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Review

Insights into Parkinson's disease models and neurotoxicity using non-invasive imaging

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Abstract

Loss of dopamine in the nigrostriatal system causes a severe impairment in motor function in patients with Parkinson's disease and in experimental neurotoxic models of the disease. We have used non-invasive imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (MRI) to investigate in vivo the changes in the dopamine system in neurotoxic models of Parkinson's disease. In addition to classic neurotransmitter studies, in these models, it is also possible to characterize associated and perhaps pathogenic factors, such as the contribution of microglia activation and inflammatory responses to neuronal damage. Functional imaging techniques are instrumental to our understanding and modeling of disease mechanisms, which should in turn lead to development of new therapies for Parkinson's disease and other neurodegenerative disorders.

Keywords: Parkinson disease; Neurotoxicity; Imaging; Dopamine

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Neurotoxic models of Parkinson's disease

The capacity of a number of pharmacological agents and environmental toxins to lesion specific neural populations has been used extensively to mimic the pathological and functional alterations that characterize neurodegenerative disorders. These experimental models are useful for the evaluation of therapeutic strategies directed to obtain symptomatic relief and to slow down the degenerative

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process (neuroprotection). On the basis of experimental and clinical findings, Parkinson's disease (PD) was the first neurodegenerative disease to be modeled (Ungerstedt, 1968). In PD, there is a progressive loss of dopamine (DA) neurons in the substantia nigra (SN) that causes a deficiency of this neurotransmitter in the main projection area of SN neurons, the dorsal (motor) striatum. In the striatum, DA modulates the cortico-thalamic motor system and the lack of DA in this region is responsible for the characteristic motor impairment in PD (Marsden, 1992). Certain substances have the ability to disrupt the catecholaminergic systems and induce a quite selective loss of midbrain DA neurons and corresponding PD-like motor symptoms in different animal species, mainly rodents and non-human primates.

6-Hydroxydopamine (6-OHDA) was the first chemical agent used for its specific neurotoxic effects on catecholaminergic pathways (Ungerstedt, 1968; Ungerstedt and Arbuthnott, 1970). Different models have been developed using 6-OHDA, most of them unilateral (as bilateral administration is associated with adipsia and aphagia and high mortality) in various species, mainly rodents and small monkeys as marmosets (Bankiewicz et al., 1999). 6-OHDA needs to be delivered locally, by stereotactic injection that can be performed at different sites within the nigrostriatal system.

Different models can be created by targeting the DA system at different levels (Bankiewicz et al., 1999): quite restricted lesions result from administration into the substantia nigra (cell bodies), more widespread lesions are achieved by injecting the toxin into the nigrostriatal tract (in the medial forebrain bundle where DA axons are tightly packed), and progressive lesions are obtained by delivering 6-OHDA into the striatum (DA terminals). Most 6-OHDA models are limited by their acute toxic nature, but following administration into the striatal terminal field, degeneration progresses over several weeks (Oiwa et al., 2003; Sauer and Oertel, 1994) providing a useful model for protection and mechanistic studies. The toxic effect of 6-OHDA is related to its capacity to generate reactive oxygen species (ROS) (Betarbet et al., 2002). Toxicity is pronounced in DA neurons due to selective uptake of the toxin by the DA transporter (DAT) system, presence of monoamine oxidase, and low tolerance of this neuronal population to oxidative stress. Indeed, ROS and oxidative stress have been pointed out as key factors in the pathogenic cascade leading to loss of midbrain DA neurons in PD (Greenamyre and Hastings, 2004) (Fig. 1).

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was discovered as a result of observations of the PD-like syndrome caused by intravenous administration of MPTP-contaminated heroin (Davis et al., 1979; Langston et al., 1983) in drug addicts. MPTP crosses the blood–brain barrier and is metabolized in the astrocytes to its toxic metabolite 1-methyl-4-phenyl-2,3-dihydropyridinium (MPP^+), by monoamine oxidase-B (MAO-B). This toxic metabolite is selectively taken up by DA neurons, due to its affinity to

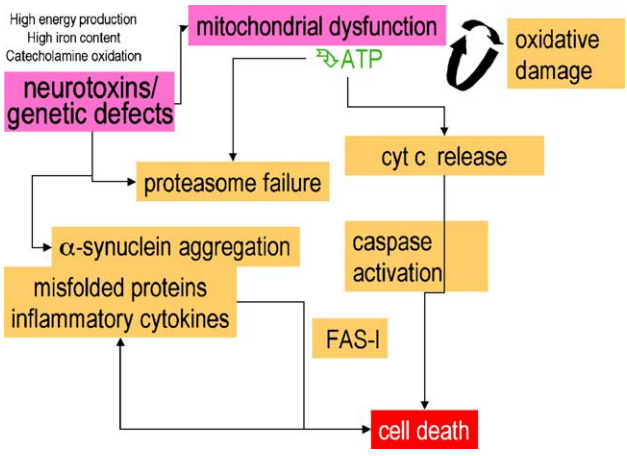

Fig. 1. Mitochondrial failure and oxidative stress are induced by several dopamine (DA) neurotoxins, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). MPTP is metabolized to its toxic metabolite 1-methyl-4-phenyl-2,3,-dihydropyridinium (MPP^+), which is taken up by DA neurons through the dopamine transporter and concentrated in the mitochondria blocking complex I of the respiratory chain. Similar pathogenic mechanisms are involved in dopamine neuronal loss in idiopathic and genetic forms of Parkinson's disease.

the DAT, and concentrated in the mitochondria where it inhibits complex I of the electron transport chain leading to oxidative stress and death of DA neurons (Langston et al., 1984). Rodents show variable susceptibility to MPTP. Rats are resistant and mice from different strains show variable susceptibility and usually transient DA depletion with variable behavioral correlation. In contrast, primates are rather susceptible and develop a motor syndrome closely resembling PD. Chronic (repeated) administration of low doses of MPTP to macaques reproduces all the signs of PD (tremor, bradykinesia, rigidity, hypokinesia, and postural impairment) and mimics, to a certain extent, the progressive nature of PD (Brownell et al., 1998a, 2003). Proteinaceous inclusion bodies have been reported in aged primate neurons following MPTP exposure, although these aggregates were unlike typical Lewy bodies (Forno et al., 1988) and have not been observed in macaques.

Other inhibitors of mitochondrial complex I, including pesticides such as rotenone (Betarbet et al., 2000), and herbicides like 1,1′-dimethyl-4,4′-bipyridinium (paraquat) (Corasaniti et al., 1998) and manganese ethylene bisdithiocarbamate (maneb) have also been used to induce DA neurotoxicity and PD models (Betarbet et al., 2002) and investigated as environmental toxins in relation with sporadic PD. The relevance of toxic models for pathogenic studies is variable, as experimental toxins might act through either similar or unrelated mechanisms to those implicated in the human disorders (Hornykiewicz et al., 1988). Interestingly, genetic mutations identified in familial forms of the PD appear to converge into common pathogenic mechanisms involving mitochondrial dysfunction, oxidative stress, and protein mishandling (Fig. 1). Indeed, mutations in two genes, DJ-1 (Bonifati et al., 2003) and PINK-1 (Valente et al., 2004), recently identified by genetic linkage analysis and

positional cloning in familial forms of early onset PD (PARK7 and PARK6, respectively), are hypothesized to be implicated in cellular response to oxidative stress (Bonifati et al., 2004; Greenamyre and Hastings, 2004) acting therefore through pathogenic mechanisms similar to DA neurotoxins.

In vivo functional imaging of DA neurotoxicity

Functional neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) make it possible to evaluate in vivo specific neural circuits in the brain before and after administration of a neurotoxin. Predictive models of disease progression are required for testing disease-modifying hypothesis and for this purpose non-invasive imaging techniques can play a fundamental role (Brownell et al., 1998a, 1999). Studies combining the use of different PET tracers that target critical proteins increase our insight into the progression of the degeneration, disease mechanisms, and effect of novel therapies. PET studies can aim to evaluate the severity of the DA loss by using presynaptic DA tracers and other toxic and adaptive changes in systems related to the DA system. The flexibility to label different compounds provides the ability to investigate effects at different levels (Sanchez-Pernaute et al., 2002): presynaptic loss of DA terminals, using, for example, 2β-carbomethoxy-3β-(4-fluorophenyl) tropane (CFT), a selective ligand for the DAT (Fig. 2),

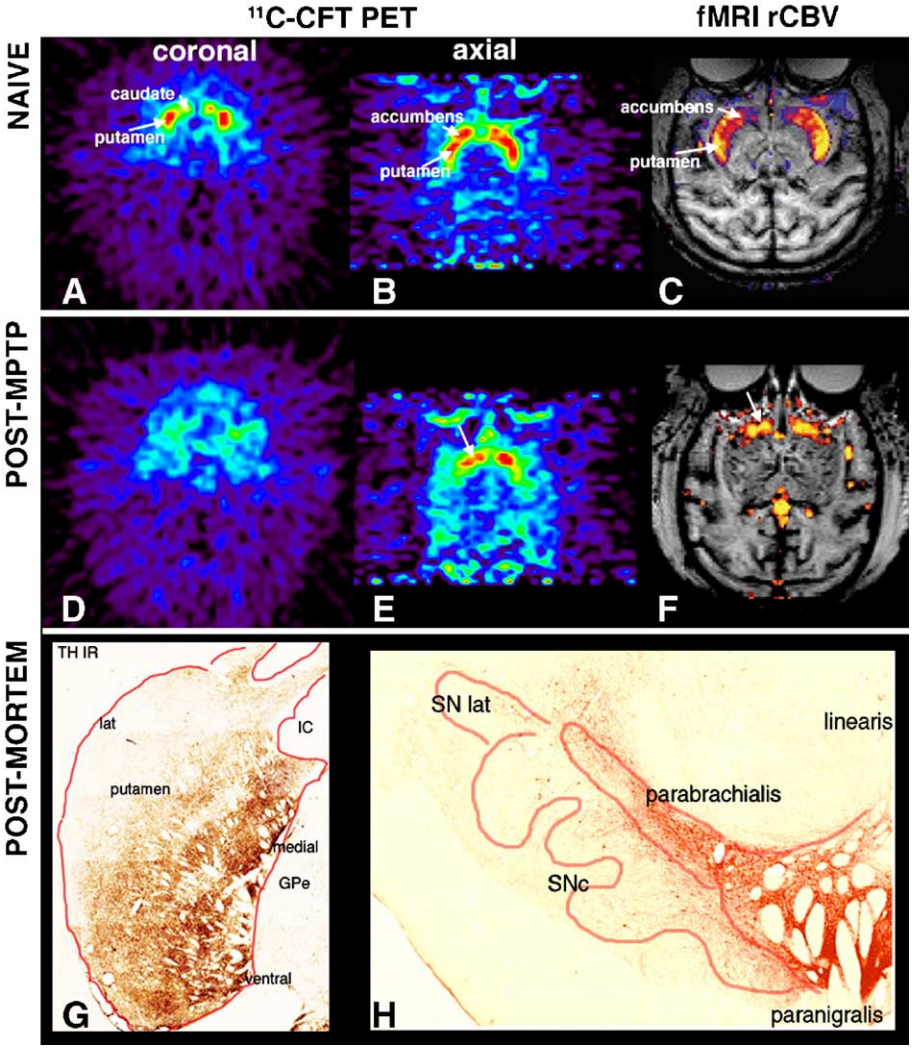

Fig. 2. Functional imaging techniques document in vivo the differential susceptibility of the mesostriatal and mesolimbic dopamine systems to MPTP. PET imaging using the specific ligand for the dopamine transporter 2β-carbomethoxy-3β-(4-fluorophenyl) tropane (CFT) in coronal (A, D) and axial (B, E) reconstructions of the primate striatum: note the loss of binding in the caudate and putamen (63%) after MPTP administration (D, E) with preservation of the binding in the nucleus accumbens (E). Functional MRI using an amphetamine challenge to measure regional cerebral blood volume (CBV) change in response to dopamine release (C, F) shows a relative preservation of the hemodynamic changes in the nucleus accumbens (arrowhead). The average loss of signal rCBV changes was 86–90% in putamen and caudate and 36% loss in the nucleus accumbens (Jenkins et al., 2004). These findings are confirmed by the postmortem analysis: Computer-assisted generated images (virtual slice, Neurolucida software, MicroBrightField, Williston, VT) of tyrosine hydroxylase (TH) immunoreactivity (G, H) show a pronounced loss of TH immunoreactive fibers in the posterolateral striatum (65% normalized to accumbens optical density) and loss of dopamine neurons in the substantia nigra (60%) more severe in the nigrosomes in the pars compacta (A9) than in the A10 groups (parabrachialis and paranigralis).

adaptive postsynaptic changes in DA receptors using selective DA receptor antagonists, and synaptic release of DA using displacement paradigms (Laruelle et al., 1995). Metabolic changes in related regions of the motor circuitry can be evaluated using PET and glucose and oxygen indices (Brownell et al., 2003). However, it is required to take into account biological and pharmacological factors that may lead to under- or overestimation of the extent of DA degeneration, such as enzymatic regulation, competition for transporters, and associated metabolic factors. DA decrease caused by 6-OHDA (in rodents) or MPTP (in primates) administration can be assessed in vivo using PET and ^{11}C-CFT (Brownell et al., 1998a, 2003; Hantraye et al., 1992) and these studies correlate and are validated by postmortem evaluation of loss of tyrosine hydroxylase (TH) positive neurons in the SN and DA fibers in the striatum (Hantraye et al., 1992) (Fig. 2).

The specific PET signal can be restored by transplantation of DA cells (Brownell et al., 1998b) and by embryonic stem cells (Bjorklund et al., 2002) but not after transplantation of non-DA cells (Brownell et al., 1998b). Using fMRI, we can also characterize both local changes in the DA system and downstream changes in cortico-subcortical associated areas. fMRI is based on the principle that neuronal activation induces a hemodynamic response (neurovascular coupling) to match the increase in metabolic demand caused by the increase in oxygen/glucose consumption that is generated by synaptic activity (Heeger and Ress, 2002). The hemodynamic response can be measured using several fMRI techniques such as BOLD (blood oxygenation level dependent) signal (Ogawa et al., 1990), cerebral blood flow (CBF), and regional cerebral blood volume (rCBV) (Heeger and Ress, 2002). Recent studies show that DA function can be evaluated using MRI techniques in rats, monkeys, and humans (Chen et al., 1997, 1999a, 2001; Honey et al., 2003; Zhang et al., 2001). fMRI studies using iron oxide-based superparamagnetic agents and CBV measures (Mandeville et al., 1998) provide an optimal temporal and spatial resolution even in deep brain structures.

For neuronal activation in anesthetized animals, pharmacological challenges using selective agonists and antagonists of a neurotransmitter allow to characterize in vivo dynamic changes in function. We have used amphetamine to induce DA release in the nigrostriatal system and measured the changes in CBV with fMRI (Bjorklund et al., 2002; Chen et al., 1997; Jenkins et al., 2004) (Fig. 2). The loss of DA cells induced by 6-OHDA in rats was accompanied by a parallel decrease in the CBV response to both amphetamine and to CFT (Chen et al., 1997). Moreover, as in the PET studies mentioned above, we could demonstrate restoration of DA function after transplantation of fetal DA cells or embryonic stem cells using fMRI with an amphetamine challenge (Bjorklund et al., 2002; Chen et al., 1999b).

Increasing evidence suggests that an inflammatory reaction accompanies the pathological processes seen in many neurodegenerative disorders, including PD (Hirsch et al., 1998; McGeer and McGeer, 1998; McGeer et al., 2003). The contribution of inflammation to the progression of neurodegenerative disorders has become an active field of research in recent years as it may provide alternative therapeutic opportunities for such chronic diseases. Microglial cells are the macrophages of the brain and respond to noxious stimuli by changing morphology and expression of cell-surface markers and releasing pro-inflammatory cytokines (Minghetti and Levi, 1998). Activated microglial cells may play a major role in the extension of neuronal loss after a lesion or an insult, such as neurotoxin exposure. Migration of activated microglia and macrophages towards the lesion site correlates with the secondary damage after an acute neurotoxic event (Ullrich et al., 2001). Moreover, a similar mechanism might amplify and perpetuate neuronal damage in chronic neurodegenerative disorders, such as PD (Hirsch et al., 1998).

Recently, we have used a ^{11}C-labeled radioactive tracer that binds to the peripheral benzodiazepine receptor ^{11}C-PK11195 [*N*-sec-butyl-1-(2-chlorophenyl)-*N*-methylisoquinoline-3-carboxamide] (Camsonne et al., 1984) to study activated microglia in PD models. This ligand has been used in human studies to characterize microglia activation in several brain pathologies including encephalitis, stroke, and degenerative disorders (Banati, 2003; Banati et al., 1997, 1999; Cagnin et al., 2001, 2002). We found that intrastriatal administration of 6-OHDA induced a microglial reaction (Cicchetti et al., 2002) that may participate in the progression or extension of neuronal loss caused by the neurotoxin. Using PET and ^{11}C-PK 11195, we were able to detect an increase of specific binding along the ipsilateral nigrostriatal system in the 6-OHDA-lesioned rat (Cicchetti et al., 2002). Anti-inflammatory drugs such as the selective inhibitors of the inducible form of cyclooxygenase (COX-2) can reduce ^{11}C-PK-11195 binding and perhaps provide neuroprotection. We have investigated the protective effect of COX-2 inhibitors on the DA system and used PET combining DA specific tracers, such as the DAT ligand ^{11}C -CFT, in conjunction with inflammation markers and immunohistochemistry in a recent study (Sanchez-Pernaute et al., 2004). We found that chronic treatment with a selective COX-2 inhibitor constrained the inflammatory response induced by striatal 6-OHDA and limited, to a certain extent, the progressive DA neuronal death in the SN. Similar protective effects of selective COX-2 inhibitors have been reported in excitotoxicity and ischemia models (Kunz and Oliw, 2001; Nakayama et al., 1998; Nogawa et al., 1997; Scali et al., 2003).

Conclusions

In summary, current methodology using non-invasive imaging techniques allows detailed in vivo investigation of the DA system in normal and disease states. It is possible to

quantify the extent of DA neuronal loss, the development of compensatory changes, and the involvement of other (non-DA) brain regions. These studies are important to estimate biological variables like the rate of progression of the disease, in order to evaluate the impact of therapeutic and neuroprotective interventions. In addition, these imaging techniques are contributing to our understanding and modeling of disease mechanisms, which should in turn lead to development of new therapies.

Acknowledgments

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