

## Basal ganglia: New therapeutic approaches to Parkinson's disease

### Ann M. Graybiel

**As the search for molecular therapies for basal ganglia disorders, such as Parkinson's disease, accelerates, new neurobiological information is also leading to renewed interest in neurosurgical approaches.**

Address: Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Building E25, Room 618, Cambridge, Massachusetts 02139, USA.

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The motor symptoms of basal ganglia disorders fall at two extremes. In Parkinson's disease and related parkinsonian states, patients have difficulty in initiating movements. In Huntington's disease and related choreoathetotic disorders, patients make unwanted movements. Evidence has long placed two brain structures at the center of research on these disorders: the dopamine-synthesizing substantia nigra of the midbrain, which degenerates in Parkinson's disease, and the striatum of the forebrain, which degenerates in Huntington's disease. How neurodegeneration in these two nuclei could bring about such different symptoms has so far not made much neurobiological sense. The dopamine-containing cells of the substantia nigra innervate the striatum, so it appears that loss of dopaminergic innervation of the striatum produces the hypokinetic disorder of Parkinson's disease; and yet the loss of striatal cells themselves produces hyperkinetic disorders such as Huntington's disease. New neurobiological clues to the functional organization of the basal ganglia are now helping with both molecular biological and more classical approaches to treating these debilitating neurological disorders.

The potential of the molecular approach is demonstrated by the recent cloning of the Huntington's disease gene [1] and identification of proteins that interact with the gene's product, Huntingtin [2]. These represent major steps towards the development of a gene-based therapy for Huntington's disease. But what about Parkinson's disease, which is not associated with a clear genetic defect? The success of L-DOPA in relieving symptoms of Parkinson's disease was a pioneering example of a successful molecular-replacement therapy in neurology; L-DOPA is the biosynthetic precursor of dopamine. L-DOPA-based therapies tend, however, to lose effectiveness with time, and L-DOPA itself can induce abnormal and debilitating motor side effects (dyskinesias). Even without a clear genetic basis for Parkinson's disease, new molecular approaches to manipulating the dopamine system are being developed.

By targeted gene inactivation, 'knockout' mice have been generated that lack single dopamine receptor subtypes [3–7], or the dopamine transporter [8]. The receptor mutants demonstrate clear receptor-specific effects of dopamine on neurotransmission and behavior, and the transport mutants show remarkable behavioral changes as well. These mutant mice will be of great value in speeding the development of new pharmacological treatment of dopamine-based disorders. They also bring surprises about the molecular events responsible for the effects of addictive drugs such as amphetamine and cocaine.

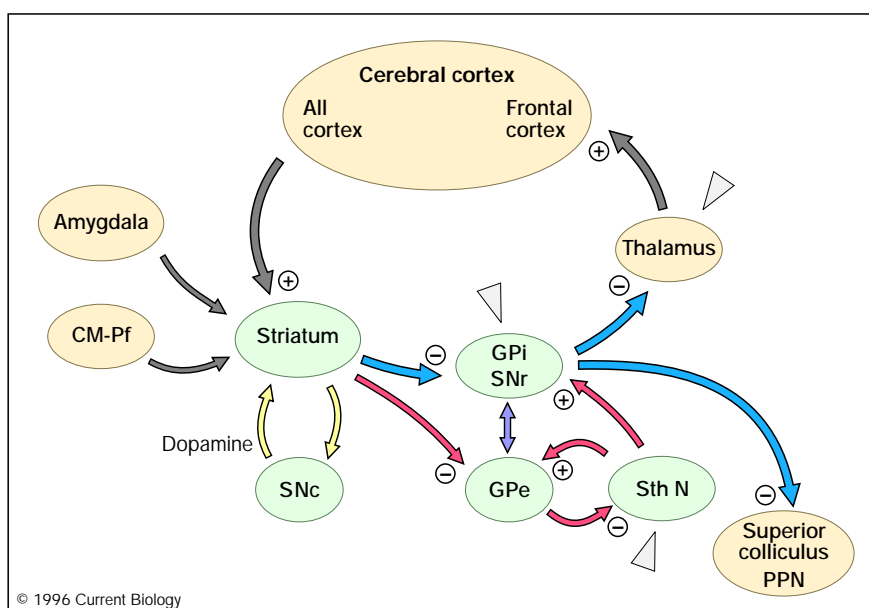
Zhou and Palmiter [9] have used an imaginative combined knockout/transgene strategy to generate mutant mice that specifically lack dopamine in the substantia nigra. They first generated knockout mice lacking tyrosine hydroxylase, an enzyme involved in synthesis of catecholamines such as dopamine and noradrenaline. The knockout mice die as embryos, but could be rescued by a tyrosine hydroxylase transgene that conferred synthesis of noradrenaline, but not dopamine, in neurons of the noradrenergic locus coeruleus. The rescued mice showed the classical signs of dopamine deficiency, dying at about two weeks of age. If given L-DOPA therapy, however, the mice lived and showed great improvement on all but the most complex motor tasks. Even more selective targeting strategies, using cell- or region-specific promoter sequences, offer great potential for devising new gene-based therapies.

A development in molecular biology that has clear therapeutic potential for treating Parkinson's disease is the cloning of genes encoding neurotrophins and growth factors. For example, glial-derived neurotrophic factor (GDNF) has been reported to halt the progression of degeneration in the substantia nigra induced by the neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) [10] or by axotomy [11], and preliminary tests of GDNF infusion to reduce symptoms in primate parkinsonian models are reported as being promising [12]. Even the signalling molecule Sonic hedgehog, known to have important roles in a number developmental contexts, may be an important player — it can induce neurons of the developing midbrain to differentiate with a dopaminergic phenotype *in vitro* [13]. These results suggest new therapeutic strategies in which molecules that promote the differentiation or survival of dopaminergic neurons are delivered to appropriate targets by using infusion techniques or transplantation.

At a time when molecular genetic techniques are advancing so rapidly and seem so promising, it is ironic that neurosurgery, a traditional and often last-hope approach to

Figure 1

Summary of basal ganglia circuits. Five key nuclei of the circuit are shown in pale green. Major inputs to the circuit lead to the striatum from the cerebral cortex, the amygdala and the intralaminar thalamus (CM-Pf). The striatum (which degenerates in Huntington's disease) is the source of three key pathways through the basal ganglia: First, the direct pathway (blue), which has two GABAergic inhibitory links in a row, so that activation of the striatum is thought to disinhibit ('release') the motor thalamus and subsequently the frontal cortex, as well as midbrain structures such as the superior colliculus and pedunculopontine nucleus (PPN). Second, the indirect pathway (red), which is thought to work in opposition to the direct pathway because of the added link through the subthalamic nucleus (Sth N) which excites direct pathway inhibitory function. And third, the striatonigral pathway to the pars compacta of the substantia nigra (SNc), which forms a loop (yellow) with the dopamine-containing nigrostriatal pathway that degenerates in Parkinson's disease. The two segments of the pallidum are also interconnected (purple). For clarity, a number of subcircuits have been omitted. Grey arrows point to sites of neurosurgical intervention by



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lesions or stimulation in Parkinson's disease patients; the arrow pointing to the globus pallidus (Gpi) indicates the site of posteroventral pallidotomy discussed in text.

Most growth factor/neurotrophin and transplant strategies are directed toward the nigrostriatal system. SNr, non-dopaminergic (reticular) part of the substantia nigra.

basal ganglia disorders, is re-emerging as a major way of treating Parkinson's disease [14–22]. The renewed interest in neurosurgical treatments for Parkinson's disease is based on the use of new neurobiological information to determine precise targets for the brain lesions. The central idea prompting the neurosurgical effort is that the extremes of motor disability found in hypokinetic and hyperkinetic basal ganglia disorders reflect imbalances between two major basal ganglia pathways: a 'direct' pathway (or family of pathways) from the striatum to motor executive regions, and an 'indirect' pathway that modulates the direct one (Fig. 1) [23–25].

Both the direct and the indirect pathways lead to parts of the globus pallidus and to the non-dopaminergic (reticular) part of the substantia nigra. The direct pathway leads on to the thalamus and frontal cortex or, *via* the substantia nigra, to the brainstem. The neocortex can excite this direct pathway by releasing an excitatory amino acid, such as glutamate, from corticostriatal terminals, and because two inhibitory —  $\gamma$ -amino-butyric acid (GABA)-releasing — synapses then follow in a row (Fig. 1), the circuit is thought to activate cortical and brainstem movement centers. The indirect pathway is supposed to have exactly the opposite effect, because it includes an excitatory link in a small but pivotal nucleus, the subthalamic nucleus. The subthalamic nucleus turns on inhibition in the direct pathway. This push-pull system, so current notions go,

works by enhancing movement through activity in the direct path and diminishing it through activity in the indirect path ([23,24], but see [26]). This notion has shifted the therapeutic focus away from the dopaminergic substantia nigra and striatum to the pallidum and subthalamic nucleus.

Neurosurgical lesions are being made — first in MPTP-treated parkinsonian monkeys [27] and now in patients with Parkinson's disease [14,16–18,21,22] — to increase mobility by decreasing tonic direct pathway inhibition of the thalamus. Localized high-frequency stimulation delivered by portable stimulators is also being vigorously pursued as a way of making reversible, 'functional lesions' [15,19,20]. The targets for the lesions are the subthalamic nucleus, the thalamus and now (the preference of many groups) the internal segment of the globus pallidus (Fig. 1). Dramatic and immediate symptomatic relief can occur with a posteroventral pallidal lesion, as originally documented by Leksell [14] and Laitinen [16] and their coworkers. Most patients remain on L-DOPA, however, and reports based on careful ongoing studies (for example [22]) do not make claims of complete reversal of symptoms. Long-term follow-ups have not yet been possible. A key feature of the pallidotomy procedure appears to be to confine the lesion to the most strictly 'motor' (posteroventral) part of the pallidum and/or associated fiber bundles. This requires demanding collaborative efforts of

neurosurgeons, neurologists and physiologists to identify the critical target site with extracellular recording methods.

Following posteroventral pallidotomy, a striking normalization of metabolic activity in the premotor/supplementary motor cortex has been demonstrated by positron emission tomography (PET) scans [18,28]. This finding strongly supports the notion that the pallidal lesion decreases inhibition of thalamo-cortical circuits. Ironically, however, one of the great successes of the posteroventral pallidotomy procedure calls into question some of the notions on which the surgery is based. Opinion is growing that the procedure is strikingly effective in reducing L-DOPA-induced dyskinesias (for example [21,22]), and it is not at all clear how this could fit with enabling movement in Parkinson's patients. Another puzzle is how the symptomatic relief can be so great when the treatment does not, apparently, involve the reticular part of the substantia nigra, which contains many direct path neurons affecting movement (Fig. 1). Finally, there are questions about whether the pallidal lesions have cognitive effects as well — and, if so, what mechanisms might underlie such effects.

Molecular therapies based on this notion of direct and indirect pathways are also rapidly being developed. Glutamate receptors are reasonable targets for such efforts to control interactions between the direct and indirect pathways [29], as are receptors for peptides coexpressed with GABA in the direct and indirect pathways [25,30]. Interest is also shifting back to the nigrostriatal system, especially as studies of knockout mice clearly show that dopamine D<sub>1</sub> and D<sub>2</sub> receptors can selectively control the expression of direct and indirect pathway neuropeptides. D<sub>1</sub> receptor mutants have sharply diminished basal ganglia expression of dynorphin [3] and substance P [3,4], the neuropeptides coexpressed with GABA in the direct pathway, whereas D<sub>2</sub> receptor mutants show loss of basal ganglia expression of enkephalin, the neuropeptide coexpressed with GABA in the indirect pathway [7]. These contrasting effects suggest that dopamine, acting at D<sub>1</sub> and D<sub>2</sub> receptors, can selectively affect the functioning of the direct and indirect pathways.

Perhaps the most optimistic view to take is that, while gene- and growth-factor-based therapies are being devised to prevent neurodegeneration, strategies aimed at symptomatic relief of Parkinson's disease and other basal ganglia disorders can profit from innovative combinations of molecular biology and neurosurgery. There is, moreover, a real possibility that, as more is learned about the neurobiology of the basal ganglia, these strategies can be applied to conditions involving, not only the motor symptoms of basal ganglia dysfunction, but the cognitive and affective symptoms as well.

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