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Pharmacology of Mesocortical Dopamine Neurons

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I. Introduction

THIS review attempts to summarize our current knowledge of the biochemistry and pharmacology of the dopamine (DA) innervation to the frontal cortex, a rapidly expanding area of brain research which has existed for less than a decade (for an earlier review, see Ref. 148). Most of the studies reviewed were conducted with rats, although relevant data from other species are also cited. Brief discussions of the role of the prefrontal cortex in behavior and of behavioral and anatomical studies on the mesocortical DA neurons are also included in order to consider the possible functional significance of this DA system.

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II. The Prefrontal Cortex and Dopamine

Berger et al. (19) observed that the field of dopaminergic projections to the rat cerebral cortex coincided closely with the rat prefrontal cortex, a neocortical area

defined as the projection field of the mediodorsal thalamic nucleus (115, 46). This observation was confirmed by the systematic study of Beckstead (16). A similar parallel between mesocortical DA neuron terminal fields and the area defined as the prefrontal cortex has since been documented in many other species, including nonhuman primates (88, 47, 23, 28).

The prefrontal cortex is involved in the temporal organization of behavior, and ablations of the prefrontal cortices of many different species induce similar functional deficits including: 1) detrimental effects on behavioral tests such as discrimination and delayed response tasks; 2) a difficulty in suppressing attention to irrelevant internal and external stimuli, resulting in hyperreaction and motor hyperactivity; and 3) a diminution in affective and social behavior (for comprehensive reviews, see Refs. 60, 61). In addition, neuropharmacologists have focused attention on the prefrontal cortex because the DA projection to this area is selectively activated by footshock stress and shows a qualitatively different response to chronic antipsychotic drug treatment (see section VI).

The experiments summarized in this review focus primarily on the anteromedial (pregenual) frontal cortex, because this area represents a large portion of the anatomically defined and behaviorally important prefrontal cortex, and because it contains higher levels of DA and neurochemical markers of dopaminergic function than any other frontal lobe cortical region. In addition, this area apparently receives an innervation from a more discrete, localized group of DA cells than other cortical areas (see section IV). In accordance with some previous anatomical and biochemical/pharmacological investigations, this area will simply be termed the "prefrontal cortex," and the DA projection to this area will be called the "mesocortical DA system." Investigations that involved examination of a slightly more inclusive terminal area (e.g. to include the most rostral pole or lateral aspects of the frontal cortex) are also discussed. Other (especially earlier) studies that have involved more gross or whole cortical dissections without regard to the different cortical DA projections are not reviewed at length. Likewise, details of the other more extensively studied brain DA systems are not reviewed here, but discussed only in comparison to the mesocortical DA system.

III. Discovery of a Dopaminergic Projection to the Cerebral Cortex

The first evidence for a dopaminergic projection to the rat cerebral cortex was obtained from biochemical studies. Thierry et al. (146) reported that cortical DA levels were unaltered by lesions of the central noradrenergic system. These investigators subsequently demonstrated the continued synthesis of ^{3}H-DA from ^{3}H-tyrosine in cortical slices and synaptosomes after 6-hydroxydopamine (6-OHDA) lesions which nearly totally abolished ^{3}H-norepinephrine (^{3}H-NE) synthesis (143). Shortly thereafter, specific high affinity ^{3}H-DA uptake (141) and DA-sensitive adenylate cyclase (152, 25) were identified in the cortex. Dopaminergic projections to the cortex, described as thin unmyelinated fibers with a smooth appearance and irregularly spaced varicosities, were shown by histochemical studies (in combination with lesions and pharmacological manipulations) to innervate primarily the frontal, cingulate, piriform, and entorhinal cortices (18, 73, 90, 19). Distinct cortical innervations were suggested early on by the data of Lindvall et al. (90), who reported that lesions of the DA cell bodies in the lateral portion of the substantia nigra (SN) completely removed the DA innervation of the anterior cingulate cortex while sparing the frontal cortical DA projection. Conversely, lesions of the dorsal part of the ventral tegmental area (VTA) DA cell group eliminated the frontal cortical DA innervation, but not the projections to the cingulate cortex.

IV. Anatomy of the Mesocortical Dopamine Projection and Its Relationship to the Prefrontal Cortex

The origin and distribution of dopaminergic projections to the frontal cortex and other forebrain areas has since been investigated in great detail by using anterograde transport and autoradiographic tracing, anterograde degeneration, retrograde transport of horseradish peroxidase or fluorescent dyes, pharmacological manipulations, and discrete brain lesions. This literature is vast, and the data and methodological considerations are to some extent too complex to review here. These data are briefly summarized below, in the hope of facilitating an understanding of the pharmacology of the mesocortical DA cells (see fig. 1). For a more detailed discussion, see Swanson (135).

Most studies have reported that the caudate is innervated primarily by DA cells originating from throughout the SN, but also receives projections of VTA origin. The nucleus accumbens and olfactory tubercle are innervated primarily by DA cells in the VTA, but more laterally by fibers from the medial SN (57, 17). There has been less agreement about the origins of the DA projections to the cerebral cortex. The DA innervations to the cingulate cortex (also called the anteromedial supragenual area) and the piriform cortex seem to arise primarily from cells in the lateral VTA and/or medial SN (90, 130, 36, 87–89, 57, 101). Likewise, a discrete origin for the DA innervation of the entorhinal cortex has not been established, although most reports have suggested that this DA projection arises primarily from the VTA (36, 87, 89, 57, 58, 101, 17, 135). In contrast to these other cortical areas, and confirming an earlier report (90), the dopaminergic innervation to the prefrontal cortex (anteromedial pregenual area) apparently derives primarily from the medial VTA (130, 36, 87–89, 57, 132, 17, 135).

There is some controversy over the extent to which unidentified midbrain neurons innervating forebrain

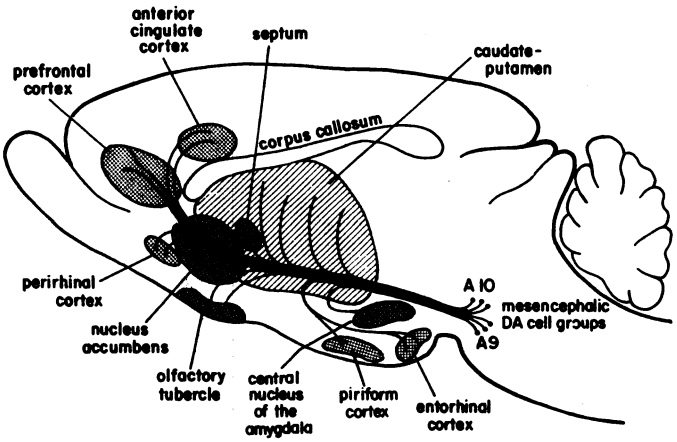

FIG. 1. Schematic diagram depicting the distribution of nigrostriatal, mesolimbic, and mesocortical dopaminergic neuronal systems in brain. The stippled regions indicate the major nerve terminal areas. The cell groups in this figure are named according to the nomenclature of Dahlstrom and Fuxe (Acta Physiol. Scand. **62:** Suppl. 232, 1, 1965).

areas colateralize to two or more different terminal fields (150, 151, 56, 135). However, there is general agreement that cells originating in the VTA are rarely double labeled after the retrograde transport of fluorescent dyes from terminal fields; thus the majority of cells projecting to the prefrontal cortex would not be expected to collateralize. It has been pointed out that the DA neurons of the SN and VTA are formed as a single unit ontogenetically, and constitute a continuous group in the adult (57). It has been argued, therefore, that the distinction between mesolimbic and mesocortical systems is "an artificial distinction with little to recommend it" (101). While it is true that such terms have been ill defined, dopaminergic projections to various cortical and "limbic" areas do apparently differ to some extent in terms of the origin of their DA innervation, as outlined above. Perhaps more importantly, various forebrain DA projections can be clearly distinguished by using biochemical, electrophysiological, and pharmacological criteria, as will be discussed below.

V. Biochemical Characteristics of the Mesocortical Dopamine System

A. Dopamine Levels

Until recently, the study of mesocortical DA functioning has been hampered by the fact that the content of DA in the prefrontal cortex is only approximately 1% of the DA concentration in the striatum. DA metabolite levels are similarly low in the prefrontal cortex. The development of more sensitive and specific techniques, especially liquid chromatography with electrochemical detection and radioenzymatic assays, has greatly facilitated the routine determination of DA and related compounds in the prefrontal cortex. DA levels in the range of approximately 70 to 125 ng/g wet weight or 0.6 to 2 ng/mg protein are generally reported in the rat prefrontal or frontal cortices (78, 52, 136, 138, 107, 110, 111, 126, 131, 53, 55, 9, 12–14, 98, 3, 113, 69, 139, 38). These DA levels are approximately 25 to 60% of the norepinephrine (NE) values in the corresponding cortical region. The DA levels and DA enrichment relative to NE are critically dependent on anterior-posterior localization of the area examined ("whole" frontal, prefrontal, or cingulate cortex (52, 136, 107). In addition, the DA levels in the prefrontal cortex increase substantially from superficial to deeper cortical layers, while NE levels remain constant (52, 136). Lesion experiments, analogous to those described above with the histochemical studies, have been performed prior to the measurement of frontal cortical DA and NE. Lesions of the ascending noradrenergic system which markedly deplete NE do not decrease prefrontal cortical DA (129, 9), and, in fact, often paradoxically increase frontal cortical DA by as much as 40% (52, 138, 126). Electrolytic or 6-OHDA lesions of the VTA dramatically reduce prefrontal cortical DA while having lesser effects in adjacent areas (52, 126, 131). In contrast, 6-OHDA lesions of the SN decrease cingulate but not frontal cortical DA (52, 126).

B. Tyrosine Hydroxylase

Tyrosine hydroxylase is the rate-limiting enzyme in the synthesis of DA and NE. The distribution of tyrosine hydroxylase activity (TH) in the frontal cortex parallels the distribution of DA. Thus, 1) TH is higher in the prefrontal cortex than in surrounding cortical areas; 2) TH follows the laminar distribution of DA (and not NE) in the prefrontal cortex; 3) lesions that deplete approximately 90% of the cortical NE decrease prefrontal cortical TH by only 20% to 30%; 4) lesions which cause 60% to 75% depletions of DA cause a 50% to 60% loss of TH (52, 129, 110). Emson and Koob (52) concluded that the amount of TH in DA terminals in this area is 2 to 3 times higher than in noradrenergic terminals. Schmidt and Bhatnagar (129) calculated that the TH activity relative to catecholamine content in the mesocortical DA system is approximately 10-fold higher than in the cortical noradrenergic terminals.

C. ^{3}H-Dopamine Uptake

The reuptake of DA and NE into the nerve terminal is a primary mechanism for the inactivation of catecholamines released into the synaptic cleft. Tassin et al. (141) described a specific DA uptake process in rat cerebral cortex, defined as the ^{3}H-DA uptake which was resistant to lesioning of noradrenergic innervation to this region or NE uptake blockers such as desipramine, and sensitive to the somewhat selective DA uptake inhibitor benztropine. As with other measures of dopaminergic innervation, ^{3}H-DA uptake is highest in the prefrontal cortex, both in absolute amounts and relative to ^{3}H-NE uptake, compared to adjacent cortical regions (52, 136, 111). ^{3}H-DA uptake in the prefrontal cortex, as well as in other DA terminal regions, is more potently inhib-

ited by *d*-amphetamine than by *l*-amphetamine (94), indicating most DA uptake occurs in DA nerve terminals.

D. Dopamine-sensitive Adenylate Cyclase

A DA-sensitive adenylate cyclase, linked to postsynaptic DA receptors and distinct from NE (β-adrenergic)-sensitive adenylate cyclase, was first characterized in whole rat cortex (152). The cortical distribution of DA-sensitive adenylate cyclase parallels the distribution of other indices of dopaminergic innervation: the highest cortical activity is found in the prefrontal cortex and, within this area, the most activity is localized ventrally in the deeper cortical layers (25, 136, 80, 48). The prefrontal cortical adenylate cyclase has been extensively characterized (25). When this system was compared with striatal DA-sensitive adenylate cyclase, some slight differences between the apparent affinities of these two systems for some DA antagonists was reported, although the significance of this observation is not known. Different degrees of prefrontal cortical DA-sensitive adenylate cyclase supersensitivity are induced by various lesions of the mesocortical DA neurons. It has been suggested that these differences are related to the degree of concurrent noradrenergic observation (139).

E. ^{3}H-Ligand Binding

The binding of tritiated ligands to neuroleptic receptors in the rat frontal cortex has not yet contributed significantly to our knowledge of the role of DA in the prefrontal cortex. Laduron et al. (82) reported that ^{3}H-spiperone (spiroperidol) labeled more binding sites in the frontal cortex (both in vivo and in vitro) than in other cortical areas, paralleling the distribution of other dopaminergic markers. However, ^{3}H-spiperone apparently labels both serotonin (5-HT) and DA binding sites, with the former predominating in the frontal cortex (40, 86, 93, 74, 3). These investigators have shown that the binding site(s) labeled depends on the specificity of the displacing agent used. Since some of the commonly used displaced drugs have nearly equal affinity for 5-HT and DA binding sites, much of the frontal cortical ^{3}H-spiperone binding literature is difficult to interpret (see section VI B 5). However, the autoradiographic localization of ^{3}H-spiperone frontal cortical binding sites after in vivo coadministration of ^{3}H-spiperone and the serotonergic antagonist pipamperone does parallel other indices of DA receptor localization (103).

F. Dopamine Metabolites

Under many conditions brain DA metabolite levels reflect the physiological activity of dopaminergic neurons. Dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) are both important DA metabolites in rat brain. In addition, both DOPAC and HVA are found in unconjugated and conjugated forms (for a review, see Ref. 39). Frontal cortical free DOPAC levels in the range of 0.28 to 0.65 ng/mg protein (84, 70, 24, 113) or approximately 30 to 100 ng/g wet weight (158, 121, 54, 149, 160, 153, 53, 55, 9, 98, 3, 95, 12–14, 38) have been reported. Frontal cortical free HVA in the range of 30 to 90 ng/g have been measured (158, 121, 160, 3, 2, 3, 4). In very large areas of cortex, as well as in striatum, free and conjugated DOPAC levels change in a similar manner in response to DA agonists and antagonists and to electrical stimulation, i.e., both free and conjugated DOPAC seem to be good measures of dopaminergic activity (51). Most investigations involving more defined cortical regions have measured only free DOPAC; the levels of conjugated DOPAC in very discrete cortical regions are not known with certainty (since the conjugated DOPAC/free DOPAC ratio changes in different brain regions), but conjugated DOPAC may constitute better than 50% of total DOPAC in the frontal cortex (50, 5).

In contrast to the similar alterations in free and conjugated DOPAC, Westerink and Korf (158) found that free DOPAC and free HVA did not change in parallel following certain pharmacological manipulations. The discrepancies were most striking in the mesolimbic areas and the frontal cortex. The authors suggested that DOPAC levels more closely reflected changes in DA metabolism than HVA levels did. They ascribed the difference to the fact that under basal conditions only a small fraction of DOPAC is O-methylated to HVA in mesolimbic regions (159); under conditions of altered dopaminergic activity, the percentage of O-methylation of DOPAC may be altered (158). More recent results obtained by parallel HVA and DOPAC determinations in the frontal cortex and mesolimbic DA system support this contention (3) (see section VI B).

Lavielle et al. (84) have suggested that the DOPAC/DA ratio is a sensitive index of changes in dopaminergic activity. Objections can be raised to this method of expressing experimental results since it may obscure which levels (i.e. DOPAC and/or DA) are altered, and turnover data (e.g. DOPAC levels) are generally considered more difficult to interpret under nonsteady state (i.e. changing DA levels) conditions. This is of special concern in view of the paradoxical changes in DA synthesis seen in response to a cessation of dopaminergic impulse flow in some (but not all) DA systems (see Refs. 116, 12). Nevertheless, DOPAC/DA ratios, at least under basal conditions, may suggest regional differences in the rate of DA utilization. DOPAC/DA reported by these investigators (84, 132, 92, 24) in the frontal cortex (0.41 to 0.5), olfactory tubercle (0.30), nucleus accumbens (0.18 to 0.30), and striatum (0.12 to 0.25) would suggest that the DA turnover in these regions is as follows: frontal cortex > olfactory tubercle ≥ nucleus accumbens ≥ striatum.

Recent studies, in which HVA/DA ratios in striatal, limbic, and cortical areas of human brain have been used to estimate DA turnover, also revealed a more rapid turnover of DA in frontal and cingulate cortex than in olfactory cortex and striatal and limbic areas (83a). These observations are very similar to those reported in

TABLE 1

Some electrophysiological and biochemical characteristics of subtypes of midbrain dopamine neurons.[1]

Type of DA Neuron	Basal Discharge Rate* (spikes/second)	Relative Degree of Bursting‖	DA Auto-receptors	DOPAC/DA†
Mesoprefrontal	9.3 ± 0.6‡ (3.7–13.2)	53.9 ± 9.1 (10)	No	0.413 ± 0.078 (10)
Mesocingulate	5.9 ± 0.5§ (3.9–7.8)	37.8 ± 6.0 (10)	No	0.617 ± 0.096 (8)
Mesopiriform	4.3 ± 0.3 (2.9–5.8)	7.8 ± 3.1 (10)	Yes	0.279 ± 0.059 (9)
Nigrostriatal	3.1 ± 0.5 (1.1–5.6)	1.8 ± 0.3 (10)	Yes	0.101 ± 0.005 (11)

Data taken in part from Chiodo et al. (38).

* Data represent the mean ± SEM. The numbers in parentheses represent the range.

‖ Data represent the percent of spikes occurring in bursts out of the total number of action potentials sampled (500 per cell) (mean ± SEM). The numbers in parentheses represent the number of cells sampled. All groups significantly differed from each other at $P < 0.01$; analysis of variance and post-hoc Scheffe comparison.

† Data represent the mean ± SEM DOPAC/DA ratio in the projection area. The numbers in parentheses represent the number of separate experiments (4 to 8 rats/experiment).

‡ $P < 0.01$ relative to mesopiriform and nigrostriatal.

§ $P < 0.01$ with respect to mesoprefrontal and $P < 0.05$ relative to mesopiriform and nigrostriatal; analysis of variance and post-hoc Scheffe comparison.

rat brain and are consistent with the possibility that DA terminals in human frontal and cingulate cortices lack DA autoreceptors (see section VI B). Table 1 summarizes some of the electrophysiological and biochemical characteristics of midbrain DA neurons.

G. Dopamine Depletion Rates

It has been reported (147, 3) that the depletion of DA 30 to 45 min after administering the TH inhibitor α-methyltyrosine (AMT) is more pronounced in the frontal cortex than in other forebrain areas. This is consistent with the DOPAC/DA measurements, which also suggest a faster mesocortical DA turnover. Agnati et al. (1), by using a photographic method to quantity DA fluorescence at various times after AMT, have calculated a DA half-life of 1.73 hr in the SN and 0.52 hr in the medial VTA. As mentioned above (section IV), the DA innervation to the striatum originates primarily from the SN, while the mesocortical DA system probably originates primarily from the medial VTA. It is of interest, then, that the calculated half-life of striatal DA is 2.51 hr, while the prefrontal cortical DA half-life is only 0.65 hr (9). The half-life of DA in the olfactory tubercle and in lateral VTA DA cells (which may be the DA cells innervating the olfactory tubercle; see section IV) falls within an intermediate range (1, 9). Thus, the DA turnover rate of the mesocortical DA system is apparently twice as fast as that of the mesolimbic DA system and four times faster than nigrostriatal DA turnover (9).

VI. Biochemical Response of the Mesocortical Dopamine System to Physiological/ Pharmacological Manipulations

A. Possible Sites of Action of Dopaminergic Drugs on Various Dopamine Systems

The regulatory mechanisms operative in central dopaminergic neurons have been elucidated in large part through the use of pharmacological agents. Some drugs act presynaptically to alter the fate of DA. Monoamine oxidase inhibitors, for example, prevent DA catabolism, thereby decreasing DA metabolite levels, increasing the intraneuronal DA concentration, and inhibiting DA synthesis. Other drugs such as DA receptor antagonists ("antipsychotic drugs") act primarily at the level of membrane receptors. DA antagonists increase nigrostriatal and mesolimbic DA cell activity and increase DA synthesis, release, and catabolism (for a general review, see Ref. 39). These drugs may exert their effects on nigrostriatal/mesolimbic DA systems through multiple sites of action (75) including: 1) the blockade of postsynaptic DA receptors (fig. 2, site 1) with a subsequent increase in DA activity mediated via a neuronal feedback mechanism (32); and 2) the blockade of nerve terminal autoreceptors (fig. 2, site 2) (116). In addition, DA antagonists may increase DA cell activity through the blockade of soma/dendritic autoreceptors (fig. 2, site 3) (66), although this remains a matter of controversy (see Ref. 31). These drugs also increase the number of dopamine cells that are physiologically active. However, the mechanism responsible for this action is at present unclear (31).

To examine the effect of dopaminergic agents on *nerve terminal* DA autoreceptors (fig. 2, site 2) in vivo, a pharmacological method for eliminating dopaminergic impulse flow is often used. Administration of γ-hydroxybutyrate or its lactone precursor, γ-butyrolactone (GBL), reversibly blocks DA impulse flow, resulting in an increase in tyrosine hydroxylation and DA levels in nigrostriatal and mesolimbic DA systems. Identical neurochemical effects are seen after the use of mechanical lesioning (axotomy) or local anesthetic application to block the impulse flow of these DA systems (76, 116). It has been hypothesized that these changes result from a decreased DA autoreceptor activation secondary to the

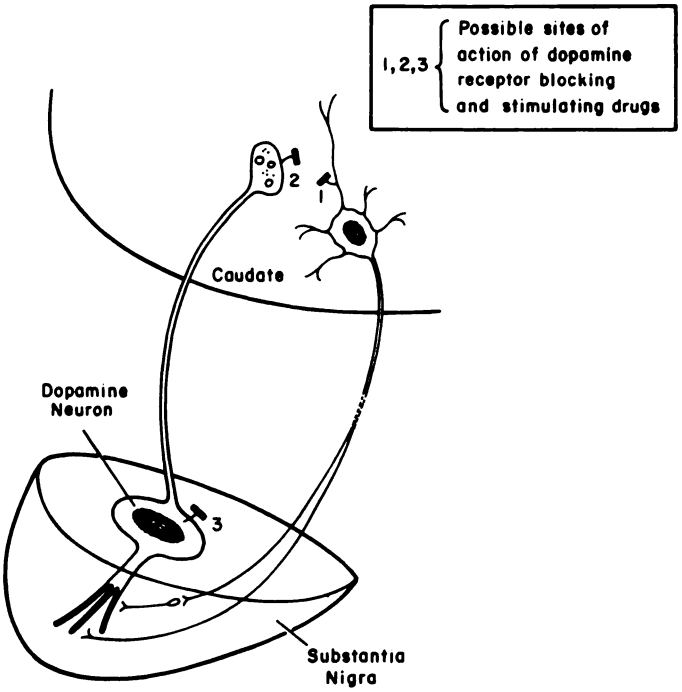

FIG. 2. Schematic diagram of nigrostriatal dopamine system illustrating some possible sites for drug interactions with dopamine receptors.

decreased amount of DA released into the synaptic cleft by neuronal discharge (77). Direct-acting DA agonists prevent this increase in DA synthesis through the stimulation of DA nerve terminal autoreceptors, since the influence of postsynaptic DA receptors and cell body DA autoreceptors on DA synthesis have been eliminated (154, 10; for a review, see Ref. 116). Single cell in vivo electrophysiological recording techniques coupled with microiontophoresis have been used to study the interaction of drugs with somatic/dendritic DA autoreceptors (fig. 2, site 3) which can modulate DA cell activity (for reviews, see Refs. 34, 31). The microiontophoretic application of DA onto the cell bodies and dendrites of nigrostriatal and mesolimbic DA neurons decreases the firing rate of these cells through the activation of autoreceptors. In addition, low (parenterally administered) doses of the DA agonist apomorphine selectively act at midbrain DA cell autoreceptors without stimulating postsynaptic DA receptors (134). The properties of DA autoreceptors are listed in table 2.

In contrast to the results obtained in the nigrostriatal and mesolimbic DA systems, the GBL- or axotomy-induced inhibition of mesocortical DA impulse flow does not elicit an increase in prefrontal cortical DA synthesis (12). The increase in DA levels that occurs in this system after the blockade of impulse flow is not due to an increased DA synthesis, and is not reversible with DA agonists (12–14, 118, 119, 38). These data strongly suggest that mesocortical DA neurons projecting to the prefrontal cortex lack functional terminal autoreceptors. Likewise, the firing rate of DA cells positively identified as innervating the prefrontal cortex (by antidromic activation techniques) is unaltered by drugs which activate cell body autoreceptors (11, 38). These data demonstrate that these mesocortical DA neurons lack somatic/dendritic (as well as terminal) autoreceptors (see section VII A).

B. Response to Acute and Chronic Dopamine Agonists and Dopamine Antagonists

1. ^{3}H-DA Synthesis. Early studies by Scatton et al. (127) investigated the effects of dopaminergic agents on ^{3}H-DA synthesis (from ^{3}H-tyrosine) in slices prepared from hemicortices (including frontal, cingulate, and parietal areas). In vivo pretreatment with the DA agonist apomorphine decreased ^{3}H-DA synthesis in brain slices. Pretreatment with the DA antagonist thioproperazine increased both striatal and cortical ^{3}H-DA synthesis; however, a 10-fold higher dose was required to obtain the same effect in the cortex as in the striatum. These investigators reported that tolerance to the activation of ^{3}H-DA synthesis by DA antagonists developed in the nigrostriatal but not mesolimbic and mesocortical DA systems following chronic DA antagonist administration (124, 125). A later analysis of the time course of activation following a single depot injection of the DA antagonist pipotiazine revealed the following: 1) in the striatum, DA synthesis was initially accelerated, followed by a marked and prolonged decrease in synthesis (i.e., the development of tolerance); 2) in olfactory tubercle/nucleus accumbens, synthesis of DA was accelerated for a longer time, followed by an inhibitory phase of lesser duration and extent than that seen in the striatum; and 3) in the cortex, only an increase in DA synthesis was observed at all times, i.e., no tolerance developed (123). Although these studies did not involve a very precisely defined area of cortex, they have provided the impetus for further research on the mesocortical DA system.

2. DA Metabolites. There are some discrepancies regarding the reported effects of the DA agonist apomor-

TABLE 2
Properties of dopamine autoreceptors.

1. Nerve terminal autoreceptors modulate the impulse-induced synthesis and release of DA.
2. Cell body/dendritic autoreceptors regulate the physiological activity (firing) of the DA cell.
3. In any particular DA system, autoreceptors are either present on or absent from both the nerve terminals and cell bodies/dendrites.
4. Within any given DA system, nerve terminal and cell body/dendritic autoreceptors appear to have similar or identical pharmacological properties.
5. Nerve terminal autoreceptors on the mesolimbic dopamine neuron appear to be more sensitive to dopamine agonists than autoreceptors on nigrostriatal nerve terminals.
6. Autoreceptors differ from postsynaptic DA receptors in their pharmacological responsiveness (e.g. the enhanced sensitivity of autoreceptors to DA agonists).
7. The responsiveness of autoreceptors is altered following chronic exposure to various pharmacological agents.

phine on frontal cortical DA metabolites but these are most likely related to dosage, timing, and dissection, although most data point to a similar conclusion. Westerink and Korf (158) reported that a very high dose (5 mg/kg) of apomorphine depressed frontal cortical and striatal free DOPAC to a small and equal extent, while lowering HVA to a greater extent. In a large frontal cortical dissection, Elchisak et al. (51) found that free DOPAC was depressed to a lesser extent by a relatively high dose (2 mg/g) of apomorphine than was striatal free DOPAC. While striatal conjugated DOPAC was also significantly decreased, frontal cortical conjugated DOPAC was unaltered by apomorphine. Recently, Bacopoulos and Roth (7) found that while apomorphine depressed total (conjugated plus free) DOPAC and HVA levels and reversed the haloperidol-induced increase in DA metabolites in the striatum and olfactory tubercle in a dose dependent manner, the effects of apomorphine on DOPAC and HVA in a large frontal cortical region were minimal or absent. Similarly, low (autoreceptor stimulating) doses (30 to 50 μg/kg) of apomorphine, which significantly decreased free HVA levels in the striatum and olfactory tubercle, did not alter HVA levels in a discrete prefrontal cortical region (14, 118, 119).

Likewise, some discrepancies have arisen regarding the effect of DA antagonists on frontal cortical DA metabolism. The acute administration of DA antagonists increases striatal levels of the DA metabolites DOPAC and HVA by approximately 250% to 400%. The responsiveness of the mesocortical DA system to DA antagonists has been harder to determine definitively. In studies involving rather large frontal cortical dissections (in some cases possibly contaminated with mesolimbic tissue), frontal cortical DOPAC increases on the order of approximately 150% to 200% have been reported (7, 95, 96). However, in other experiments involving more discrete frontal/prefrontal cortical dissections, much smaller responses, on the order of only 30% to 95% increases in DOPAC, have been found (158, 121, 160, 13, 14, 118, 119). The change in DA metabolite levels seen also apparently depends on the metabolite measured. HVA levels are usually increased in response to DA antagonist to a greater extent (ranging from 50% to 400% increases) than DOPAC levels, even in somewhat more defined frontal cortical regions (158, 121, 160, 2, 3). However, when analyses are carried out in a carefully defined area of prefrontal cortex (14, 160), a region receiving innervation from dopaminergic neurons devoid of autoreceptors, the HVA response to acute treatment with antipsychotic drugs is minimal and comparable to the response of DOPAC. An enhanced response of HVA relative to DOPAC is also seen in mesolimbic areas (158, 3), and may reflect a change in the fraction of DOPAC converted to HVA under conditions of increased DA activity (see section V F).

DA antagonists alter in vivo tyrosine hydroxylation (DOPA accumulation after DOPA decarboxylase inhibition) in a manner similar to DA metabolism. DOPA accumulation is accelerated by as much as 400% in the striatum by haloperidol. Since this increased DA synthesis is only partially attenuated by the pharmacological inhibition of DA impulse flow, it appears that the effect of DA antagonists on striatal DA synthesis is due both to an increase in nigrostriatal DA impulse flow and to the blockade of striatal terminal autoreceptors (12). In contrast, only about a 30% increase in DOPA accumulation is seen in prefrontal cortex after haloperidol challenge. This modest increase in DA synthesis is totally prevented by the blockade of mesocortical DA impulse flow, consistent with the proposal that the effect of haloperidol on the mesocortical DA system is solely due to alterations in DA cell firing and does not involve an interaction with nerve terminal DA autoreceptors (12).

Scatton (121) observed that chronic treatment with a moderate dose of the DA antagonist haloperidol (0.2 mg/kg) elicited striatal tolerance to DOPAC elevation within 11 days, and olfactory tubercle/nucleus accumbens tolerance by 40 days; the frontal cortex actually increased in responsiveness by this time (40 days). Similarly, it has been reported that 0.5 mg/kg of haloperidol induces a diminished responsiveness to acute haloperidol challenge in the striatum and olfactory tubercle, but not in the prefrontal cortex, after 28 days of treatment (13). The interesting observation was made that tolerance could be induced within 11 days in all brain areas studied if halperidol was administered in supermaximal doses (1 to 2 mg/kg haloperidol for mesolimbic area, 5 mg/kg for frontal cortex; 121). Similar results have been obtained with high doses of other neuroleptics (160, 2, 3).

The development of tolerance in the striatum (and often in mesolimbic areas), but a lack of tolerance (or even reverse tolerance) in the frontal cortex, in response to moderate doses of DA antagonists has also been demonstrated in other species, including primates (26, 27, 81, 4, 6, 117). A recent postmortem study (8) on human brain demonstrated that following chronic neuroleptic treatment, HVA levels were not significantly increased in the projection areas of the nigrostriatal and mesolimbic DA systems; this suggests the development of tolerance to the effects of DA antagonists in these systems. In contrast, several cortical areas, including the prefrontal cortex, contained elevated HVA levels, thereby suggesting that tolerance did not develop in these brain regions.

After chronic DA antagonist treatment schedules that result in the development of tolerance to subsequent DA antagonist challenge, DA autoreceptor supersensitivity has been directly demonstrated in subcortical DA systems (64, 104, 104a, 62a, 10, 13). Even after such treatment, no autoreceptor activity was demonstrable on the DA nerve terminals in the prefrontal cortex (13).

3. Relationship between DA Autoreceptors and the Response to Dopaminergic Drugs. The interaction of DA agonists and antagonists with DA autoreceptors appar-

ently plays a prominent role in determining the output of the various DA systems in response to acute and chronic treatment with these drugs, as summarized below. DA neurons that lack DA autoreceptors show little response (as in the case of the mesocortical system) (see section VI B 2) or no response (e.g., the tuberoinfundibular system) (42) to acute DA antagonist or agonist challenge. DA systems that possess autoreceptors (nigrostriatal, mesolimbic, and tuberohypophyseal systems) respond dramatically to the administration of DA agonists and antagonists (see section VI B 2, and Ref. 42). In the mesocortical system, no tolerance to DA antagonists develops following chronic treatment, while tolerance does develop in DA systems possessing autoreceptors (see section VI B 2). Further, the time course for the development of tolerance to DA antagonist challenge parallels the development of autoreceptor supersensitivity (section VI B 2). Finally, both the acute response to DA antagonists and agonists, and tolerance development occurs in the nigrostriatal system, even after brain lesions which eliminate striatal postsynaptic DA receptors, but which leave autoreceptors intact (63, 44, 45, 37, 20, 162, 163, 15, 122). These observations further strengthen the belief that drug interaction with autoreceptors, as opposed to postsynaptic receptors, play a major rather than a minor role in influencing dopamine metabolism.

In summary, the unique characteristics of the mesocortical DA neurons (compared to nigrostriatal/mesolimbic DA systems), such as the greatly diminished effect of DA antagonists and DA agonists (sections VI B 2, VII A), as well as the increased DA turnover (section V, F, G), the altered pattern and increased rate of cell firing (section VII A), and the selective activation by certain stresses (VI C), may be explained by the absence of nerve terminal/cell body DA autoreceptors (see table 3). However, the importance of other dissimilarities between the mesocortical and other DA systems, such as differences in feedback pathways and neuronal inputs (section VI D), has yet to be determined.

4. Protein Carboxylmethylation. Recent experiments have uncovered a possible link between DA autoreceptor activation and presynaptic protein carboxylmethylation (PCM) (119, 21). DA apomorphine, and the putative selective DA autoreceptor agonist 3-(3-hydroxyphenyl)-N-n-propyl-piperdine (3-PPP) all produce a stimulation of PCM in synaptosomes prepared from DA-rich terminal areas such as striatum and olfactory tubercle, but not in the hippocampus. This DA-sensitive PCM is blocked by DA antagonists and by the prior destruction of DA neurons and their autoreceptors. The lack of DA-sensitive PCM in the prefrontal cortex is consistent with other evidence for the absence of mesocortical DA autoreceptors.

5. ^{3}H-Ligand Binding. After chronic neuroleptic treatment, the binding of ^{3}H-spiperone in both rat and human striatum and mesolimbic areas increases significantly (increased B_{max}), while frontal cortical binding is unaltered (142, 2, 3, 114). However, as discussed above (section V E), only a small percentage of the ^{3}H-spiperone binding in the frontal cortex may be bound to DA receptors under the conditions used in these studies, making these results difficult to interpret.

TABLE 3

Unique characteristics of mesocortical dopamine neurons compared to other dopamine systems: possible consequences of the lack of nerve terminal and cell body/dendritic autoreceptors.

1. A higher DA turnover rate.
2. A higher rate of physiological activity (firing) and different pattern of activity (more bursting).
3. Greatly diminished responsiveness to DA agonists and antagonists.
4. Lack of tolerance development following chronic antipsychotic drug administration.
5. Resistance to the development of depolarization-induced inactivation following chronic treatment with antipsychotic drugs.
6. Selective activation by footshock stress.

C. Response to Footshock Stress

Thierry et al. (147) made the interesting observation that 20 min of footshock stress caused a large, selective increase in DA (but not NE) utilization in the frontal cortex of AMT pretreated rats. A smaller activation was seen in the nucleus accumbens, and no change was observed in olfactory tubercle or striatum. Other investigators have since used changes in DOPAC as an index of activation. Frontal cortical DOPAC is consistently elevated 60% to 100% by 20 min of stress (54, 84, 149, 24, 113), an effect being seen as early as 3 min (54, 24). The DOPAC/DA ratio has also been used in some of these stress experiments, but as discussed above (section V F), this measure may obscure some important information. Thus, in response to DOPAC-elevating stress, frontal cortical DA levels have been reported to decrease (84, 24), increase (113), or remain unaltered (54, 149). In addition, the time course for the reported decrease in frontal cortical DA does not follow the elevation of DOPAC (84, 24).

Cingulate cortex DOPAC-DA is also elevated (by 60%) after footshock stress, an effect due to both an increase in DOPAC and a decrease in DA (84). In agreement with the initial experiments of Thierry et al. (147), it has been shown that the DOPAC in the nucleus accumbens is elevated by approximately 35% after footshock stress (54, 149). Lavielle et al. (84) report no change in nucleus accumbens DOPAC/DA, but in this case both DOPAC and DA were elevated equally. Under the stress conditions used, no changes in DA turnover in the olfactory tubercle, septum, amygdala, medial basal hypothalamus, or striatum have been reported (147, 54, 84, 149, 113).

Tissari et al. (149) report that conditions that elevate frontal cortical DOPAC do not alter the V_{max} of frontal cortical TH or the K_m of TH for pteridine cofactor. However, under the same conditions, Reinhard et al. (113) have demonstrated an increase in tyrosine hydroxylation in vivo (DOPA accumulation). The selective na-

ture of the mesocortical DA activation is supported by the lack of effect of this footshock stress on frontal cortical 5-hydroxytryptophan accumulation, 5-HT, and 5-hydroxyindoleacetic acid levels, NE levels, and NE utilization (113). Benzodiazepines reverse the footshock-induced increase in frontal cortical DOPAC (54, 113), DOPAC/DA ratio (84), or DOPA accumulation (113). The stress-induced increase in DA was unaltered by benzodiazepine pretreatment (113).

Interestingly, indirect evidence has suggested that the substance P projection innervating the VTA may be activated by the application of footshocks that selectively activate the mesocortical DA system (92). In contrast, just as the nigrostriatal DA system is unaffected by the footshock stress used, the substance P projection to the SN is apparently not activated under these conditions (92). Recently, it has been demonstrated (11a) that preinfusion into the VTA of monoclonal antibodies directed against substance P prevents the footshock-induced increase in prefrontal cortical DOPAC, providing direct evidence for a role of substance P VTA afferents in mediating this response. Distinct afferents to different areas within the VTA and SN may also account for the selective responses of various DA systems to several brain lesions (see section VI D).

Similar effects of footshock stress on DA metabolism are seen in mice. Frontal cortical (but not striatal) DOPAC and HVA are increased by stress, with a time course similar to that reported in rats (71, 79). Frontal cortical DA levels have been reported to decrease (71) or increase (79). Interestingly, much more dramatic increases in frontal cortical DOPAC/DA are seen in Balb/C mice (high rate self-stimulators/high emotionality) than in C57 BL/C mice (low rate self-stimulators) (71). Surprisingly, when ^{3}H-DA synthesis is measured in slices in vitro following the in vivo stress, an increase in mouse frontal cortical (but not striatal) ^{3}H-DA synthesis is observed, without any change in ^{3}H-NE synthesis (49, 79). Since this stress-induced activation of ^{3}H-DA synthesis is blocked by dexamethasone pretreatment and mimicked by intracerebroventricular injection of ACTH, Dunn and coworkers have suggested that endogenous ACTH release may mediate the effect of stress on the frontal cortical DA system, although they point out that alternatively the injection of ACTH may itself act as a stressor (49, 41, 79). In a quite distinct paradigm—isolation induced fighting in mice—mesocortical (but not nigrostriatal) ^{3}H-DA uptake is reportedly significantly increased (68).

D. Response to Various Brain Lesions

Lisoprawski et al. (91) also reported that electrolytic lesions of the entire habenula resulted in an activation of the mesocortical DA system, as evidenced by an increase in the DOPAC/DA ratio. DOPAC/DA was unchanged in the nucleus accumbens, olfactory tubercle, and striatum. The authors concluded that some neurons originating or passing through the habenula exert a selective inhibitory influence on mesocortical DA neurons. These authors (70) also reported that electrolytic lesions of the dorsal raphe caused an increase in DOPAC/DA in the nucleus accumbens, and to some extent in the striatum, but not in the frontal cortex. In the nucleus accumbens, significant increases in both DOPAC and DA were seen. The authors suggested that the DA neurons projecting to the nucleus accumbens are under a selective tonic inhibition exerted by neurons originating from the dorsal raphe nucleus.

The studies of Phillipson (108, 109) have demonstrated that different VTA regions in some cases receive quite distinct neuronal inputs. For example, the majority of the VTA region receives afferents from the lateral habenula and the dorsal raphe. In contrast, the anterior midline area of the VTA, which may correspond to the site of origin of the mesocortical DA cells (see section IV), receives afferents from the medial habenula and medial raphe. The differential activation of various DA projections following the lesions of different VTA afferents might possibly be explained by the existence of these distinct VTA inputs. Before any firm conclusions along these lines can be reached, the arduous task of examining the localization of VTA afferents relative to that of the DA cells projecting to different terminal regions must be undertaken.

E. Response to Miscellaneous Drugs

Bowers and Salomonsson (27a) assessed the effects of a very low dose (0.05 μmole/kg) of *d*-lysergic acid diethylamide (LSD) on prefrontal cortical and striatal HVA. Acutely, LSD more than doubled prefrontal cortical HVA without changing striatal HVA. After chronic intermittent treatment, LSD challenge elicited a lesser, but still significant, increase in the prefrontal cortex. This latter treatment schedule also increased striatal HVA by approximately 30%. Brom-LSD had an acute effect on HVA in either prefrontal cortex or striatum.

The effects of intracerebroventricular injection of $ACTH_{1-24}$ and lysine vasopressin on subsequent ^{3}H-DA accumulation from ^{3}H-tyrosine in brain slices has been examined, as mentioned above (section VI C). Both $ACTH_{1-24}$ and lysine vasopressin are reported to selectively activate ^{3}H-DA accumulation in frontal cortex, while $ACTH_{1-24}$ does not alter (and lysine vasopressin actually inhibited) striatal ^{3}H-DA accumulation. Direct in vitro incubation with $ACTH_{1-24}$ or lysine vasopressin does not significantly alter ^{3}H-DA accumulation in frontal cortical or striatal slices.

Fadda et al. (53) have reported that the acute oral administration of ethanol raised striatal but not frontal cortical DOPAC. A concomitant increase in striatal DOPA accumulation was observed. DA levels were unaltered in both areas. Following chronic ethanol administration, however, frontal cortical (but not striatal) DA was elevated by 60%. DOPAC in both areas was unaf-

fected. Finally, following chronic treatment plus ethanol challenge, increased DOPAC and decreased DA were reported both in striatum and frontal cortex. Striatal DOPA accumulation was no longer accelerated.

Both acute and chronic morphine treatment cause increases in the firing rate of nigrostriatal DA neurons, and increases in striatal DOPAC and DOPA accumulation (105, 158). In contrast, acute morphine reportedly does not raise frontal cortical DOPAC levels (158). Conversely, it has been reported that morphine does not accelerate AMT-induced decline of striatal DA, but does enhance DA decline in a large area of forebrain cortex (99, 100).

Fadda et al. (55) also investigated the effects of lithium on dopaminergic systems. While acute lithium had no effect on DOPAC in any region, chronic lithium raised striatal and nucleus accumbens DOPAC by approximately 45%. Frontal cortical DOPAC remained unaltered. DA levels were constant in all regions after both acute and chronic treatment.

Waldmeier (153) has reported that the 5-HT receptor blocker mianserin attenuates the effect of subsequently administered haloperidol on frontal cortical DOPAC and HVA. Conversely, a 5-HT reuptake inhibitor (CGP 6085 A) potentiates the effect of low dose haloperidol on frontal cortical metabolites. Similar results were obtained in the striatum and mesolimbic area (nucleus accumbens/olfactory tubercle). The muscarinic agonist oxotremorine elevates striatal and frontal cortical DOPAC to a similar extent (158). The monoamine oxidase inhibitor pargyline dramatically decreases both striatal and cortical DOPAC (51) and HVA (14) and attenuates DA synthesis in both regions (12).

VII. Electrophysiological Characteristics and Pharmacological Responsiveness of the Mesocortical Dopamine Neurons and Dopamine-sensitive Cells in the Frontal Cortex

A. Mesocortical Dopamine Cells

The biochemistry of the different DA systems has been evaluated in detail, in part owing to the ease with which distinct DA projection areas can be isolated for subsequent analysis. A distinction between different subpopulations of DA cells at the level of the mesencephalon, where the DA cell bodies are essentially contiguous, is more difficult, and, in fact, this question has been addressed only very recently (11, 38). While the electrophysiology of SN DA neurons has been thoroughly studied (for reviews, see Refs. 34, 31), many fewer studies have been conducted on presumed VTA DA cells. Even less is known about the electrophysiology of *identified subpopulations* of VTA DA cells that innervate different terminal fields (in this case, the prefrontal cortex). Only these data will be briefly discussed here.

Deniau et al. (43) antidromically activated VTA cells from the frontal cortex (as well as the septum, nucleus accumbens, and striatum) which they divided into either fast conduction velocity (>2 m/sec) or slow conduction velocity (<1 m/sec) mesocortical cells. This second group exhibited a mean conduction velocity of 0.53 m/sec. The firing rate of this group of cells was not reported; the range of discharge rates for all mesocortical cells was 0 to 8 sec. Interestingly, less than 2% of all VTA slow conduction neurons (possible DA neurons) were found to project to more than one forebrain structure (branching); none of these cells projected to the frontal cortex. This is in good agreement with the anatomical evidence for a lack of collateralization of VTA cells (see section IV). These same investigators (144) found that these unidentified slow-conducting mesocortical cells were reduced in number following local 6-OHDA lesions, whereas the relative number of fast-conducting neurons was increased. No further electrophysiological or pharmacological characterization of these cells was reported.

Wang published a series of papers (155–157) on VTA DA neurons, the majority of which were antidromically activated by electrical stimulation of the nucleus accumbens. However, a few VTA DA cells ($N = 11$) could be antidromically activated from a large area of the frontal and anterior cingulate cortices (157). These DA cells resembled other DA cells in terms of firing pattern, discharge rate (2.87 ± 0.82/sec), spike duration (3.2 ± 0.4 msec), and conduction velocity (0.45 m/sec). Recently, VTA DA cells antidromically activated from the prefrontal cortex have been studied in some detail by Chiodo, Bunney, and coworkers (11, 38). These cells are localized to some extent to the medial VTA, in agreement with most anatomical studies (see section IV). The conduction velocity (0.5 m/sec) and long duration action potential (>2.5 msec) characteristic of DA neurons are seen with these identified mesocortical DA cells. One striking difference, however, is the much faster firing rate of mesocortical DA neurons (9.3 ± 0.6/sec) projecting to the prefrontal cortex as compared to VTA DA cells innervating the cingulate and piriform cortices (5.9 ± 0.5/sec and 4.3 ± 0.3/sec, respectively) and SN DA cells innervating the striatum (3.1 ± 0.5/sec). The mesocortical cells projecting to the prefrontal and cingulate cortices also exhibit significantly more bursting than other DA cells (Table 1), although the physiological significance of this difference is unknown at present.

DA cells identified as projecting to the prefrontal cortex are readily inhibited by the indirect-acting DA agonist *d*-amphetamine (157, 11, 38). This inhibition is reversed by the administration of haloperidol (38). In contrast, the mesocortical cells are not inhibited by low (autoreceptor-selective) doses of apomorphine or the putative selective DA autoreceptor agonist 3-PPP (11, 38). Likewise the firing rate of these neurons is unaffected by the microiontophoretic application of DA (11, 38). These neurons are thus strikingly different in their responsiveness to DA agonists in comparison to other VTA

and SN DA cells. These data provide direct electrophysiological evidence that mesocortical DA cells innervating the prefrontal cortex lack soma/dendritic autoreceptors (see section VI A). These identified mesocortical cells are also resistant to the induction of depolarization inactivation (which is seen electrophysiologically with other A9 and A10 DA cells) after chronic neuroleptic treatment (38a). The mechanisms involved in this phenomenon are currently under investigation.

B. *Dopamine-sensitive prefrontal cortical cells*

Only a few studies have assessed the effects of DA drugs on the physiological activity of cells in the rat frontal cortex. Mora et al. (102) simultaneously recorded the activity of cells in the prefrontal cortex and an area generally considered not to receive a prominent DA innervation (somatosensory cortex or hippocampus). Of the prefrontal cortical cells tested, 42% were inhibited by intravenous apomorphine, while the activity of the control cells was not decreased. *d*-Amphetamine and L-DOPA (when given with a peripheral DOPA decarboxylase inhibitor) also inhibited prefrontal cortical cells. No attempt was made to correlate the response to DA agonists with the cortical layer of the cell tested. Anatomical studies have shown that, while the noradrenergic innervation to the prefrontal cortex is relatively uniform, the DA innervation is localized primarily to layers V and VI (see section V A).

Bunney and Aghajanian (33) established a clear correspondence between the response of a prefrontal cortical cell to DA or NE and the localization (cortical layer) of that cell. Cells in the more superficial layers (layers II and III) were depressed by iontophoretically applied NE but were minimally responsive to DA, whereas cells in layers V and VI responded primarily to iontophoretically applied DA and not NE. The NE reuptake blocker desmethylimipramine, when microiontophoretically applied, potentiated the NE-induced inhibition in layers II and III, but not the DA-induced depression in deeper layers. Conversely, the iontophoretic application of the DA reuptake blocker benztropine potentiated the DA- but not NE-induced depression. The iontophoretic application of the DA antagonist trifluoperazine blocked the DA depression seen in layers V and VI, but not the NE-induced inhibition seen in layers II and III.

Likewise, few studies have been conducted on the electrophysiological responsiveness of cells in DA terminal areas after chronic drug treatment. In the caudate nucleus of the rat, a supersensitive response to iontophoretic DA is evident during and/or after chronic neuroleptic treatment (165, 133). It has been reported that the responsiveness of cat frontal cortical neurons is unaltered after chronic neuroleptic treatment; however, in this study, the responsiveness of cat striatal neurons was also unchanged (22). The methodological differences among these studies have been discussed at length (133).

VIII. Involvement of the Mesocortical Dopamine System in Various Behaviors

A. *Intracranial Self-Stimulation*

It has been hypothesized that the mesocortical, mesolimbic, and/or nigrostriatal DA systems may be involved in the mediation of intracranial self-stimulation. While the role of the various DA systems in self-stimulation has been intensively investigated, an in depth discussion of this research area is beyond the scope of this review. It does not appear, however, that either the mesocortical or the other DA projections are critical in maintaining self-stimulation from various brain regions, although they may serve a modulatory role (for reviews, see Refs. 59, 161). It is of interest that following a 10-min session of bilateral intracranial self-stimulation of the VTA region, frontal cortical DOPAC was increased by approximately 90% and DA depleted by almost 30%, while a smaller increase in nucleus accumbens DOPAC and no change in nucleus accumbens DA was observed (132). This is a similar response to that seen following a period of footshock stress (see section VI C).

B. *Stress*

It is now well documented that the mesocortical DA system is activated by footshock stresses which do not activate most other brain catecholamine systems. The biochemistry and pharmacology of this response are discussed in section VI C. More severe or chronic stresses can alter noradrenergic, serotonergic, and dopaminergic turnover in several brain regions (e.g., Refs. 145, 83).

C. *Cognitive Function/Locomotor Activity*

In a delayed response or delayed alternation paradigm, the appropriate behavioral response is determined by a previously presented stimulus. During the period that separates the two stimuli, a slow surface negative potential (also called the contingent negative variation), associated with a state of anticipation, can be recorded from the prefrontal cortical region in primates and man. Electrophysiological recording of the activity of prefrontal cortical neurons reveals that most of these cells are activated during some phase of this delay period (for reviews, see Refs. 60, 61). Likewise, local cerebral glucose utilization (as determined with ^{14}C-2-deoxyglucose) is selectively increased in the prefrontal cortex (but not other brain regions of monkeys trained in a delayed response task, as compared to untrained animals (30).

Lesions of the rat VTA induce a permanent syndrome characterized by "locomotor hyperactivity, hyperreactivity, difficulties in suppressing previously learned responses or in tolerating frustrating situations, disappearance of freezing reaction, disturbances of organized behaviors and hypoemotivity" (85, 62, 140). Likewise, food search strategies are impaired following such lesions (106). There is a very good correlation between the

increase in locomotor activity seen and the decrease in frontal cortical DA resulting from VTA lesions (140). Similarly, after 6-OHDA lesions in the VTA, which greatly reduce frontal cortical DA, more collateral or irrelevant behaviors and an enhanced distractibility or responsiveness to environmental stimuli are seen (131). Rats with these lesions exhibit a severe impairment in the retention of delayed alteration (131). Local injection of 6-OHDA into the prefrontal cortex of rats pretreated with desipramine (to protect the noradrenergic projections), which causes a dramatic local depletion of DA, elicits the same hyperactivity (35, 111). Interestingly, these authors reported that several biochemical measures of the activity of the subcortical DA systems are increased following these lesions (35, 110, 111). Similar local 6-OHDA/desipramine lesions in the prefrontal cortex have been performed in monkeys (29). An impairment in spatial delayed alternation performance nearly as severe as that induced by surgical ablation of the prefrontal cortex was reported. However, 6-OHDA-induced deficit can be pharmacologically reversed with dopamine agonists (29).

D. Prefrontal Cortical/Subcortical Dopamine Interaction: A Speculative Synthesis

It has been known for many years that lesions of the frontal cortex alter the effects of dopaminergic drugs on behaviors thought to be mediated by subcortical DA systems (see Ref. 128 and references therein). For instance, frontal cortical lesions enhance DA-agonist (*d*-amphetamine or apomorphine)-induced stereotypy, locomotor activity, and circling; conversely these lesions attentuate DA-antagonist-induced catalepsy (128). Interestingly, a recent report suggests that large frontal cortical ablations induce oral dyskinesia and greatly potentiate haloperidol-induced dyskinesia (67). These data are consistent with the possibility of a lesion induced increase in ipsilateral subcortical DA transmission. However, basal and drug-induced changes in striatal DOPAC levels are reportedly unaltered following frontal cortical lesions (122, 128). Pycock and Carter and co-workers (110, 111, 35) have reported that selective prefrontal cortical DA lesions also apparently enhance subcortical DA transmission, since these more selective lesions also increase DA-agonist-induced behaviors. In addition, after prefrontal cortical DA lesions, biochemical evidence of increased subcortical DA turnover was also obtained.

An increase in the activity of subcortical DA systems in response to lesioning of either the entire frontal cortex or the DA innervation to the prefrontal cortex may thus account for the increased locomotor activity generally seen following such lesions, as suggested by Pycock and coworkers. Consistent with this suggestion, behavioral manipulations (e.g. isolation) which decrease prefrontal cortical DOPAC/DA result in a concurrent increase in subcortical DOPAC/DA (24). In addition, the placement of different mouse strains in an open field apparatus has an inverse effect on prefrontal cortical DOPAC/DA and locomotor activity, i.e. the smaller the increase in prefrontal cortical DOPAC/DA evoked, the greater the increase in locomotor activity (137).

As mentioned above, in many species lesions of the prefrontal cortex induce functional deficits including 1) dramatic deficits on certain "cognitive" tasks, 2) a difficulty in suppressing attention to irrelevant internal and external stimuli, and (a possibly related) motor hyperactivity, and 3) a diminution in affective and social behavior (see Refs. 60, 61, 106). These changes parallel most of the predominant symptoms of schizophrenia, including a disruption of higher cognitive functions, difficulty of attention, increased and stereotypic motor behavior, and disturbances in affective response and withdrawal from interaction with other people (see 120, 106). These data may seem at odds, since the effects of prefrontal cortical lesions are often mimicked by selective *reductions* in prefrontal cortical DA, while schizophrenia has been thought to be somehow linked to a relative *excess* of cortical or limbic DA influence. However, the animal experiments on prefrontal cortical/subcortical DA interaction could help to reconcile these data. If schizophrenia involved some disturbance of frontal lobe function, as has been previously suggested, the subcortical or other cortical DA systems normally modulated by the prefrontal cortex might in turn be activated. The increased activity of these other DA systems could account for some of the schizophrenic symptomology observed, and the efficacy of antipsychotic agents could be due to DA blockade at these sites. Yet the cognitive/attentional (prefrontal cortical) deficits might be expected to persist even in patients who otherwise show clinical improvement. In fact, such deficits have been reported even in schizophrenics on antipsychotic drug treatment or in remission (see Ref. 164 and references therein, 106).

IX. Summary

The current information on the pharmacology and function of the DA innervation to the prefrontal cortex is a synthesis of data from several initially distinct areas of research. Some possible functions of the mesocortical DA system are suggested from the extensive studies conducted on the role of the prefrontal cortex in behavior, and also from the data on prefrontal cortical modulation of the output of subcortical DA systems. Meanwhile, anatomical, behavioral, biochemical, and electrophysiological studies on mesocortical DA neurons have largely resulted from interest in determining the site(s) and mechanism(s) of action of various psychotropic drugs, and particularly the antipsychotic drugs (DA antagonists). An interrelated field of study has investigated the functional role of DA autoreceptors.

The mesocortical DA system possesses many unique characteristics compared to the nigrostriatal/mesolimbic DA systems, including 1) a higher DA turnover rate, 2)

a higher rate and different pattern of neuronal discharge, 3) a greatly diminished responsiveness to DA agonists and antagonists, 4) a lack of tolerance to the effect of chronically administered DA antagonists, and 5) a selective activation by footshock stress. These characteristics may be due to the fact that the DA cells projecting to the prefrontal cortex lack DA autoreceptors, an important site for the physiological and pharmacological modulation of subcortical DA systems. This contention is further supported by recent studies on two distinct DA systems innervating, respectively, the anterior cingulate and piriform cortices: the former system, which lacks DA autoreceptors, responds much like the prefrontal cortical DA system; the latter system, which possesses functional DA autoreceptors, manifests a pharmacological responsiveness similar to the nigrostriatal/mesolimbic DA systems (11, 14, 118, 119, 38).

Autoreceptors may be an important target for future rational drug design. For example, DA agonists more selective for DA autoreceptors (65, 72) may be useful agents in the treatment of schizophrenia. If, however, these drugs prove ineffective in schizophrenic patients, it might help to explain the equivocal results obtained to date in the treatment of schizophrenia with low (autoreceptor-specific) doses of less selective DA agonists (for a review, see Ref. 97). A lack of clinical efficacy of DA autoreceptor agonists might also suggest that if a DA system is indirectly involved in schizophrenia the site of therapeutic action of antipsychotic drugs is a DA system (such as that innervating the prefrontal cortex) that lacks autoreceptors.

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