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15 Diseases of the Basal Ganglia

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Parkinson's Disease (PD)

In 1817 a general practitioner in Shoreditch, London, wrote an essay on the shaking palsy describing a neurological disorder in some of his patients which has become associated with his name. The main features are:

(1) Slowness and loss of movements known as bradykinesia or akinesia
(2) Muscle stiffness and rigidity
(3) Tremor of the limbs mainly at rest (but not in sleep)

These result in a shuffling gait, an inability to initiate even simple movements like turning, a stooped posture and micrographia (small handwriting). It is a slowly progressing degenerative disease affecting, at most, some 1% of the population above 55 years.

PATHOLOGY

It was known for most of the twentieth century that the brains of PD patients lacked the dark pigmentation characteristic of neurons in the substantia nigra. Such colouring is caused by melanin granules in their cell bodies and although its role is uncertain it is only found in humans and primates and they alone can develop the symptoms of PD. The substantia nigra (SN) is also characterised by round eosinophilic intraneuronal inclusions known as Lewy bodies, which are increased in PD. Neither neuromelonin nor Lewy bodies are confined solely to the SN but it is the neurons of the SN which degenerate in PD.

Since these neurons form the dopaminergic nigrostriatial tract (Fig. 7.1) it is not surprising that PD patients also show a loss of striatal DA. This was first detected in post-mortem studies in 1960 by Hornykiewicz and numerous studies since have shown that not only is PD associated with and presumably caused by a loss of striatal DA, but at death that loss actually reaches more than 80%. Within the striatum DA loss is greater in the putamen which has predominantly motor links with the cortex than in the caudate mucleus with its connections to cortical association areas.

Recently PET studies with 6-fluorodopa, which is taken up by DA nerve terminals in the striatum and is therefore presumably a measure of both the number of functional DA neurons in the nigrostriatal tract to it as well as its DA content, show that this is more like 50% of normal at the start of symptoms, not the 80% observed at PM (see

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Fig. 15.1). In fact sequential PET measurements in selected patients as the disease progresses followed by extrapolation backwards suggests that DA loss may start some 5 years before symptoms first appear. Nevertheless it is surprising that in all PM studies of normal and PD brains the concentration of striatal DA is either normal or only 10-20% of it.

Three questions need some consideration.

(1) Is the DA loss confined to the nigrostriatal tract?
(2) Are other NTs affected?
(3) Why do the symptoms only occur when DA loss is so marked?

There is some loss (40–60%) of DA in the nucleus accumbens of the mesolimbic system in the ventral tegmentum (A10) and cortex at post-mortem but nowhere is it as marked as in the striatum. Some loss of NA, 5-HT, CCK and the enkephalins and of the markers GAD and ChAT (for GABA and ACh) have been reported in the striatum, SN and other areas but these rarely exceed 50% and could be secondary to DA loss.

The ability of the striatum to apparently function normally until it has lost much of its DA can be ascribed in part to denervation supersensitivity, the degeneration of the DA input resulting in an increase in postsynaptic DA receptors and partly to the remaining neurons producing more DA. This is supported by measurements in humans which show that the HVA:DA ratio, a measure of DA turnover, is much greater in Parkinsonism patients and by microdialysis in rats with 6-OHDA lesions of the nigrostriatal tract, when the reduction in perfusate (released) DA is very much less than that of neuronal (stored) DA.

Thus initially the nigrostriatal tract is able to compensate for the loss of neurons but eventually this fails and the symptoms of PD emerge.

ANIMAL MODELS

Since PD is caused by a relatively specific degeneration of the DA nigrostriatal tract and as there are specific toxins, for DA neurons, i.e. 6-OHDA and MPTP, it should be possible to produce appropriate experimental models. Certainly both toxins cause rotational behaviour in rats (Fig. 7.7) but no rodent shows a syndrome suggestive of PD. Tremor and akinesia can be seen, however, in primates after such toxins and these are being more widely used in experimental studies of PD and drug evaluation. Reserpine causes a depletion of all brain monoamines and produces motor defects in rats, which, even if not PD-like, do respond to DA manipulation.

BASAL GANGLIA CIRCUITRY (Fig. 15.2)

In order to understand how the symptoms of PD could arise from a loss of striatal DA and what can be done to replace it and treat PD, it is necessary to know something of basal ganglia circuitry and the role of DA in it. The scheme to be outlined should, however, be regarded as a working template rather than fully proven fact but there is much evidence for it (Fig. 15.2). Certainly the striatum, i.e. the putamen and caudate nucleus, is accepted as the main receiving area in motor circuits. Information coming to

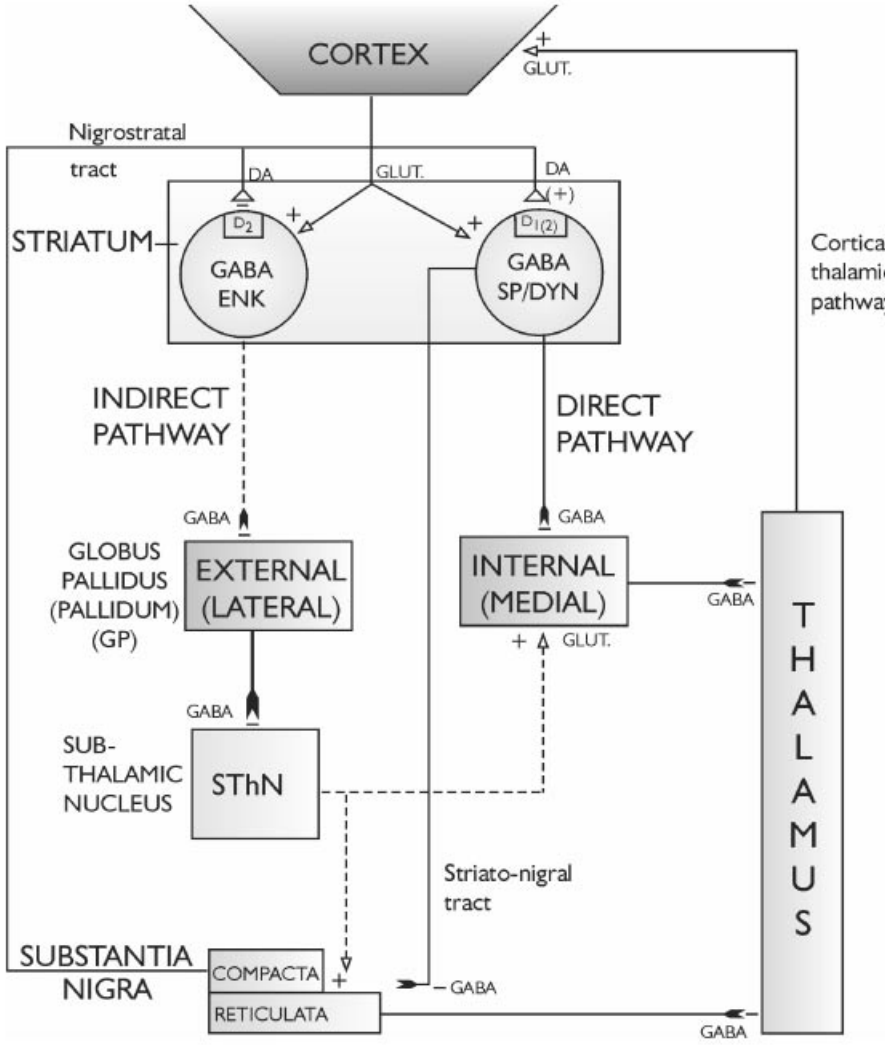

Figure 15.2(a) A schematic presentation of possible normal basal ganglia circuitry. Activity in the cortico-thalamic pathway is modulated by striatal control of the globus pallidus (pallidum) through two pathways, the indirect pathway (Ind Path) to the external pallidum/globus pallidus (GPext) and the subthalamic nucleus (SThN) and the direct pathway (Dir Path) to GPint. Scheme based on that of Chesselet and Delfs (1996) but see text. Pathway activity: ---- low; — normal; **—** high

it from the cortex and thalamus is processed and channelled to the pallidum (globus pallidus, GP) and to the substantia nigra reticulata.

There are two main output pathways from the striatum to the globus pallidus.

(1) The *direct pathway* (Dir Path) which makes monosynaptic contact with the internal (medial) globus pallidus (GPint) and to a lesser extent the substantia nigra reticulata (SNr).

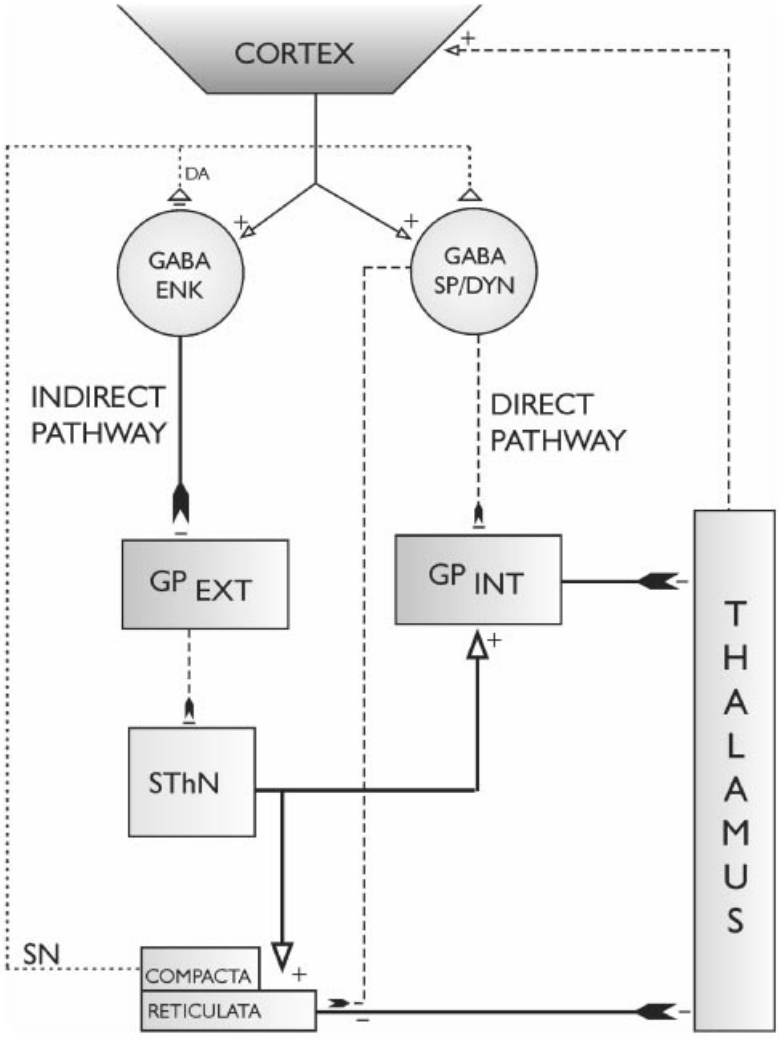

Figure 15.2(b) A schematic presentation of possible basal ganglia circuitry in Parkinson's disease. In PD there is little or no inhibitory nigrostriatal input to the striatum so the Ind Path is active and GPext is inhibited. This will then have less depressant effect on the SThN which will be free to drive the GPint (and SNr) and so reduce cortico-thalamic traffic and produce akinesia. See text for detail. Pathway activity: ---- low; — normal; ═ high

(2) The *indirect pathway* (Ind Path) which also influences GPint and SN but only after going through the external (lateral) GPext and the subthalamic nucleus (SThN).

The GPint and, to a lesser extent, the SNr modulate activity through the thalamo-cortical motor pathways (Fig. 15.2a). These outputs and both the direct and indirect pathways appear to be inhibitory.

The axons of both pathways arise from the medium spiny neurons that constitute 80% of striatal cells. These neurons release GABA but those to the Ind Path have

metenkephalin as a co-transmitter and express only D_2 receptors while those to the Dir Path have dynorphin and substance P (the latter mainly to SNr) and express both DA receptors but D_1 predominates. Activation of D_2 receptors results in inhibition of the GABA/ENK neurons of the Ind Path, and probably of the Dir Path, but the D_1 effect could be excitatory on the neurons of the Dir Path as there is a reduction in substance P mRNA in the striatum after blocking its DA input.

Normally (Fig. 15.2(a)) DA inhibits the Ind Path to GPext so that this is then free to inhibit the SThN. This latter system can then no longer drive, through glutamate release, the SNr or GPint whose inhibitory outputs are reduced. The assumption is that the thalamo-cortical pathway can then function properly and movement is normal.

The role of the Dir Path is less clear. When it is active it should inhibit Gpint (and SNr) and so reduce their suppression of the thalamo-cortical pathway. If it is inhibited by DA in the striatum then the converse applies, GPint will be active and thalamo-cortical traffic will be reduced. On balance it seems, however, that DA stimulates the neurons of the Dir Path so that the GPint is inhibited and thalamo-cortical flow facilitated. Some evidence for this comes from the finding that in Huntington's Chorea when the GABA/ENK (Ind Path) neurons degenerate and the Dir Path dominates the patient suffers from dyskinesias-facilitated movement.

Whatever the precise activity of these pathways, DA obviously has a pivotal role in their control. Thus in PD (Fig. 15.2(b)) when there is little DA to inhibit the Ind Path there is more inhibition of GPext which frees the SThN to drive GPint and SNr to inhibit the thalamo-cortical link and motor activity, i.e. produce hypokinesia. The fact that lesion of GPext causes some rigidity in animals supports this. Also if the Dir Path is not driven in the absence of DA, this will also free GPint to inhibit motor activity.

So how can the abnormal pattern of striatal activity that causes akinesia be restored to normal?

THERAPY

Parkinsonism is unique among diseases of the CNS, in that it results from the known loss of a particular NT, i.e. DA, resulting from the degeneration of a particular pathway, the nigrostriatal. Dopamine also has a relatively limited distribution in the brain and few peripheral effects. It should therefore be amenable to therapy based on augmenting its function. Also since the role of DA appears to be to maintain a tonic inhibitory control on GABA output pathways from the striatum, possibly in part by an extra synaptic action (Chapter 6), it may not be necessary for it to be released physiologically from nerve terminals. Thus it may be adequate to just provide DA extracellularly.

Nevertheless it must also be expected that anything which increases DA function not only controls extrapyramidal function but also reproduces the other central effects of DA; i.e. vomiting, a reduction in prolactin secretion and some psychotic manifestations. In excess it may also cause dyskinesias. Despite these problems, the therapy of PD is one of the success stories of neurology.

It is generally assumed that DA itself cannot be used because it does not cross the blood–brain barrier although some recent mocrodialysis studies following intravenous DA indicates that this may not be so, in rats anyway. Thus PD may be treated by

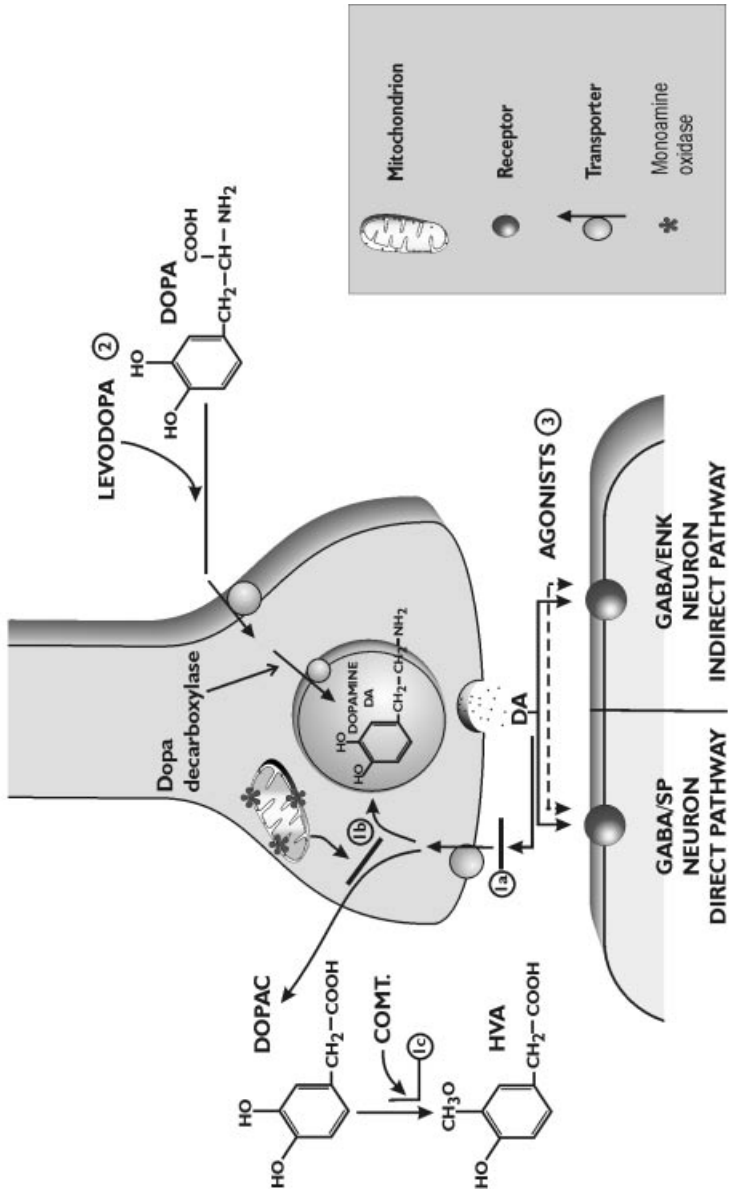

Figure 15.3 Mechanisms of augmenting dopamine function at synapses in the striatum. Synaptic DA levels may be increased by blocking its neuronal uptake (1a), inhibiting the metabolising enzymes MAO_B (1b) or COMT (1c) or by providing its precursor dopa in its levo form (2). The DA receptors may also be stimulated by appropriate D_2/D_1 agonists (3)

(A) Augmenting the action of DA (Fig. 15.3)
(B) Modifying the action of other NTs that could oppose or augment DA function
(C) Non-pharmacological approaches, e.g. grafts

Within these approaches one can:

(A) (1) Increase the action of the remaining DA by reducing its destruction
(2) Replenish DA by giving its precursor levodopa
(3) Mimic the action of DA with appropriate DA receptor agonists
(B) (4) Block the action of any NT released from the neurons of striatal output pathways that are normally inhibited by DA (Fig. 15.8)
(5) Reduce or increase the effects of any NT that could be either antagonising or augmenting the action of DA in the striatum (Fig. 15.9)
(C) (6) Transplant appropriate neural tissue into the striatum
(7) Lesion the pathways that DA no longer inhibits or stimulate opposing ones

In addition to therapy it is hoped that the cause of PD can be established and degeneration of DA neurons stopped or even reversed by pharmacological (including trophic) means or genetic manipulation.

(A) (1) INCREASING THE EFFECTIVENESS OF THE REMAINING DA

Dopamine is removed from its site of action by uptake into nerve terminals and metabolism by MAO and COMT. Drugs are available to block all these processes. The DA neuronal uptake transporter can be distinguished from that for NA and is blocked preferentially by nomifensine. Also unlike NA, which is a substrate for MAO_A, dopamine is a substrate for MAO_B for which selegiline (deprenyl) is an effective inhibitor. The efficacy of both nomifensine and selegiline might be augmented initially by supersensitivity to the remaining DA (increased receptor number) but this decreases with time and augmenting synaptic DA increases the likelihood of stimulating terminal autoreceptors and inhibiting DA release. In view of these problems and the progressive degeneration of DA neurons it is not surprising that nomifensine has little effect but selegiline does produce some improvements in the early stages of the disease and there has been much interest in the possibility that it can prevent, or at least reduce, further degeneration (see section on Aetiology).

O-methylation of DA is a secondary line of metabolism and its inhibition has little effect on the removal of DA but drugs that block this enzyme are gaining a place in prolonging the action of levodopa.

(A) (2) REPLENISHING DA: LEVODOPA

Early use

Irrespective of whether or not DA can cross the blood-brain barrier it will certainly be destroyed after oral administration by MAO and COMT in the gut and liver before achieving an adequate plasma concentration. Levodopa, by contrast, is not a good substrate for MAO, although metabolised by COMT (Fig. 15.4) and is transported across the gut and blood–brain barrier.

Early attempts to treat PD with dopa failed because the doses used were too small. This arose partly from the fear that it would be converted to NA as well as DA and so

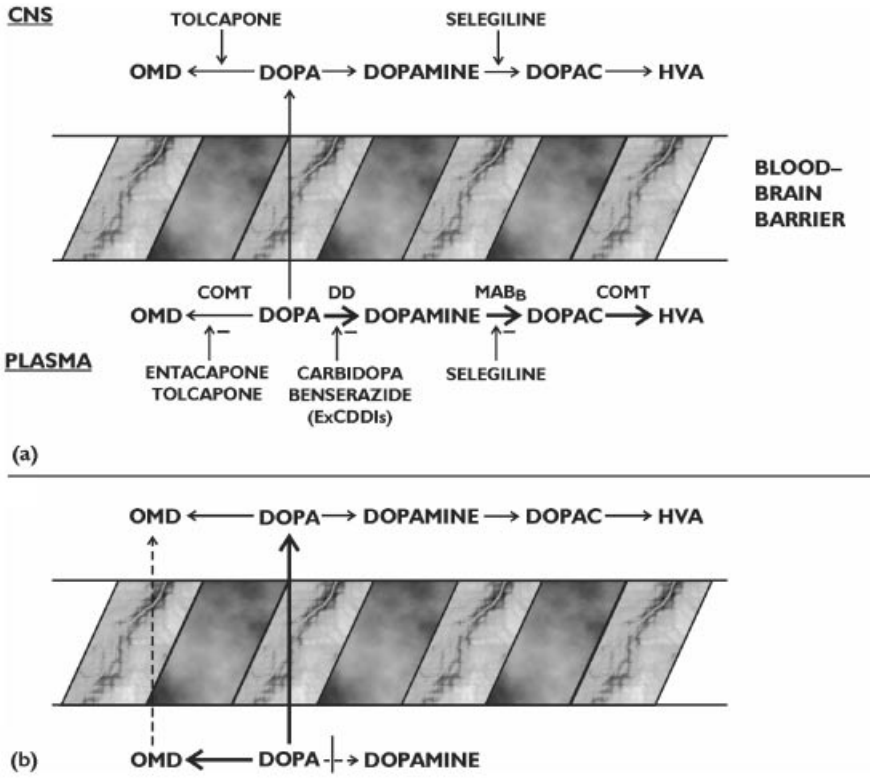

Figure 15.4 The central and peripheral metabolism of levodopa and its modification by drugs. (a) **Levodopa** alone. After oral administration alone most dopa is rapidly decarboxylated to DA in the gut and blood with some *o*-methylated (COMT) to *o*-methyl/dopa (OMD). Only a small amount (3%) enters the CNS to be converted to DA. (b) **After an extracerebral dopa** decarboxylase inhibitor. Blocking just the peripheral dopa decarboxylase (DD) with inhibitors like carbidopa and benserazide, that cannot enter the CNS (extra cerebral dopa decarboxylase inhibitors, ExCDDIs), stops the conversion of levodopa to DA peripherally, so that more enters the CNS or is *o*-methylated peripherally to OMD.

The deamination of DA to DOPAC can be prevented by MAO_B inhibitors such as selegiline while COMT inhibitors stop its further *o*-methylation to HVA and the conversion of dopa to OMD. COMT inhibitors can act just peripherally (entacapone) or in the CNS as well (tolcapone). DD — dopa decarboxylase; MAO — monoamine oxidase; COMT — catechol-*o*-methyl transferase

raise BP. In fact DA synthesis is favoured, since dopa decarboxylase is widely distributed and never saturated, but further synthesis to NA is limited by the restriction of dopamine *B*-hydroxylase to vesicles in NA nerve terminals.

Fortunately Cotzias and his colleagues (1967), after finding that large doses of levodopa (in excess of 3 g) were effective in South American miners suffering from manganese poisoning and showing symptoms akin to PD, tried them successfully in Parkinsonism patients. Subsequently lower doses (0.5–1.0 mg) were tried universally and found to be effective. It is generally accepted that the improvement is very good in 35% of patients, good in 30% and moderate in 30% with some ($<5\%$) not really responding. Indeed its effect is so dramatic that the validity of PD diagnosis in the non-responders is questioned.

It is not the object of this text to cover the detailed pharmacology and use of drugs but levodopa must be an exception. Its use in PD illustrates the problems that still have to be overcome even after the cause of a disease of the CNS has been established and a treatment devised.

Mode of action

Levodopa itself has virtually no affinity for DA receptors and if its conversion to DA is stopped by inhibiting its decarboxylation in the brain then it has no behavioural (DA-like) effects in animals. More importantly, it loses its efficacy in primates with experimental (MPTP) Parkinsonism. Thus it must be converted to DA. Unfortunately most of the DA nerves that would normally do that in the striatum have degenerated and the remainder are already working overtime. Nevertheless it is known from experimental studies, after virtually complete destruction of the nigrostriatal tract, that systemic dopa can still increase striatal DA. Presumably conversion must take place in other neurons or as dopa crosses the blood-brain barrier. Whichever is correct, dopa will increase DA not only in the striatum but elsewhere in the brain and so side-effects occur such as vomiting (60% of patients), dyskinesia (80%), some psychoses (25%) and a reduction in prolactin secretion. Although some phasic hypertension may be seen, the dominant cardiovascular effects are cardiac arrythmias and hypotension (50%) probably through reduced sympathetic activity either due to DA displacing NA in peripheral sympathetic nerve terminals or a reduction in central sympathetic outflow.

Unfortunately levodopa (only the levo form of dopa is active) has a very short plasma half-life ($\frac{1}{2}t$) of 1½–2 hours. Also it is estimated that only 30% of an oral dose reaches the circulation and less than 10% of that gets into the CNS. How, then, can the efficacy of levodopa be improved?

Adjuncts

Decarboxylase inhibitors

A glance at Fig. 15.4 will show that levodopa is metabolised primarily by dopa decarboxylase to DA and by COMT to 3-methoxy tyrosine, but usually referred to as OMD (*o*-methyldopa).

Blocking the conversion to DA would appear stupid unless this could be restricted to the periphery. More dopa would then be preserved for entry into the brain, where it could be decarboxylated to DA as usual. Drugs like carbidopa and benserazide do precisely that and are used successfully with levodopa. They are known as extracerebral dopa decarboxylase inhibitors (ExCDDIs). Carbidopa (α-methyldopa hydrazine) is structurally similar to dopa but its hydrazine group ($NHNH_2$) reduces lipid solubility and CNS penetration (Fig. 15.4).

ExCDDIs certainly improve the efficacy and duration of action of levodopa so that it can be given in a smaller dose (e.g. 25%) and generally in a 4:1 ratio, levodopa:ExCDDI. As might be expected, some DA side-effects such as dyskinesia and psychoses are worse, but hypotension is less (no peripheral effects of DA) and vomiting is actually much reduced or abolished. This is because the chemoreceptor trigger zone of the vomiting centre while in the brain is on the blood side of the blood–brain barrier and will not be stimulated since no DA is formed peripherally (Fig. 15.5). That an

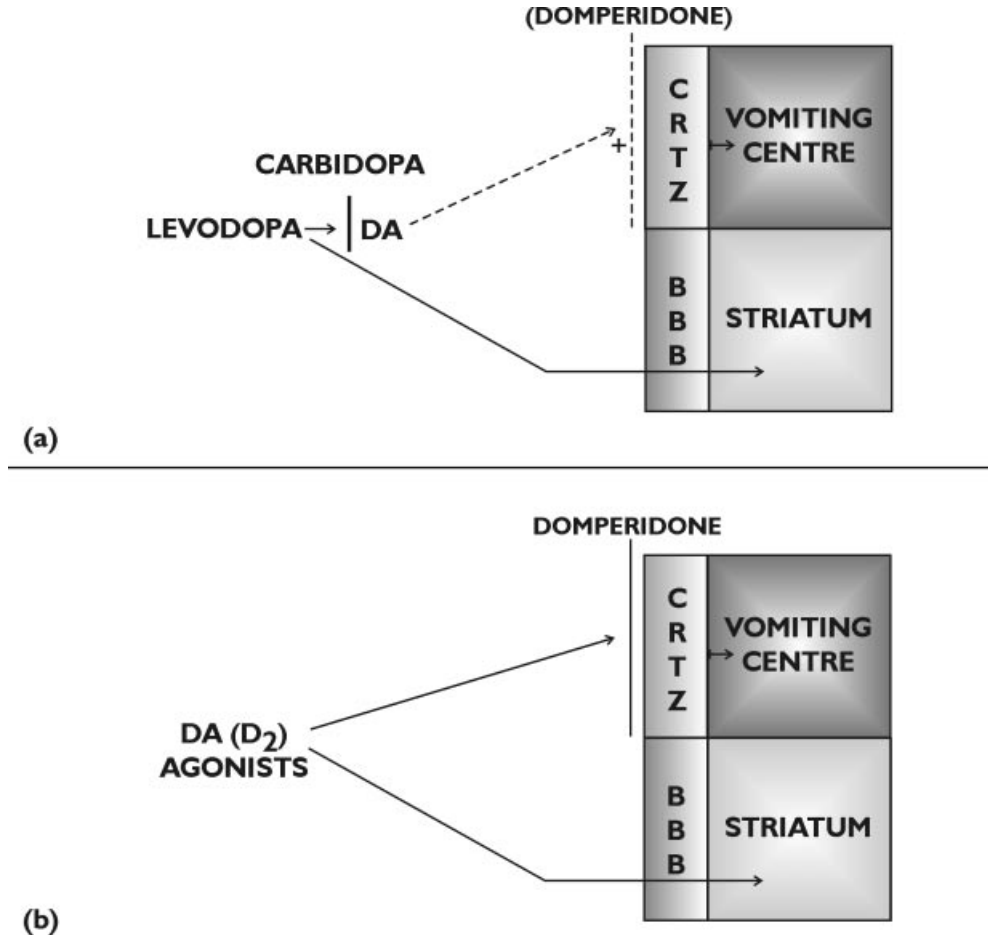

Figure 15.5 Counteracting the emetic effect of (a) levodopa and (b) a dopamine agonist in the therapy of PD.

DA produces vomiting by acting on the chemo receptor trigger zone (CRTZ) of the vomiting centre (VC) outside, on the blood side, of the blood–brain barrier. When levodopa is given with an extracerebral dopa decarboxylase inhibitor like carbidopa it is not converted to DA peripherally and so there is no stimulation of the CRTZ. The emetic effect of a DA (D_2) agonist can be prevented by a D_2 antagonist like domperidone which acts only peripherally. This could also prevent the emetic effect of any DA formed peripherally from levodopa. Since neither carbidopa nor domperidone enter the CNS they do not modify the central effect of either levodopa or a DA agonist

ExCDDI does reduce the peripheral metabolism of dopa in humans and increase the amount entering the brain in animals is shown in Fig. 15.6.

COMT inhibitors

Levodopa is a better substrate for COMT than MAO and when given with an ExCDDI most of it is *o*-methylated to OMD (Fig. 15.4). Recently COMT inhibitors have been developed which act either just peripherally (entacopone) or centrally as well

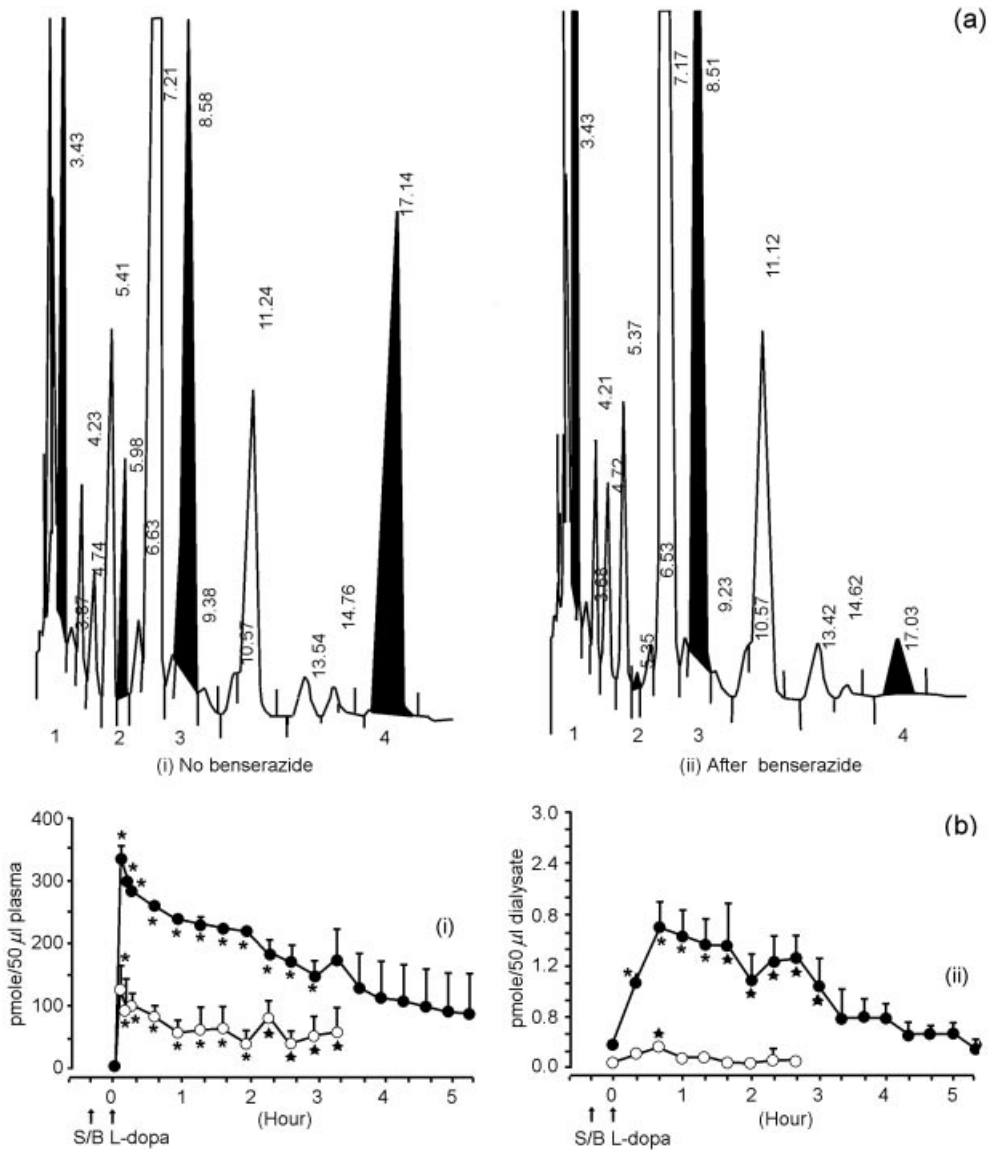

Figure 15.6 The effect of the extra cerebral dopa decarboxylose inhibitor, benzerazide, on the metabolism of levodopa. (a) HPLC chromatogram of human plasma pooled after being taken at varying times over 4 h after levodopa given orally (250 mg) either alone (i) or (ii) following benserazide (50 mg) to a PD patient. Peaks 1 = dopa, 2 = DOPAC, 3 = OMD, 4 = HVA. These peaks have been filled in to highlight them. Dopamine is not seen in either trace due to its rapid metabolism to DOPAC and HVA. Peaks for both these metabolites are seen in (i) but they are much reduced in (ii) indicating that in the presence of benserazide very little DA had been formed peripherally. The OMD peak is much greater after benserazide, which again indicates that dopa has been *o*-methylated (by COMT) rather than decarboxylated. (Unpublished data, Bovingdon, M and Webster, RA). (b) Time-course of dopa levels in microdialysates from the striatum of an anaesthetised rat after 15 mg/kg levodopa given intravenously 20 min after saline (open circles) or 5 mg/kg benserazide (filled circles). After benserazide dopa CSF levels rose eight times. (Unpublished figure, Wan Ya Chang and Webster, RA)

(tolcopone). Both have been tried clinically and shown to prolong the plasma half-life and effect of dopa (+ExCDDI).

Long-term effects

After some 5 years of treatment, most patients show

(1) Abnormal involuntary movements (AIMs), manifest mainly as dyskinesias at the peak plasma level of dopa.
(2) End-of-dose akinesia, i.e. a quicker return to the symptoms of PD.
(3) The ON–OFF effect in which patients experience abrupt swings, perhaps in a matter of minutes, between the extreme of AIMs (1) and akinesia (2). A patient may be walking fairly well but then become suddenly akinetic and fixed before quickly moving again.

These effects could result from the progression of the disease but as they are a feature of levodopa therapy a change in the central response to levodopa or changes in its peripheral kinetics are more likely. The latter does not occur since the maximum plasma concentration, the time to reach it and the plasma half-life are still similar after 10 years of treatment to those achieved initially, although continuous infusion of dopa can smooth out the swings.

As the disease progresses there will presumably be a further loss in the ability of striatal neurons to synthesise DA whether from endogenous or exogenous dopa but the occurrence of dyskinesias suggests that enough DA can somehow still be formed. In view of the complexity of the striatal output pathways and the critical role of DA in controlling the balance between them it is perhaps not surprising that sudden swings in motor function can occur especially with a drug like levodopa that affects both outputs (see below).

Attention has been given to the possibility that some of the above motor effects may arise from a metabolite of levodopa. The prime suspect is OMD which has a half-life of some 20 hours and reaches plasma concentrations three- to fourfold those of dopa. Suggestions that it may compete with dopa for entry across the blood–brain barrier or act as a partial agonist (effective antagonist) have not been substantiated experimentally although it does reduce DA release from rat striatal slices. Also if free radical production through deamination of DA is neurotoxic (see below) then this would be increased by levodopa.

Despite all these problems, levodopa improves the life of the PD patient, effectively slows progession of the disease and prolongs life.

(A) (3) DA AGONISTS

Since there is no reduction in striatal postsynaptic DA receptors in PD then drugs acting directly on them should be effective and in theory present some advantages over levodopa. They do not have to be converted to DA, they can be designed to be long-acting, cross the blood–brain barrier and act on specific DA receptors. In practice they have been somewhat disappointing.

Despite the fact that in quantitative studies of motor performance they often appear to produce more benefit than levodopa and are less likely to cause dyskinesia and ON–OFF fluctations, patients tend to prefer levodopa. Possibly unless DA function is

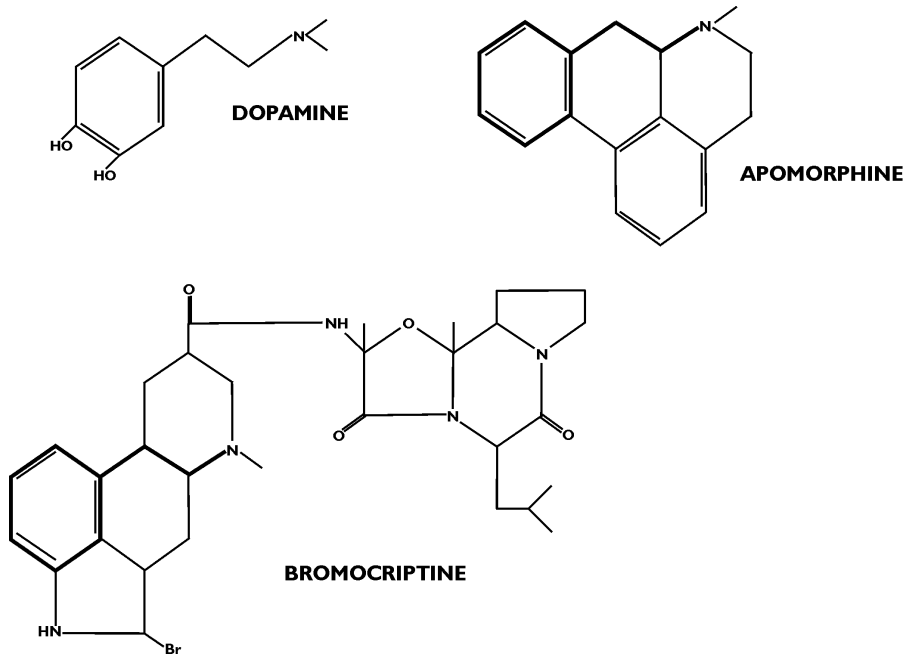

Figure 15.7 Chemical structure of some DA agonists. The structure of DA is shown for comparison and its configuration emphasised in the agonist structure where appropriate

pushed towards the extreme of causing dyskinesia, as with levodopa, there is inadequate release from akinesia. Dyskinesia seems preferable to akinesia.

With most DA agonists there are the other expected signs of increased DA activity such as hallucinations, psychosis and hypotension which can be worse than with levodopa. Fortunately vomiting can be countered by giving the DA antagonist domperidone. This does not cross the blood–brain barrier and so counteracts only the peripheral (chemoreceptor trigger zone) effect of the DA agonist (Fig. 15.5).

Bromocriptine was the first DA agonist used followed by pergolide and lisuride and more recently the very long-acting cabergoline. They are all erot derivatives (Fig. 15.7) and act predominantly on D_2 receptors. Other non-ergolines under test include ropinirole and pramipexole. Apomorphine is a D_2 and D_1 receptor agonist which was tested in PD long before any other agonist but abandoned because of vomiting. Recently with anti-emetic (domperidone) back-up it has been shown to be effective and even reduce the ON–OFF fluctuations of levodopa. Unfortunately it is ineffective orally.

DA agonists have rarely been used alone or before levodopa although there is interest in whether this latter approach would avoid the early use of levodopa and so reduce the time over which it was given and delay the appearance of its side-effects. Generally monotherapy, especially long term, with DA agonists is not considered adequate. This may be because there is some evidence that they still require the presence of endogenous DA to be fully effective. In fact studies in marmosets with experimental (MPTP-induced) Parkinsonism show that after inhibition of central dopa decarboxylase and thus the synthesis of striatal DA, specific D_1 and D_2 agonists were inactive alone and

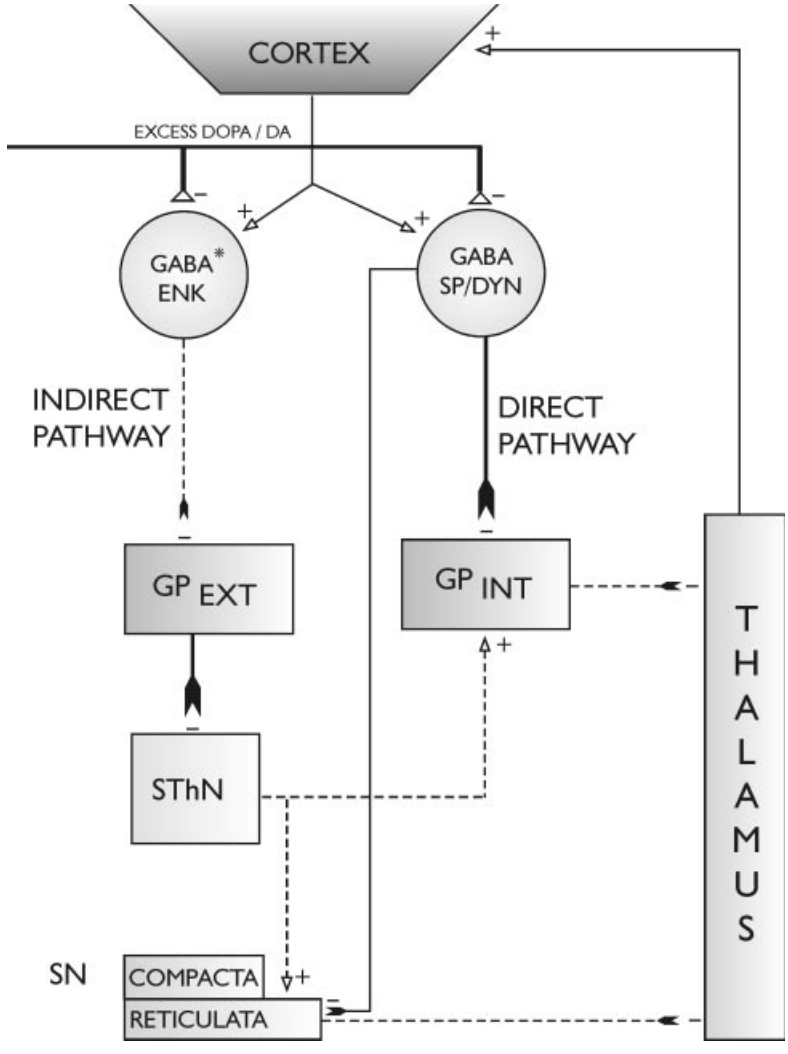

Figure 15.8 A schematic presentation of possible basal ganglia circuitry after excess dopa. High DA levels formed from excess levodopa could so depress the Ind Path that there is little inhibition of GPext which is then able to control the SThN leaving it unable to drive GPint or SNr. Cortico thalamic traffic will then be facilitated and dyskinesias could develop. This may possibly be augmented by DA driving the Dir Path and further inhibiting GPint. See text for detail. *Neurons lost in Huntington's Chorea. Pathway activity: ---- low; — normal; ═ high

less effective in combination unless given in high doses that could be inappropriate clinically (Treseder, Jackson and Jenner 2000).

DOPA, DA AGONISTS AND STRIATAL FUNCTION (Fig. 15.8)

The production of DA from levodopa should restore the normal striatal picture from that proposed for PD by inhibiting striatal output pathways (Fig. 15.8). It may

probably also reduce glutamate release from the excitatory cortical input to the striatum which drives the output pathways. However, too much dopa (DA) could swing the balance in favour of the Dir Path and so facilitate thalamo-cortical activity to produce dyskinesias (see Fig. 15.8). The possible importance of the D_1 effects of levodopa is substantiated by the finding that after treating rats with levodopa and carbidopa for four weeks it was the decrease in substance P mRNA expression on neurons of the D_1-controlled Dir Path rather than the increase in ENK mRNA expression of neurons on the D_2-controlled Ind Path, induced by 6-OHDA leisons, that was reversed (Jolkkonen, Jenner and Marsden 1995).

Since D_2 (but not D_1) receptors are expressed on neurons of the Ind Path, then D_2 agonists will have the same effect on this pathway as levodopa and overcome the hypokinesia. Their inability to activate D_1 receptors could mean, however, that while they are less likely to cause dyskinesias, for the reasons given above, their ability to dampen the GPint may also not be sufficient to give the required facilitation of motor function. Conversely, the absence of D_1 receptors on the Ind Path explains why their agonists cannot influence it and so appear unable to reduce hypokinesia.

Although D_1 agonists alone are considered to have little value in the treatment of PD, the knowledge that the mixed agonist apomorphine (and indeed levodopa) appears to be more effective than a D_2 agonist alone and as experimental evidence indicates that the full DA behavioural effect can only be achieved by stimulating both D_2 and D_1 receptors (Chapter 7, Fig. 7.9), the obsession with D_2 stimulation in PD is perhaps surprising. There are as many D_1 as D_2 receptors in the striatum and it is unlikely that they are all redundant. Unfortunately few specific full D_1 agonists have been available for evaluation until recently (see Hagan *et al.* 1997). Some show promise in both animal models and humans, although the reported absence of dyskinesias is perhaps surprising in view of the considered role of D_1 receptors in their initiation (see above). Nevertheless, treatment with specific D_1 and D_2 agonists in controlled combinations could be useful.

The efficacy of DA agonists, even if not total, does show that striatal function can be reinstated to some extent by merely flooding it with the equivalent of DA and that this does not have to be released physiologically.

Summary: DA augmentation

Clearly there are a number of ways of treating PD based on the concept of augmenting DA but clinical advice is not the object of this text. There is much discussion and no little disagreement on the subject. Views are conditioned by the knowledge that the disorder is progressive, requiring long-term therapy and tempered by the cost of some agonists. Perhaps the consensus now is to start therapy as late as possible, keep it to the minimum and only increase dose or add drugs as is absolutely necessary. Hardly any patient avoids polypharmacy but the order of prescription is probably to augment existing DA with MAOI, then either replenish with levodopa or use DA agonist. There is a developing consensus that since levodopa so frequently causes motor complications (e.g. dyskinesias) it is better to keep that in hand and start with a D_2 agonist. In fact a recent multicentre 5-year trial of ropinirole compared with levodopa showed it to have similar efficacy to levodopa but producing fewer dyskinesias. To these approaches must be added adjuncts such as ExCDDIs, antiemetics, antimuscarinics and possibly amantidine.

Amantidine

This is an anti-viral agent that has weak levodopa-like effects but its mode of action is not really known. Since the most likely effect is considered to be the release of DA it is not surprising that its value is limited when most DA neurons have been destroyed.

Co-transmitters

Although CCK is known to co-exist with DA in nigrostriatal nerve terminals its precise role is not yet sufficiently understood to be manipulated to advantage.

(B) (4) MODIFYING STRIATAL OUTPUT

Knowledge of the striatal output pathways could provide another approach to therapy either by inhibiting the effects of GABA, at different points along the indirect or direct pathways, or those of its co-transmitters, enkephalin, dynorphin and substance P. Since GABA is, of course, widely distributed and its antagonism is primarily proconvulsant manipulating its function specifically in the basal ganglia is not a current option, unless molecular biology establishes a distinct subset of receptors there and drugs can be found to block them. Much the same might be said of the peptides but some recent research requires consideration.

There is evidence from some experimental studies that metENK can decrease GABA release in the GPext while dynorphin reduces GLUT release in GPint. The former effect would reduce the inhibition of GPext neurons by the Ind Path (just as DA would in the striatum) leaving them with greater control of the SThN and hence reduced stimulation of GPint. Dynorphin inhibition of glutamate release within GPint would have the same effect (Fig. 15.9). Since the increased output of this nucleus is believed to cause akinesia these processes could be of benefit in PD.

Preliminary data indicate that in the reserpinised rat or MPTP marmoset, the enkephalin agonist (SNC80) reduces PD-like symptoms without causing increased activity, i.e. no trend to dyskinesias. Enadoline, a dynorphin-like kappa opioid agonist also has similar effects in the same models. Whether it would be similar in humans remains to be seen.

Despite the fact that neither delta nor kappa agonists caused hyperkinetic (dyskinesia-like) activity in the above studies, antagonism of these receptors with naloxone can apparently diminish such activity induced in animals by long-term dosage with levodopa and has been shown to work in preliminary human studies (Henry and Brotchie 1996). Of course, levodopa-produced DA might be expected to inhibit striatal GABA/ENK output to GPext sufficiently to ensure that very little met ENK was actually released to be antagonised, although dynorphin release from the Dir Path could be maintained so that blocking its inhibitory effects on glutamate release would result in decreased output from GPint and a shift away from dyskinesia.

Clearly many more data are needed on the release of these peptides and their function in GP before their possible role in PD can be properly evaluated but they illustrate an interesting alternative approach to therapy.

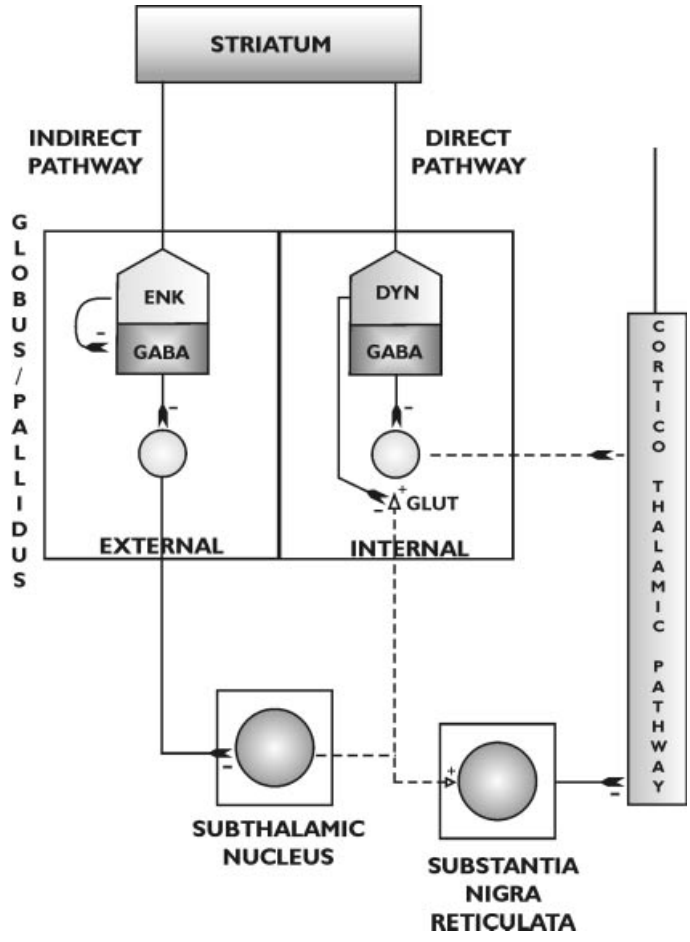

Figure 15.9 Peptide modulation of striatal input to the globus pollidus. Enkephalin released from axon terminals of neurons of the indirect pathway (see Fig. 15.2 for details) is thought to inhibit GABA release from the same terminals so that feedback (auto) inhibition is reduced. This will free the neurons to inhibit the subthalamic nucleus (SThN) and its drive to GPint and SNr which in turn will have less inhibitory effect on cortico-thalamic traffic and possibly reduce akinesia. Dynorphin released from terminals of neurons of the direct pathway may also reduce glutamate release and excitation in the internal globus pallidus and further depress its inhibition of the cortico-thalamic pathway. High concentrations of these peptides may, however, result in dyskinesias. (See Henry and Brotchie 1996 and Maneuf *et al.* 1995)

(B) (5) MANIPULATING OTHER STRIATAL NTs

Acetylcholine

Antimuscarinic drugs such as atropine have been used to modest effect in the treatment of PD for more than a century attenuating tremor and rigidity but with little effect on akinesia. Currently benzhexol and benztropine are sometimes added to levodopa therapy but peripheral effects such as dry mouth, blurred vision and constipation are unpleasant. They are also often used to counteract neuroleptic-induced extrapyramidal effects.

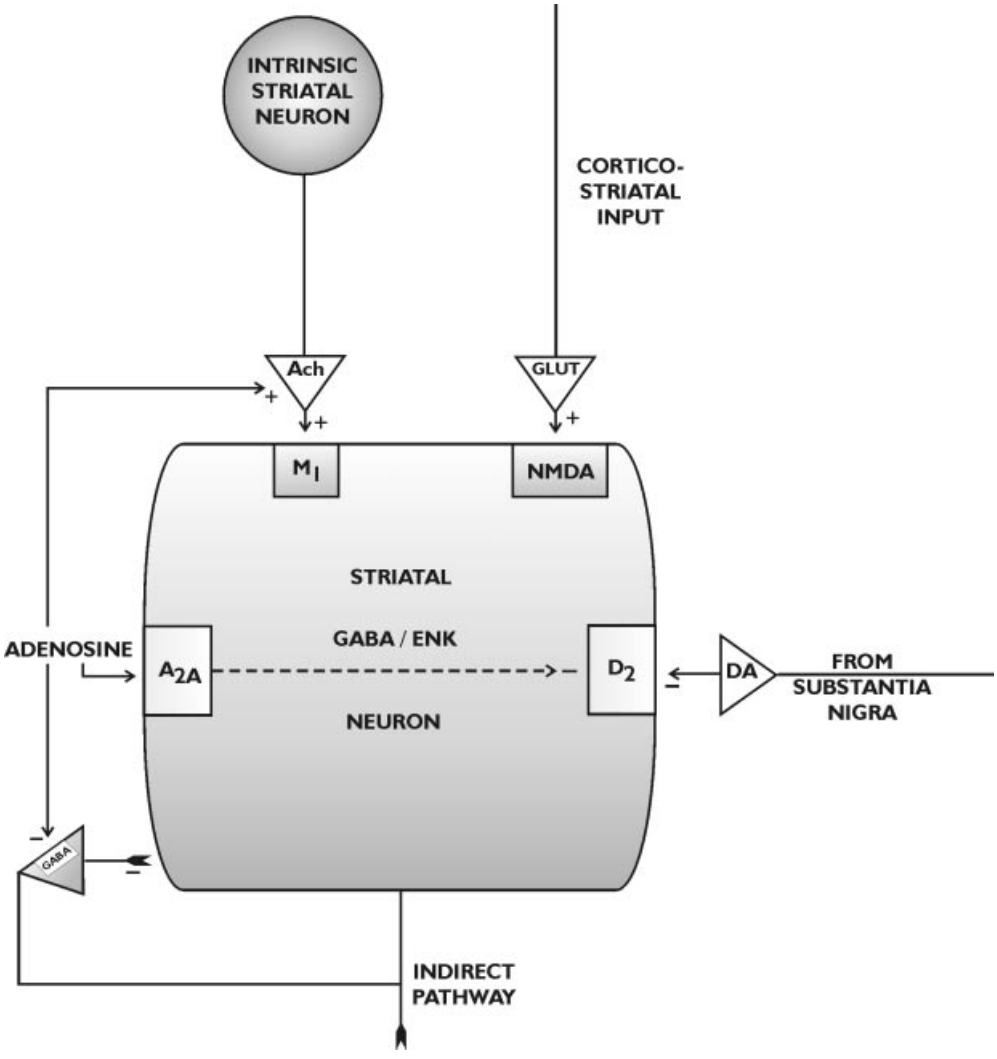

Figure 15.10 Neurotransmitter interactions on the striatal GABA (ENK) neurons of the indirect pathway to globus pallidus. Stratal GABA (ENK) neurons are normally inhibited by both DA, released from nigrostriatal nerve terminals and GABA from their recurrent collaterals. Excitation is mediated by ACh released from intrinsic interneurons and glutamate from cortico-striatal afferents. To compensate for the absence of DA-mediated inhibition in PD the excitation could be reduced by antagonising the actions of ACh (a) at M_1 receptors (antimuscarinics), glutamate (NMDA antagonists) (b) or possibly adenosine. Through its A_{2A} receptor adenosine (c) appears to counter D_2 receptor activity and increase ACh and reduce GABA release, all of which would increase neuron excitability. (See Ferre *et al* 1997 and Richardson *et al* 1997)

ACh is released from the large non-spiny striatal interneurons (Fig. 15.10) which only represent some 5% of total striatal neuron number. Since ACh is excitatory and DA inhibitory on striatal neurons, various schemes have been proposed to balance their antagonistic action but the role of ACh in striatal function (and PD) appears to be relatively minor.

Dopamine inhibits cholinergic neuron firing and ACh release in the striatum predominantly through D_2 receptors. Released ACh probably stimulates the GABA/ENK neurons through M_1 receptors opposing the inhibitory action of DA on them. Clearly in the absence of DA more ACh will be released and its excitatory effect on the GABA/ENK neurons will not be counteracted. Since these neurons and the Ind Path are mainly associated with the akinesia of PD it is perhaps surprising that antimuscarinics have little effect on this symptom.

The excitatory muscarinic receptors on GABA/ENK neurons are M_1 but those on the GABA/SP neurons are probably M_4 and inhibitory. A study of more specific M_1 and M_4 antagonists in PD therapy may be appropriate.

Excitatory amino acids

It would be surprising if these were not implicated in PD. Although most striatal neurons release GABA they are driven by cortical and thalamic inputs releasing glutamate. So in the absence of DA to inhibit them in PD the antagonism of glutamate is an alternative possible approach, providing it can be restricted to the striatum. Certainly intrastriatal (and pallidal) injections of NMDA and AMPA receptor antagonists alleviate motor symptoms in rodent and primate models of PD. The fact that striatal NMDA receptors belong to the subgroup NMDA-2RB, which have a high affinity for antagonists of the glycine and polyamine site (Chapter 10), provides an opportunity for some selectivity of action. The non-competitive antagonist at the NMDA receptor polyamine site, ifenprodil, can in fact reduce PD-like symptoms when injected either intrastriatally or even intravenously in 6-OHDA bilaterally lesioned marmosets, but proved ineffective systemically in humans. Other drugs acting on NMDA receptors may be better.

Adenosine

Binding and mRNA measurements show A_{2A} receptors on the GABA/ENK neurons with D_2 receptors and A_1 receptors on the GABA/SP neurons which express mainly D_1 receptors (Fig. 15.9). The A_{2A} receptors have been most studied.

Activation of the A_{2A} receptor has been shown to increase ACh and reduce GABA release from striatal synaptosomes. Both effects could increase the activity of the striatal GABA neurons, the latter by reducing their inhibition through GABA released by recurrent collaterals. There are also studies which show that the A_{2A} receptor activation is associated with both reduced D_2 receptors binding and DA-induced behaviour. Thus blocking these effects with an A_{2A} antagonist should augment DA inhibition of GABA/ENK neurons and A_{2A} antagonists have been shown to reverse DA antagonist-induced increases in proenkephalin mRNA in those neurons.

The A_{2A} antagonist KF1787 has also been found to improve the motor impairment in marmosets after MPTP while the non-selective adenosine antagonist theophylline augmented levodopa effects in Parkinsonian patients. Whether these responses reflect a specific effect in the striatum is unclear but in order to be effective, these drugs would require ongoing adenosine activity which, it must be remembered, is mainly depressant on neurons. The role of the A_1 receptor, more concentrated on GABA/SP neurons and linked to D_1 receptors, is even less clear although there is evidence that these two adenosine receptors have reciprocal effects. Whether A_1 activation would result in

reduced activity of the Dir Path and possibly alleviate levodopa-induced dyskinesias remains to be seen, but it does counteract D_1-driven GABA release in that pathway.

Summary of therapy

Apart from dopamine many NTs such as glutamate, GABA, various peptides, adenosine and ACh are all involved in striatal function but their wide distribution in the CNS makes it difficult to restrict any manipulation of their activity to the striatum after systemic drug administration.

By contrast, the unique loss of DA in PD and its relative restriction to the striatum makes it more amenable to manipulation and augmenting dopamine function is currently the only realistic and effective therapy for PD. Nevertheless, increasing knowledge of basal ganglia circuitry and modifying other NTs involved could lead to some improvement in overall therapy while DA-based therapy itself could be improved. The swings in response to levodopa might be avoided by using DA agonists that are not simply the most potent and specific for D_2 receptors, as this may overcompensate for DA loss, while if levodopa-induced dyskinesias depend on D_1 receptor stimulation then using levodopa with a D_1 antagonist or partial agonist might overcome them.

(C) (6) TRANSPLANTS AND CELL REPLACEMENT

Perhaps all the problems of drug therapy would be avoided if neural tissue capable of synthesising DA could be inserted into the striatum. Foetal mesencephalic tissue has been implanted in the striatum of PD patients and it survives sufficiently for axons to extend, branch and innervate neurons. Experimental studies show DA is formed and in patients PET scans show increased fluorodopa uptake, some function is restored and the dose of levodopa can be reduced. Although DA release cannot be measured directly in patients, there is in fact indirect evidence for it from studies in one transplant patient (Piccini *et al*. 1999). These showed that 10 years after a graft into one putamen the number of D_2 receptors there as measured by PET scans of the binding of the specific D_2 antagonist (^{11}C) raclopride was normal but upregulated (by 44%) in the non-grafted putamen. Since postsynaptic DA receptors are known to increase in number if DA release is reduced this was taken to indicate that DA release was still reduced on the untreated side but restored to normal on the graft side. Also amphetamine, which releases DA to compete with and reduce raclopride binding, did this more effectively on the grafted side — another indication of greater DA release.

Unfortunately transplants require 6–7 foetal brains to obtain enough transplantable material for one patient, which itself raises ethical considerations, and as the tissue cannot diffuse its influence is restricted, even with multiple injection sites, and only a fraction (approx. 20%) of the neurons survive. Also without knowledge of the cause of PD the transplant could meet the same fate as the original neurons. The concept, however, demands perseverance and a number of variants are being tried.

Some ethical and practical concerns may be overcome by the use of porcine rather than human foetal cells and their potential is on trial. Certainly xenotransplants can survive in the human brain partly because it does not show the same immunoreactivity as the rest of the body but recipients will still require some immunosuppressant drugs. Attempts are also being made, with some success, to expand mesencephalic dopamine

neurons *in vitro* by the use of nerve growth factors, and so produce large numbers for transplant.

Non-neuronal transplants such as adrenal chromaffin cells have been tried but do not survive although some L-dopa-producing cell lines (e.g. PC12) or glomus cells of the carotid body do produce DA *in vivo* and may provide the equivalent of a continuous infusion of dopa (and DA) directly into the brain. Expression of tyrosine hydroxylase to promote dopa and DA synthesis in striatal cells by direct gene transfer *in vivo* or in cultures for subsequent transplanting, may also be possible. (See Dunnett and Bjorklund 1999 for a review of these approaches.)

(C) (7) LESIONS

The therapeutic strategies outlined above are aimed primarily at blocking the activity of the striatal indirect output pathway so that the SThN drive to GP and its output inhibition of thalamo-cortical transmission is reduced (Fig. 15.2). The same effect could be achieved quite specifically and permanently by lesioning the SThN or GP. Both have been tried in limited numbers and shown to have some success. Surprisingly, stimulation of SThN and GP through chronically implanted electrodes is also effective but since this required high-frequency stimulation (100 Hz) it is possible that this is blocking rather than initiating impulse flow and is like a temporary lesion.

AETIOLOGY AND PREVENTION

If the symptoms of PD arise when nigra cell loss results in a particular depletion of striatal DA (e.g. 50% or more) and, as is generally assumed, there is a gradual loss of nigra cells during ageing then we should all develop PD if we live long enough. Fortunately this is not the case as many people can reach 90 or 100 years without developing PD. In fact, PM studies show that in normal subjects nigra DA cell loss proceeds at 4–5% per 10 years but in PD sufferers it occurs at almost ten times this level (Fearnley and Lees 1991).

Thus either the gradual loss of nigral cells and striatal DA is accelerated for some reason in certain people, so that these markers fall to below 50% of normal around 55–60 years, or some people experience a specific event (or events) during life which acutely reduces DA concentration. This could be to a level which is not enough to produce PD at the time but ensures that when a natural ageing loss of DA is superimposed on it the critical low level will be reached and PD emerge before natural death. The first possibility is likely to have a genetic basis but although examples of familial PD are rare there is typically an increased incidence (2–14) of the disease in the family of a PD patient and initial PET studies show a much higher (53%) loss of DA neuron labelling in the monozygotic than the dizygotic twin of a PD sufferer even if the disorder is not clinically apparent.

While a number of gene markers have been identified in different families there is no consistent mutation although parkin on chromosome 6 and α synuclein on 4 have aroused most interest. Mutations of the gene encoding the latter, such as threonine replacing alanine on amino acid 53 (A53T) or phenylalanine for alanine on 30 (A30P) have certainly been established in particular families with inherited PD. In fact ablation of the gene encoding α synuclein has been shown to produce locomotor defects in mice

and surprisingly in the fruitfly *Drosophila melanogaster*. By expressing normal human α synuclein in all the nerve cells of *Drosophila*, Feany and Bender (2000) found no neuronal abnormalities but with wild-type α synuclein or the mutants A53T and A30P they observed premature and specific death of dopaminergic neurons. Additionally some neurons showed intracellular aggregates that resembled Lewy bodies and were composed of the α synuclein filaments seen in the human counterpart. Of course, flies cannot be said to develop PD but unlike normal ones, the transengic fly found it more difficult to climb the sides of a vertical vial.

The fact that some schizophrenics show PD symptoms when given DA antagonists has been considered to indicate that they already have a reduced DA function and are asymptomatic potential PD patients but the high incidence of PD side-effects after neuroleptics and its occurrence in young people (20–30 years) argues against this. A viral infection can lead to PD as evidenced by its high incidence (50%) in survivors of an outbreak of encephalitic lethargica in Europe around 1920. Toxins can also be inducers.

In 1982 there was a small outbreak of PD among Californian heroin addicts taking what was thought to be a methadone substitute, but due to a mistake in synthesis turned out to be a piperidine derivative MPTP (1-methyl-4-phenyl-1,2,3,6-tetra hydropyridine). By any route, even cutaneous or inspired, this causes a specific degeneration of nigral DA neurons in humans and primates but not in rodents, which may indicate some link with melanin (not found in rodents). MPTP itself is not the active factor but requires deamination by mitochondrial MAO_B to a charged pyridium MPP^+ which is taken up specifically by DA neurons. MAO_B inhibitors such as selegiline prevent MPTP-induced PD in primates. The production of MPP^+ generates free radicals as does the oxidation of DA itself.

Free radicals and peroxides are highly reactive substances and can damage DNA, membrane lipid and cell protein and initiate lipid peroxidation to destroy all membranes. Hydrogen peroxide (H_2O_2) can actually be produced by the oxidation of DA, under the influence of MAO_B and is potentially toxic to SN neurons (Fig. 15.11). Normally such H_2O_2 would be detoxified by glutathione but glutathione activity is low in brain so that H_2O_2 can accumulate. While a reduction in glutathione itself is not sufficient to destroy nigral cells, since its direct inhibition alone does not have that effect, the rise in H_2O_2 coupled with its conversion to toxic radicals could do so. This process is also favoured by the high levels of free iron in the substantia nigra which are augmented in PD patients. Iron is normally bound in the body by ferritin but as this is low in the brain the iron will increase and facilitate the production of free radicals. Thus the SN, sitting as it does with high DA levels, ample MAO for converting it to H_2O_2, little chance to detoxify it but plenty of iron for free radical production, is ready to self-destruct. Whether this is enhanced by dopa therapy and the provision of more DA is uncertain but it has been shown that systemic L-dopa does undergo auto-oxidation in rat striatum to a semiquinone (Serra *et al.* 2000). This process is inhibited by antioxidants and enhanced by manganese and, of course, miners of this element are known sometimes to develop Parkinsonism-like symptoms and as indicated above, were the first patients to be shown to respond to L-dopa therapy. Whether antioxidants should be given with L-dopa may bear investigation although when one such agent, tocopherol, was tested alone, i.e. on otherwise untreated PD patients, it failed to retard the development of symptoms.

The reliance of free radical and MPP^+ production on MAO_B activity stimulated considerable interest in the possibility that blocking this enzyme could prevent the

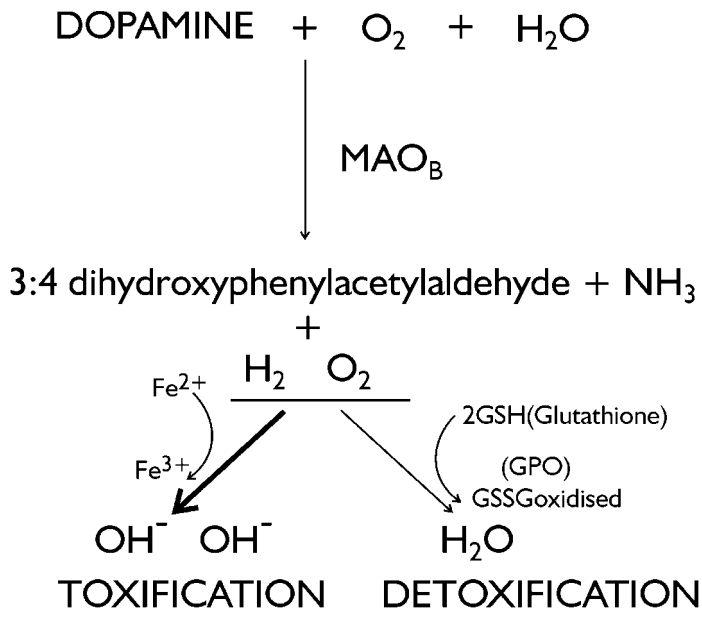

Figure 15.11 Possible scheme for the formation of free radicals from the metabolism of dopamine. Normally hydrogen peroxide formed from the deamination of DA is detoxified to H_2O along with the production of oxidised glutathione (GSSG) from its reduced form (GSH), by glutathione peroxidase. This reaction is restricted in the brain, however, because of low levels of the peroxidase. By contrast the formation of the reactive OH-radical (toxification) is enhanced in the substantia nigra because of its high levels of active iron and the low concentration of transferin to bind it. This potential toxic process could be enhanced by extra DA formed from levodopa in the therapy of PD (see Olanow 1993 and Olanow *et al.* 1998)

progression of PD. Trials with selegiline (deprenyl) on hundreds of new untreated patients initially suggested that this was the case since almost twice as many patients in the control group needed to receive levodopa in the first year compared with those on the MAO_B inhibitor. Unfortunately analysis after discontinuing the inhibitor showed no difference in the subsequent development of PD, implying that the inhibitor was just relieving the symptoms (i.e. levodopa-like effects). Nevertheless interest in the possible preventive effects of MAO_B inhibition persists. Certainly the slow progression of PD and neuronal loss means that if the cause can be established and countered, it might be possible to stop disease development especially if treatment could start in the very early or preclinical stages. In fact neurotrophic factors such as glial cell line or brain-derived neurotrophic factors (GDNF or BDNF) have shown some beneficial effect on 6-OHDA or MPTP-depleted DA function when injected intracerebrally in animals.

Nitric oxide has also been implicated in PD. Thus animals with MPTP-induced Parkinsonism not only show extensive gliosis in the substantia nigra (like humans) in which the glial cells produce NO, but Liberatore and colleagues have found that in iNOS (inducible nitric oxide synthase) knock-out mice the toxicity of MPTP is halved. Since NO releases iron from ferritin and produces toxic peroxinitrate in the presence of superoxide radicals it could accelerate, even if it does not initiate, dopaminergic cell death (see Hirsch and Hunot 2000 for further details).

Huntington's Chorea

This disease takes its name from George Huntington who observed and studied it in families in New York at the end of the nineteenth century. It is an inherited autosomal dominant disease with the child of an affected parent having a 50% chance of inheriting the gene and then unavoidably suffering from the disease. It is characterised by choreas (dyskinesias) which start in the extremities (fingers) but spread to the face, limbs and whole body even though they disappear during sleep. Akinesia develops as in PD and like that disease HC is initially a disorder of the basal ganglia but starts earlier (30–45 years). It is more progressive, invariably resulting in death within 20 years, as motor impairment makes any function difficult and emotional disturbances and dementia develop. Fortunately it affects only 0.01% of the population and hopefully prenatal diagnosis will become available and its occurrence further reduced.

Early neuron loss occurs in the striatum and especially of the GABA/ENK neurons which project to the GPext (Fig. 15.2) and referred to as the indirect pathway in the discussion on PD. This would leave the GABA/DYN neurons and the direct pathway dominant, which appears to be the requirement for dyskinesia (Fig. 15.8). Thus, unlike PD, there is no loss of neuronal input to the striatum or of DA levels but a marked reduction in striatal GABA as well as its co-transmitting peptides, especially metenkephalin but also dynorphin and substance P. It is not possible to replace adequately the lost GABA but the early dyskinesias can be reduced by using DA antagonists which would primarily block the D_2 inhibitory effect on the remaining GABA/ENK neurons and so help to restore balance. Knowledge of basal ganglia circuitry (Fig. 15.2) suggests, however, that the antagonists probably need to have some effect on the D_1 receptors and GABA neurons of the direct pathway as well. Whether adenosine A_1 agonists or opiate antagonists (see above) could usefully reduce the activity of those neurons remains to be evaluated. Unfortunately any process reducing dyskinesias could encourage akinesia. This is the opposite problem to that in PD but a reminder of the pivotal role of the striatum and DA in movement control (see Fig. 7.8).

Since HC is such a progressive disorder with clear neuronal loss, it is not surprising that NT manipulation has been of little value in therapy and that there is no drug treatment of any significance. More hope rests on a genetic approach and the mutated gene has in fact been identified and cloned but its precise role remains uncertain. For details of its structure, possible actions and appropriate models see Reddy, Williams and Tagle (1999).

ADDENDUM

The first proper double blind trial of embryonic implants in 40 PD patients (20 undergoing just surgery without any implant), has shown no improvement in patients over 60 years but some clinical benefit (fewer symptoms between levodopa dosing) in those below that age. Unfortunately some of these responders eventually developed dyskinesias, a sign of too much dopamine, and further implants were halted until the technique has been re-evaluated, see Freed, CR *et al. N Engl J Med* 2001, **344**: 710–719.

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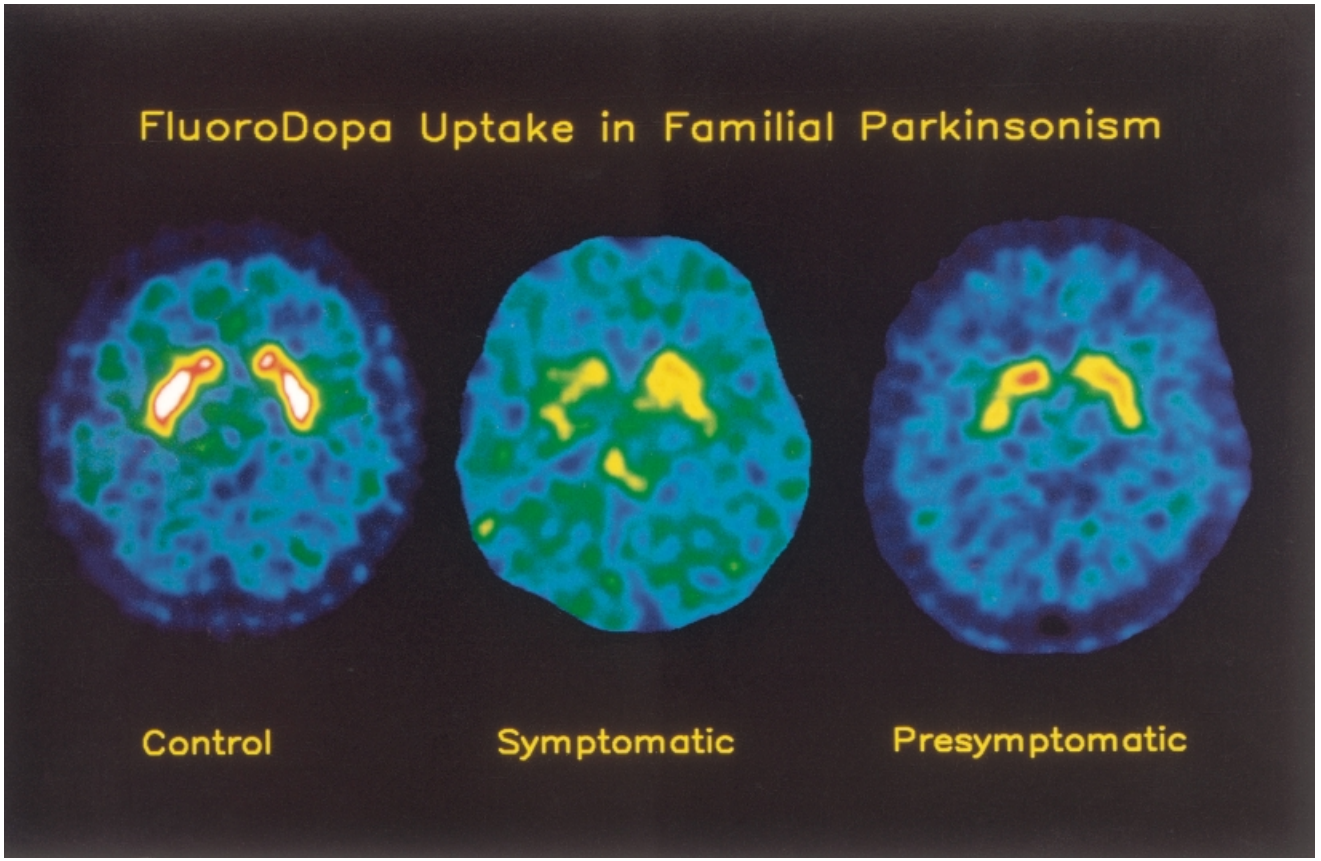

Figure 15.1 PET scans in normal and Parkinsonian patients.
A PET scan with [^{18}F] fluorodopa in a control subject shows that the striatum is heavily labelled whilst in a Parkinson patient with established symptoms there is little labelling. This patient's twin, whilst free of symptoms, also showed some loss of labelling and subsequently developed the disorder. Reproduced by kind permission of D Brooks, MRC Cyclotron Unit, Hammersmith Hospital, UK.