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).

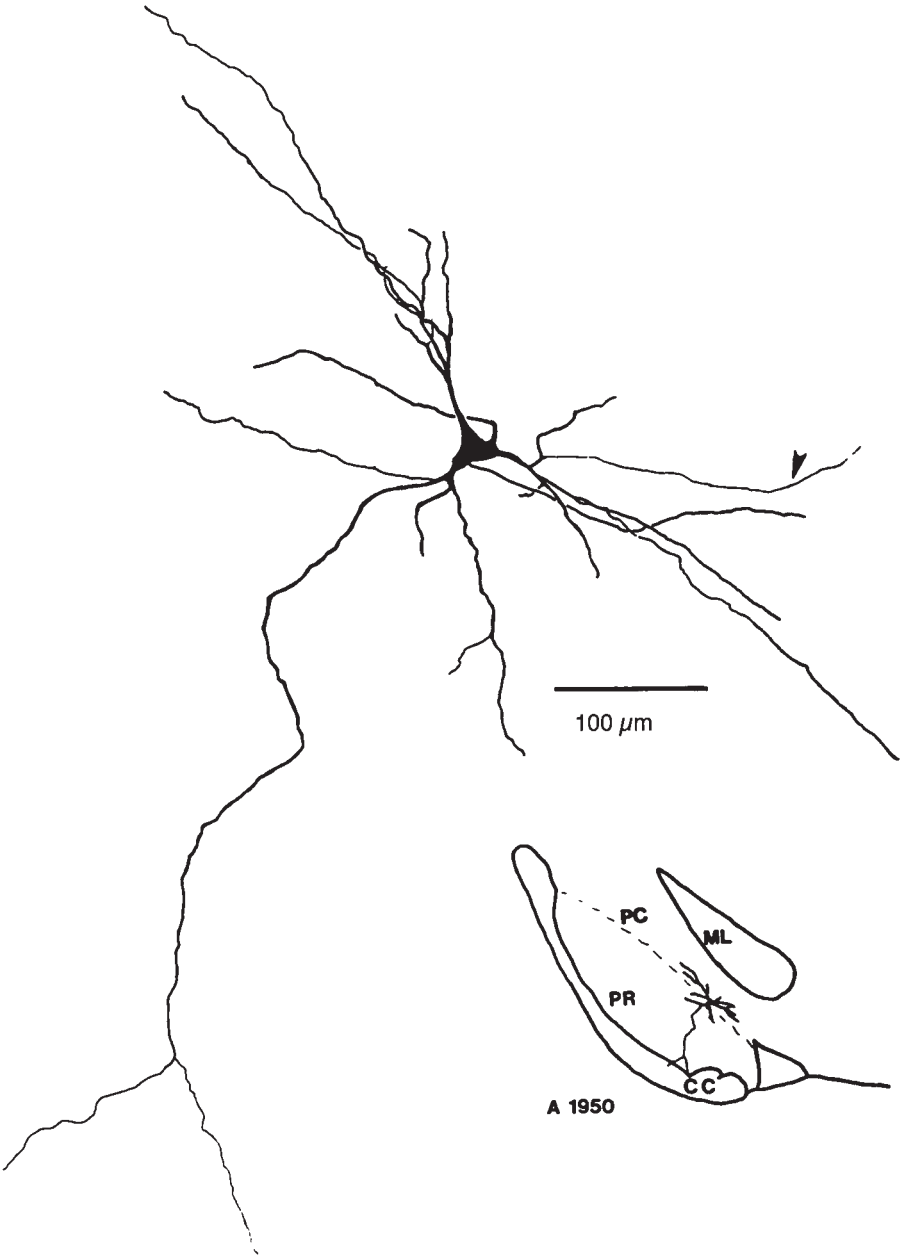

Fig. 1. Drawing tube reconstruction of an HRP-filled substantia nigra pars compacta neuron that was antidromically activated from both ipsilateral globus pallidus and neostriatum. The *inset* is drawn approximately to scale to illustrate the location of the dendritic arborization of the neuron within 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

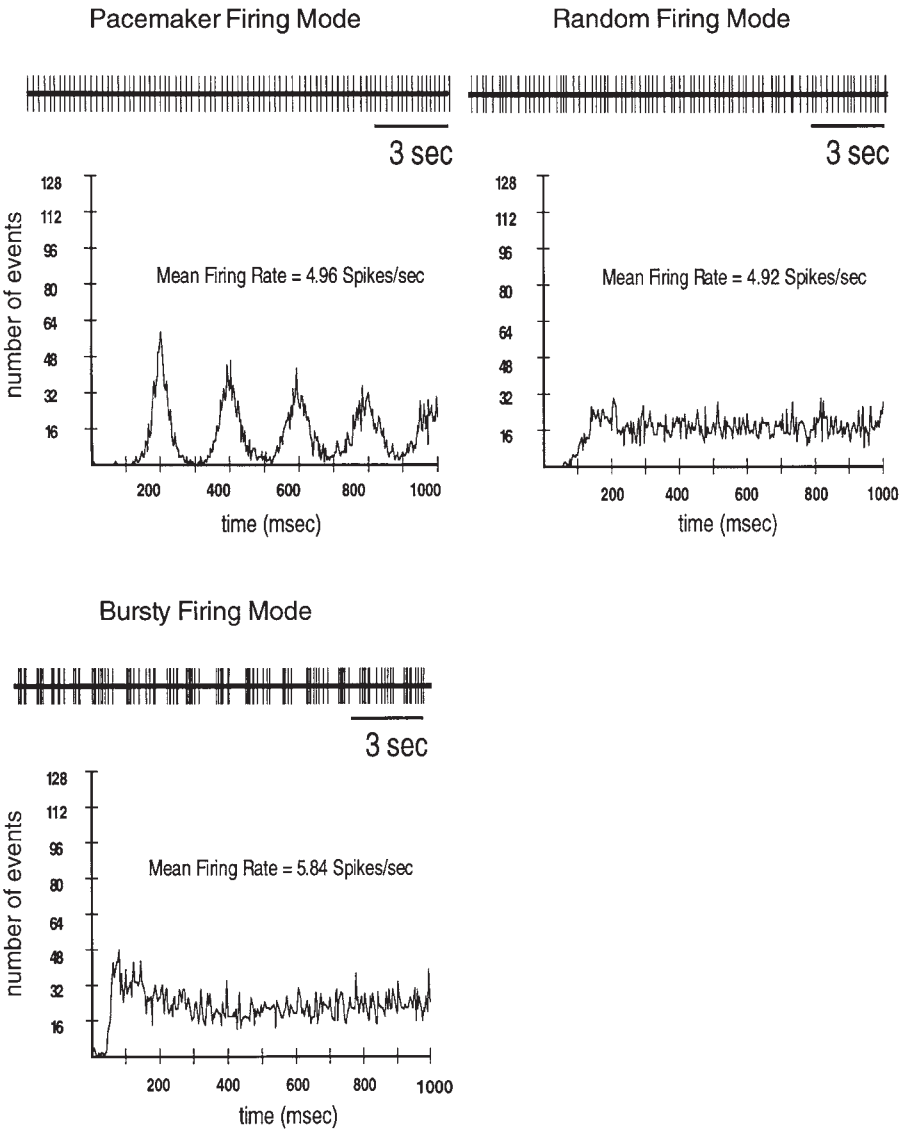

Fig. 2. Autocorrelograms of representative neurons exhibiting the three firing modes of dopaminergic neurons in vivo. Above each autocorrelogram is the first approximately 15 s of the spike train used to create the autocorrelogram. Bin width = 3 ms. (Reproduced from TEPPER et al. 1995 with permission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