et al. 1984; Grenhoff et al. 1986, 1988; Charlety et al. 1991). Despite this consistent difference, the mean firing rates of A9 and A10 dopaminergic neurons are usually reported to be about the same (e.g., Wang 1981a,b; Grenhoff et al. 1986, 1988; Freeman and Bunney 1987; Gariano et al. 1989b; Shepard and Bunney 1988; Charlety et al. 1991; but see also Chiodo et al. 1984). One reason put forth for the difference in proportion of burst firing neurons is a difference in autoreceptor number and/or sensitivity (Chiodo et al. 1984), but for reasons discussed below (see discussion in Sect. E.IV) this does not seem the most likely explanation. Rather, as suggested previously (e.g., Grenhoff et al. 1988) a difference in afferent inputs may be responsible. Various afferents to midbrain dopaminergic neurons and the effects they have on firing rate and pattern are discussed below (see Sect. D). In that context, it is interesting to note that one of the most striking qualitative differences between A9 and A10 neurons is that dopaminergic neurons in the VTA appear to receive a significantly greater number of glutamatergic asymmetric, presumably excitatory, synaptic contacts than those in the substantia nigra (Smith et al. 1996).

II. Intracellular Recordings

The first data from intracellular recordings from identified rat dopaminergic neurons were published by Grace and Bunney in a memorable series of papers in the early 1980s (Grace and Bunney 1980, 1983a,b, 1984a,b). This accomplishment was rendered even more impressive by the fact that these were in vivo recordings from the substantia nigra, a structure deep in the midbrain where the dopaminergic neurons are situated in a layer only a few cells thick. These recordings verified that the unusually long duration action potential was not an artifact of damage or extracellular recording. The action potential had an inflection that, upon digital differentiation, was virtually identical to the IS-SD break previously noted in extracellular recordings. Furthermore, the small antidromic spike observed extracellularly could be seen intracellularly and converted to a full spike by injecting depolarizing current, consistent with its tentative extracellular identification as an IS spike. Spontaneous spikes were seen to arise from a slow depolarization and were followed by large amplitude, long-lasting spike afterhyperpolarizations. Application of hyperpolarizing current pulses revealed a slowly developing inward rectification, and the episodes of slow-burst firing first seen with extracellular recordings were observed to occur superimposed upon large spontaneous depolarizations (Grace and Bunney 1980, 1983a,b, 1984a,b).

Subsequent in vitro recordings revealed that the long, slow afterhyperpolarization was due to a calcium-activated potassium conductance and that the slowly developing inward rectification was blocked by tetraethylammonium (TEA), suggesting its mediation by I_h (Kita et al. 1986). The slow after-

hyperpolarization is very sensitive to apamin, and plays a significant role in regulating the firing pattern of dopaminergic neurons (Shepard and Bunney 1988; Ping and Shepard 1996). A number of pharmacologically and electrophysiologically distinct low- and high-threshold calcium conductances have been identified in midbrain dopaminergic neurons (e.g., Llinás et al. 1984; Nedergaard et al. 1988, 1993; Nedergaard and Greenfield 1992; Kang and Kitai 1993a,b; Cardozo and Bean 1995; Galarraga and Bargas 1995; Wilson and Callaway 2000). Dopaminergic neurons also exhibit several different types of voltage-dependent potassium channels (Silva et al. 1990). A transient, 4-aminopyridine (4-AP)-sensitive, TEA-insensitive A-current that is largely inactivated at the most stable subthreshold membrane potentials is expressed, as is a sustained outward current and at least two different types of calcium-activated potassium current (Silva et al. 1990; Cardozo and Bean 1995), plus the inwardly rectifying I_h mentioned above. Although the conductances responsible for the bursty and random firing patterns have not yet been identified conclusively, it appears that the pacemaker firing pattern emerges as a result of an intrinsic membrane potential oscillation, resulting from a low threshold, non-inactivating calcium conductance, and a calcium-activated potassium conductance (Harris et al. 1989; Yung et al. 1991; Nedergaard and Greenfield 1992; Kang and Kitai 1993a,b; Wilson and Callaway 2000). A single action potential is fired at the peak of the oscillation and the resulting calcium-dependent spike afterhyperpolarization is sufficient to prevent any further spiking. Although results from early studies suggested that the dopaminergic cell bodies were electrically inexcitable (Grace and Bunney 1983b), excised patch clamp recordings from the soma and dendrites of dopaminergic neurons have revealed voltage-gated inward and outward currents underlying active propagation of spikes in the soma and dendrites of these neurons (Hausser et al. 1995).

The biggest difference between dopaminergic neurons recorded in vivo and in vitro is the absence of the random or bursty firing patterns in the slice preparation, likely due to the loss of afferents in the slice (Grace 1987; Lacey et al. 1989; but see also Mereu et al. 1997). Another difference is the higher input resistance observed in vitro (70–250 MΩ; Kita et al. 1986) compared to in vivo (18–35 MΩ; Grace and Bunney 1983a) also presumably due to the reduced number of functional afferents in the slice preparation (Fig. 3).

D. Afferents to Dopaminergic Neurons

I. GABAergic Afferents

The vast majority of afferent boutons synapsing on dopaminergic perikarya and dendrites in substantia nigra, perhaps as much as 70%–90%, are γ-aminobutyric acid (GABA)ergic. Most of the GABAergic input originates from the striatum, globus pallidus, and the pars reticulata of the substantia nigra (Ribak et al. 1976, 1980; Somogyi et al. 1981; Nitsch and Riesenberg

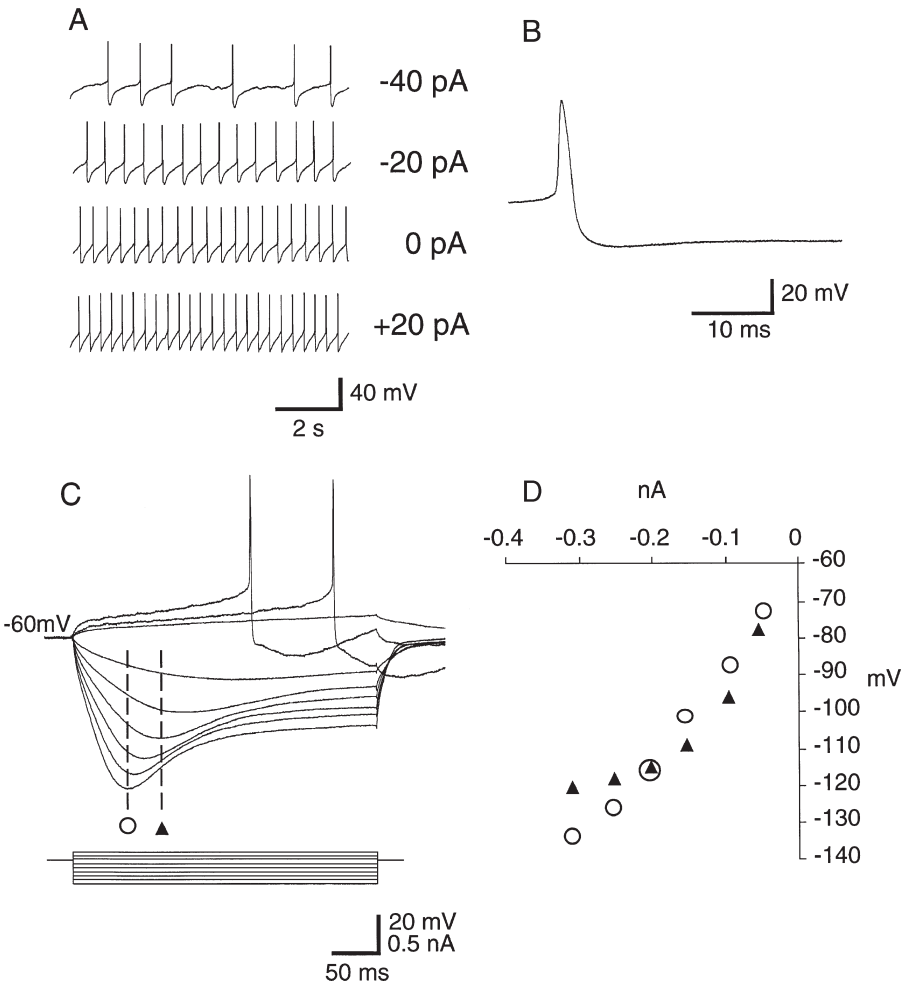


Fig. 3A–D. Electrophysiological identification of substantia nigra dopaminergic neurons in vitro. **A** Spontaneously active dopaminergic neuron firing in the typical pacemaker-like mode seen in vitro. Constant current injection of hyper- and depolarizing pulses manipulated pacemaker-like firing between 0.8 and 4 Hz. Action potential amplitudes are truncated due to aliasing. **B** Action potentials were of long duration (>2 ms) and exhibited large afterhyperpolarizations. **C** Intracellular injection of current pulses revealed a slow depolarizing ramp potential in the depolarizing direction and a strong time-dependent inward rectification when the membrane was hyperpolarized. **D** Current–Voltage plots show nearly linear slope and minimal inward rectification at the onset of hyperpolarizing current pulses (*open circles*) and a much more pronounced slowly activating inward rectification when I_h begins to activate after about 100 ms (*solid triangles*). (Reproduced from Iribe et al. 1999 with permission of the publishers)

1988; Smith and Bolam 1989; Tepper et al. 1995). Dopaminergic neurons express both of the two principal subtypes of GABA receptor, $GABA_A$ and $GABA_B$ receptors, and are quite effectively hyperpolarized by bath application of $GABA_A$- or $GABA_B$-selective agonists in vitro (Lacey 1993).

There is a massive GABAergic input to the substantia nigra from the neostriatum, both the dorsal and ventral parts. Although most of these fibers synapse on the non-dopaminergic neurons in the pars reticulata (Grofova and Rinvik 1970), there are monosynaptic inputs to dopaminergic neurons (Somogyi et al. 1981; Bolam and Smith 1990). Early in vivo recording studies showed that striatal stimulation produces monosynaptic inhibitory postsynaptic potentials (IPSPs) that could be blocked by picrotoxin in substantia nigra, thus suggesting that striatonigral inhibition was mediated by $GABA_A$ receptors; however, the neurons were not identified in these studies and appear to have been pars reticulata GABAergic neurons (Precht and Yoshida 1971; Yoshida and Precht 1971).

Later in vivo intracellular recording studies from identified substantia nigra dopaminergic and non-dopaminergic neurons also revealed a monosynaptic inhibitory postsynaptic potential evoked by striatal stimulation that is also mediated by a $GABA_A$ receptor (Grace and Bunney 1985), and the striatal-induced inhibition of antidromically identified nigrostriatal dopaminergic neurons recorded extracellularly in vivo is abolished by the $GABA_A$ receptor antagonist, bicuculline, but not by the $GABA_B$ receptor antagonist, CGP-55845 A (Paladini et al. 1999a).

In contrast, in vitro studies show that both $GABA_A$ and $GABA_B$ IPSPs are elicited in substantia nigra and VTA dopaminergic neurons following stimulation of various places within the slice (Hausser and Yung 1994), although it is difficult to be certain of the origin of these responses. However, activation of D_1 receptors in substantia nigra has been shown to selectively facilitate $GABA_B$ responses elicited by high frequency trains of stimuli delivered locally to dopaminergic neurons in vitro (Cameron and Williams 1993). Since only the striatonigral afferents to nigra are known to express D_1 receptors (Harrison et al. 1990), these data suggest that at least some of the $GABA_B$ IPSPs are mediated via the striatonigral pathway (Cameron and Williams 1993). One possible explanation for the different results obtained in vivo and in vitro is that most of the in vivo studies used single-pulse stimuli, whereas Cameron and Williams (1993) used trains. However, attempts to evoke $GABA_B$-mediated responses in vivo by stimulating the striatum with high frequency trains similar to those used in vitro were unsuccessful (Paladini et al. 1999a). It is also possible that for some reason the stimulus-evoked release of GABA has better access to $GABA_B$ receptors in the slice preparation than it does in vivo, perhaps because of reduced GABA uptake, or because the stimulation in vitro causes activation of a population of GABAergic afferents that is not activated in vivo. Along these lines it is interesting to note that spontaneous miniature IPSPs in dopaminergic neurons appear to be exclusively $GABA_A$-mediated (Hausser and Yung 1994).

Although the origin of the $GABA_B$ responses in vitro remain unclear, the bulk of the data suggest that in vivo, striatal GABAergic inhibition of dopaminergic neurons is mediated largely or exclusively by $GABA_A$ receptors.

There is also a significant input to substantia nigra from globus pallidus. Although the pallidal projection also appears to terminate preferentially on non-dopaminergic neurons of the substantia nigra pars reticulata (Smith and Bolam 1989), there is also a significant projection to pars compacta (Hattori et al. 1975). Stimulation of the globus pallidus elicits monosynaptic IPSPs in dopaminergic neurons in vivo (Tepper et al. 1987b), and like striatal-evoked inhibition, inhibition of nigrostriatal neurons evoked by electrical stimulation of the globus pallidus can be completely blocked by $GABA_A$, but not $GABA_B$ antagonists (Paladini et al. 1999a).

The third major GABAergic input to dopaminergic neurons arises from axon collaterals of pars reticulata neurons. Grace and colleagues (Grace and Bunney 1979, 1985; Grace et al. 1980) provided an important clue to understanding synaptic responses in substantia nigra by showing that there is a reciprocal relation between the spontaneous firing of non-dopaminergic neurons in the pars reticulata and dopaminergic neurons of the pars compacta. A second important finding was that very low intensity stimulation of neostriatum produced excitation of dopaminergic neurons (Grace and Bunney 1985). These data were interpreted to indicate that there exists a monosynaptic pathway between a population of GABAergic neurons in pars reticulata and dopaminergic neurons in pars compacta.

The pars reticulata neuron observed to fire reciprocally with dopaminergic neurons in vivo in extracellular recordings was not identified in the first studies except to note that the neurons fired between 15 and 40 Hz, exhibited brief-duration (~0.5 ms) spikes, were excited by tail pinch, were more sensitive to inhibition by GABA than dopaminergic neurons, could not be antidromically activated from thalamus, and comprised a subpopulation of non-dopaminergic pars reticulata neurons (Grace and Bunney 1979; Grace et al. 1980). However, subsequent reports tentatively identified the neuron as an interneuron (e.g., Grace and Bunney 1985, 1986; Smith and Grace 1992; Grace et al. 1997). This suggestion of a class of pars reticulata interneurons that mediate a number of indirect effects on dopaminergic neurons has by now been generally accepted and is widely cited by a number of physiologists and pharmacologists (e.g., Mereu and Gessa 1985; Johnson and North 1992; Santiago and Westerink 1992; Zhang et al. 1992, 1993). However, although suggested on the basis of Golgi staining studies (e.g., Schwyn and Fox 1974; Juraska et al. 1977; Francois et al. 1979) the existence of one or more classes of nigral interneurons has never been conclusively identified, an admittedly difficult task.

Pars reticulata projection neurons that send their main axons to tectum or thalamus issue axon collaterals within both substantia nigra pars reticulata and pars compacta (Deniau et al. 1982; Grofova et al. 1982). These collaterals synapse on other non-dopaminergic pars reticulata neurons (Deniau et al.

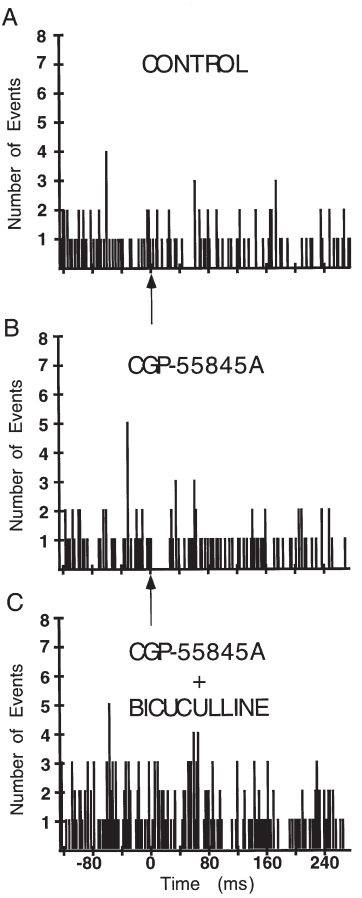


Fig. 4A–C. Presynaptic inhibitory $GABA_B$ receptors present on the terminals of local collaterals of pars reticulata nigrothalamic neurons are responsible for masking the inhibitory effects of antidromic activation of nigrothalamic neurons on dopaminergic neurons. The presynaptic inhibition is unmasked by local application of the selective $GABA_B$ receptor antagonist, CGP-55845 A. **A** Stimulation of thalamus (1.0 mA) fails to affect the firing of a nigrostriatal dopaminergic neuron. **B** Application of CGP-55845 A reveals an inhibition (suppression to 0% of control for 24 ms duration). **C** Application of bicuculline together with CGP-55845 A abolishes the unmasked inhibition. Peri stimulus time histograms (PSTH) consist of 100 trials each with 2-ms bin width. (Reproduced from Paladini et al. 1999a with permission of the publishers)

1982) as well as on dopaminergic neurons (Tepper et al. 2002). When these pars reticulata neurons are selectively activated antidromically by electrical stimulation of the thalamus or tectum, most dopaminergic neurons are inhibited (Tepper et al. 1995). This inhibition is blocked by the selective $GABA_A$ receptor antagonist, bicuculline, but not by the selective $GABA_B$ receptor antagonists, 2-hydroxysaclofen or CGP-55845 A (Tepper et al. 1995; Paladini et al. 1999a). Thus, pars reticulata GABAergic projection neurons provide an important monosynaptic GABAergic input to nigral dopaminergic neurons.

In contrast to $GABA_A$ receptor blockade, $GABA_B$ receptor blockade not only failed to block inhibition elicited by electrical stimulation of striatal, pallidal, or nigral reticulata afferents, but rather potentiated it (Paladini et al. 1999a), as shown in the example in Fig. 4. This is likely due to the presence of inhibitory presynaptic $GABA_B$ receptors on the terminals of GABAergic afferents to the dopaminergic neurons. These presynaptic receptors serve to

inhibit evoked release of GABA (Giralt et al. 1990) and reduce IPSP/C amplitude (Hausser and Yung 1994; Shen and Johnson 1997). There is apparently enough endogenous GABA in the substantia nigra in vivo to activate these autoreceptors such that when they are blocked by local application of $GABA_B$ antagonists, GABA release is enhanced and the postsynaptic $GABA_A$-mediated inhibition is increased (Paladini et al. 1999a).

In addition to their inhibitory effects on the rate of spontaneous activity, the GABAergic inputs contribute significantly to the regulation of the firing pattern of midbrain dopaminergic neurons. Local application of the $GABA_A$ receptor antagonists, bicuculline or picrotoxin, causes dopaminergic neurons to switch to the bursty firing pattern (Tepper et al. 1995; Paladini and Tepper 1999). The transition is quite robust, and is independent of the baseline firing rate, firing pattern, or the change in firing rate due to application of the drug, suggesting that it is not due simply to increased depolarization and/or firing rate caused by blocking $GABA_A$ receptors. The effect is specific to blocking $GABA_A$ receptors; blockade of $GABA_B$ receptors with 2-OH-saclofen or CGP-55845 A produces a slight but consistent and statistically significant reduction in firing rate and regularization of the firing pattern (Tepper et al. 1995; Paladini and Tepper 1999). This latter effect appears due to increased GABA release as a result of blockade of the presynaptic $GABA_B$ receptors discussed above. This results in increased stimulation of postsynaptic $GABA_A$ receptors on dopaminergic neurons and decreased burst firing, probably due to the $GABA_A$-mediated decrease in input resistance (Canavier 1999; Paladini et al. 1999b). Subsequent experiments revealed that a significant source of the GABAergic input that was blocked by bicuculline or picrotoxin resulting in burst firing was the pars reticulata, and that the reticulata efferents could be effectively modulated by output from the globus pallidus (Celada et al. 1999). Thus, increased activity in pallidum led to inhibition of reticulata GABAergic projection neurons and disinhibition of nigrostriatal dopaminergic neurons resulting in burst firing. Conversely, decreased activity in pallidum led to increased firing of reticulata neurons and the abolition of burst firing in dopaminergic neurons (Celada et al. 1999). Although the mechanism or mechanisms underlying endogenous burst firing in dopaminergic neurons are incompletely understood (see below), it is clear that GABAergic afferents, acting at postsynaptic $GABA_A$ receptors on dopaminergic neurons can modulate the firing pattern of these neurons in vivo in an extremely powerful and consistent manner.

The roles and physiological significance of postsynaptic $GABA_B$ receptors on mesencephalic dopaminergic neurons are less clear. The receptors are certainly present, and dopaminergic neurons respond to selective $GABA_B$ agonists in vitro with a large conductance increase to potassium and a hyperpolarization (Lacey et al. 1988; Lacey 1993), and local electrical stimulation in slices of substantia nigra can elicit $GABA_B$ IPSPs or IPSCs (e.g., Sugita et al.1992; Cameron and Williams 1993). On the other hand, neither the striatal, pallidal, nor pars reticulata inputs appear to stimulate $GABA_B$ recep-

tors on dopaminergic neurons in vivo to any significant degree as discussed above (Paladini et al. 1999a), so the source(s) of the input to $GABA_B$ postsynaptic receptors remains unclear. In vivo, application of the $GABA_B$ agonist, baclofen, reduces dopaminergic neuron firing rate and leads to a regularization of firing pattern (e.g., Engberg et al. 1993). However, although intravenous administration of the selective GABA antagonist, CGP35348, antagonized the effects of baclofen, it was without effect on firing rate or firing pattern when given alone, suggesting that the receptor was not effectively stimulated in vivo under the conditions of the experiment, consistent with the results of Tepper et al. (1995) and Paladini and Tepper (1999). On the other hand, in a more recent study, SCH 50911, a novel $GABA_B$ antagonist, was shown to increase the firing rate and burstiness of dopaminergic neurons when administered intravenously, suggesting that the postsynaptic $GABA_B$ receptors were effectively stimulated by endogenous GABA (Erhardt et al. 1999). GABA, as well as $GABA_B$ agonists and antagonists will act both on pre- and postsynaptic receptors, and it is likely that methodological differences, possibly differences in the potencies and/or tissue distribution of the different $GABA_B$ antagonists, accounts for these discrepancies by altering the balance of effects on the pre- and postsynaptic $GABA_B$ receptors. Thus at present, the source(s) of inputs that activate $GABA_B$ receptors as well as the physiological significance of $GABA_B$ receptor activation in midbrain dopaminergic neurons remain to be determined.

II. Glutamatergic Afferents

The best characterized glutamatergic (i.e., excitatory amino acid) afferents to substantia nigra arise from the frontal cortex (Usunoff et al. 1982; Usunoff 1984; Sesack and Pickel 1992; Naito and Kita 1994), subthalamic nucleus (STN; Chang et al. 1984; Kita and Kitai 1987; Damlama and Tepper 1993) and pedunculopontine nucleus (PPN), which also sends cholinergic afferents to substantia nigra (Moon-Edely and Graybiel 1983; Sugimoto and Hattori 1984; Clarke et al. 1987; Rye et al. 1987; Gould et al. 1989; Damlama and Tepper 1993; Futami et al. 1995). Midbrain dopaminergic neurons express both *N*-methyl-D-aspartate (NMDA) and non-NMDA glutamate receptors (Mereu et al. 1991) and respond to local application of glutamate in vivo with an increase in spontaneous firing rate (Scarnati and Paciti 1982). As the principal mediators of excitatory synaptic transmission in substantia nigra, these afferents have been the subject of considerable study. Moreover, glutamate application induces an increase in burstiness in dopaminergic neurons (Grace and Bunney 1984b; Overton and Clark 1992, 1997) as does intracellular loading with calcium (Grace and Bunney 1984b), and the incidence of spontaneous burst firing has been reported to be decreased by NMDA antagonists (Chergui et al. 1993). In addition, stimulation of NMDA receptors on dopaminergic neurons in vitro produces a stereotyped form of a calcium-independent rhythmic burst firing that appears to be dependent on sodium

influx through the NMDA channel and the operation of an electrogenic sodium pump (Johnson et al. 1992). Thus, it is as a potential mechanism for inducing burst firing that the glutamatergic afferents, especially those originating in frontal and prefrontal cortex, have received special interest (Overton and Clark 1997).

Glutamate also acts on dopaminergic neurons through metabotropic receptors which are divided into eight subgroups (De Blasi et al. 2001). Although it is unclear if all these subgroups are present on dopaminergic neurons (Bonci et al. 1997) there have been reports describing the action of metabotropic glutamate receptor agonists on the electrophysiological properties of dopaminergic neurons in vitro and in vivo. In vitro intracellular recordings studies obtained from rats slices, have reported that stimulation of metabotropic glutamate receptors with Trans-1-amino-cyclopentane-1,3-dicarboxylate (t-ACPD), a selective agonist for the R1 subtype of the metabotropic glutamate receptor, produces a depolarization (Mercuri et al. 1992) and a sustained increase in firing rate (Mercuri et al. 1993). This depolarization seems to be mediated by a cation-mediated inward current independent of calcium mobilization (Guatteo et al. 1999). In contrast, other studies have reported an IPSP after stimulation of mGluR1 (Fiorillo and Williams 1998) and a blockade of this effect by amphetamine (Paladini et al. 2001). Furthermore, in the only published study on the role of metabotropic glutamate receptors on dopaminergic neurons in vivo (Meltzer et al. 1997), an inhibition followed by excitation of firing rate was reported after microiontophoretic application of 1-aminocyclopentane-1,3-dicarboxylate (1 S,3R-ACPD), a putative metabotropic glutamate receptor selective agonist and both these effects were antagonized by application of the metabotropic glutamate receptor antagonist (S)-4-carboxy-phenylglycine. These findings would imply that glutamate is not solely an excitatory neurotransmitter in the midbrain but that its actions have to be viewed in a broader sense. At present is unclear if the metabotropic glutamate receptor-mediated IPSP is due to the particular stimulating conditions employed (Fiorillo and Williams 1998) or really represents an effect of physiological importance. If the latter turns out to be the case, it will add considerably to the role of glutamate on the regulation of dopaminergic neurons and their response to drugs.

In the first report to implicate cortex (frontal and anterior cingulate) in the elicitation of bursting in nigrostriatal neurons, cortical stimulation in urethane-anesthetized rats was shown to elicit burst discharges that closely resembled spontaneous bursts (Gariano and Groves 1988). However, this response occurred only in a very small proportion of nigral dopaminergic neurons (5%), at a latency of over 200 ms, and was preceded by a substantial inhibition of firing (Nakamura et al. 1979; Gariano and Groves 1988). No attempts to block the bursts with glutamate antagonists were made and given the long latency, mediation by a monosynaptic glutamatergic input from cortex seemed unlikely. Soon after, inactivating the prefrontal cortex by local cooling was shown to abolish bursting and induce pacemaker-like firing in dopami-

nergic neurons (Svensson and Tung 1989). On the other hand, lesions of medial prefrontal cortex were largely without effect on the spontaneous activity of substantia nigra dopaminergic neurons, although there was a significant reduction in the number of VTA neurons encountered per track (Shim et al. 1996), consistent with a greater innervation of VTA dopaminergic neurons by glutamatergic afferents compared to substantia nigra (Smith et al. 1996). Interestingly, the prefrontal lesions were associated with a slight increase in the spontaneous firing rate of substantia nigra dopaminergic neurons (Shim et al. 1996), perhaps due to the preferential site of termination of corticonigral afferents on GABAergic pars reticulata neurons thereby activating feedforward inhibition onto the dopaminergic neurons (Hajos and Greenfield 1994; Tepper et al. 1995). Subsequent studies replicated the finding of initial inhibition followed by extremely long latency burst responses after frontal cortical stimulation. They showed that the burst response could be blocked by NMDA but not by non-NMDA antagonists (see Overton and Clark 1997 for review), providing strong evidence for a role of the glutamatergic corticonigral projection in the modulation of dopaminergic neuron firing pattern.

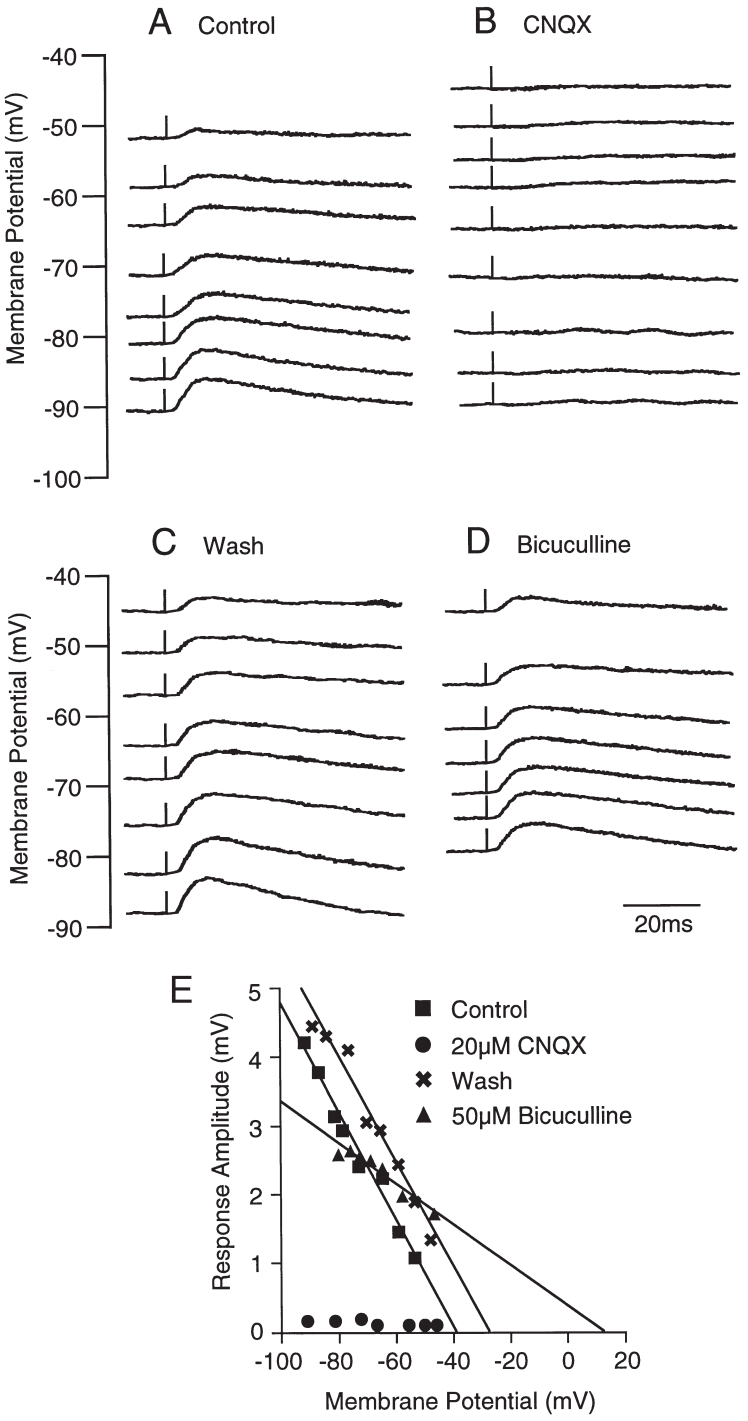
Reports of the effects of STN stimulation on the activity of substantia nigra dopaminergic neurons in vivo have been, perhaps surprisingly, more contradictory. In the earliest report, electrical stimulation of the subthalamic nucleus was found to be excitatory to dopaminergic and non-dopaminergic nigral neurons (Hammond et al. 1978). In a subsequent study that used local infusions of bicuculline to stimulate the subthalamic nucleus pharmacologically, approximately equal numbers of excitatory and inhibitory responses were found among dopaminergic neurons, although almost all of the non-dopaminergic neurons in pars reticulata were excited (Robledo and Féger 1990). More recently, biphasic effects of electrical or pharmacological stimulation of subthalamic nucleus on nigral dopaminergic neurons were again reported, with an initial inhibition predominant following electrical stimulation that was followed in 35% of the neurons by a burst-like response (Smith and Grace 1992). Pharmacological activation of the subthalamic nucleus by bicuculline infusion led to an initial decrease in firing rate and the incidence of burst firing with the opposite biphasic effects following inactivation of the subthalamic nucleus with muscimol (Smith and Grace 1992). In another study, local infusions of GABA or bicuculline into subthalamic nucleus produced decreases and increases in firing rate and burst firing in nigral dopaminergic neurons, but these effects were observed in only about half of the neurons, with the other half showing the opposite effects (Chergui et al. 1994).

The STN-evoked inhibitory responses seen in the in vivo studies are almost certainly an indirect effect, resulting from subthalamic stimulation-induced activation of GABAergic axons or neurons synaptically activated by the stimulus. In vitro studies revealed that the depolarizing response seen in response to subthalamic stimuli in dopaminergic neurons (Nakanishi et al. 1987) was composed of a nearly superimposed monosynaptic excitatory postsynaptic potential (EPSP) comprising both NMDA and non-NMDA compo-

nents, and a monosynaptic and/or polysynaptic $GABA_A$-mediated IPSP (Iribe et al. 1999). The monosynaptic IPSP arose from stimulation of descending GABAergic striatonigral and/or pallidonigral fibers and was eliminated by hemisection of the brain anterior to the subthalamic nucleus several days before the in vitro recordings. In some cases, however, an IPSP remained after the hemisection that could be abolished with bicuculline or 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX; Fig. 5). The latter effect indicates that the IPSP arose from glutamatergic excitation of a GABAergic neuron whose subthalamic input and outputs to dopaminergic neurons remained intact in the slice preparation, most likely the pars reticulata GABAergic projection neurons (Tepper et al. 1995; Iribe et al. 1999).

Stimulation of the PPN in vivo induces short latency excitation in a significant fraction of nigral dopaminergic neurons (Scarnati et al. 1984). In brain slices, stimulation of the PPN produces monosynaptic EPSPs that consist of both glutamatergic and cholinergic components that appear to converge on single dopaminergic neurons (Futami et al. 1995). The pharmacology of the glutamatergic component is not well established; however, in one extracellular recording study, NMDA-selective antagonists were ineffective at blocking excitatory effects of pedunculopontine stimulation which were blocked by broad spectrum glutamate antagonists, suggesting that in vivo the predominant effect may be mediated principally by non-NMDA glutamate receptors (DiLoreto et al. 1992). Compared to the subthalamic nucleus and prefrontal cortex, inhibitory responses are relatively rare with pedunculopontine stimulation. This may be because a larger proportion of pedunculopontine afferents terminate on dopaminergic neurons and dendrites as opposed to pars reticulata GABAergic neurons. For example, only about 10% of subthalamic afferents terminate on tyrosine hydroxylase-positive cells and dendrites in substantia nigra, the remainder synapsing on non-dopaminergic pars reticulata neurons, whereas almost 38% of boutons originating in the pedunculopontine nucleus synapse on dopaminergic dendrites (Damlama 1994). Thus, the balance of input is shifted more towards the monosynaptic pedunculopontine–dopaminergic neuron pathway than the disynaptic pathway through pars reticulata (Iribe et al. 1999). Thus, although not yet as well studied as the subthalamic afferents, the excitatory input from the pedunculopontine nucleus may prove to be at least equally important as a source of monosynaptic excitation of dopaminergic neurons.

Although there are many reports that NMDA agonists elicit burst firing in dopaminergic neurons in vivo and in vitro (Grace and Bunney 1984b; Johnson et al. 1992; Overton and Clark 1992), and that kynurenate, a broad-spectrum excitatory amino acid antagonist, inhibits burst firing (Charlety et al. 1991), there are other reports that NMDA or *l*-glutamate, acting through NMDA receptors as demonstrated by blockade of their effects with selective NMDA antagonists, produced increases in midbrain dopaminergic neuron firing rate without significantly increasing bursting in vitro (e.g., Seutin et al. 1990; Wang and French 1993; Connelly and Shepard 1997). In addition, non-


A Control
B CNQX
C Wash
D Bicuculline
Membrane Potential (mV)
-40
-50
-60
-70
-80
-90
-100
20ms
E
Response Amplitude (mV)
Membrane Potential (mV)
Control
20μM CNQX
Wash
50μM Bicuculline
0
1
2
3
4
5
-100
-80
-60
-40
-20
0
20

NMDA, mGluR1 agonists have been reported to induce burst firing in dopaminergic neurons (Meltzer et al. 1997), even in the presence of NMDA receptor antagonists (Zhang et al. 1994). Blockade of the long-lasting spike afterhyperpolarization by apamin also induces burst firing in vitro (Shepard and Bunney 1988). Finally, rhythmic burst firing induced by NMDA or NMDA plus apamin in vitro is abolished by $GABA_A$ receptor agonists (Paladini et al. 1999b), suggesting that in vivo, NMDA-related burst firing may be controlled or gated in a permissive fashion depending on the level of activity in GABAergic afferents.

There is little doubt that the glutamatergic afferents to dopaminergic neurons are the most important source of their excitatory input. However, while it is virtually certain that glutamatergic inputs play an important role in the modulation of dopamine neuron firing pattern (Overton and Clark 1997), it is probably not the case that NMDA receptor stimulation of dopaminergic neurons is exclusively or perhaps even primarily responsible for evoking bursty firing in vivo. There is also good evidence that dopaminergic neuron firing pattern is modulated to an important extent by other transmitter/receptor systems including GABAergic (Tepper et al. 1995; Celada et al. 1999; Paladini and Tepper 1999), cholinergic (Grenhoff et al. 1986; Futami et al. 1995; Kitai et al. 1999), and non-NMDA glutamatergic systems (Zhang et al. 1994; Meltzer et al. 1997).

III. Cholinergic Afferents

The substantia nigra is rich in acetylcholinesterase, and choline acetyltransferase-positive synapses are made onto the dendrites of dopaminergic neurons (Beninato and Spencer 1988). The principal source of the cholinergic input is likely the pedunculopontine and laterodorsal tegmental nuclei (Gould et al. 1989; Damlama and Tepper 1993). A number of nicotinic receptor subunits are expressed by mesencephalic dopaminergic neurons including α3, α4, α5, α7, β2, and β3 (Sorenson et al. 1998), and bath application of nicotine produces an inward current and depolarization that exhibits

Fig. 5A–E. The IPSP component of the subthalamic nucleus-evoked depolarizing postsynaptic potential (DPSP) in some dopaminergic neurons is polysynaptic. Under control conditions, subthalamic stimulation produced a DPSP with a reversal potential of –38.8 mV (**A**, **E**) indicating that it is composed of an EPSP and near simultaneous IPSP. Addition of CNQX to the bath completely abolished both components of the DPSP (**B**, **E**) indicating that the IPSP resulted from glutamate-dependent synaptic activation of an inhibitory neuron whose inputs and outputs remained intact in the slice. After a 1-h wash, the DPSP returned and still exhibited a hyperpolarized reversal potential as before drug application (**C**, **E**). Subsequent application of bicuculline shifted the reversal potential in the positive direction to 12.6 mV (**D**, **E**) showing that the IPSP component of the DPSP was $GABA_A$-mediated. Traces in A–D are each the average of four single sweeps. (Reproduced from Iribe et al. 1999 with permission of the publishers)

desensitization with a time course of tens of seconds (Calabresi et al. 1989; Sorenson et al. 1998). The response is sensitive to κ-bungarotoxin but not α-bungarotoxin and is thus more similar to the nicotinic response seen at peripheral autonomic ganglia than at the neuromuscular junction (Calabresi et al. 1989). In vivo, local or systemic administration of nicotine agonists produces excitation of nigrostriatal (Lichtensteiger et al. 1982) and VTA dopaminergic neurons (Mereu et al. 1987) together with an increment in burst firing of dopaminergic neurons (Grenhoff et al. 1986). It is interesting to note that the increase in firing rate and increase in burst firing were only poorly correlated, suggesting a possible nicotinic effect on firing pattern independent of its effect on firing rate (Grenhoff et al. 1986).

Dopaminergic neurons also express muscarinic receptors, and are depolarized by muscarinic agonists in vitro with a pharmacological profile resembling that of the M_1 receptor, although the mechanism of the response appears different from that of the classic m-current closure of potassium channels (Lacey 1993). In addition to these postsynaptic actions, acetylcholine (ACh) acts presynaptically in substantia nigra to inhibit release of GABA from GABAergic afferents through an M_3 receptor (Grillner et al. 2000).

Stimulation of the pedunculopontine nucleus in vivo produces mostly excitation of dopaminergic neurons at short latencies ranging from 3 to 5 ms (Scarnati et al. 1984), consistent with the conduction time of cholinergic neurons from the pedunculopontine nucleus to the substantia nigra (Futami et al. 1995; Takakusaki et al. 1996). The EPSP that underlies the excitation seen extracellularly in vivo is composed of both nicotinic and pirenzepine-sensitive muscarinic components (Futami et al. 1995). Pedunculopontine stimulation also produces burst firing in nigral dopaminergic neurons in vivo (Lokwan et al. 1999). The bursts observed were brief (averaging two spikes) and occurred at extremely long latency (~100 ms). As no antagonists were tested, the transmitter and receptor underlying the evoked bursts remains to be determined. The bursting could be glutamate-mediated as suggested by the authors, cholinergic, or might depend on an interaction of the two transmitter systems (e.g., Futami et al. 1995; Kitai et al. 1999).

IV. Monoaminergic Afferents

A projection from the dorsal raphé nucleus to the substantia nigra has been described on the basis of anatomical, electrophysiological, and pharmacological bases. Retrograde and anterograde tract tracing studies both reveal a significant input to substantia nigra and VTA from the dorsal raphé nucleus (Fibiger and Miller 1977; Corvaja et al. 1993), and the ventral regions of the substantia nigra and VTA are rich in serotonergic axons and boutons that make asymmetric synapses onto both dopaminergic and non-dopaminergic dendrites (Hervé et al. 1987; Mori et al. 1987; Corvaja et al. 1993). In early studies, stimulation of the dorsal raphé was shown to inhibit the firing of both pars compacta (dopaminergic) and pars reticulata (non-dopaminergic)

neurons in vivo (Dray et al. 1976; Fibiger and Miller 1977), effects that were abolished by depletion of serotonin (Fibiger and Miller 1977). A later study revealed more modest effects, with dorsal raphé stimulation exerting modest inhibitory effects only on dopaminergic neurons firing at less than 4 Hz; more rapidly firing neurons were unaffected (Kelland et al. 1990b). 5-Hydroxytryptamine $(5HT)_{1A}$ agonists exerted effects consistent with this, leading at high doses to excitation of slowly firing cells without affecting more rapidly firing neurons, while $5HT_{1B}$ agonists were without effect (Kelland et al. 1990b).

These inhibitory effects of serotonin are difficult to reconcile with the asymmetric synapses made by dorsal raphé neurons on dopaminergic dendrites, which are usually associated with excitatory synaptic actions. Furthermore, serotonin has been found to enhance the release of dopamine from substantia nigra in vivo (Glowinski and Cheramy 1981) and the VTA in vitro (Beart and McDonald 1982). In vitro, serotonin has been found to facilitate a dendritic calcium conductance (Nedergaard et al. 1988), and produces a clear depolarization and excitation of substantia nigra dopaminergic neurons (Nedergaard et al. 1991). These effects are mediated postsynaptically, but not by $5HT_{1A}$ or $5HT_2$ receptors. These data also seem inconsistent with a classical inhibitory action of serotonin on mesencephalic dopaminergic neurons.

Perhaps some of the discrepancy can be resolved by data showing that stimulation of the dorsal raphé with short trains of pulses reduces the dendritic excitability of dopaminergic dendrites, as measured by somatodendritic invasion of antidromic spikes (Trent and Tepper 1991). The depression in dendritic excitability was unrelated to changes in the mean firing rate or to the strength or duration of neostriatal-evoked inhibition. This effect was abolished by depletion of serotonin with para-chlorophenylalanine for 3 days prior to recording and could be reinstated by administration of 5 hydroxytryptophan and was also blocked by systemic administration of the non-specific serotonin antagonist, metergoline, indicating that it was serotonergic in nature. In addition, the depression in dendritic excitability could be, perhaps surprisingly, also blocked by haloperidol. These data were interpreted to indicate that the raphé inputs to nigral dopaminergic dendrites produced a local depolarization that resulted in local release of dopamine that subsequently activated somatodendritic autoreceptors which led to a local hyperpolarization of the dendrites and a reduction in dendritic excitability, without grossly affecting the firing rate of the neuron as a whole (Trent and Tepper 1991). This interpretation is consistent with the asymmetric character and location of the serotonergic synapses on the dopaminergic neurons, the previously observed increase in dopamine release following serotonergic stimulation in substantia nigra and VTA, and the serotonergic facilitation of dendritic calcium entry, and it could account for the generally inconsistent and weak effect of serotonergic agonists and dorsal raphé stimulation on dopaminergic neuron firing rate.

In addition, pars reticulata GABAergic neurons are excited by serotonin via both pre- and postsynaptic mechanisms (Stanford and Lacey 1996). Given

the feedforward inhibition of nigral dopaminergic neurons from pars reticulata (Hajos and Greenfield 1994;Tepper et al. 1995), the effects of serotonergic agonists and raphé input on dopaminergic neurons may also depend to an extent on the ratio of the opposing effects of direct activation of dopaminergic neurons and disynaptic input through pars reticulata, as well as on a balance between the action of serotonin on autoreceptors and different postsynaptic receptors.

Although not as well characterized nor as dense as the serotonergic input from the dorsal raphé, some retrograde tracing studies reveal a modest projection from the locus coeruleus to the VTA (Phillipson 1979). Stimulation of the locus coeruleus produces excitatory responses in dopaminergic neurons recorded extracellularly in substantia nigra and VTA in vivo (Grenhoff et al. 1993). Although α_1 adrenoceptor binding and message levels are extremely low or non-detectable in the midbrain (Jones et al. 1985; Pieribone et al. 1994), these responses were abolished by catecholamine depletion and were blocked by prazosin, indicating that they were mediated by an α_1 receptor. In vitro recordings provided largely consistent results, showing that about 60% of mesencephalic dopaminergic neurons respond to α_1 receptor stimulation with a depolarization due to a potassium conductance decrease (Grenhoff et al. 1995). In addition, the α_2 agonist clonidine has been reported to promote a regularization of firing pattern in both substantia nigra (Grenhoff and Svensson 1988) and VTA neurons (Grenhoff and Svensson 1989), most likely by its presynaptic inhibitory effects on norepinephrine release.

E. Autoreceptor-Mediated Effects on Dopaminergic Neurons

I. Somatodendritic Autoreceptors

In 1973 Bunney and colleagues (Bunney et al. 1973a,b; Bunney and Aghajanian 1973; Aghajanian and Bunney 1973) published the first recordings from identified substantia nigra and VTA dopaminergic neurons. One of the key observations was that apomorphine, a direct-acting dopamine receptor agonist, potently inhibited dopaminergic neurons even when applied iontophoretically (Aghajanian and Bunney 1977). This finding demonstrated that dopaminergic neurons possessed receptors for their own transmitter, dopamine, on their cell body and/or dendrites (somatodendritic region). These receptors were termed somatodendritic autoreceptors, to distinguish them from the axon terminal autoreceptors also expressed by dopaminergic neurons that play a role in the local regulation of dopamine release and synthesis (for review see Starke et al. 1989).

The earliest pharmacological characterization of dopamine somatodendritic autoreceptors predated the current molecular biologically defined classification of dopamine receptors and indicated simply that they exhibited a pharmacological profile distinct from either α or β adrenoceptors, i.e., that they

were a unique type of dopamine receptor (Aghajanian and Bunney 1977). When dopamine neurons were classified into D1 or D2 subtypes (Kebabian and Calne 1979), it became clear, based on the sensitivity of the receptor to haloperidol (Groves et al. 1975), a moderately selective D_2 antagonist, that the dopamine autoreceptor was a D2 receptor. This was later confirmed with the use of highly selective D2 receptor agonists and antagonists in in vitro intracellular recordings (Lacey et al. 1987, 1988; Lacey 1993) and receptor binding (Morelli et al. 1988). With the advent of the widespread use of molecular biological methods to isolate and identify neurotransmitter receptors in the last decade came the discovery that there are in fact two families of dopamine receptors, D1 and D2. Within each family exist subtypes, D_1 and D_5 for the D1 family and D_2 (both long and short isoforms), D_3 and D_4 for the D2 family (see for review, Sibley and Monsma 1992). Although the most recent electrophysiological data confirm that the autoreceptor is a member of the D2 receptor family (Devoto et al. 1995), there remains some controversy as to whether the autoreceptor is exclusively a D_2 receptor, as suggested on the basis of experiments with transgenic D_2 (Mercuri et al. 1997) or D_3 (Koeltzow et al. 1998) knockout mice, or instead comprises both D_2 and D_3 receptors, as suggested based on experiments localizing D_3 message and/or protein to midbrain dopaminergic neurons (Tepper et al. 1997; Shafer and Levant 1998; Stanwood et al. 2000) or electrophysiological experiments in rats after antisense knockdown of dopamine D_2 and/or D_3 receptors (Tepper et al. 1997). Using a very sensitive and specific polyclonal antibody raised against a synthetic peptide reflecting the amino acid sequence of the third cytoplasmic loop of the D_3 receptor, Sokoloff and associates have recently reported that all rat mesencephalic dopaminergic neurons express the D_3 receptor (Diaz et al. 2000), which supports the notion that autoreceptors belong to both subclasses: D_2 and D_3.

In any event, somatodendritic autoreceptor stimulation leads to an hyperpolarization of dopaminergic neurons that is caused by an increase in conductance to potassium (Lacey et al. 1987, 1988). It is this hyperpolarization which can reach about 12 mV in vitro in response to a maximal concentration of quinpirole (Bowery et al. 1994) that is responsible for the inhibition of spontaneous activity seen after local or systemic administration of autoreceptor agonists. The potassium channel linked to the dopamine autoreceptor in situ appears to be the same one that is opened by activation of $GABA_B$ receptors since the autoreceptor-mediated potassium current is reversibly occluded by maximal stimulation of the $GABA_B$ receptor by baclofen (Lacey et al. 1988).

The D_2 somatodendritic autoreceptor is G-protein coupled and its function is disrupted by pertussis toxin (Innis and Aghajanian 1987; Shepard and Connelly 1999). Although the specifics of the G-protein coupling to D_2 or D_3 autoreceptors is unknown at present, it appears to be independent of protein kinase A or C pathways (Cathala and Paupardin-Tritsch 1999). Transfection studies in MES-23.5, a dopaminergic neuroblastoma cell line in which D_2

receptor stimulation increases a potassium conductance, have revealed that the D_{2S} receptor is linked via a $G_{s\alpha}$ whereas the D_{2L} is linked via a $G_{o\alpha}$ (Liu et al. 1999).

Although commonly termed the somatodendritic autoreceptor, the D_2 autoreceptor may be preferentially located in the dendrites rather than the soma or pericellular region. Although electron microscopic immunocytochemistry revealed cellular D_2 receptor labeling in substantia nigra and VTA, the labeling of perikarya and large proximal dendrites was very weak compared to that of dendrites (Sesack et al. 1994). Almost exactly the same distribution of labeling was seen for the autoreceptor potassium channel subunit, Kir3.2 (Ianobe et al. 1999). Finally, in vivo extracellular recordings of dopaminergic neurons following local pressure injection of autoreceptor agonists showed that the neurons were more effectively inhibited when the drugs were applied several hundred micrometers distal to the recording site than when applied right at the recording site which was most often presumably at or near the soma (Akaoka et al. 1992). Thus, the somatodendritic autoreceptor may be, in reality, principally expressed on the dendrites rather than the somata of dopaminergic neurons.

II. Axon Terminal Autoreceptors

As mentioned above, the first dopamine autoreceptors to be discovered were receptors located on the axon terminals of nigrostriatal fibers in slices of rat striatum (Farnebo and Hamberger 1971; for review see Starke et al. 1989). When rat striatal slices were incubated with ^{3}H-tyrosine and subjected to field electrical stimulation, radiolabeled dopamine was released. Addition of apomorphine to the bath significantly reduced the dopamine efflux. These data were correctly interpreted to mean that there existed a population of dopamine receptors on or near the release sites on dopaminergic axons in the dopamine terminal fields that served to inhibit the release of electrically evoked dopamine. Subsequent studies showed that release evoked by depolarization of the slices by high potassium was also subject to autoreceptor regulation but that release elicited by agents that interfered with the dopamine transporter, for example, amphetamine, was not subject to autoregulation (Kamal et al. 1981). This turned out to be related to the calcium dependence of the releasing stimuli. Release that is calcium dependent, such as that evoked by electrical stimulation or high potassium, is subject to autoregulation, whereas calcium-independent release (e.g., by amphetamine) (Arnold et al. 1977; Meyerhoff and Kant 1978) is not under autoreceptor control (Kamal et al. 1981).

In addition to modulating the release of dopamine, dopamine terminal autoreceptors can also modulate the synthesis of dopamine by altering the rate of tyrosine hydroxylation (Walters and Roth1976; Roth et al. 1978). A thorough discussion of autoreceptor effects on dopamine synthesis is beyond the scope of the present chapter and the reader is referred to Wolf and Roth (1990) for a comprehensive review.

The terminal autoreceptor appears similar or identical in all respects to the somatodendritic autoreceptor. The axon terminal autoreceptor subtype is D_2 (Boyar and Altar 1987; Tepper et al. 1984a), and is a G-protein coupled receptor sensitive to pertussis toxin (Bean et al. 1988). Stimulation of terminal autoreceptors in vivo produces an increase in the amount of current needed to evoke an antidromic action potential, indicating that autoreceptor activation is associated with a decrease in the excitability of the dopaminergic nerve terminals in the striatum (Groves et al. 1981; Tepper et al. 1984a,b, 1985), nucleus accumbens (Mereu et al. 1985), and cortex (Gariano et al. 1989a). This is most likely due to an hyperpolarization of the terminal similar to that seen at the cell body, and can be reversed by local application of selective D_2 receptor antagonists including sulpiride (Tepper et al. 1984a; Tepper and Groves 1990). In addition, application of D_2 antagonists by themselves results in an increase in the excitability of dopaminergic terminals indicating that the extracellular concentrations of dopamine in striatum, nucleus accumbens, and cortex are high enough to cause at least partial occupancy of the terminal autoreceptors in vivo (Tepper et al. 1984a,b; Mereu et al. 1985; Gariano et al. 1989a). In addition, there have been two reports of decreases in dopamine terminal excitability following D_1 receptor agonist SKF 38393 local administration that could be partially reversed by the D_1 selective antagonist SCH 23390 (Diana et al. 1988, 1991a), But in view of the bulk of in vivo and in vitro electrophysiological, receptor binding, and in situ hybridization evidence it is unlikely that these effects reflect the presence of D_1 terminal autoreceptors.

III. Are D_2 Autoreceptors Different from Other D_2 Receptors?

It is often claimed that dopamine autoreceptors are "more sensitive" than other, postsynaptic D_2 receptors. One piece of evidence cited in support of this is the relatively low doses or concentrations of D2 agonists required to inhibit dopaminergic neuron firing (in the range of 4–8 µg/kg, i.v. for apomorphine; Chiodo and Antelman 1980; Tepper et al. 1982), or to induce hyperpolarization of dopaminergic neurons in vitro (ED_{50} for quinpirole: 77 nM; for apomorphine 205 nm; Bowery et al. 1994). The doses of D2 antagonists required to block the effects of dopamine or D2 agonists are similarly low; the selective D2 antagonist, sulpiride shows an apparent K_d of 13 nM for antagonizing the effects of the selective D2 agonist, quinpirole (Lacey et al. 1987). This is indeed sensitive, but it is difficult to find something against which to compare this, since even though many other central neurons express postsynaptic D_2 and/or D_3 receptors, in most of them the receptor is not linked to the opening of a ligand-gated potassium channel as it is in substantia nigra (Lacey et al. 1988), but rather acts to modify the kinetics or gating of voltage gated channels (e.g., Surmeier et al. 1992, 1996; Surmeier and Kitai 1993). This difference creates problems when trying to compare the physiological effects of stimulating the dopamine autoreceptor with other populations of D_2 receptors.

For example, in one study that is widely cited as evidence that the dopamine autoreceptor is more sensitive than the postsynaptic D2 receptor, the ability of iontophoretically applied dopamine or intravenously administered apomorphine to inhibit the spontaneous activity of substantia nigra dopaminergic neurons or striatal neurons was compared (Skirboll et al. 1979). In both cases the dopaminergic neurons were inhibited at much lower doses of agonist than the striatal neurons. However, since the dopamine receptors are linked to different effectors in the two neuronal populations (Lacey 1993; Surmeier and Kita 1993; Usiello et al. 2000), it is not valid to compare the ability of drugs to inhibit the spontaneous firing of striatal and dopaminergic neurons, nor to use differences in their ED_{50} as evidence that the autoreceptor is more sensitive than the postsynaptic D_2 receptor (Skirboll et al. 1979). Studies which conclude that the autoreceptor is the same as the postsynaptic receptor from experiments comparing the ability of dopamine agonists to inhibit dopamine release with their ability to inhibit ACh release are similarly flawed (e.g., Helmreich et al. 1982).

However, there is at least one place in which postsynaptic D_2 receptor signaling/linkage appears to be similar or identical to that in the dopaminergic neuron, and that is the lactotroph cells of the pituitary gland. Among these cells, dopamine acts through a D_2 receptor (Vallar and Meldolesi 1989) to open a potassium channel in concentrations as low as 100 nM (Israel et al. 1987), the same range as that required for activation of the autoreceptor (Lacey 1993). Based on these data, it seems likely that when coupled to a potassium conductance, the D_2 autoreceptor and the D_2 postsynaptic receptor exhibit similar or identical sensitivities.

IV. Are Autoreceptors Ubiquitous Among Dopaminergic Neurons?

Although the majority of the studies of dopamine autoreceptor pharmacology have been conducted in the nigrostriatal system, there have also been a large number of studies focusing on the mesoaccumbens and mesocortical dopaminergic projections. Although there is unanimous agreement about the existence of somatodendritic and axon terminal autoreceptors on dopaminergic neurons of the substantia nigra pars compacta, the situation has been more controversial with respect to the dopaminergic neurons of the VTA. The controversy arose when it was found that the turnover of dopamine was significantly faster in the frontal cortex than in the striatum and that the synthesis of dopamine in cortex appeared unaffected by apomorphine (Bannon et al. 1981, 1982). It was concluded that these neurons lacked "synthesis-modulating autoreceptors." Similar results and conclusions were reported for dopamine terminals in the amygdala, hypothalamus, and bed nucleus of the stria terminalis (Kilts et al. 1987). Furthermore, a subsequent study reported that iontophoretic application of dopamine failed to inhibit the spontaneous activity of dopaminergic neurons projecting to the prefrontal or cingulate cortices, whereas neurons projecting to the striatum or piriform cortices were

readily inhibited (Chiodo et al. 1984). In addition, the mean spontaneous firing rates of the medial mesocortical dopaminergic neurons were reported to be relatively high (mesoprefrontal: 9.3 ± 0.6 Hz; mesocingulate: 5.9 ± 0.5 Hz), and the incidence of burst firing much higher than in nigrostriatal or mesopiriform neurons (Chiodo et al. 1984). Thus, it was concluded that these neurons were devoid of both "impulse-regulating somatodendritic and synthesis-modulating nerve terminal autoreceptors," although the possibility that these neurons might still possess terminal autoreceptors that modulate dopamine release was left open (Chiodo et al. 1984).

Subsequently, two groups reported that dopaminergic neurons that projected to prefrontal or cingulate cortex were inhibited by low "autoreceptor-specific" doses of apomorphine (5–6 μg/kg) to the same extent as nigrostriatal or meso-accumbens dopaminergic neurons (Shepard and German 1984; Gariano et al. 1989a). Furthermore, these two studies reported that the mesocortical neurons also exhibited the same range of spontaneous firing rates as nigrostriatal neurons (Shepard and German 1984; Gariano et al. 1989a), results that agreed well with earlier studies of the electrophysiological properties of VTA dopaminergic neurons in which the projection targets were not identified (e.g., Wang 1981a,b).

How can one resolve these discrepancies? It is possible that the electrophysiological results of Chiodo et al. (1984) derive from a small subpopulation of mesocortical dopaminergic neurons, located very close to the midline which were not sampled in the other studies. It should be noted that the cell bodies of origin of the nigrostriatal, mesolimbic, and mesocortical neurons reported in Chiodo et al. (1984) showed a much more restricted localization and projection topography with essentially no overlap than that reported by others (see for example, Fallon and Laughlin 1995). Regardless, based on in situ hybridization studies and D_2 and/or D_3 receptor autoradiography, the dopaminergic neurons of origin of the nigrostriatal, mesolimbic, and mesocortical projections all express dopamine D_2 and/or D_3 mRNA and/or receptor protein (Morelli et al. 1988; Meador-Woodruff et al. 1989; Diaz et al. 2000), indicating the ubiquitous expression of the D_2 and/or D_3 autoreceptor on mesencephalic dopaminergic neurons. In vivo recording studies clearly show evidence for the existence of D2-family somatodendritic autoreceptors on VTA neurons projecting to prefrontal cortex (Shepard and German 1984; Gariano et al. 1989b). Finally, retrograde tracing studies show clearly that a number of neurons in the substantia nigra and VTA collateralize to the striatum and cortical areas including prefrontal cortex (Fallon 1981). Although these results are in direct contradiction to those of Chiodo et al. (1984), the bulk of the evidence points strongly towards the idea that most or, more likely, all mesencephalic dopaminergic neurons express D_2 and/or D_3 somatodendritic autoreceptors.

What about nerve terminal autoreceptors? A large number of in vitro experiments have consistently shown that stimulus-evoked release of dopamine from all terminal regions, including prefrontal and cingulate

cortices (Plantje et al. 1985, 1987) is modulated by D_2 and/or D_3 nerve terminal autoreceptors (for review see Starke et al. 1989), although the sensitivity of release to autoreceptor agonists and antagonists in cortex is sometimes reported to be less than in striatum (e.g., Cubeddu et al. 1990). In vivo electrophysiological experiments of changes in the excitability of dopamine nerve terminals in response to local infusion of D2 receptor agonists or antagonists or changes in impulse flow revealed that mesoprefrontal dopaminergic neurons responded exactly as did nigrostriatal neurons, reinforcing the idea that these mesoprefrontal dopaminergic neurons also possessed nerve terminal autoreceptors (Tepper et al. 1984a,b; Gariano et al. 1989a; Tepper and Groves 1990). It is still unclear why, if the cortical and mesolimbic dopaminergic terminals possess autoreceptors as they appear to, dopamine metabolism is different in the prefrontal cortex. One intriguing possibility is that the much lower levels of tissue dopamine (Kilts et al. 1987) and dopamine overflow (Abercrombie et al. 1989), coupled with the far fewer functional reuptake sites in these structures (e.g., Cass and Gerhardt 1995; Letchworth et al. 2000) interact to blunt autoinhibition. Interestingly, recent studies in a mouse mutant lacking the dopamine transporter show that interfering with the transporter severely attenuates autoreceptor function (Jones et al. 1999), although the mechanism for this is as yet unclear.

In any event, the bulk of the evidence now favors the conclusion that all mesencephalic dopaminergic neurons express D_2 and/or D_3 dopamine autoreceptors. Whether there are actually different "synthesis-modulating autoreceptors," "impulse-modulating autoreceptors," and "release-modulating autoreceptors" as proposed by some (see, for example, Kilts et al. 1987 or Wolf and Roth 1990), or simply one autoreceptor (that may comprise both D_2 and D_3 receptors) that serves different functions depending on its subcellular location remains to be determined.

V. What Are the Physiological Roles of Autoreceptors?

The functional role of the axon terminal autoreceptor seems relatively clear. By making it possible to modulate dopamine release (and synthesis) locally, dopaminergic synaptic transmission can be fine-tuned to an extent simply not possible by modulating impulse activity along the main axon when each axon may give rise to several hundred thousand release sites (Tepper et al. 1987a).

But what of the somatodendritic autoreceptor? Among the earliest ideas as to the physiological function of somatodendritic autoreceptors on dopaminergic neurons was the "self-inhibition" hypothesis of Groves and associates (Groves et al. 1975). According to this hypothesis, dopamine released from the dendrites of dopaminergic neurons activated somatodendritic autoreceptors thereby participating in a local negative feedback regulation of the electrophysiological and biochemical activity of the neurons. The self-inhibition hypothesis was consistent with the slow firing rate of dopaminergic neurons (Bunney et al. 1973a), the location of dopamine within dendrites of

nigral dopaminergic neurons (e.g., Bjorklund and Lindvall 1975), and the inhibitory effects of dopamine or dopamine receptor agonists on the spontaneous activity of dopaminergic neurons (e.g., Bunney et al. 1973a,b). Furthermore, administration of dopamine receptor antagonists alone produced increases in the firing rate of dopaminergic neurons in vivo, suggesting that the neurons were under a tonic inhibition mediated by dopamine (Bunney and Aghajanian 1973; Bunney et al. 1973a,b). Since there are no dopaminergic afferents to substantia nigra, and no local axon collaterals from the dopaminergic neurons (Juraska et al. 1977; Wassef et al. 1981; Tepper et al. 1987b), the source of the endogenously released dopamine was most likely to be the dendrites of the dopamine neurons themselves. This hypothesis was borne out by subsequent demonstration that depolarizing stimuli such as high potassium (Geffen et al. 1976) as well as dopamine-releasing agents such as amphetamine (Paden et al. 1976) elicited dopamine release from slices of substantia nigra.

From the earliest extracellular recordings in vivo, midbrain dopaminergic neurons were known to fire spontaneously at very low rates, rarely averaging more than eight spikes per second for prolonged periods, and it was natural to wonder if dopaminergic self-inhibition as originally proposed (Groves et al. 1975) played a role in the slow firing and long post-spike refractoriness seen in autocorrelograms (Wilson et al. 1977). The earliest intracellular recordings from dopaminergic neurons revealed spontaneous action potentials that were followed by large, long-lasting afterhyperpolarizations (Grace and Bunney 1980, 1983a,b) that seemed consistent with this idea, and administration of haloperidol was shown to alter the pattern of firing of these neurons in vivo, making the occurrence of shorter interspike intervals more common, a result that could sometimes be observed in the absence of a change in firing rate (Wilson et al. 1979). However, as described above, subsequent electrophysiological studies revealed that the prolonged spike afterhyperpolarization and long interspike intervals were due largely to a calcium activated potassium conductance (Kita et al. 1986; Shepard and Bunney 1988; Ping and Shepard 1996), and not to dopamine. Interestingly enough, autoreceptor stimulation in dissociated dopaminergic neurons has been shown to reduce calcium entry through ω-conotoxin and w-AgaIVA-sensitive calcium channels which leads to a reduction in the calcium-activated potassium current (Cardozo and Bean 1995).

The dendritic tree of dopaminergic neurons is relatively sparse, but individual dendrites often extend for distances of a millimeter or more (Juraska et al. 1977; Tepper et al. 1987b; Hausser et al. 1995). One possible role for the autoreceptor-mediated hyperpolarization/conductance increase is to respond to dendritically released dopamine by attenuating or blocking the effects of afferent input or intrinsic voltage-dependent conductances (e.g., Cardozo and Bean 1995; Wilson and Callaway 2000) of a dendrite or dendritic segment on which the autoreceptor is located. This type of action would be far more subtle than the more generally assumed classical function whereby auto-

receptors function to limit or regulate the overall activity of dopaminergic neurons.

The classical idea of autoreceptor function derives from the many experiments in which autoreceptor agonists, administered either systemically or locally, have the effect of significantly hyperpolarizing the neuron and suppressing or completely inhibiting its spontaneous activity (Bunney et al. 1973a,b; Groves et al. 1975; Lacey et al. 1987). In these experimental situations, exogenous application of autoreceptor agonists or dopamine releasing agents is likely to produce levels of autoreceptor occupancy that are significantly greater than those that obtain in vivo under normal physiological conditions. Evidence in support of a more subtle and localized physiological effect of somatodendritic autoreceptor activation comes from several lines of evidence.

The electrophysiological response of dopaminergic neurons to autoreceptor antagonists exhibits certain vagaries. Although early studies showed that systemic administration of chlorpromazine or haloperidol at low doses (1.25 mg/kg and 25–50 μg/kg, i.v., respectively) to unanesthetized, immobilized rats consistently produced large (approximately 100%) increases in the spontaneous firing rate (Bunney et al. 1973a,b; Wilson et al. 1979), this effect appeared to be mediated, at least in part, through the striatum since striatal lesions blunted or abolished the effect (Kondo and Iwatsubo 1980). In a recent re-examination of the effects of systemically administered haloperidol or sulpiride on dopaminergic neuron activity, Pucak and Grace (1994) did not find evidence of striatal involvement in the effects of autoreceptor antagonists, as there were no large difference between the effects of these drugs in hemitransected and intact rats. On the other hand, only about 50% of the dopaminergic neurons in their study were excited at all by haloperidol, even at 500 μg/kg, and in the excited cells the mean increase in firing rate was relatively modest, less than 20%. Although firing rate increases up to 56% were seen after administration of 4 mg/kg haloperidol, the significance of the response to such extremely high doses is unclear.

When administered locally in substantia nigra, autoreceptor antagonists (e.g. haloperidol) have been reported to be without effect (Bunney et al. 1973b; Lacey et al. 1990) or to cause large (Groves et al. 1975) or modest (Pucak and Grace 1996) increases in firing of nigral dopaminergic neurons. Although it is clear that general anesthetics can interfere with the response of dopaminergic neurons to autoreceptor blockade (Mereu et al. 1984b), these inconsistent and surprisingly modest effects of D_2 receptor antagonists are hard to reconcile with the generally accepted idea that somatodendritic autoreceptors play a significant role in modulating the firing rate of dopaminergic neurons under physiological conditions.

Furthermore, when the autoreceptors are partially or completely inactivated by treatment with pertussis toxin or antisense knockdown, there are no significant changes in the spontaneous firing rate or pattern of substantia nigra dopaminergic neurons recorded in vivo (Innis and Aghajanian 1987; Tepper et al. 1997; Shepard and Connelly 1999).

Experiments in which somatodendritic autoreceptors are stimulated by endogenous dopamine release by synaptic stimulation reveal changes in dendritic excitability with no significant alteration in mean firing rate (Trent and Tepper 1991). The absence of a gross change in neuronal activity is likely due to a more modest and localized activation of autoreceptors than is achieved by application of exogenous drugs, and is consistent with the functional compartmentalization of the dopaminergic neuron into different electroresponsive regions that may function independently (Grace 1990). Thus, somatodendritic dopamine autoreceptors may serve as a mechanism for altering the excitability and/or response of specific dendritic segments of a neuron in a local manner in response to phasic afferent inputs, and in this way alter the way the neuron integrates its afferent inputs in a subtle and graded fashion.

F. Miscellaneous Neuropharmacology

I. Gamma-Hydroxybutyric Acid

Gamma-hydroxybutyric acid (GHBA) is a normal constituent of the mammalian brain and has been proposed as a putative neurotransmitter and/or neuromodulator (see Maitre et al. 2000 for a recent review). GHBA administration has been shown to modify neuronal activity of dopaminergic neurons of the pars compacta in various ways. In chloral hydrate anesthetized rats, GHBA inhibits impulse flow and this inhibition is blocked by the selective $GABA_B$ antagonist, SCH 50911, but not by the selective GHBA-antagonist NCS-382, suggesting an action on $GABA_B$ receptors (Erhardt et al. 1998). On the other hand when administered in low doses to unanesthetized rats, GHBA was found to increase the firing rate of pars compacta dopaminergic neurons (Diana et al. 1991b) and to produce heterogeneous responses in non-dopaminergic pars reticulata cells (Diana et al. 1993b). Unfortunately, no antagonism studies were performed, thus leaving open the possibility that GHBA in low doses may act through GHBA receptors (see Maitre et al. 2000) to produce excitation of pars compacta neurons and $GABA_B$ receptors to produce inhibition and regularization of firing.

II. Glycine

Dopaminergic neurons respond to bath application of glycine in vitro with a chloride-dependent membrane hyperpolarization. This response is sensitive to strychnine and insensitive to bicuculline or picrotoxin, indicating that it is mediated by a glycine-specific receptor (Mercuri et al. 1990). The source of the glycinergic input is unknown, and could originate in as yet unidentified nigral interneurons and/or from the brainstem (McGeer et al. 1987).

III. Neuropeptides

Cholecystokinin-8 (CCK-8) is the carboxyterminal octapeptide of the peptide cholecystokinin, and is found in some dopaminergic neurons in rat VTA and

substantia nigra (Skirboll et al. 1981; Kalivas 1993). CCK is co-released with dopamine from dopaminergic dendrites (Freeman et al. 1991), and when administered systemically in vivo or locally in vitro, CCK-8 excites dopaminergic neurons. In vivo, CCK-8 increases firing rate and burst firing (Skirboll et al. 1981; Freeman and Bunney 1987). Thus, dopaminergic neurons may be considered to express a second class of autoreceptor, a CCK autoreceptor that acts to facilitate rather than depress the excitability of the neuron. In vitro studies in dissociated dopaminergic nigral neurons show that CCK-8 acts through CCK-A receptors to activate an inward G-protein coupled current. The current was insensitive to pertussis toxin but was abolished by intracellular heparin or calcium chelators, suggesting that it is mediated by IP_3-induced calcium release (Wu and Wang 1994). However, in addition to its excitatory effects, CCK also appears to potentiate the inhibitory effects of dopamine autoreceptor stimulation through an unknown mechanism (Hommer and Skirboll 1983; Freeman and Bunney 1987; Kalivas 1993), so the physiological significance of CCK release in substantia nigra remains to be determined.

Neurotensin and the related peptide, neuromedin N are also present in dopaminergic neurons in rat mesencephalic dopaminergic neurons, some of which also contain CCK. These neurons also express neurotensin receptors. In addition, neurotensin is contained in afferents to the substantia nigra and VTA. Similar to CCK, application of neurotensin in vivo or in vitro leads to increased firing rates of dopaminergic neurons (see Kalivas 1993 for review). Part of this excitatory effect is due to the opening of a G-protein coupled nonselective inward cation conductance (Chien et al. 1996). However, neurotensin also affects autoreceptor responses, but in contrast to CCK, neurotensin attenuates the effects of dopamine autoreceptor agonists (Werkman et al. 2000) and does so by acting to close the same potassium conductance that is opened by dopamine autoreceptor and $GABA_B$ receptor agonists (Lacey et al. 1988; Farkas et al. 1997).

Despite being contained in striatonigral neurons that synapse on dopaminergic neurons in substantia nigra (Mahalik 1988), substance P has little or no effect when applied locally to substantia nigra dopaminergic neurons (Collingridge and Davies 1982; Pinnock and Dray 1982), presumably because levels of substance P receptor binding are low or undetectable in substantia nigra (Rothman et al. 1984). On the other hand, iontophoretic application of substance K or kassinin excites dopaminergic and nondopaminergic nigral neurons in vivo (Innis et al. 1985), and senktide, a selective selective neurokinin NK3 receptor agonist excites dopaminergic neurons in vitro (Keegan et al. 1992). The source and identity of the endogenous ligand is unclear, although nigral levels of both substance P and substance K decrease following excitotoxic lesions of striatum (Arai et al. 1985). Since essentially all electrophysiological changes in nigral neurons following striatal stimulation appear to be due to GABA release, the physiological significance of these tachykinin effects is unclear at present.

G. Acute and Chronic Effects of Antipsychotics on Dopaminergic Neurons

I. Differences Between Effects of Typical and Atypical Antipsychotics

As discussed above, acute systemic administration of antipsychotics increases the activity of dopaminergic neurons in the different subdivisions of the midbrain. One potentially important difference that is apparent between A9 and A10 neurons is the response to "atypical" antipsychotics of which clozapine represents the prototype. These neuroleptics are distinguished from the "typical" antipsychotics because they have a much lower incidence of inducing extrapyramidal side effects (see Meltzer et al. 1999 for a recent review) and thus represent a pharmacological class with enormous clinical potential. One widely accepted hypothesis for the lack of extrapyramidal side effects from the atypical antipsychotics has been that the former have a preferential site of action in the mesolimbic and/or mesocortical dopaminergic system. Early in vivo recording studies following acute administration showed that these compounds increased the firing rate selectively in the A10 region without affecting neuronal activity in A9, whereas their chronic administration led to a reduction in the proportion of spontaneously active neurons as indexed by the cells per track ratio (see below) solely in A10 (Chiodo and Bunney 1983; White and Wang 1983). Subsequent studies suggested a possible difference in interaction of the atypical antipsychotics with autoreceptors in A9 and A10 (e.g., Stockton and Rasmussen 1996). On the other hand, in vitro studies generally have not revealed a differential response of A9 and A10 neurons to typical and atypical antipsychotics (e.g., Suppes and Pinnock 1987; Bowery et al. 1994) and a recent in vivo study showed that intravenous administration of clozapine increased the firing rate of nigrostriatal dopaminergic neurons to the same extent as seen in VTA neurons, but only in unanesthetized rats (Melis et al. 1998). Thus, it is not yet clear that there is a preferential site of action of atypical antipsychotics for the mesolimbic versus nigrostriatal system, at least as far as autoreceptor blockade goes, nor what the pharmacological basis of such a preference might be. Alternative explanations include, for example, differences between the two classes of antipsychotics with respect to interaction with alpha$_2$ adrenergic receptors (Hertel et al. 1999), a relatively more potent blockade of 5HT$_{2A}$ receptors coupled with a weak blockade of D$_2$ receptors (Meltzer et al. 1989, 1999), or a combination of properties (Kinon and Lieberman 1996), which may be the substrate for the differential incidence of extrapyramidal side effects resulting from chronic treatment with typical and atypical neuroleptics.

II. Effects of Chronic Antipsychotic Drug Administration – The Depolarization Block Hypothesis

While the acute administration of dopamine receptor antagonists leads to increased spontaneous firing of dopaminergic neurons (Bunney and Aghajanian 1973; Groves et al. 1975; Wang 1981b), chronic administration of antipsychotics has been suggested to reduce dopaminergic synaptic transmission not only by blocking postsynaptic dopamine receptors, but by a relatively novel mechanism in which a state of chronic depolarization of dopaminergic neurons is induced which, over time, renders a population of neurons unable to fire action potentials thereby reducing the population of spontaneously active dopaminergic neurons. This phenomenon was termed depolarization block (Bunney and Grace 1978) and was measured experimentally by counting the number of neurons displaying the characteristics of dopaminergic neurons encountered while lowering an extracellular recording electrode through the region of the substantia nigra and/or VTA. Following chronic, but not acute antipsychotic treatment, the mean number of presumed dopaminergic neurons encountered per electrode track was found to be less than in controls. Iontophoresis of GABA or dopamine which would be expected to hyperpolarize the neurons reversed these effects. It was therefore proposed that the reduction in the number of cells encountered per track following chronic antipsychotic drug administration was a result of depolarization inactivation of the neurons (Bunney and Grace 1978).

Considerable interest in this theory arose quickly as it provided the first compelling explanation of why the antipsychotic effects of neuroleptics usually take weeks to develop, despite the fact that the blockade of dopamine receptors occurs immediately upon drug administration. Subsequently, numerous reports consistent with the initial phenomenological description emerged (e.g., Chiodo and Bunney 1983; White and Wang 1983; Skarsfeldt 1988, 1995). With additional evidence from intracellular and extracellular recordings consistent with the existence of depolarized dopaminergic neurons in animals chronically treated with neuroleptics (Grace and Bunney 1986), the depolarization block theory gained widespread, although not universal (see Mereu et al. 1994, 1995), acceptance as the principal mechanism by which neuroleptics exert their clinically therapeutic antipsychotic action. The phenomenon appears to be fully reversible, as after withdrawal for 8–14 days after up to 14 months of chronic treatment with haloperidol there are no longer any changes in the number of cells per track or in any other measures of dopaminergic neuron activity compared to controls (Chiodo and Bunney 1987; Gariano et al. 1990). The actual substrates of the depolarization inactivation are not known, although it appears that intact afferent input from the forebrain is essential for the development and maintenance of the phenomenon (see Grace et al. 1997 for review).

There are actually two separate issues to consider with respect to the role of depolarization block in the clinical response to chronic administration of

antipsychotic drugs. The first is whether depolarization block actually occurs in dopaminergic neurons in animals and/or humans chronically treated with neuroleptic drugs. The second is whether depolarization inactivation (assuming it occurs) accounts for the therapeutic action of antipsychotic drugs.

Much of the evidence for the existence of depolarization block relies on measurements of cells per track data described above. While drug-induced changes in the number of cells per track might well indicate changes in the proportion of spontaneously active neurons, alternative explanations have been proposed including changes in firing rate and/or changes in the extent to which the action potential invades the dendrites thereby altering the size of the extracellular field potential of the neuron. Both of these would alter the probability of encountering a neuron while lowering a microelectrode through a designated region of the brain (see discussions in Diana et al. 1995a and Dai and Tepper 1998). For example, a reduction in the number of dopaminergic cells per track was observed after chronic ethanol administration and subsequent withdrawal and attributed to a reduced number of spontaneously active neurons due to depolarization block (Shen and Chiodo 1993). Subsequent experiments (Diana et al. 1995a), however, revealed that during withdrawal, dopaminergic neurons exhibited reduced spontaneous activity (i.e. lower firing rates and burst firing) which could account for more difficult detection and hence a lower number of cells per track even though the neurons were not in depolarization block as evidenced by their slow spontaneous activity and the inability of apomorphine to increase the number of cells per track. Thus, although an interesting and potentially valuable tool, the interpretation of changes in the number of cells per track is complex and may be due to factors other than or in addition to a change in the number of spontaneously active neurons.

As to the second issue, although able to replicate the reduction in cells per track following chronic dopamine antagonists in anesthetized rats, Mereu et al. (1994, 1995) found no reduction in the number of cells per track in locally anesthetized, immobilized, and artificially respired rats. These authors argued that the appearance of depolarization block is an artifact of some type of interaction between general anesthetics and the neuroleptics, and hence is unlikely to account for the therapeutic effects of neuroleptics in (unanesthetized) humans. In addition, some predictions of the depolarization block hypothesis, for example the expected reduction in extracellular dopamine levels in striatal and/or cortical terminal fields following chronic neuroleptic treatment, have been difficult to demonstrate experimentally (e.g., Hernandez and Hoebel 1989; Zhang et al. 1989; Hollerman et al. 1992; Moghaddam and Bunney 1993 but see also Moore et al. 1998). Furthermore, manipulations that increase dopaminergic neuron firing and dopamine release in normal animals also increase extracellular dopamine levels after chronic haloperidol treatment, although the hypothesis would seem to predict that dopaminergic neurons in depolarization block should be unable to respond to excitatory stimuli with an increase in firing rate and dopamine release (Klitenick et al. 1996).

In conclusion, although there is electrophysiological evidence in support of the development of depolarization block in dopaminergic neurons following chronic neuroleptic treatment, some of these data, particularly the cells per track data, are open to alternative interpretations. In addition, the apparent dependency of the development of depolarization inactivation on anesthetic state or other aspects of the experimental preparation, coupled with the inability of a number of experiments to demonstrate the expected decrease in extracellular dopamine levels following chronic neuroleptic treatment, point toward the need for more research before a definitive conclusion about the role of depolarization inactivation in the therapeutic effects of neuroleptics can be reached.

H. Dopaminergic Neurons and Drugs of Abuse: Acute and Chronic Studies

I. Acute Effects of Drugs of Abuse on Dopaminergic Neurons

Dopaminergic systems of the mammalian brain are a major target of drugs of abuse and represent cellular systems which are considered crucial in conveying affect-related effects of various addicting drugs. Thus, dopaminergic neurons have been extensively studied in recent years and much is now known about their response to administration of drugs of abuse (White 1996; Diana 1998; Pulvirenti and Diana 2001).

In vivo, drugs as structurally and pharmacologically diverse as ethanol (Gessa et al. 1985), nicotine (Lichtensteiger et al. 1982; Grenhoff et al. 1986; Mereu et al. 1987), morphine (Iwatsubo and Clouet 1977; Gysling and Wang 1983; Matthews and German 1984) and cannabinoids (French 1997; French et al. 1997; Gessa et al. 1998) increase the firing rate and bursting activity of mesencephalic dopaminergic neurons, resulting in augmented dopamine outflow in terminal areas when acutely administered (Di Chiara and Imperato 1988). In contrast, psychostimulants such as amphetamine and cocaine decrease dopaminergic neuronal activity, principally through indirect actions at the somatodendritic autoreceptor (Bunney et al. 1973a,b; Groves et al. 1975; Einhorn et al. 1988), although their effects on dopamine outflow in terminal regions are not dissimilar from other addicting compounds, i.e., they promote an increase in extracellular dopamine levels by blocking and/or reversing the dopamine uptake transporter (Kuczenksi 1983).

In vitro recordings have provided useful insights into the cellular mechanisms which lead to the excitation of dopaminergic neurons after acute administration of drugs of abuse. Morphine does not act directly on dopaminergic neurons which lack μ-opioid receptors, but rather acts on μ-opioid receptors located on pars reticulata GABAergic neurons producing a potassium-mediated hyperpolarization, which in turn, leads to a depolarization and consequent excitation of dopaminergic neurons through disinhibition (Lacey

et al. 1989; Johnson and North 1992; Kalivas 1993). Although the pars reticulata neuron mediating the disinhibitory effect of μ-opioids has not been conclusively identified and could be an interneuron (Johnson and North 1992), other anatomical and electrophysiological studies have demonstrated that nigrothalamic and nigrotectal neurons exhibit the requisite synaptic arrangement to underlie the disinhibitory effect (Hajos and Greenfield 1994; Tepper et al. 1995, 2000).

A similar mechanism was proposed for the action of ethanol when it was demonstrated that the excitation of dopaminergic neurons induced by ethanol (Mereu et al. 1984a; Gessa et al. 1985) was accompanied by a reduction in pars reticulata non-dopaminergic neuronal activity (Mereu and Gessa 1985) of similar proportions. However, this is unlikely to be the sole mechanism of action of ethanol on dopaminergic neurons, since ethanol activates dopamine-containing cells even when these are mechanically dissociated or studied in slices (Brodie et al. 1999a,b; Brodie and Appel 1998), and ethanol has been shown to have direct effects on the calcium-dependent potassium current in dopaminergic neurons. (Brodie and Appel 1998; Brodie et al. 1999a,b).

Nicotine has been reported to activate dopaminergic neurons in vivo (Lichtensteiger et al. 1982; Grenhoff et al. 1986; Mereu et al. 1987) and in vitro (Calabresi et al. 1989; Pidoplichko et al. 1997), but in contrast to ethanol and opiates, its action is mediated by a direct action on nicotinic receptors located on dopaminergic neurons. Most of the nicotine-induced inward current in dopaminergic neurons is carried by β2-subunit-containing receptors with a minor component contributed by α7 subunit-containing receptors, and even when exposed to concentrations of nicotine found in the blood of smokers, exhibits rapid desensitization (Pidoplichko et al. 1997; Dani et al. 2000).

Among various classes of drugs of abuse, cannabinoids rank high in the list especially in terms of spread of their use and recently have received much attention possibly owing to their social popularity. The actions of Δ^9-tetrahydrocannabinol (THC), the active principle of marijuana, and its synthetic analogues have been recently described in central dopaminergic systems. After acute administration, dopamine outflow is increased in the nucleus accumbens (Gardner and Lowinson 1991) and prefrontal cortex (Chen et al. 1990) while dopaminergic neuronal activity in anesthetized rats is increased in the VTA and substantia nigra (French 1997; French et al. 1997) by an action on CB1 receptors. In unanesthetized rats, cannabinoids similarly activate mesolimbic (Gessa et al. 1998) and mesoprefrontal dopaminergic neurons (Diana et al. 1998b) by a selective action on CB1 receptors. Although there is general agreement about the systems level effects of CB1 stimulation on dopaminergic systems (but see Gifford et al. 1997), their cellular site(s) of action remain controversial. Autoradiographic studies combined with 6-OHDA lesions of the ascending dopaminergic pathways have indicated that CB1 receptors are not expressed by dopaminergic neurons (Herkenham et al. 1991) while these receptors have been detected in high amounts on pars

reticulata GABAergic neurons and on the terminals of striatonigral projection neurons in substantia nigra (Herkenham et al. 1991). The existence of CB1 receptors on pars reticulata GABAergic neurons coupled with the results of in vivo microdialysis studies in the shell of the nucleus accumbens has led to the suggestion that cannabinoids may increase dopaminergic transmission by acting through μ-opioid receptors in a disinhibitory fashion (Tanda et al. 1997) similar to that described above for opioids. However, such a mechanism seems incompatible with direct experimental evidence that shows that cannabinoid agonists increase rather than decrease pars reticulata neuronal activity (Tersigni and Rosenberg 1996; Miller and Walker 1995; see Melis et al. 2000 for discussion on this point) and that the cannabinoid-induced stimulation of firing rate of dopaminergic neurons is not antagonized by naloxone (French 1997; Melis et al. 2000). Thus, at present, the cellular site of action for cannabinoid-induced increase of dopaminergic neuronal activity remains to be determined.

II. Chronic Effects of Drugs of Abuse on Dopaminergic Neurons

While studies of the acute effects of drug of abuse on dopaminergic neurons are extremely informative to identify primary sites of actions of addicting compounds, they are less helpful when trying to understand the general phenomenon of drug addiction. Drug addiction is induced by chronic administration of various substances and is now widely accepted as an example of drug-induced alterations in neuronal plasticity (Nestler 1993; Diana 1996, 1998; Pulvirenti and Diana 2001). Thus, the study of the activity of dopaminergic neurons after chronic administration of drugs of abuse is considered more pertinent and relevant in the context of drug dependence.

Chronic administration of psychostimulants such as cocaine and amphetamine have been shown to affect mesolimbic dopaminergic neurons at various levels (Henry et al. 1989; Ackerman and White 1990; White et al. 1995; White 1996). Firing rate appears to be higher in rats chronically treated with cocaine (Zhang et al. 1992a), perhaps due to the reduced sensitivity of somatodendritic autoreceptors (Ackerman and White 1990; Zhang et al. 1992a), although administration regimen seems to be an important factor as it could affect differently A9 and A10 neurons (Gao et al. 1998). Chronic treatment with amphetamine leads to a reduction in the sensitivity of dopaminergic neurons to autoreceptor-mediated inhibition by apomorphine or amphetamine in a dose-dependent manner (Kamata and Rebec 1983, 1984a,b). Further, an increased sensitivity to iontophoretically applied glutamate, which could push the cells to an apparent depolarization block (Zhang et al. 1997), has been described after both cocaine and amphetamine, although it is unclear if these effects are related to the chronic regimen with cocaine and/or amphetamine or to their withdrawal, as investigations were carried out at variable lengths of time after last drug administration (for review see White 1996). In addition, chronic amphetamine treatment affects dopaminergic neurons not only at the soma but also at the level of the synaptic endings. The ability of

amphetamine to induce a decrease in striatal dopamine terminal excitability (Tepper et al. 1984a) is blunted or eliminated in animals following 2 weeks of treatment with amphetamine (Garcia-Munoz et al. 1996).

Morphine, when administered repeatedly, also produces a number of effects on the mesolimbic dopaminergic system. The firing rate of dopaminergic neurons is within control values 2 h after the last morphine administration, but firing rate and burst firing are drastically reduced when the opiate antagonist, naloxone, is administered at this time (Diana et al. 1995b). Further, the relative refractory period is consistently prolonged, supporting an increased refractoriness of the dopaminergic neuron in generating action potentials (Diana et al. 1995b). In addition, dopaminergic cell bodies appear to "shrink" (Sklair-Tavron et al. 1996) after chronic morphine administration, an effect consistent with the prolongation of refractory periods of these units (Diana et al. 1995b,c; Diana 1996) although is unclear if the reduction in cell body size is induced by chronic morphine or by its withdrawal. These effects, in any event, all point to a vulnerability of the mesolimbic dopaminergic system after chronic administration of morphine.

Ethanol, when chronically administered, has been shown to increase the basal activity of dopaminergic neurons projecting to the nucleus accumbens and no tolerance seems to develop (Diana et al. 1992) to its stimulating properties on dopaminergic neurons (Gessa et al. 1985). Chronically administered nicotine, on the other hand, appears to affect dopaminergic neurons differently. In vitro studies have shown that the stimulating properties of nicotine upon dopaminergic neurons are rapidly lost after repeated exposure due to desensitization of nicotinic receptors present in the somatic region of dopaminergic neurons and helping in explaining acute tolerance to nicotine's rewarding effects (Pidoplichko et al. 1997).

Another commonly abused drug is Δ^9-THC, the active principle of marijuana. Its actions on dopaminergic neurons have been recently elucidated and are similar from those reported above for other drugs, at least in terms of neuronal activity, in spite of the fact that cannabinoids are frequently considered only mildly addicting (Grinspoon and Bakalar 1997). Chronic administration of Δ^9-THC alters dopaminergic neuronal functioning in the limbic system in a way similar to that reported for morphine, and tolerance to the stimulating properties of Δ^9-THC seems to develop only in A9 but not in A10 neurons (Wu and French 2000). Firing rate and burstiness are reduced after chronic exposure and are further reduced if the selective antagonist SR 1417116 A is administered (Diana et al. 1998a). In contrast, overt behavioral signs of withdrawal are evident only in rats in which the selective antagonist, SR 141716 A, was administered, suggesting that the lack of withdrawal symptoms might be due to the presence of residual Δ^9-THC, which would counteract abstinence signs. This fact may also help in explaining why cannabinoids are traditionally considered devoid of withdrawal signs (Grinspoon and Bakalar 1997).

In conclusion, while acute administration of addicting drugs stimulates the activity of dopaminergic neurons and in particular the mesolimbic system,

chronic administration alters neuronal functioning in various ways which indicate the mesolimbic dopaminergic pathway as a major target in the actions of chronic administration of addicting drugs, and provide the rationale for drug addiction viewed as an example of drug-induced alterations in neuronal plasticity (Koob and Bloom 1988; Nestler 1992, 1993, 2001; Diana 1996, 1998; Koob and Le Moal 1997; Pulvirenti and Diana 2001).

III. Withdrawal Following Chronic Administration

While repeated administration forms the basis of neurobiological changes induced by drugs of abuse, withdrawal is often a time-window which reveals enduring effects produced by the continued exposure. Indeed, drug-withdrawal offers the unique opportunity to study neurobiological alterations induced by chronic administration of addicting drugs in a drug-free condition, in which the abused substance may act as a potential confounding factor. It is often very difficult to discriminate between effects induced by the drug, when chronically administered, or by its absence after chronic administration. Thus, it is advisable to carefully discriminate between effects induced by drugs themselves and effects induced by their absence since interpretations are often opposite (Diana 1996; Sklair-Tavron et al. 1996; Diana et al. 1999).

The effect of withdrawal from various addicting drugs has recently been described in dopaminergic neurons. Ethanol withdrawal reduces the spontaneous activity (firing rate and burstiness) of dopaminergic neurons projecting to the nucleus accumbens, in rats in vivo (Diana et al. 1993a) and in mice in vitro (Bailey et al. 1998), and these effects are accompanied by an elongation of refractory periods and a reduction of dopamine dialysate in the nucleus accumbens (Fig. 6) (Diana et al. 1993a). The reduction in neuronal activity does not seem to be due to the depolarization block proposed for cocaine withdrawal (Ackerman and White 1990, 1992) as it persists in rats anesthetized with chloral hydrate which show the same sensitivity to apomorphine as unanesthetized rats (Diana et al. 1995a, but see Shen and Chiodo 1993). Further, hypofunctioning of dopaminergic neurons outlasts the behavioral manifestations of withdrawal, suggesting a role for dopaminergic neurons in subtle but reproducible and enduring modifications in cell physiology unrelated to somatic withdrawal but more closely linked to longer lasting changes occurring after ethanol withdrawal (Diana 1996, 1998).

Morphine withdrawal also produces a depression in firing rate and burst firing in dopaminergic neurons with no evidence of depolarization block (Diana et al. 1995b). These data are consistent with the hyperpolarization due to an increased GABA release seen in dopaminergic neurons in vitro during acute morphine withdrawal (Bonci and Williams 1997). In addition, morphine withdrawal produces a reduction in glutamatergic EPSCs in VTA dopaminergic neurons due to reduced glutamate release (Manzoni and Williams 1999). Furthermore, as in the case of ethanol, the reduction of dopaminergic activity after opiate withdrawal persists for 14 days, while behavioral measures

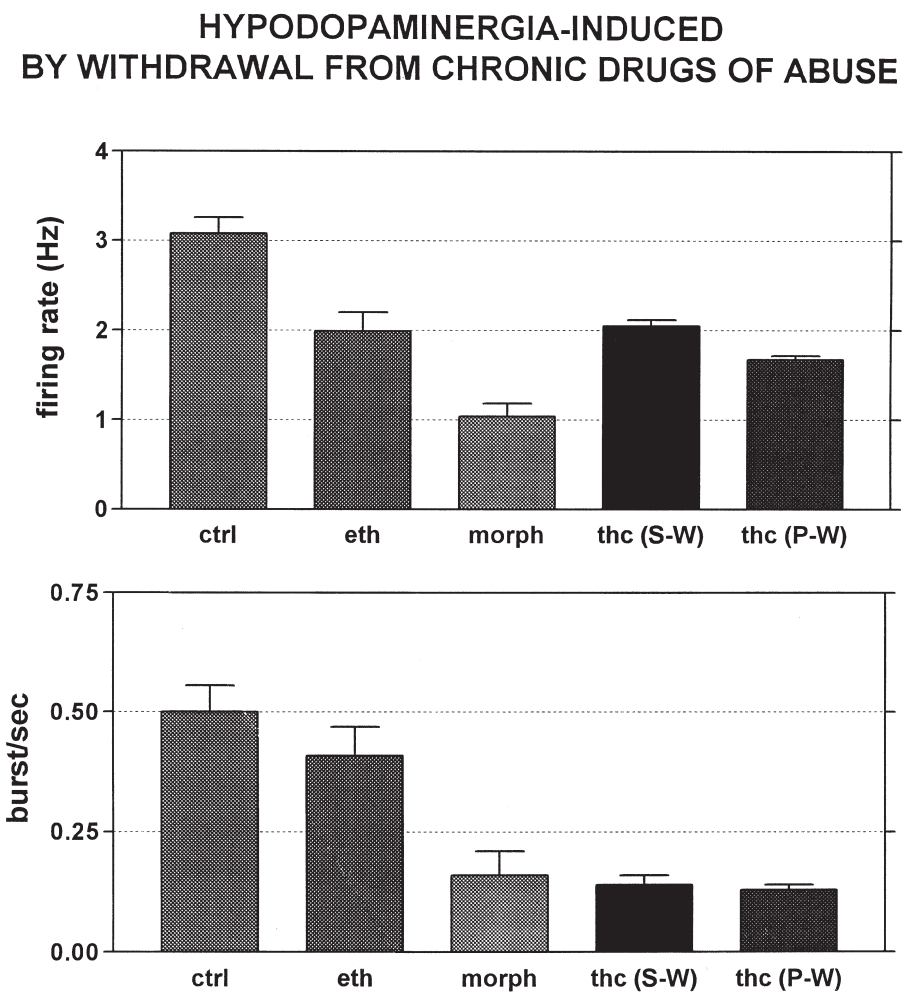


Fig. 6. Extracellular electrophysiological properties of mesolimbic dopaminergic neurons projecting to the nucleus accumbens in vivo after withdrawal from chronic administration of ethanol (*eth*), morphine (*morph*), and Δ^9-THC (*thc*) spontaneous (*S-W*) and pharmacologically precipitated (*P-W*). Note the parallel decline in firing rate (*top*) and bursting activity (*bottom*) irrespective of the substance administered. Due to the different baseline activity in treated and control rats, number of bursts is expressed as bursts per second. See details in Diana et al. (1995c) and Diana (1998)

of abstinence are within control values at 3 days (Diana et al. 1999). Once again, these results would suggest that hypofunction of the mesolimbic dopaminergic system is related to the long-term consequences of chronic opiate abuse and not to behavioral signs of withdrawal (but see Harris and Aston-Jones 1994). Furthermore, administration of morphine to rats with a history of morphine addiction results in an activation of dopaminergic firing

rate far greater than that observed in saline-treated counterparts (Diana et al. 1999). This suggests that although dopaminergic neurons have returned to apparent normality (extracellular electrophysiological indices are within control values), the mesolimbic dopamine system remains hyper-responsive (i.e., vulnerable) to opiates even longer, with profound implications for the phenomenon of relapse into opiate addiction in humans. Nicotine, the principal constituent of tobacco, seems to produce different effects upon discontinuation of chronic exposure (Rasmussen and Czachura 1995), at least in vivo. Indeed, chronic administration seems to produce a reduction of firing rate in the A10 region but not in the A9, whereas withdrawal restored control firing rates in A10 and increased above control in A9 (Rasmussen and Czachura 1995). Although stimulating, these results are flawed by the lack of antidromic identification of the neurons, which hampers firm conclusions on the regional selectivity of the effects observed, and thus we await confirmation in light of contrasting results obtained in vitro (Pidoplichko et al. 1997) and in vivo with the microdialysis method (Carboni et al. 2000).

Cannabis derivatives have long been seen as only mildly addicting and consequently as devoid of withdrawal manifestations. Recently, however, with the advent of appropriate pharmacological tools, it has been possible to demonstrate behavioral manifestations of cannabinoid withdrawal (Aceto et al. 1995, 1996; Tsou et al. 1995). On this basis we investigated the possibility that chronic treatment with Δ^9-THC affects the function of the mesolimbic dopamine system. We found that both withdrawal conditions (spontaneous and pharmacologically precipitated) reduced the firing rate of dopaminergic neurons projecting to the nucleus accumbens with behavioral manifestations of withdrawal evident only in the pharmacologically precipitated withdrawal group (Diana et al. 1998a). These facts suggest that hypofunction of the dopaminergic mesolimbic system may participate in the neurobiological basis of long-term consequences of cannabinoid dependence, allowing us to extend this conclusion to the general phenomenon irrespective of the chemical class abused and further suggest that the failure to observe behavioral signs of cannabinoid withdrawal could be due to high lipophilicity of cannabinoids, which hampered observation of an abrupt somatic withdrawal (Diana et al. 1998a).

I. Conclusions

In the last decade, electrophysiological studies have added significantly to our knowledge of the physiological activity and pharmacological responsiveness of dopaminergic neurons. Many of the intrinsic mechanisms that lead to action potential generation and the generation of different firing patterns, both under normal physiological conditions and after various pharmacological manipulations, have been described. Considerable advances have been made in understanding the pathways, neurotransmitters, and receptors that form the substrates for the afferent regulation of central dopaminergic systems.

These central dopaminergic systems have been demonstrated to be a major target for many psychotropic drugs including psychotherapeutic antipsychotics and drugs of abuse. Dopaminergic systems play a role in the response to drugs of abuse not only when administered acutely but, perhaps more importantly, following chronic administration and withdrawal. Under withdrawal, regardless of the specific drug, there is a depression in the spontaneous activity and burst firing of dopaminergic neurons projecting to the nucleus accumbens. This "hypodopaminergia" outlasts the behavioral signs of withdrawal and suggests that dopaminergic systems play an important role in the long-term consequences of prolonged drug intake and provides an example of drug-induced alterations in neuronal plasticity affecting the mesolimbic dopaminergic system. Identification of the etiological factors leading to the abnormal cellular physiology following chronic administration of, and withdrawal from, addictive drugs may pave the way for future pharmacological treatments of drug addiction.

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