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Emerging Treatments in Parkinson's Disease

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Abstract
This paper provides a critical review on the most recent developments in the treatment of Parkinson's disease. New symptomatic therapies include the use of catechol-O-methyltransferase (COMT) inhibitors, new dopamine agonists and of surgical treatments (such as pallidotomy or deep brain stimulation). Protective strategies include the use of COMT and monoamine oxidase B inhibitors, of dopamine agonists and of trophic factors. The main preclinical premises, on which the usage of newly developed therapies is based, are discussed. Symptomatic therapy has been greatly refined in recent years and has gradually become a polytherapeutic approach. Protective therapy, which will attract the interest of fundamental and clinical research in the field of Parkinson's disease, is the real future challenge.

Introduction

Parkinson's disease (PD) is a progressive degenerative condition that cannot be cured yet. Currently available therapies are very useful in treating parkinsonian signs and symptoms, but do not prevent the occurrence or delay the progression of the disease. Symptomatic treatment is by no means satisfactory, as it often requires complex daily schedules of different drugs. After several years of treatment, PD patients develop motor fluctuations which tend to increase in severity to become a specific clinical problem to be dealt with.

Symptomatic Therapy

Improvement of Levodopa-Based Therapy

Levodopa, a precursor of dopamine and of other catecholamines, is the most active drug for PD. Response to levodopa therapy is a specific feature of PD and all PD patients are candidates for levodopa during the course of the disease.

Levodopa is commonly prescribed in association with peripheral inhibitors of aromatic amino acid decarboxylase, such as carbidopa or benserazide, that block the production of dopamine on the periphery allowing larger amounts of levodopa to reach the brain (fig. 1). Without such inhibition, about 70% of levodopa is decarboxylated to form dopamine; about 10% is methylated to form 3-O-methyldopa (3-OMD) and the remainder is probably used in the synthesis of melanin [1, 2]. When decarboxylation is blocked by peripheral inhibiotors, O-methylation becomes the prominent metabolic pathway, and 3-OMD is the major plasma metabolite of levodopa [3]. This shift of levodopa metabolism toward the production of 3-OMD has several drawbacks:

(1) The plasma half-life of 3-OMD is 15 h, compared to about 1 h for levodopa, and plasma concentrations of 3-OMD during chronic therapy rise to several times that of levodopa [4].

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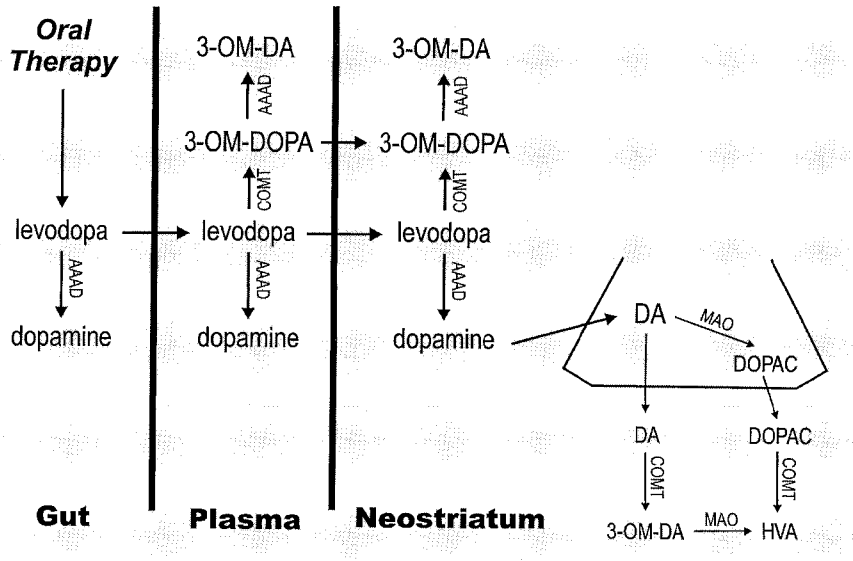

Fig. 1. Metabolism of levodopa after oral intake. Levodopa can readily cross biological membranes, such as the gut wall and the blood-brain barrier, while dopamine cannot. For this reason, levodopa is commonly administered in association with an inhibitor of AAAD, such as benserazide or carbidopa. If COMT metabolism is not inhibited, the methylated compound 3-methoxy-DOPA (3-OM-DOPA) is formed; this easily crosses the blood-brain barrier to reach the neostriatum. 3-OM-DOPA is thought to be toxic to dopaminergic neurons. In the neostriatum, methylation of dopamine produces 3-methoxy-dopamine (3-OM-DA), which may also be neurotoxic. MAO activity produces di-hydroxyphenylacetic acid (DOPAC) from dopamine and homovanillic acid from 3-OM-DA.

(2) There is not therapeutic benefit from 3-OMD; instead, it has been shown to decrease the efficacy of levodopa therapy in PD [5, 6].

(3) 3-OMD competes with levodopa for transport into the brain via the large neutral amino acid transport system [7, 8]. It has not been demonstrated that, in the concentrations achieved during chronic levodopa therapy, 3-OMD actually influences levodopa transport [9, 10]; however, the reduction of circulating 3-OMD could theoretically increase delivery of levodopa to the brain.

A reduction of 3-OMD could be achieved by inhibiting catechol-O-methyltransferase (COMT) in patients with levodopa preparations.

Catechol-O-Methyltransferase Inhibition. O-methylation of dopamine and levodopa by COMT is an important enzymatic pathway for the metabolism of these catecholamines. Consequently, manipulation of O-methylation may influence the antiparkinsonian effects of levodopa. The development of new COMT inhibitors during the past 10 years enables performing clinical investigations of the role played by peripheral and central O-methylation in the antiparkinsonian action of levodopa.

On the periphery, COMT activity is present in most tissues but is particularly high in the liver, the kidney, and the intestinal mucosa [11–13]. In the central nervous system it is found in neurons and in the glia [1]. In any compartment, the enzyme has a cellular distribution (i.e., it is not found in plasma or in the cerebrospinal fluid).

Central inhibition of COMT could potentially be useful in the symptomatic therapy of PD by blocking the termination of dopamine actions in the brain and preventing the metabolism of levodopa in the periphery. O-methylation of dopamine is one method of metabolically inactivating the neurotransmitter. Inhibition of this pathway by a central COMT inhibitor could prolong the synaptic action of endogenously generated dopamine and thus enhance its effects. Potentially of greater importance than the effects on endogenous brain dopamine metabolism may be the effects exerted by COMT inhibitors on levodopa pharmacokinetics. There are several possible interactions: (1) the gut and the liver contain high concentrations of COMT; thus, inhibition of first-pass metabolism of levodopa by COMT could increase bioavailability of the drug [11–13]; (2) since O-methylation is the major metabolic discarding route when aromatic amino acid decarboxylase (AAAD) is inhibited [3], inhibition of systemic COMT may play a major role in reducing clearance of levodopa from plasma; (3) brain capillary endothelial COMT, in combination with AAAD and monoamine oxidase (MAO), constitutes an enzymatic barrier to levodopa entry into the brain [14, 15]; therefore, inhibition of brain capillary endothelial cell COMT would have the effect of enhancing levodopa entry into the brain, and (4) inhibition of brain COMT should allow more levodopa to be available for decarboxylation to dopamine.

Two second-generation nitrocatechols will be readily available for the treatment of PD patients: entacapone is a

Table 1. Most common stereotactic lesions placed in the basal ganglia or adjacent regions to relieve parkinsonian signs and symptoms

Denomination	Lesioned site	Clinical signs expected to improve
Ansotomy	Ansa lenticularis	Akinesia and rigidity
Campotomy	Forel's fields H_1 and H_2	Rigidity
Pallidotomy[1]	Globus pallidum	Akinesia, rigidity, tremor
Subthalamic lesion[1]	Subthalamic nucleus	Akinesia, rigidity, tremor
Subthalamotomy[2]	Zona incerta or Forel's fields H_1 and H_2	Rigidity
Thalamotomy[1]	Thalamus (usually the VIM nucleus)	Tremor and on state dyskinesias

[1] Deep brain stimulation of the same nucleus is an alternative to lesion.
[2] Classical subthalamotomy must not be confused with modern subthalamic lesion.

peripheral COMT inhibitor that does not cross the blood-brain barrier, while tolcapone acts centrally as well as peripherally. In initial clinical studies in patients with PD, both entacapone and tolcapone strengthened and prolonged the therapeutic effects of levodopa. The effect of entacapone and tolcapone in levodopa-treated parkinsonian patients is to prolong the effects of single doses of levodopa by 20–70% without affecting the maximum plasma levodopa concentration or the time to maximum concentration [16–21]. Whether this can be attributed to the slowed elimination of levodopa from plasma is not clear. The magnitude of the increase in duration of action appears to be roughly the same for entacapone and for tolcapone; thus the contribution of central inhibition of COMT to the therapeutic effect of tolcapone is unknown. In addition to the peripheral action, tolcapone also enhances striatal dopamine neurotransmission by central inhibition of O-methylation and by blocking the central conversion of dopamine into 3-methoxytyramine [22]. It is presently unclear if there are different clinical indications for the use of peripheral COMT inhibitors as compared to those acting on the central nervous system as well. It is foreseen, however, that in the near future levodopa preparations will be normally associated with COMT inhibitors.

New Surgical Techniques

The first attempts to relieve symptoms of PD by surgery occurred more than 50 years ago [23, 24]. The first unequivocal accomplisment was the relief of parkinsonian tremor by stereotactic thalamotomy according to the anatomical landmarks set by Hassler and Reichert [25]. Early stereotactic lesions proved that most parkinsonian signs could be alleviated by the appropriate placement of discrete lesions in different deep nuclei of the brain (table 1) [26]; shortly afterwards, however, in the 1960s, the advent of levodopa provided the most powerful treatment for all parkinsonian signs but tremor. Thus, stereotactic thalamotomy for tremor was the only surgical approach performed in the postlevodopa era, until recently. The interest in surgical techniques has been revived following the discovery that PD patients treated chronically with antiparkinsonian drugs develop motor fluctuations and dyskinesia. These complications of drug therapy usually become a therapeutic issue of its own. Based on solid expermental evidence, in the 1980s grafts of brain tissue have been performed on severely fluctuating PD patients. More recently, stereotactic lesions have received a new momentum and deep brain stimulation has been proposed as a reversible alternative to lesions.

Transplantation. Basic and clinical research on neural transplantation is by no means limited to PD. Clinical experimentation in PD has so far focused on the implant of autologous adrenal medullar tissue and of heterologous fetal tissue. Adrenal medullar grafts are no longer performed for several reasons, the most important being the unreliability of clinical outcome [27] and the evidence that adrenal medulla of PD patients is not normal [28].

Compared to the initial expectations, fetal tissue grafts have not represented a major breakthrough in the therapy of PD. Initial reports of significant improvements in the clinical outcome [29] have not been confirmed. The issue as to whether fetal grafts survive in the human brain, as they do in lower species, has attracted scientific interest until it has been shown that this is indeed the case, at least in selected patients [30]. More recently, it has been observed that fetal tissue grafts improve motor performance in patients with 1-methyl-4-phenyl-1,2,3,6-tetra-

Table 2. The basal ganglia: synopsis of physiological changes in parkinsonian states

Anatomical site	Physiological changes in parkinsonism
Neostriatum (caudate nucleus, putamen)	Hyperactivity (matrix: indirect path)
	Hypoactivity (patch: direct path)
Globus pallidum (medial part)	Hyperactivity
Globus pallidum (lateral part)	Hypoactivity
Subthalamic nucleus	Hyperactivity
Substantia nigra pars compacta	Hypoactivity (degeneration in Parkinson's disease)
Substantia nigra pars reticulata	Hyperactivity
Ventral tegmental area	Hypoactivity
Pedunculopontine nucleus	Hypoactivity (?)

hydropyridine (MPTP)-induced parkinsonism thus showing results similar to those obtained in MPTP-poisoned monkeys [31]. A reason for the difficulty in observing improvement after fetal tissue grafts may be that, for ethical reasons, mainly complicated cases and aged parkinsonian patients have been implanted so far. This was not the case for MPTP-poisoned patients who had a relatively younger age. Notwithstanding, even the strongest advocates of brain grafts admit that the clinical improvement of patients with idiopathic PD, who received fetal tissue grafts, is not enough to improve motor fluctuations to a significant degree. Due to unsolved ethical issues and to such unsatisfactory results, newer research programs are evaluating the posssibility to implant xenogenic or engineered cells in the brain of parkinsonian patients [32]. Such implants may not only provide a source of viable neurons, but also some trophic factors required for cell survival and brain repair [33].

Deep Brain Lesion and Stimulation. Deep brain stimulation (DBS) is a functional inactivation produced by a high-frequency current pulse. DBS is comparable to a small lesion but, at variance with a lesion, it is reversible and can be graded by adjusting the physical parameters. Thalamotomy, which has been used for a number of years, is remarkably efficacious in tremor and also provides relief from some on-state dyskinesias [34]. The pathophysiology of the latter effect has not been unequivocally elucidated. Thalamotomy has been replaced in part by thalamic stimulation, a technique originally developed to avoid the side effects associated with thalamic lesions [35].

Following the elucidation of basal ganglia functional changes occurring in parkinsonian and dyskinetic states [36], the possibility to correct hyperactivity of specific brain nuclei became a hypothesis worth considering. The first comfirmation came from the observation of a parkinsonian patient who improved following a small infarct of the subthalamic nucleus [37]. Experimental subthalamic lesions were then successfully performed in monkeys suffering from MPTP-induced parkinsonism [38].

Surgical correction of hyperactivity cannot be performed in all hyperactive deep brain nuclei (table 2). For example, the substantia nigra reticulata cannot be lesioned or stimulated in its entirety without affecting the neighboring structures. The globus pallidum and the subthalamic nucleus, instead, are easy targets for stereotactic surgery and are well demarcated anatomically. Lesions of the globus pallidum were already performed in Sweden in the late 1950s, but became unfashionable following the universal acceptance of thalamotomy as the standard surgical procedure for PD. Posteroventral pallidotomy, aimed at the medial globus pallidum, has been recently replicated with improved technology and has proven to ameliorate parkinsonian signs and reduce dyskinesias [39–41].

The medial globus pallidum can be inhibited by a direct lesion or a high-frequency stimulation, but the subthalamic nucleus should rather be approached with the latter technique, as subthalamic lesions are prone to produce hemichorea or ballism. Due to its flexibility, deep brain stimulation is the method of choice to directly inhibit the subthalamic nucleus. This approach has proven useful in a number of patients [42–44]. We have also observed that subthalamic nucleus stimulation yields impressive improvement of akinesia, rigidity and tremor in parkinsonian patients.

Although surgical therapy of PD constitutes a promising therapeutic tool, the specific indications and the long-term results of modern stereotactic techniques are not available yet. Preliminary evidence indicates that medial pallidotomy (or stimulation) reduces dyskinesias to a significant extent and brings about a certain improvement in all parkinsonian signs. Subthalamic stimulation, instead, greatly improves all parkinsonian signs, but is prone to bring about dyskinesias. In either case, drug therapy can be reduced to a variable extent. The first treatment is preferred for patients who prevalently suffer from dyskinesias, particularly of the diphasic type, the latter is chosen as a therapy for off-related motor phenomena.

Protective Therapy

The mechanism leading to cell degeneration in PD has been the object of intense investigation during the last 10 years. The desire to introduce neuroprotective therapy for PD has begun to focus attention on the pathogenic mechanisms responsible for cell death. Although the cause of neuronal death in PD remains unknown, a hyperoxidation phenomenon has been implicated as a potential cytotoxic mechanism. Oxidant stress, due to the formation of hydrogen peroxide and oxygen-derived free radicals, can cause cell damage due to chain reactions of membrane lipid peroxidation. Catecholaminergic neurons containing neuromelanin, an autoxidation byproduct of catecholamines, are more vulnerable in PD than nonmelanized catecholaminergic neurons. Because the substantia nigra is rich in dopamine, which can undergo both enzymatic oxidation via monoamine oxidase and nonenzymatic autoxidation, hydrogen peroxide and oxyradicals (superoxide anion radical and hydroxyl radical) are generated. Although proof that oxidant stress actually causes the loss of dopaminergic neurons in patients with PD is lacking, there is a considerable body of evidence from studies in both animals and humans that support the concept.

(1) Neurotoxins that selectively destroy the dopaminergic neurons in the nigra, such as 6-hydroxydopamine and MPTP, appear to act via oxidant stress.

(2) The substantia nigra of patients with PD reveals evidence of oxidant stress by the findings of increased lipid peroxidation and decreased reduced glutathione.

(3) Total iron is increased and ferritin is reduced in the substantia nigra pars compacta of patients with PD. This combination suggests that this transition metal is, in a low molecular weight form, capable of catalyzing nonenzymatic oxidative reactions, especially the conversion of hydrogen peroxide to hydroxyl radical, which is the most reactive of the oxygen radicals.

(4) Neuromelanin, a product of dopamine autoxidation, can serve as a reservoir for iron, promoting the generation of oxyradicals.

(5) Antioxidant defense mechanisms appear to be reduced in the parkinsonian substantia nigra with the findings of decreased activities of glutathione peroxidase and catalase.

(6) The findings of decreased activity of NADH-CoQ reductase, a mitochondrial complex I enzyme, in substantia nigra and platelets in patients with PD, can also be interpreted to be a cause or product of oxidant stress. The identical enzyme abnormality occurs with MPTP toxicity, and this has been associated with increased superoxide anion radical formation.

The evidence favoring the oxidant stress hypothesis is convincing but not yet fully established. The ideal treatment for PD is one capable to interfere with the process leading to progressive degeneration of dopaminergic neurons. Such a treatment has not been found yet. Notwithstanding, a large number of molecules have been evaluated in different experimental conditions, in order to test a protective action on cell degeneration and, particularly, on the degeneration of dopaminergic neurons. Experiments carried out in vitro and in vivo suggested that a number of drugs, some of which are already available in the clinic, have scavening or protective features that qualify them for a possible role in the etiologic therapy of PD. The most relevant evidence will be summarized here, with the warning that the data so far collected are scanty and inconclusive.

Experiments in vitro have shown that nitecapone (a molecule related to entacapone) is a scavenger of nitric oxide [45]. A fallout of this line of research may be the finding that COMT inhibitors have antiscavenging properties. These drugs are already supposed to reduce the metabolic stress of dopaminergic neurons by limiting the production of methylated catechol compounds.

MAO-B Inhibitors

Following the discovery that, at variance with lower mammals, the human brain contains MAO B, the clinical effects of using selegiline, a selective MAO-B inhibitor, were evaluated (fig. 2). Early studies showed that selegiline prolongs the symptomatic efficacy of levodopa, as expected from the inhibitory action on dopamine catabolism [46]. About at the same time, however, it was observed that patients treated with selegiline had an increased life expectancy [47]. These observations were replicated in part by North American neurologists [48] and were the object of the large DATATOP multicenter double-blind study [49] that reported that PD progresses more slowly in patients who take selegiline. The DATATOP study was harshly criticized on methodological and clinical grounds [50]. The problem with all studies aimed at evaluating a putative neuroprotective effect is that a clinical endpoint is usually extrapolated to draw conclusions on a neurobiological feature (such as protection from neural degeneration), the two being heterogeneous in nature. This type of inconsistency cannot by avoided based on currently available methodology and must be accepted as such. The DATATOP results were not confirmed by a recently published open multicenter British study [51].

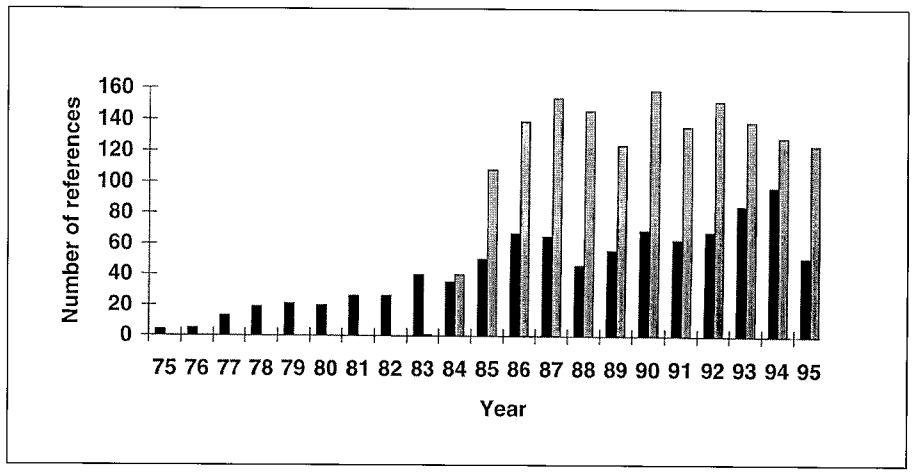

Fig. 2. Number of references containing the text word selegiline or deprenyl (solid bars) or MPTP (hatched bars). It can be observed that the number of publications on selegiline has increased gradually from the mid-1970s and has received a specific momentum after the discovery of MPTP-induced parkinsonism. Source: Medline.

Selegiline is a nonreversible MAO-B inhibitor, giving rise to active metabolites that may affect the interpretation of clinical results [52, 53]. Lazabemide, a new selective and reversible MAO-B inhibitor, has been developed recently and will be shortly available for clinical practice. Preliminary data show that lazabemide exerts clinical effects on the progression of PD similar to those of selegiline [54]. Lazabemide has not active metabolites that can alter the interpretation of clinical results.

Dopamine Agonists

The long-lasting diatribe on the possible protective action of selegiline in PD patients prompted the search for similar effects of drugs already available. The dopamine agonist lisuride was considered a possible candidate for protective action [55], but very little research to support these data was performed. The most suggestive evidence was instead collected on two other ergoline derivatives currently used for the symptomatic therapy of PD: pergolide and alpha-dihydroergocriptine. An in vitro study showed that pergolide is capable to induce soluble superoxide dismutase in the rat striatum, while having no effect on the mitochondrial form of the enzyme [56]. In addition, an in vivo experiment on 6-hydroxydopamine-lesioned mice revealed that pretreatment with pergolide prevented loss of dopamine in the striatum [57]. In monkeys rendered parkinsonian with MPTP it was shown that dihydroergocriptine exerts a protective effect, as demonstrated by the morphology of substantia nigra [58]. A similar action has also been demonstrated by a biochemical study in MPTP-treated monkeys [59].

Taken together, the available data on dopamine agonists indicate that some sort of protective action may be exerted by ergot alkaloids, probably due to a direct stimulation of presynaptic dopamine receptors and to the induction of soluble superoxide dismutase. The recent availability of non-ergot dopamine agonists will enable evaluating if the protective action is shared by molecules with a different chemical structure but similar activity on dopamine receptors. Additional clinical data are also necessary for these compounds.

Other Compounds

GM1 Gangliosides. Some evidence has been collected on the possibility that GM1 ganglioside exerts some form of neuroprotection in experimental parkinsonism induced by MPTP. Following early evidence in the mouse [60], a remarkable biochemical and morphological recovery was observed in monkeys poisoned with MPTP [61]. These data were denied in part by other groups, who observed an increase in tyrosine hydroxylase activity [62]. No data are available in man.

NMDA Antagonists. In recent years excitatory amino acids have gained considerable interest since they can cause excitotoxic lesion of neurons under a number of pathological conditions. The discovery that Parkinons's disease is associated with an increased glutamatergic activity [63] prompted the search for new therapeutic tools acting on glutamate receptors. Different groups independently showed that MK-801, an N-methyl-*D*-aspartate (NMDA) antagonist previously investigated for the therapy of ischemia, protects against MPTP-induced toxicity [64–68]. This protection appears to be partial and time-dependent. A similar activity has been reported for R(–)-3-(2-carboxypiperazine-4-yl)-propyl-l-phosphonic acid, a competitive NMDA antagonist [69]. MPTP-

induced degeneration of dopaminergic neurons is likely to involve glutamate-mediated toxicity; noncompetitive or competitive NMDA antagonist may protect nigral neurons from MPTP-induced degeneration whereas their striatal terminals still seem to degenerate. Interestingly, amantadine, an antiparkinsonian drug that has long been available in the clinic [70], has recently been shown to possess low-affinity noncompetitive NMDA receptor antagonist activity [71]. Amantadine has been used for many years for the treatment of PD. Therefore, a wealth of experience has been collected with this drug. Further studies are warranted to evaluate the putative protective action of amantadine and related compounds.

Trophic Factors. Brain-derived neurotrophic factor protects dopamine neurons against neurotoxicitiy induced by 6-hycaroxydopamine, by MPTP and other agents [72–75]. A similar action has been demonstrated for basic fibroblast growth factor [76, 77] and for glial-derived neurotrophic factor [78, 79].

COMT Inhibitors. Experiments in vitro have shown that nitecapone (a molecule related to entacapone) is a scavenger of nitric oxide [45]. A fallout of this line of research may be the finding that COMT inhibitors have antiscavenging properties. As discussed before, these drugs are already supposed to reduce the metabolic stress of dopaminergic neurons by limiting the production of methylated catechol metabolites.

Conclusion

The number of drugs available for the treatment of PD is progressively increasing. The availability of many new molecules does not seem to have settled the number of problems facing the clinician who deals with complicated cases. Clinical practice has slowly drifted toward a more complex therapeutic approach, where different treatments are combined to form separate layers of therapy. By this way it is believed that a summation of therapeutic benefit can be achieved with a minimum of side effects. Most PD patients will be treated in the future with a combination of dopamine agonists, levodopa, MAO-B inhibitors and COMT inhibitors. Many of them will also receive a surgical treatment.

The vast majority of the available treatments are symptomatic. However, it is believed that the strong neurobiological investment in protective therapy will soon provide a fallout to clinical practice.

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