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Evidence for Plasticity of the Dopaminergic System in Parkinsonism

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Abstract

A series of compensatory mechanisms within the dopaminergic system have been shown to maintain clinical function in the presence of dopamine loss. Experimental evidence for increased presynaptic dopamine turnover owing to increased dopamine synthesis, release, and reduced reuptake exists. Direct evidence that these mechanisms maintain extracellular dopamine levels is provided by intracerebral microdialysis techniques. Postsynaptic denervation supersensitivity clearly occurs with D_2 dopamine receptors, although this is less evident with D_1 receptors.

Similarly, mechanisms of plasticity have been shown to be relevant in human postmortem and Positron Emission Tomographic studies of patients with Parkinson's disease. However, although presynaptic increases in dopamine turnover are well documented, postsynaptic D_1 and D_2 receptor changes have been more difficult

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to establish, mainly because of methodological difficulties. D_2, but not D_1, receptor increases have been documented in drug naive Parkinsonian patients with PET techniques. In transplantation of adrenal gland to striatum in animal models and patients with Parkinsonism where clinical improvement occurs, plasticity of host response may be as important as plasticity of the graft.

Although some elements of the compensatory mechanism of dopamine plasticity may be deleterious, such as dyskinesias owing to dopamine receptor supersensitivity, the overall effect of delay and minimization of the clinical expression of disease is advantageous. An even greater understanding of the mechanisms involved may assist in developing future therapeutic strategies.

Introduction

As information about the dopaminergic system has accrued over the last 30 years, it has been apparent that it has a remarkable plasticity in response to injury and disease. This facility to adapt to environmental change under the stresses of experimental manipulation and disease acts as a paradigm for other neurochemical systems. In this article, the experimental and clinical evidence for plasticity within the dopaminergic system in the face of deficient dopamine levels resulting from injury, toxic or degenerative change will be examined. Plasticity seen in graft and host during transplantation of catecholaminergic cells to the striatum will also be discussed.

The Dopaminergic System Under Physiological Conditions

The mesostriatal, mesocortical, and mesolimbic components of the dopaminergic system have cell bodies residing in substantia nigra compacta and ventral tegmental area of the mesencephalon. The nigrostriatal tract plays a critical role in modulating movement (Marsden, 1982). Dopamine is generated by the rate-limiting enzyme tyrosine hydroxylase (TH), excreted into the synaptic cleft in response to burst firing of dopaminergic nigral cells (Grace and Bunney, 1984; Nisenbaum et al., 1988). Within the striatum, the message is then transmitted through postsynaptic dopamine receptors (D_1 and D_2). D_1 receptors are adenyl cyclase linked, whereas D_2 receptors are either inhibitory or not coupled to this enzyme (*see* Anderson et al., 1990 for recent review). Evidence that a more complex array of dopamine receptors exists is now emerging as a result of molecular biological techniques. D_3, D_4 (D_2-like), and D_5 (D_1-like) receptors have been cloned and characterized, but whether they have any role in motor function is, as yet, unclear (Sokoloff et al., 1990; Sunahara et al., 1991; Van Tol et al., 1991). Negative feedback on the rate-limiting enzyme tyrosine hydroxylase (TH) is via presynaptic D_2 autoreceptors located in the striatum, thus preventing excessive dopamine production under physiological conditions. Presynaptic D_2 autoreceptors are located on dendrites and cell bodies, as well as on terminals, and may be more sensitive to dopamine and its agonists than postsynaptic D_2 receptors, although the evidence for this is questioned (Drukarch and Stoof, 1990). When the message is completed, dopamine is rapidly removed from the synaptic cleft by an efficient dopamine uptake system (Horn, 1990). This dopamine transporter, which is energy and sodium dependent, is probably the most important mechanism for inactivation of the synaptic effects of dopamine and its recycling. Postsynaptically, classical synapses are made with medium spiny neurons that are GABergic (Groves, 1980; Pickel et al., 1981), whereas tonic inhibition of cholinergic cells by dopamine is more likely via nonclassical synapses (DeLong and Georgopoulos, 1981). Striatal cells are supported by a glial network that may also absorb modest amounts of dopamine by passive diffusion (Paterson and Hertz, 1989). Glial cells also contain the enzyme monoamine oxidase B (MAOB), which is critically important under physiological conditions in degrading excess dopamine, but may also be

important in the generation of toxic moieties from pyridine derivatives, such as *N* methyl-4-phenyl 1,2,3,6-tetrahydro-pyridine (MPTP) (Langston et al., 1983; Markey et al., 1984).

Plasticity in Clinical and Experimental Models of Dopamine Depletion

The majority of motor symptoms of Parkinson's disease result from degeneration of mesencephalic dopaminergic neurons and their striatal projections (mesostriatal dopaminergic system). It is less clear to what extent the mesolimbic and mesocortical systems contribute to the clinical triad of bradykinesia rigidity and tremor, or the role of other neurotransmitter systems, particularly the neuropeptides (Agid, 1991). The development of a model of a relatively pure loss of dopaminergic cells of the mesostriatal system in animals has been helpful in determining the clinical expression of dopamine depletion. For example, 6OH dopamine lesions of nigrostriatal tract in rats causes ipsilateral circling behavior (Ungerstedt, 1971), and systemic MPTP administration to primates results in a clinical syndrome very similar to Parkinson's disease, although tremor is usually less prominent (Burns et al., 1983). Inadvertent MPTP administration in humans has also produced a clinical syndrome almost indistinguishable from Parkinson's disease (Langston et al., 1983). In both animal models and human forms of Parkinsonism, there is considerable evidence to suggest that the clinical expression of dopamine depletion may be minimized or delayed by a series of compensatory mechanisms.

Experimental Models

One of the early findings during the development of the 6OH dopamine rat model of Parkinsonism was that a loss of 90% or more of striatal dopamine was necessary before the clinical expression of circling was seen (Ungerstedt, 1971). Since then, a series of potential compensatory mechanisms have been identified, many of which have been recently reviewed (Schultz, 1982; Zigmond et al., 1990; Calne and Zigmond, 1991).

Presynaptic Mechanisms

These can be broadly categorized into increased dopamine turnover resulting from increased dopamine synthesis/release in the remaining neurons and reduced reuptake. Increased TH activity has been demonstrated in 6OH-dopamine lesioned rats (Zigmond et al., 1984) and may be seen as early as 5 d postsurgery. A correlation between TH activity and dopamine depletion exists, and an increase in TH activity is seen after destruction of at least 50% of the dopaminergic innervation to the striatum. The increase in TH activity may be possible by virtue of phospholyation of stores of previously inactive enzyme as demonstrated in adrenal catecholamine systems (Meligeni et al., 1982). Altered TH function under these conditions is presumably under D_2 autoreceptor control, although direct evidence for this is lacking. Increased catecholamine turnover is inferred by the observation that increased Dopac/dopamine ratios may be seen within 60 h of lesioning of the nigrostriatal tract in the 6OH dopamine rat model (Zigmond et al., 1984). Similar increases in dopamine turnover have been seen after systemic administration of MPTP to C57 black mice (Heikkila et al., 1984; Hallman et al., 1984). Two possible explanations for the observed increase in dopamine turnover have been advanced (Zigmond et al., 1990). First, increased rate and pattern of firing of the remaining neurons may occur (Grace and Bunney, 1984). Second, increased dopamine release in response to each burst is observed in the presence of lesions of 90% or more of the nigrostriatal tract (Stachowiak et al., 1987; Snyder et al., 1990).

Direct evidence that these presynaptic compensatory mechanisms would maintain extracellular levels of dopamine at adequate levels was lacking until the recent development of intracere-

bral dialysis techniques. Robinson and Whishaw (1988) showed that extracellular concentrations of dopamine were normal on the 6OH-dopamine lesioned side of the rat model of Parkinsonism, even after that side was depleted of up to 99% of the dopamine measured in postmortem tissue. In rats with <95% depletion of tissue dopamine, amphetamine was still able to induce a large increase in extracellular dopamine on the lesioned side, but if tissue depletion was >95%, amphetamine produced a steady decline in extracellular dopamine. Abercrombie et al. (1990) showed similar maintenance of extracellular dopamine levels in the presence of lowered tissue dopamine levels, but found reduction in extracellular levels after only 80% depletion of tissue levels.

A further presynaptic mechanism contributing to the maintenance of extracellular dopamine levels is reduced reuptake through sodium-dependent channels. Zigmond et al. (1984) measured dopamine uptake in synaptosomes prepared from the lesioned side of 6OH-dopamine-treated rats, and showed that [^{3}H] dopamine uptake was significantly reduced compared to controls and that this strongly correlated with reduction in endogenous dopamine levels. This reduction in uptake may lead to a more prolonged dopamine action with a wider sphere of influence owing to diffusion (Zigmond et al., 1990). This diffuse, more widespread action of dopamine as a neurotransmitter is consistent with observations that its action is a tonic modulatory one on the striatum (Orr et al., 1986), and exogenous replacement of dopamine in the form of its precursor L-Dopa reverses neurological deficits in animal models and patients with Parkinson's disease (Cotzias et al., 1987).

The role of striatal glial cells in dopamine compensatory mechanisms is unclear. Some controversy exists as to whether these cells have the ability to take up catecholamines actively, although more recently Paterson and Hertz (1989) presented convincing evidence that uptake is by a facilitated diffusion mechanism. Overall, the contribution of glial cells to dopamine storage and release is likely to be small under conditions of dopamine depletion, although their role during exogenous L-dopa administration needs to be examined further.

Postsynaptic Mechanisms

Although the concept of denervation supersensitivity was well known in the peripheral nervous system, it was not until 1971 that Ungerstedt demonstrated in the 6OH dopamine rat model of Parkinsonism that it definitely existed in the central nervous system (Ungerstedt, 1971). He showed that both apomorphine and L-dopa induced a strong rotational behavior and that the direction of the rotation (contralateral) indicated that the denervated striatum was more sensitive to dopamine-receptor-stimulating drugs than the innervated striatum. Creese, Burt, and Snyder (1977) showed that the number of dopamine receptor binding sites, using [^{3}H] haloperidol as a radioligand, increased by 20–100% on the lesioned side, indicating that the apparent receptor supersensitivity behavior seen was reflected by an actual increase in postsynaptic receptors. The change in postsynaptic dopamine receptor numbers was not present 4 d post lesion, but had developed by at least 21 d using [^{3}H] apomorphine as a radioligand (Creese and Snyder, 1979).

It has recently become clear that interaction between D_1 and D_2 receptors is necessary for motor behavioral expression, since adequate control of motor response to dopaminergic treatment only occurs when both D_1 and D_2 receptors are intact (Robertson and Robertson, 1986; Waddington, 1986; Carlson et al., 1987). The true role of D_1 receptors in motor response is as yet unclear, although it is of interest that Viola et al., (1989) found both D_1 and D_2 receptors to be increased in MPTP-exposed monkeys. However, in the rat 6OH dopamine denervation model, D_1 receptors have been unaltered (Savasta et al., 1988), unless post lesion delays were as long as 90 d (Buonamici

et al., 1986). The recent cloning and characterization of a further series of dopamine receptors, including D_5 with D_1-like characteristics (Sunahara et al., 1991), D_3 with D_2–like autoreceptor and postsynaptic characteristics (Sokoloff et al., 1990), and D_4 with D_2 features (Van Tol et al., 1991), may mean that a further reinterpretation of existing postsynaptic plasticity concepts may be necessary.

Clinical Studies

Although the mechanisms of plasticity of the dopamine system in experimental systems have been evolving, some parallels have been documented in cases of Parkinson's disease. The evidence may be broadly classified into in vitro postmortem studies and in vivo studies using Positron Emission Tomography (PET).

Postmortem Studies

PRESYNAPTIC. The most important original contribution was that of Bernheimer et al., who demonstrated, based on extrapolations of postmortem assay of dopamine levels, that at least 80% of striatal dopamine loss was necessary before symptoms of Parkinson's disease developed (Bernheimer et al., 1973). However, these reductions in dopamine levels vary throughout the striatum, being much more marked in putamen than caudate (Kish et al., 1988). Dopamine uptake sites have also been used as an index of dopamine terminal loss in Parkinson's disease and found to be markedly less than dopamine loss when radioligands, such as [^{3}H] cocaine (Pimoule et al., 1983) or [^{3}H] GBR 12935 (Maloteaux et al., 1988; Pearce et al., 1990), were used on membrane preparations. We have been able to demonstrate marked regional reductions in dopamine uptake site density compared to controls using [^{3}H] mazindol as a radioligand and autoradiographic techniques (Donnan et al., unpublished observations; 1991), particularly in lateral putamen (Fig. 1). Given this information, it appears likely that marked regional differences in the extent to which compensatory mechanisms come into play within the striatum exist.

As found in experimental models of Parkinsonism, HVA/dopamine ratios are markedly increased in the striatum and substantia nigra of patients with Parkinson's disease (Scatton et al., 1984; Bokobza et al., 1984), and are interpreted as overactivity of the remaining dopaminergic neurons. Of interest was the finding that the HVA/dopamine ratio was increased in putamen, caudate, and nucleus accumbens, but not in hippocampus or frontal cortex, thus suggesting that disease of mesolimbic and mesocortical projections is not severe enough to produce compensatory changes (Scatton et al., 1984).

A compensatory increase in TH activity has not been demonstrated in Parkinsonian brain (McGeer and McGeer, 1976; Javoy-Agid et al., 1981). However, Rausch et al. (1988) showed an increase in caudate TH activity when assessed in the presence of Fe^{2+} and phosphorylating agents. One recent study showed reduced mRNA TH expression in the remaining dopamine neurons of the substantia nigra in postmortem brains with Parkinson's disease (Javoy-Agid et al., 1990). Whether this reduced mRNA expression relates to increased or decreased TH enzyme turnover is uncertain, and more information concerning the regulation of TH mRNA levels is needed before this information can be fully interpreted.

POSTSYNAPTIC. There have been numerous studies of dopamine receptors in postmortem brain, and both increases and decreases in striatal D_1 and D_2 density have been reported in both L-dopa-treated and untreated patients (*see* reviews by Hassan and Thankar, 1988; Pierot et al., 1988). Agid et al. (1987) averaged all available studies and found there was evidence for a significant increase in D_2 receptors in putamen, but not caudate or accumbens, and a significant reduction in D_1 receptors in the substantia nigra. An approach that is obviously needed is autoradiographic analysis of receptors adjacent to the most severe presynaptic loss as documented by autoradiographic distribution of dopamine uptake sites.

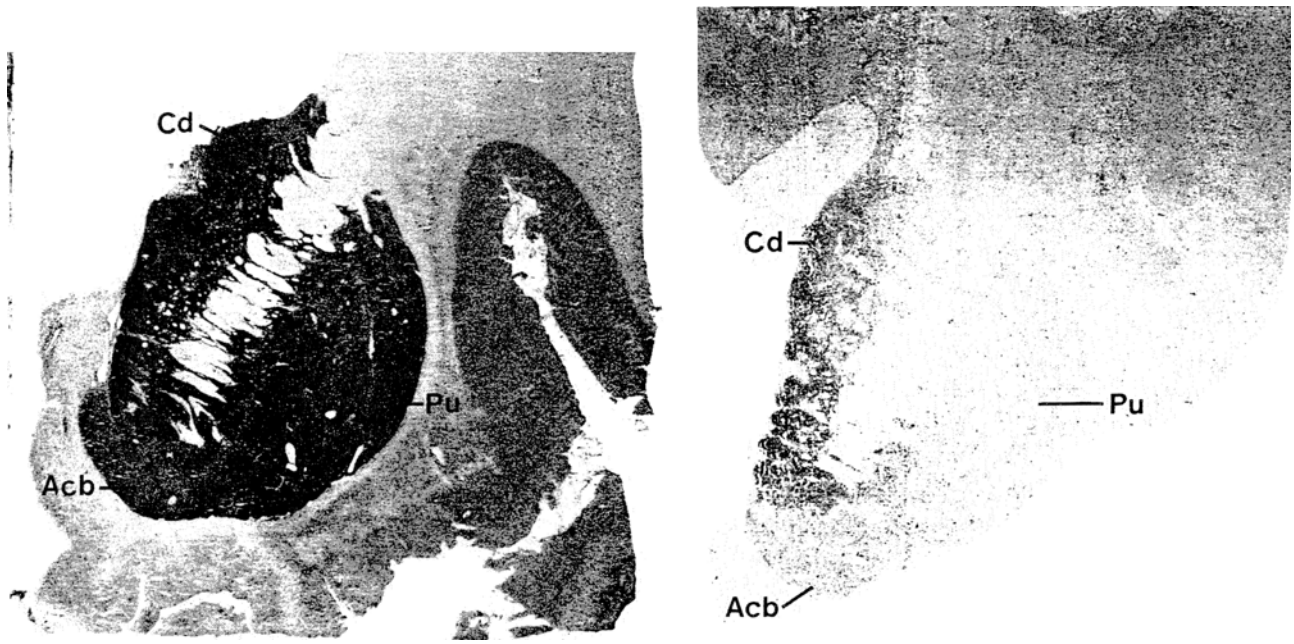

Fig. 1. Dopamine uptake sites' distribution in human striatum using [^{3}H] mazindol autoradiography—control (left panel) and Parkinsonian (right panel) brain. A marked loss of dopamine uptake sites is seen laterally in both caudate and putamen. Cd caudate, Pu putamen, Acb n. accumbens.

In Vivo Studies with Positron Emission Tomography (PET)

The loss of presynaptic dopaminergic function has been documented with PET using radioligands [^{18}F]-6-F-dopa (Garnett et al., 1984; Nahmias et al., 1985; Leenders et al., 1986). This technique most likely measures the storage capacity of presynaptic terminals, but also measures extracellular dopamine. An index of remaining terminal density may be better gaged by imaging of dopamine uptake sites with [^{11}C] nomifensine, the levels of which have been shown to be reduced in Parkinson's disease (Tedroff et al., 1988,1990). Quantitation of presynaptic dopamine uptake and storage using [^{18}F]-6-F-dopa have shown that less impressive levels of dopamine loss may produce symptoms than the levels of loss seen in postmortem studies (Calne and Zigmond, 1991). An explanation for the disparity between these in vivo and in vitro observations may be that PET successfully images both intra- and extracellular dopamine levels, whereas in postmortem preparations, rapid degeneration of extracellular dopamine may occur before assay can be undertaken, but intracellular levels are quite well maintained. In other words, 80–90% of intracellular dopamine may need to be lost before symptoms or signs of Parkinson's disease are experienced, whereas extracellular levels may be better preserved (Calne and Zigmond, 1991). These findings are consistent with experimental data measuring extracellular dopamine levels using microdialysis techniques discussed previously (Robinson and Whishaw, 1988; Abercombie et al., 1990).

Although presynaptic compensatory mechanisms within the dopaminergic system may delay the clinical expression of disease and minimize clinical deficits for many years, it is possible that they may also contribute to ongoing neuronal degeneration. Increased dopamine turnover may generate excessive free radicals, which are inad-

equately scavenged by existing enzyme systems (Agid, 1991). The possibility that these effects may be modulated by exogenous administration of free radical scavenging agents is currently being examined (Parkinson Study Group, 1989).

Postsynaptic D_1 and D_2 receptor studies have been studied using [^{11}C] raclopride as a D_2 radioligand and [^{11}C] SCH 23390 as a D_1 radioligand. There are now reports of elevated values of D_2 receptors in early untreated cases of Parkinson's disease (U. K. Rinné et al., 1989), and a further report suggesting that D_1 receptors remain unchanged in the same patients in whom D_2 receptor increases are seen (J. O. Rinne et al., 1990). Some limitation of interpretation must be placed on these studies because of the inability to quantitate D_1 and D_2 receptors absolutely owing to modeling constraints, and semiquantitative side-to-side values or referenced cerebellar values are used. However, the finding is further important evidence that plasticity in vivo in patients with Parkinson's disease does occur, as one would predict from experimental models.

Plasticity and Neural Transplantation

In recent years, transplantation of a variety of catecholaminergic tissues into animal models of Parkinsonism has resulted in partial or complete amelioration of neurochemical and clinical deficits (Björklund et al., 1981; Dunnett et al., 1981; Hefti et al., 1985; Perlow et al., 1980; Strömberg et al., 1984). Because of the ethical and potential tissue rejection issues, the tissue utilized most extensively in human studies has been autologous adrenal gland (Madrazo et al., 1987; Goetz et al., 1989), although fetal dopaminergic tissue has been used on a more limited basis (Lindvall, 1991). For these reasons, discussion will be largely limited to plasticity associated with adrenal grafts.

Adrenal grafts to the striatum of 6OH-dopamine lesioned rats have been shown to reverse apomorphine-induced circling behavior, but not spontaneous circling, unlike grafts of fetal dopaminergic tissue, which more effectively reverse motor deficits (Lindvall, 1991). Autologous adrenal grafts in humans to caudate or striatum have been only modestly successful in some patients, and in the few postmortem cases available, little or no surviving adrenal tissue has been found (Hurtig et al., 1989; Hirsch et al., 1990; Kordower et al., 1991). This raises the question of the likely mechanism of any observed improvement in animal and human studies using adrenal grafts. Is dopaminergic neuronal plasticity responsible?

Mechanism of Action of Adrenal Grafts

Early consideration of adrenal graft effectiveness included simple diffusion of catecholamine into adjacent tissue, direct synapse formation with host striatal cells, a scavenging effect on existing toxins within the striatum (particularly in human studies), or host responses to the presence of the graft (Bohn et al., 1987). The likelihood that diffusion of catechols contributes much to clinical recovery is low since experimental and clinical studies have not shown increases in CSF catecholamine levels (Becker and Freed, 1988; Lindvall et al., 1987). There is currently no evidence to support the hypothesis that the grafts may act as toxin scavenging agents. The most likely explanation may lie with both plasticity of host response and plasticity of adrenal cells themselves.

Plasticity of Host Response

There is mounting evidence to suggest that the presence of the adrenal graft may influence the host in a major way. A remarkable regeneration of host dopaminergic fibers may occur in the ipsilateral striatum in the MPTP-treated mouse after adrenal grafting (Bohn et al., 1987) and similar changes have been observed in primates (Fiandaca et al., 1988). We have also shown that the adrenal graft may induce proliferation of dopamine uptake sites using [^{3}H] mazindol as a radioligand in normal striatum (unpublished observations), but similar less pronounced changes may also be seen owing to the effects of

grafts of nonadrenal tissue (cerebral cortex) and the sham procedure. This raises the question as to whether much of the observed beneficial effect of the graft is the result of the surgical procedure itself rather than the implanted tissue. Certainly, it is well recognized that trauma to the central nervous system results in the release of a number of growth factors (Nieto-Sampedro et al., 1983; Needels et al., 1986), and relevant growth factors are also present in the adrenal gland (Blottner et al., 1989). It is of interest that resection of large parts of caudate in patients with Parkinson's disease was performed in the preL-dopa era and was shown to ameliorate disabling symptoms partially (Meyers, 1951), perhaps suggesting that similar host response mechanisms may have been responsible. The recent finding that brain-derived neurotrophic factor (BDNF) may be at least one of the growth factors specific for the dopaminergic system raises the possibility that this may be involved in the host responses observed by ourselves and others in experimental models of adrenal transplantation (Hyman et al., 1991).

Plasticity of Adrenal Cells

In experimental models of dopamine depletion, long-term survival of adrenal chromafin cells as grafts has not occurred, as in the limited evidence from human studies. However, Nishimo et al. (1988) showed the presence of TH-positive cells with the morphological characteristics of neurons around the tracts of graft insertion 14–40 wk after adrenal graft transplantation using an homogenized preparation. We have had the same experience with C57 black mice grafted with blocks of autologous adrenal gland, except that these were grafted in normal striatum and had migrated a considerable distance from the original graft site. The animals were treated with MPTP several days before sacrifice and appeared to be resistant to the toxin (Fig. 2). Whether these cells form synapses with existing striatal cells is uncertain.

The migrated cells are most likely of adrenal origin, and have transmuted from adrenal chromafin cells to neurons and also from cells producing adrenalin to dopamine (Ogawa et al., 1986). The possibility that induced transmutation of existing striatal neurons into TH-producing neurons is unlikely but cannot be completely discounted. Under normal circumstances, no TH-positive cells exist in the mouse striatum, although they have recently been described in the primate (Dubach et al., 1987). The mechanism of transmutation of adrenal cells is unclear, but considerable evidence suggests that neurotransmitters themselves may at least partly influence neuronal plasticity (Lipton and Kater, 1989). This evidence accepted, the finding of abundant cells throughout the striatum in our cases may be owing to the greater concentration of neurotransmitters in normal striatum (Prochiantz et al., 1981) compared to MPTP-treated mice where TH-positive cells were restricted to areas adjacent to the graft site (Nishino et al., 1988).

Concluding Remarks

From the preceding article, it can be seen that neuronal plasticity plays an important role in the dopaminergic system overall. Without it, the clinical expression of Parkinsonism would be seen earlier and ultimately be more profound. However, unwanted effects of plasticity also exist in the form of disabling dyskinesias (abnormal movements), which may be owing to postsynaptic dopamine receptor supersensitivity. Increased presynaptic dopamine turnover, so important in the maintenance of synaptic dopamine levels, may also have deleterious effects by generating cytotoxic products of dopamine breakdown and may be responsible for the continuation of the degenerative process. Plasticity of host and graft cells after adrenal transplantation to the striatum is likely to be one of the most important factors in the, so far, limited success of this procedure. Whatever the potential benefits or adverse effects of plasticity, an even greater understanding of its mechanisms is likely to assist the development of treatment strategies to further minimize the effects of disease.

Fig. 2. TH-positive cells in adrenal cell grafted striatum of C57 Bl mice after MPTP treatment. The cells have neuron-like morphology and were distributed a considerable distance from the graft site.

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