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Prefrontal cortical dopamine systems and the elaboration of functional corticostriatal circuits: implications for schizophrenia and Parkinson's disease

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Summary. The dopaminergic innervation of the prefrontal cortex is able to transsynaptically regulate the activity of subcortical dopamine innervations. Disruption of the prefrontal cortical DA innervation results in the enhanced biochemical responsiveness of the dopamine innervation of the nucleus accumbens. We present recent data indicating that distinct prefrontal cortical dopamine innervations can be functionally dissociated on the basis of responsiveness to stress. The ventral striatal projection target (nucleus accumbens shell) of the prefrontal cortical region that is stress sensitive is also responsive to stress. In this manner interconnected cortico-striato-pallido-mesencephalic loops can be defined on the basis of the biochemical responsive of local dopamine systems to stress and on the basis of responsiveness to antipsychotic drugs. These data suggest the functional derangement of a distinct corticofugal loops in schizophrenia and in certain aspects of Parkinson's disease.

Keywords: Prefrontal cortex, nucleus accumbens, striatum, schizophrenia, dopamine, stress, antipsychotic drugs.

> *"With few exceptions, it seems clear that psychic functions are correlated with the presence of pyramidal (psychic) cells..."*
>
> Santiago Ramon y Cajal (1906)

Ramon y Cajal's belief that cortical pyramidal neurons formed the basis for mental as well as motor processes has recently been overshadowed by an increasing awareness of the complexity and richness of behavior subserved by subcortical structures. However, Cajal's conclusions were drawn from his remarkable neuroanatomical studies; knowledge of the regulatory mechanisms governing the function of corticofugal pyramidal neurons has grown consid-

erably since the era of Cajal. If one considers cortical pyramidal neurons as part of distinct functional circuits, with discretely organized regulatory afferents and precisely ordered efferents, Cajal's proposal remains as cogent today as it was at the beginning of the century.

Among the most intensively studied of the corticofugal systems has been the corticostriatal system. This is attributable not only to the fact that the entire cerebral cortex projects topographically onto the striatal complex (Webster, 1961; Nauta, 1964; Oka, 1980; Divac, 1984; McGeorge and Faull, 1989), but also to the potential clinical significance that dysfunction of these projections may hold. Recent hypotheses of the pathophysiology of schizophrenia have suggested a derangement in certain cortico-striatal circuits (Weinberger, 1987; Goldstein and Deutch, 1992); still more recently, there has been a renewed interest in the importance of cortical mechanisms in Parkinson's disease. Thus, studies of two disorders characterized by significant, if not primary, involvement of mesotelencephalic dopamine (DA) neurons are increasingly being focused on delineation of functional alterations in corticostriatal circuits.

The cortical site that has received the most scrutiny in preclinical studies relating to schizophrenia has been the prefrontal cortex. In primate species the prefrontal cortex has been rather simply defined as the cortex anterior to the central sulcus. This cortical expanse can, of course, be further divided (Akert, 1964; Brodman, 1909; Walker, 1940). Today, we typically refer to the rostral portion of this cortical area that has a well-developed granular cell layer IV as the prefrontal cortex; other portions of the rostral cortex include diverse areas such as the premotor and supplementary motor cortices and the frontal eye fields.

The region of the rat brain generally designated the medial prefrontal cortex comprises several cytoarchitectonically distinct regions, including the medial precentral ("shoulder") cortex, the anterior cingulate (area 24 b) cortex, and the prelimbic (area 32) and infralimbic (area 25) cortices. All of these regions except for the infralimbic cortex receive afferents from the mediodorsal thalamic nucleus (Goldman-Rakic and Porrino, 1985; Groenewegen, 1988; Krettek and Price, 1977 a; Leonard, 1969); in addition, the mediodorsal thalamus projection defines the suprarhinal prefrontal cortex, which is situated dorsal to the rhinal sulcus. All of these areas also receive dopaminergic afferents from the DA neurons in the ventromedial mesencephalon (Divac et al., 1978; Lindvall and Bjorklund, 1987; van Eden et al., 1987). In addition, the basolateral amygdala projects to these cortical sites (Divac et al., 1978; Krettek and Price, 1977 b). However, the delineation of the cortical sites in the rodent that are homologous to the primate PFC is complicated by the fact that the mediodorsal thalamic projection field in the rat appears to define a number of distinct cytoarchitectonic regions that have different functional attributes (Passingham et al., 1988) as well as different connections with subcortical sites. Thus, the establishment of homologous "PFC" structures between the rodent and primate can be made on the basis of hodological, cytoarchitectonic, or functional criteria; each of

these approaches yields different results. Given the functional and cytoarchitectonic distinctions between the different parts of the rodent medial PFC, as well as the suprarhinal PFC, it is unreasonable to assume that there will be any satisfactory resolution to the dilemma of assignment of homology if one adheres to the medial PFC as a solitary construct in the rat. It is more appropriate to conceptualize the rodent medial PFC as an evolutionary step to the more elaborated primate cortex: the different regions of the medial PFC of the rodent have become spatially distinct in primate species.

Current ideas concerning the nature of information processing in the basal ganglia have focused on the presence of distinct parallel cortico-striato-thalamic circuits that emanate from different cortical regions (Alexander and Crutcher, 1990). Thus, physiological data from primate studies suggest the presence of functionally specific and anatomically segregated corticostriatal circuits that subserve different aspects of motoric function (Alexander et al., 1986). Recent studies of corticostriatal relationships in the rat have led to a similar conclusion (Groenewegen et al., 1990). Our studies of the rodent PFC suggest that functionally distinct circuits may also be defined on the basis of transmitters, such as dopamine, that are involved.

Anatomical heterogeneity of prefrontal cortical DA innervations

The dopamine innervation of the medial PFC of the rodent, while usually thought of as a functionally and anatomically homogenous system, exhibits both anatomical and functional heterogeneity. This is not surprising in light of the fact that the different regions of the rodent PFC are probably homologous to different cortical areas in primate species; the primate cortical regions have markedly different patterns of DA innervation (Lewis, 1992; Lewis et al., 1987; Levitt et al., 1984). It has been convenient to characterize the PFC DA system as a unitary system because of the difficulties in pharmacologically and functionally dissociating the different DA neurons that contribute to the prefrontal cortical DA innervation of the rat. However, anatomical methodologies have pointed to ontogenetic differences in the DA innervations of the rodent PFC, and suggested that the DA innervation of the PFC may be functionally heterogeneous as well.

Berger pioneered ontogenetic studies of the PFC DA innervation (see Berger et al.,1991). Using antibodies that recognize catecholamine biosynthetic enzymes, Berger and colleagues defined the presence of at least two different DA systems embedded in the PFC of the rat. One DA system is found in the deep layers of the PFC, and appears during the prenatal period (Verney et al., 1982), while a superficial layer DA innervation subsequently appears during the first several postnatal weeks (Berger et al., 1985 a). The superficial system is most dense in the supragenual anterior cingulate cortex, whereas the deep layer innervation is most prominent in the pregenual medial PFC. However, since the dorsal anterior cingulate cortex (area 24 b) also appears in the pregenual

(PFC) cortex, it follows that there are both laminar and regional specificities in the medial PFC.

More recent studies using antibodies generated against DA conjugates have largely confirmed the data of Berger and colleagues, and further elaborated the precise ontogenetic pattern of the DA innervation (Kahlsbeek et al., 1988). These studies clearly suggest that there are distinct differences in the development of the pregenual and supragenual cortical DA innervations, and that within the pregenual medial cortex (the PFC), the anterior cingulate compartment differs. The differences between the supragenual and pregenual cortices is also apparent in terms of axonal morphology. The DA fibers situated in the rostral area are typically smooth, whereas the supragenual fibers are markedly varicose (Lindvall and Bjorklund, 1987; Berger et al., 1985 a, b; van Eden et al., 1987).

Berger et al. (1991) have also suggested that the two systems differ with respect to the source of the DA afferents. Thus, they suggest that the deep layer (class 1) DA afferents arise from the medial aspects of the A 10 cell group, whereas the DA neurons that contribute to the superficial layers (class 2) DA system are more laterally situated, extending into the medial aspects of the A 9 (substantia nigra) cell group. We are currently investigating the precise topography of DA afferents to different cytoarchitectonic regions of the PFC.

Anatomical data indicating the presence of at least two cortical DA innervations that differ on the basis of ontogenetic considerations led Berger and associates (Berger et al., 1991; Gaspar et al., 1991) to speculate that these systems could also be differentiated on functional grounds. There are functional differences between different DA neurons innervating the PFC in regulatory controls, including the presence of impulse-modulating autoreceptors (Shepard and German, 1984). We have recently examined differences in susceptibility of mesoprefrontal cortical DA neurons to stress, and found that the DA innervations of the PFC can be functionally dissociated.

Biochemical heterogeneity of prefrontal cortical DA innervations

The DA neurons that innervate the PFC are particularly sensitive to stress (Deutch et al., 1985; Deutch and Roth, 1990; Thierry et al., 1976). Thus, mild footshock stress or conditioned fear increase DA metabolism in the PFC but not in mesolimbic areas such as the nucleus accumbens (NAS); extending the duration of stress exposure or increasing the stress intensity results in the biochemical activation of subcortical and allocortical DA systems (Deutch and Roth, 1990; Roth et al., 1988). We exploited the stress-induced activation of the mesotelencephalic DA neurons as a means through which to examine the possible functional segregation of distinct DA systems embedded in the PFC.

We originally examined the response of different midbrain DA neurons to stress using expression of the immediate early gene *c-fos* as a putative marker for those neurons that are metabolically activated by stress (Deutch et al., 1991 a). We observed that 30 min restraint stress, which increased DA metabolism in the entire PFC, and in the nucleus accumbens (NAS) and dorsal

striatum, also increased the number of DA neurons expressing Fos (the protein product of *c-fos*) in the ventral tegmental area (VTA; A 10 DA cell group), but not in the substantia nigra (A 9 cell group) or retrorubral field (A 8 cell group). The latter two groups of DA neurons innervate striatal and mesolimbic, but not prefrontal cortical, sites (Deutch et al., 1988; Lindvall and Bjorklund, 1987). The presence of Fos protein in VTA, but not nigral or retrorubral field, DA neurons therefore suggested that the A 10 neurons expressing Fos in response to stress might be DA neurons projecting to the PFC, rather than mesolimbic sites such as the nucleus accumbens. The precise topography of the A 10 DA neurons expressing Fos was consistent with this speculation: neurons in the dorsolateral parabrachial and caudal linear subnuclei of the VTA expressed Fos. These subnuclei of the VTA contain the DA neurons that provide much of the DA innervation of the PFC, but do not provide a large input to the ventral or dorsal striatum. Retrograde tracer studies confirmed that the A 10 neurons expressing Fos protein in response to stress were mesoprefrontal cortical DA neurons, and not DA neurons that project to the NAS (Deutch et al., 1991 a). Moreover, the retrograde tracing studies revealed that two populations of mesoprefrontal cortical DA neurons could be distinguished: those that express Fos in response to stress, and those that do not.

The Fos data were therefore consistent with the concept that functionally distinct DA systems could be distinguished in the medical PFC of the rat. However, it was not clear if these two populations of mesoprefrontal cortical DA neurons corresponded to the different DA innervations of the PFC defined by Berger and associates. Different regions of the PFC clearly have different concentrations of DA and metabolites (Slopsema et al., 1982). These data suggest that one approach to examine the possible functional heterogeneity of PFC DA axons in response to stress was to assess if different cytoarchitectonically-defined parts of the PFC respond biochemically in the same or different ways to stress. Mild footshock stress, at an empirically-determined threshold intensity for the stress-induced metabolic activation of the entire PFC, resulted in a marked enhancement of DA metabolism in certain areas of the PFC, while other regions within the PFC did not respond at all (Deutch, 1991). Thus, DA axons in the deep layers of the PFC increased metabolism in response to stress, whereas the superficial layer DA innervation did not; these data therefore confirmed the speculations of Berger and colleagues (Berger et al., 1984, 1991). Moreover, the infralimbic cortex (area 25) responded to stress, but the caudal prelimbic (area 32) did not, nor did the shoulder cortex/dorsal anterior cingulate (area 24 b). The mapping of response characteristics onto the different cytoarchitectonic fields of the medial PFC is quite congruent with our previous speculations concerning the functional attributes of these different cortical regions as deduced from their projection fields (Sesack et al., 1989). It should be noted, however, that we used a very mild stressor in these studies, and as such it is possible (if not likely) that more severe stressors would activate DA axons in those areas of the PFC not responsive to very mild stress.

Cortical dopaminergic regulation of subcortical dopamine systems

Dopamine axons innervating the PFC form symmetric synapses with deep layer pyramidal neurons (Goldman-Rakic et al., 1989; Sequela et al., 1988), suggesting the DA inhibits corticofugal neurons. These anatomical data are consistent with physiological data indicating that iontophoretic application of DA inhibits pyramidal neurons that project to subcortical targets (Sesack and Bunney, 1989), as does stimulation of the VTA, the source of the DA innervation to the PFC (Peterson et al., 1989; Thierry et al., 1986, 1990). The direct DA inhibition of cortical pyramidal neurons appears to act through a pharmacologically atypical D_2 DA receptor (Sesack and Bunney, 1989; Thierry et al., 1986). In addition to the direct inhibition of cortical projection neurons by DA, the monoamine may inhibit pyramidal cells indirectly, by augmenting GABA release from interneurons (Retaux et al., 1991).

The vast majority of corticofugal neurons utilize an excitatory amino acid, such as glutamate, aspartate, or sulfur-containing amino acids, as a transmitter (Carter, 1982; Christie et al., 1985; Kim et al., 1977; McGeer et al., 1977; Spencer, 1976). A large body of data suggests that excitatory amino acids in the striatum may augment DA release and metabolism (Barbieto et al., 1990; Cheramy et al., 1984; Chesselet, 1984; Giorguieff et al., 1977; Jhamandas and Marien, 1987; for a review of the issues surrounding the release of DA by excitatory amino acids, see Deutch, 1992). This action appears to be mediated in large part via a kainate/quisqualate type EAA receptor that undergoes rapid desensitization (Barbieto et al., 1990; Mayer and Vicklicky, 1989), although a NMDA-type receptor localized to interneurons may also play a role.

The removal of prefrontal cortical DA inhibition would therefore be expected to augment DA release and metabolism in subcortical sites such as the nucleus accumbens and striatum by increasing release of glutamate from disinhibited corticofugal neurons. Pycock, Carter, and associates (Carter and Pycock, 1980; Pycock et al., 1980 a, b) reported increases in various parameters of subcortical dopaminergic function following focal 6-hydroxydopamine lesions of the PFC. Consistent with these observations were a series of studies examining dopaminergic dynamics in subcortical regions using in vivo electrochemical monitoring of DOPAC following acute manipulations (Louilot et al., 1987, 1989). However, while some investigators replicated certain findings of Pycock and associates, other investigators have been unable to reproduce the changes in subcortical sites (Joyce et al., 1983; Oades et al., 1986; for review, see Deutch, 1992).

In attempts to replicate the original studies of Pycock, Carter, and colleagues, we were unable to observe any effects of cortical DA depletion on basal subcortical DA function (Deutch, 1992; Deutch et al., 1990 a; Rosin et al., 1992). However, we did observe that PFC DA lesions augment the responsiveness of the mesolimbic DA innervation to both environmental (stress) and pharmacological (haloperidol) challenges (Deutch, 1992; Deutch et al., 1990 a; Rosin

et al., 1992). Thus, focal cortical DA depletion alters subcortical dopaminergic dynamics but not basal DA tone (see Deutch, 1992). These data suggested that the critical difference between those studies that replicated the findings of Pycock and associates and those that did not was inadvertent environmental changes in the former group of studies.

One of the puzzling aspects of our studies on the effects of prefrontal cortical DA deafferentation on subcortical DA function was the fact that we observed changes only in the nucleus accumbens, and not in the dorsal striatum (Deutch et al., 1990a; Rosin et al., 1992). Most studies of glutamate-dopamine interactions have focused on the dorsal striatum, and only recently have such interactions been studied in the ventral striatum (including the nucleus accumbens). It is therefore of interest that recent studies examining the interactions of the transmitters in the NAS have noted that the doses of excitatory amino acids required to evoke DA release in the ventral striatum are considerably lower than those required in the dorsal striatum (Imperato et al., 1991; Payson and Donzanti, 1990; Youngren et al., 1992). This regionally-specific difference may in part explain our observations that only the ventral striatal DA innervation is impacted by PFC DA depletions.

Another possible factor that may contribute to the restricted effects of PFC DA depletions on the NAS, rather than the dorsal striatum, is the anatomical organization of projections from the PFC onto the striatal complex. All parts of the cortex project onto the striatum (McGeorge and Faull, 1989); the projections from the PFC to the striatal complex are topographically organized by within and across the different cytoarchitectonic fields that comprise the PFC (Sesack et al., 1989). Thus, PFC projections to the nucleus accumbens and those to the more dorsally-situated medial caudatoputamen originate from different parts of the PFC (Sesack et al., 1989). Even within the ventral striatum there appears to be a topographically-ordered origin of projections from the PFC onto different parts of the NAS (Beckstead, 1979; Berendse et al., 1991; Brog et al., 1991; Sesack et al., 1989). For example, projections from the dorsal prelimbic cortex (area 32) innervate a region of the NAS medial to the temporal limb of the anterior commissure, the so-called accumbal core. In contrast, projections from PFC neurons situated more ventrally, in the infralimbic cortex, innervated a more medial domain within the NAS that surrounds the core and has been designated the shell. These observations suggest that projections from areas of the PFC containing DA axons that respond to stress (e.g., the infralimbic cortex) innervate different aspects of the NAS than PFC areas that do not respond to stress.

The nucleus accumbens core and shell

Zahm and Heimer and collaborators have recently described a compartmental organization of the NAS that is reflected in the afferent and efferent projections of the NAS. Zaborszky et al. (1985) originally noted a distinct difference in the density of the cholecystokinin innervation of the medial and more lateral NAS;

they designated these areas the shell and core, respectively. Retrospective examination of other histochemical markers as well as new studies confirmed that "core" and "shell" regions of the NAS could be defined on the basis of histochemical markers (see Zahm and Brog, 1992). Subsequent anterograde tracer studies revealed that the NAS core projects to dorsolateral aspects of the ventral pallidum, whereas the NAS_{shell} innervates the ventromedial parts of the ventral pallidum (Heimer et al., 1991; Zahm and Heimer, 1988, 1990). Downstream projections maintain this segregation: the NAS_{core} contributes to areas associated with basal ganglia motor outflow (entopeduncular nucleus, subthalamic nucleus, and substantia nigra) whereas the NAS_{shell} recipient zone of the ventral pallidum projects to areas more closely allied with the reticular activating core, i.e., the lateral hypothalamus and ventral tegmental area. Retrograde tracer studies have continued to elaborate upon and clarify these relationships (Brog et al., 1991). These data suggest the presence of distinct circuits in which the NAS core and shell are interspersed between certain PFC fields and more caudal tragets.

We recently used biochemical methods to determine if the DA innervations of the NAS core and shell can be functionally dissociated (Deutch and Cameron, 1992). The shell has higher concentrations of both DA and serotonin than does the core; concentrations of the acidic metabolites of DA and serotonin are equal in the two NAS sectors. Examination of the rate of decline of DA following synthesis inhibition revealed that the turnover rates of DA in the core and shell are the same. We then examined the responsiveness of the accumbal core and shell DA innervations to stress. Mild stress resulted in a selective augmentation of DA metabolism in the NAS_{shell}, but not the NAS_{core}. The effects of two different antipsychotic drugs (APDs) were also examined. Haloperidol is a typical APD that has been reported to alter various parameters of DA function to a greater degree in the dorsal striatum than in the NAS (Bartholini, 1977; Zivkovic, 1977); acute haloperidol challenge increased DA metabolism to a significantly greater degree in the NAS_{core} than NAS_{shell}. The atypical APD clozapine has been noted to alter DA metabolism to an equivalent degree in the striatum and NAS (Bartholini, 1977; Zivkovic, 1977); acute clozapine administration impacted on DA metabolism to an equal degree in the core and shell. These data, in conjunction with anatomical data, suggest that the NAS_{core} may be associated with the dorsal striatum, whereas the NAS_{shell} resembles more closely a limbic sector.

Antipsychotic drug administration and the nucleus accumbens shell as a locus of antipsychotic activity

The biochemical responsiveness of the NAS_{shell} to stress and antipsychotic drugs differed from that of the accumbal core. These differences led us to speculate that it might be possible to define differences between the NAS core and shell, as well as the different dorsal striatal sectors, by examining early-immediate gene expression in response to acute APD challenge. Miller (1990) originally

noted that APDs augment striatal *c-fos* gene expression. The use of Fos immunohistochemistry to map potential sites of action of both typical and atypical APDs allowed a precise delineation of the core and shell of the nucleus accumbens, as well as other striatal sectors and compartments (Deutch et al., 1992).

The effects of four different APDs were examined. Haloperidol is a tpyical APD with a relatively high incidence of extrapyramidal side effects (EPS). Clozapine is the atypical APD, which does not appear to have EPS liability and targets negative as well as positive symptoms (for review, see Deutch et al., 1991 b). Remoxipride, a new putative APD that binds to D_2 DA receptors and the sigma site (Ogren et al., 1984, 1990), is a therapeutically effective agent (Ahlfors et al., 1990; Pflug et al., 1990; Lewander et al., 1990), that has very low EPS liability (Walinder and Holm, 1990); two controlled comparison studies have indicated that remoxipride has less or comparable EPS liability than thioridazine (McReadie et al., 1990; Phanjoo and Link, 1990). Preliminary data suggest that remoxipride may target negative as well as positive symptoms (Lewander et al., 1990), but this suggestion awaits confirmation. Finally, we examined the effects of acute administration of metoclopramide, a substituted benzamide that is an antagonist at D_2 and H-HT_3 receptors. Metoclopramide treatment is marked by a high incidence of EPS and tardive dyskinesia (Ganzini et al., 1991; Miller and Jankovic, 1989). Metoclopramide, while having parkinsonian side effect liability, may be antipsychotic at very high (at least ten fold higher than required to elicit EPS) doses (Makra et al., 1975; Stanley et al., 1980); to date there have been no controlled double-blind trials of the antipsychotic properties of metoclopramide. Thus, the four drugs tested include a typical APD (haloperidol), an atypical APD (clozapine), a new putative atypical APD (remoxipride), and a D_2 antagonist that induces EPS but does not exert antipsychotic actions at comparable doses (metoclopramide).

All three clinically effective antipsychotic drugs increased Fos expression in the NAS_{shell}; only haloperidol increased Fos expression in the NAS_{core} (Deutch et al., 1992). Metoclopramide did not enhance Fos expression in the NAS. However, metoclopramide and haloperidol (both of which have EPS liability) increased Fos expression in the dorsolateral aspects of the caudatoputamen, while neither clozapine nor remoxipride did so. These data suggest that the NAS_{shell}, but not NAS_{core}, may be a locus of antipsychotic action, whereas the dorsolateral striatum may be a locus at which D_2 antagonists act to induce EPS. The suggestion that the NAS_{shell} may be a locus of antipsychotic action was predicated on the observation that all three APDs, including haloperidol, increased Fos expression in the region. Since haloperidol is not generally effective in the treatment of negative symptoms (see Deutch et al., 1991 b), there must be additional sites at which APDs act to exert therapeutic effects of negative symptoms. In addition, there may be still other sites at which APDs act to reduce positive symptomatology.

Effects of stress on ventral pallidal dopamine systems

Stress, as noted above, increased dopaminergic metabolism and release in distinct parts of the PFC and in the NAS_{shell}. The NAS projects to the ventral pallidum (VP), with the shell innervating the ventromedial VP and the core projecting to the dorsolateral VP (Zahm and Heimer, 1990; Heimer et al., 1991). The VP receives dopaminergic projections from midbrain DA neurons (Deutch et al., 1988; Napier et al., 1991; Klitenick et al., 1992); these DA projections appear to inhibit VP neurons (Napier et al., 1991; Napier, 1992). We have recently reported that the VP dopaminergic innervation is topographically organized, such that the ventromedial VP receives projections from A 10 DA neurons situated medially, whereas the ventrolateral VP receives projections from more laterally placed VTA DA neurons (Klitenick et al., 1992). Moreover, the dopaminergic projection to the VP appears to be involved in motoric behavior (Klitenick et al., 1992).

Recent data from our laboratory suggests that the VP responds to stress in a regionally-specific manner (Bourdelais and Deutch, in preparation). We noted that stress increased the number of neurons expressing Fos protein in the ventromedial VP, but not the dorsolateral VP. Similarly, preliminary biochemical data suggest that stress increased DA metabolism in the ventromedial but not dorsolateral VP. These data suggest that the accumbal projection targets in the ventral pallidum are functionally organized in parallel with those of the NAS compartments with which they are in register.

Elaboration of functionally distinct parallel corticostriatal circuits: parallel and interactive

Anatomical data from the rat have suggested the presence of corticostriatal systems that are organized in parellel (Groenewegen et al., 1990). Similarly, data from primate physiological studies have suggested the presence of parallel cortico-striato-thalamic systems (see Alexander et al., 1986; Alexander and Crutcher, 1990). We have used responsiveness of mesotelencephalic DA neurons to stress to define the presence of what appear to be distinct stress circuits that are congruent with defined anatomical projection systems.

Stress increases DA metabolism (Deutch et al., 1985) and Fos expression (Deutch et al., 1991 a) in the VTA, but not in the SN or RRF. Studies of Fos expression have revealed that a subset of mesoprefrontal cortical DA neurons respond to stress. Biochemical analyses at the terminal field level have revealed that mild stress increases DA metabolism in distinct parts of the medial PFC (Deutch, 1991); the region that exhibited the most significant response was the infralimbic cortex, whereas the caudal prelimbic cortex did not respond. It is not clear if there are distinct DA neurons that provide the innervation of different prefrontal cortical regions in the rat, as suggested by the Fos data; we are currently investigating this possibility.

The infralimbic (stress-responsive) part of the PFC provides a major pro-

jection to the NAS_{shell}, the stress-responsive accumbal sector (Deutch and Cameron, 1992); in contrast, the NAS_{core}, which does not respond to mild stress, receives major inputs from the prelimbic area of the PFC. Thus, cortical regions that respond to stress are in register with accumbal sectors that respond to stress. This parallel organization appears to be maintained in the projection targets of the NAS: the ventromedial VP, which receives NAS_{shell} afferents, responds to stress, whereas the dorsolateral VP, a sector that does not respond to mild stress, receives afferents from the NAS_{core}. Finally, the NAS_{shell} and ventromedial VP project to the VTA (which responds to stress), while the NAS_{core} and dorsolateral VP project to the substantia nigra, which does not respond to stress. Figure 1 is a schematic illustration of a potential stress circuit involving these different sites.

It appears possible to define parallel loops that are either stress responsive or not. However, we have used relatively mild stressors for these studies. The response to stress has a number of components that can be conceptualized to involve progressively more elaborated behavior. For example, there is an orienting response to unusual auditory environmental stimuli; this orienting response may be accompanied by autonomic activation. If the auditory stimulus is accompanied by an olfactory cue indicating the presence of a predator, attention is more focused, autonomic and hormonal indices of arousal are more marked, and there is motor preparation for escape. If the auditory and olfactory stimuli are now accompanied by the visual representation of a predator within a certain distancce, flight or fight may be expected. Each of these steps represents a response to what (anthropomorphically) appears to be progressively more stressful conditions. It would seem reasonable to posit that there must be the parallel activation of different circuits subserving different aspects of the overall stress response, or that the circuits are parallel but interactive. While interpretations of electrophysiological data have favored the presence of parallel but distinct circuits, the anatomical data suggest that interactive parallel circuits are involved, and that as one circuit is activated, provided the activation is of sufficient duration or strength, another parallel circuit is recruited.

For example, suitably mild stressors may evoke autonomic activation but no overt escape behavior. The infralimbic cortex, by virtue of its efferent projections, is embedded in autonomic circuitry (Cechetto and Saper, 1990; Hurley et al., 1991; Room et al., 1985; Sesack et al., 1989). The infralimbic cortex projects to a circuit involving the NAS_{shell}, the ventromedial VP, and the VTA. However, the projections from the infralimbic cortex to the NAS_{shell}, as visualized using anterograde or retrograde tracing methods (Berendse et al., 1991; Brog et al., 1991) are not absolutely confined to the shell: a sparse input to the core can also be seen. Perhaps more importantly, the ventromedial VP projects to the medial sector of the mediodorsal thalamic nucleus, which in turn projects to the prelimbic cortex, and thereby gains direct access to the NAS_{core} (Zahm and Brog, 1992). These data would suggest that while there are parallel circuits, these operate in a coordinated fashion, not in a segregated manner.

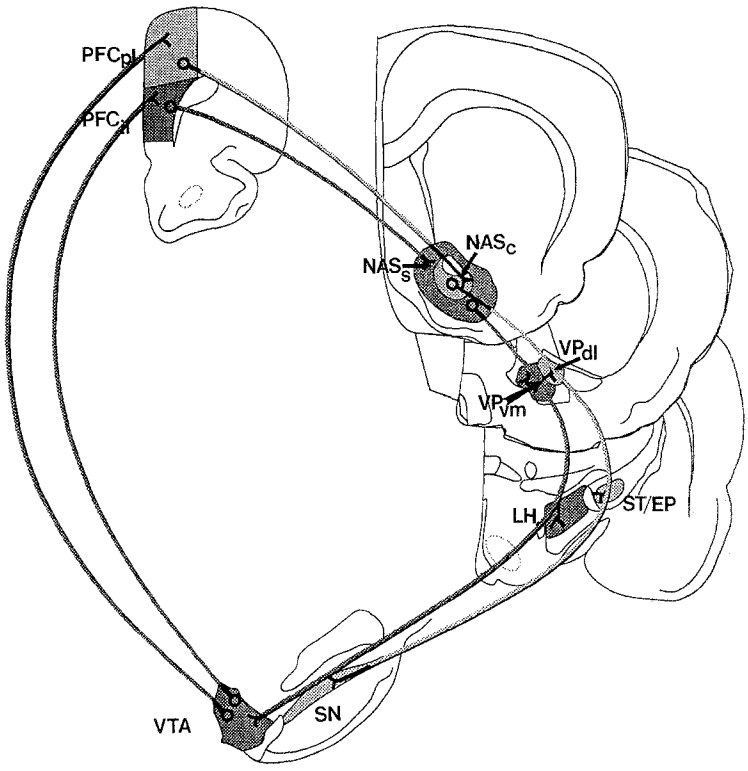

Fig. 1. Schematic illustration of the components of two stress circuits involving discrete dopaminergic innervations of the prefrontal cortex (PFC), nucleus accumbens ore (NAS_c) and shell (NAS_s), dorsolateral (VP_{dl}) and ventromedial (VP_{vm}) aspects of the ventral pallidum, lateral hypothalamus (LH), subthalamic/entopeduncular nucleus (ST/EP), substantia nigra (SN), and ventral tegmental area (VTA). The illustration is not intended to be faithful to the anatomy of the regions depicted, but simply to illustrate the concepts of two parallel corticostriatal circuits. A stress-sensitive circuit involving the infralimbic/ventral prelimbic cortex (PFC_{il}), NAS_{shell}, VP_{vm}, LH, and VTA is marked by the dark stipple. A parallel circuit that is not sensitive to mild stress (but will respond to stressors of longer duration or severity), is indicated by the lighter stippling, and involves the dorsal prelimbic/anterior cingulate aspects of the prefrontal cortex (PFC_{pl}), NAS_{core}, VP_{dl}, ST/EP, and SN

Corticostriatal circuits and schizophrenia

There has been an increasing focus over recent years on the possible involvement of corticostriatal circuits in schizophrenia (see Deutch, 1992; Goldstein and Deutch, 1992). Several factors have contributed to this interest. Weinberger and colleagues (Weinberger, 1987; Berman and Weinberger, 1990) have proposed a neurodevelopmental hypothesis of the etiology of schizophrenia. These investigators suggest that there may be a developmentally-specific dysfunction of the dopaminergic innervation of the prefrontal cortex in schizophrenic patients, and that this functional DA deafferentation of the PFC results in enhanced subcortical DA tone. This hypothesis has been very influential, in part

because it offers mechanisms to account for both negative (prefrontal cortical dysfunction) and positive (enhanced subcortical DA function) symptoms. Recent post-mortem findings suggest that the number of small interneurons in the frontal cortices is decreased in schizophrenic patients (Benes et al., 1991) and that there is a (compensatory) up-regulation of $GABA_A$ receptor sites (Benes et al., 1992). Such a loss of interneurons would be expected to decrease inhibitory tone on cortical pyramidal neurons, i.e., have effects similar to those of dopaminergic deafferentiation. In addition, recent imaging data have suggested the presence of atrophy of medial temporal lobe structures in schizophrenia (DeLisi et al., 1989; Posner et al., 1988; Shenton et al., 1992). All of these findings suggest that corticostriatal circuits originating in discrete areas of the cortex may be involved in schizophrenia.

Our data indicate that lesions of the DA innervation of the PFC result in an enhanced responsiveness of the nucleus accumbens to both environmental and pharmacological challenges. These findings thereby provide a means whereby a frontal cortical DA dysfunction, as suggested by the behavioral and functional imaging data of Weinberger and associates, can alter subcortical dopaminergic function. Moreover, a loss of GABAergic interneurons in the PFC might also be expected to enhance subcortical DA systems, since GABA release is augmented by DA in the PFC (see above). The issues of PFC DA regulation of subcortical DA systems, and the relevance of such interactions to schizophrenia, have been recently discussed (Deutch, 1992).

The subcortical target in which DA function is altered is most likely the NAS, as originally speculated by Stevens (1973). It is interesting to note that the NAS_{shell} appears to be a locus of antipsychotic activity. The NAS_{shell} not only responds to APDs, but also responds to stress. Stress-induced exacerbation of the psychotic process is well appreciated (Brown et al., 1972; Nicholson and Neufeld, 1989). Thus, the NAS_{shell} appears to be a common site at which i) stress acts, and through which stress may therefore exacerbate psychotic symptoms in schizophrenic patients, and ii) APDs act to ameliorate positive symptomatology in schizophrenic patients. As noted earlier, the therapeutic actions of clozapine (and possibly remoxipride) on negative symptomatology suggest another locus of action for APDs. Such a locus may be the prefrontal cortex. In vivo microdialysis studies examining extracellular DA concentrations have revealed that the magnitude of clozapine-induced DA release is greater in the PFC than in subcortical sites such as the NAS or striatum (Moghaddam and Bunney, 1990). These data are consistent with the findings of Robertson and Fibiger (1991), who noted in their studies of the effects of haloperidol and clozapine on Fos expression that clozapine appeared to exert a greater effect in the PFC than did haloperidol. We have also observed a clozapine-induced increase in PFC Fos expression; our preliminary observations suggest that the effect is most pronounced in the more ventral PFC aspects (infralimbic and ventral prelimbic cortices) and virtually absent in the most dorsal aspects (medial precentral cortex) of the PFC. If this is the case, then certain cortical fields in

register with distinct subcortical fields may transynaptically regulate the subcortical targets (NAS_{shell}) to alter dopaminergic function.

Such transynaptic regulation of subcortical DA systems can also derive from cortical areas outside the PFC. For example, the neuronal organization of the entorhinal cortex and adjacent structures in the temporal lobe has been suggested to be altered in schizophrenia (Altshuler et al., 1990; Arnold et al., 1991; Roberts, 1990; Suddath et al., 1989). Since the entorhinal cortex, hippocampus, and amygdala all project to the NAS (Brog et al., 1991), dysfunction in these cortical areas may impact on subcortical DA systems, in a fashion similar to that of the PFC-NAS circuits. Indeed, it is conceivable that the differences between subtypes of the schizophrenic reactions may reflect differential involvement of different corticostriatal circuits, in addition to dysfunction of a core circuit(s) involved in the generation of the core symptoms of schizophrenia.

Corticostriatal circuits and Parkinson's disease

In contrast to schizophrenia, where conclusive data indicating that the primary defect resides in DA neurons are lacking (see Goldstein and Deutch, 1992), there is no doubt that degeneration of the dopaminergic innervation of the striatum underlies the pathology of Parkinson's disease (PD). The involvement of the DA innervation of the striatal complex in PD is not uniform, however. There are clear differences in the regional and sub-regional distribution of DA depletions within the striatum in idiopathic PD. Thus, the putamen is more significantly impacted than the caudate nucleus, in a specific rostrocaudal gradient (Kish et al., 1988). However, other forms of parkinsonism, such as the post-encephalitic variant or MPTP-induced parkinsonism, exhibit a different pattern of DA deafferentation across striatal sectors (Elsworth et al., 1989; Jellinger, 1986; Pifl et al., 1990), as does the age-related decline in striatal DA concentrations (Kish et al., 1992).

While the dorsal striatum has been the focus of most studies of PD, there is also a loss of the ventral striatal DA innervation in PD and in toxin-induced parkinsonism (Elsworth et al., 1989; Hornykiewicz and Kish, 1987; Javoy-Agid et al., 1986); however, the NAS is significantly less impacted that the putamen. It is possible that this reflects the fact that the NAS core and shell have not been separately examined for differential vulnerability in PD. Certain animal data would suggest that this may the case. Injections of 6-hydroxydopamine into the VTA of the rat results in a profound rapid loss of the dopaminergic innervation of NAS_{core}, with relative sparing of the NAS_{shell} DA innervation at the same time point (Zahm and Johnson, 1991). These data are therefore consistent with the NAS_{core} being closely allied with the neostriatum, with links to basal ganglia motor outflow pathways. In addition, we have noted that 3-acetylpyridine administration to rats, which results in a relatively selective degeneration of the dorsolateral striatal DA innervation when examined six weeks after treatment (Deutch et al., 1989, 1990 b), also induces accumbal degeneration

in animals surviving for six months, with the loss of the DA innervation being restricted to the NAS_{core} (unpublished observations).

It is clear from a large body of literature that local manipulations that enhance DA tone in the NAS result in locomotor activity, while disruption of the dopaminergic innervation of the NAS markedly attenuates or eliminates the ability of psychostimulants, such as amphetamine, to elicit locomotor activation (see LeMoal and Simon, 1991). How can the role that the DA innervation of the nucleus accumbens plays be reconciled with the fact that PD is marked by relative sparing of the NAS DA system, with much more massive involvement of the dorsolateral striatum? One possibility is that the NAS, and in particular the NAS_{core}, may provide the affective drive that is necessary for volitional movement (see Iversen, 1984). Bradykinesia is perhaps the most troublesome symptom for parkinsonian patients. A number of factors contribute to the fact that PD patients have difficulties in initiation movements, but an impaired desire (motivation, affective drive) to move is not among these. The NAS_{core} may provide part of the drive that is necessary for the volitional execution of a movement. This would suggest, however, that significant disruption of the NAS_{core} DA innervation would result in profound disruption of movement, and perhaps freezing states. A threshold value for accumbal DA depletion (analogous to that required in the dorsal striatum for the emergence of parkinsonian symptoms) may have to be achieved in order for such drastic motoric impairment to be manifested.

The loss of cortical DA in PD and MPTP-induced parkinsonism is now well documented (Elsworth et al., 1990; Gaspar et al., 1991; Hornykiewicz and Kish, 1987). The loss of cortical DA in PD is both region and lamina specific (Gaspar et al., 1991); premotor, supplementary motor, motor, and prefrontal cortex all have been reported to suffer some dopaminergic loss (Elsworth et al., 1990; Gaspar et al., 1991). In certain cases the cortical DA loss can be linked to certain signs and symptoms; for example, the DA depletion in the supplementary motor area of MPTP-treated animals (Elsworth et al., 1990) may underlie the abnormalities in the *Bereitschaftspotential* seen in PD patients. Cortical DA depletions in PD have been suggested to contribute to the dementia observed in certain PD patients and to the depression rather frequently encountered in PD, but this remains speculative.

Since the prefrontal cortical dopaminergic innervation can transsynaptically regulate subcortical DA function, the assumption that cortical DA loss in PD has only negative consequences may not be correct. It is conceivable that the loss of DA in the cortical sites may improve subcortical dopaminergic tone marginally, through the transsynaptic mechanisms outlined above. In certain PD cases (e.g., those persons presenting early in the course of the disease) only slight enhancement of striatal DA release may be sufficient to significantly improve motoric function. Unfortunately, this is probably not of clinical significance, since the loss of cortical dopaminergic innervations in PD is generally associated with more advanced parkinsonian states.

However, changes in cortical function may contribute to changes in the function of striatal neurons. PD patients ultimately become refractory to the therapeutic benefits of *l*-DOPA, as well as resistant to direct DA agonist treatment. Although many factors may contribute to this problem, recent data suggest that degeneration of dendritic spines on intrinsic striatal neurons may be the major factor. The synaptic arrangement of striatal neurons is marked by a particular triadic association between cortical afferents, DA afferents, and medium spiny striatal neurons. Cortical axons terminate on striatal neurons, in particular on dendritic spine heads; DA afferents terminate on the same striatal neurons, but on dendritic shafts (Bolam, 1984; Bouyer et al., 1984). Recent morphological data have suggested that in later stages of PD there is decrease in dendritic spine density on the striatal medium spiny neurons that receive cortical and mesencephalic afferents (McNeill et al., 1988). Rearrangements of synaptic organization have been shown following unilateral disruption of cortical afferents to the striatum (Cheng et al., 1988); these changes are clearly morphological. It is conceivable that alterations in cortical function may compensate for the decrease in spine density by both morphological (synaptic plasticity) and by humoral (growth factor) mechanisms, and thereby modify the slow degeneration of post-synaptic neurons that appears to be present in PD.

Conclusions

We have presented data that defines functionally distinct corticostriatopallidal circuits that appear to be organized in a parallel yet interactive manner. These circuits may be affected to varying degrees in certain psychiatric and neurological disorders. Preclinical studies have suggested that certain of these circuits, involving distinct subdivisions of the prefrontal cortex in register with defined accumbal compartments, may be sites of dysfunction in schizophrenia. Less clear is the potential involvement of defined corticostriatal circuits in Parkinson's Disease; while parkinsonian symptomatology may involve the dorsolateral striatum, the involvement of the motor and somatosensory cortex has not been extensively characterized.

The potential dysfunction of corticostriatal circuits may suggest that therapeutic strategies for the treatment of PD be aimed at modifying excitatory amino acid transmission. Recent studies have suggested that motor function in certain animal models of PD may be altered by drugs that affect glutamatergic systems (Klockgether et al., 1991; see Greenamyre and O'Brien, 1991). Challenge protocols with ketamine have resulted in schizophreniform symptomatology (Krystal et al., 1992) and initial clinical trials of agents that act at sites on the excitatory amino acid receptor complex in schizophrenia have been performed. Unfortunately, the systemic administration of these pharmacological agents precludes the definition of sites of action (e.g, subthalamic nucleus as opposed to cerebral cortex or striatum). Although currently available drugs that act at excitatory amino acid receptors are relatively non-specific in terms of site specificity, and may therefore be expected to have unfavorable side effects profiles,

the recent advances in cloning of multiple excitatory amino acid receptor genes (see Heinemann et al., 1991), which are expressed in a regionally-specific manner in the CNS, suggest that it may be possible to develop pharmacological agents that target specific receptors in restricted central sites.

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