

# Levodopa: Past, Present, and Future

Robert A. Hauser

Departments of Neurology, Molecular Pharmacology, and Physiology, University of South Florida, Tampa, Fla., USA

## Key Words

Levodopa · Levodopa, historical perspective · Levodopa therapy, complications · Parkinson's disease · Dopa decarboxylase inhibition · Catechol-*O*-methyltransferase inhibition

## Abstract

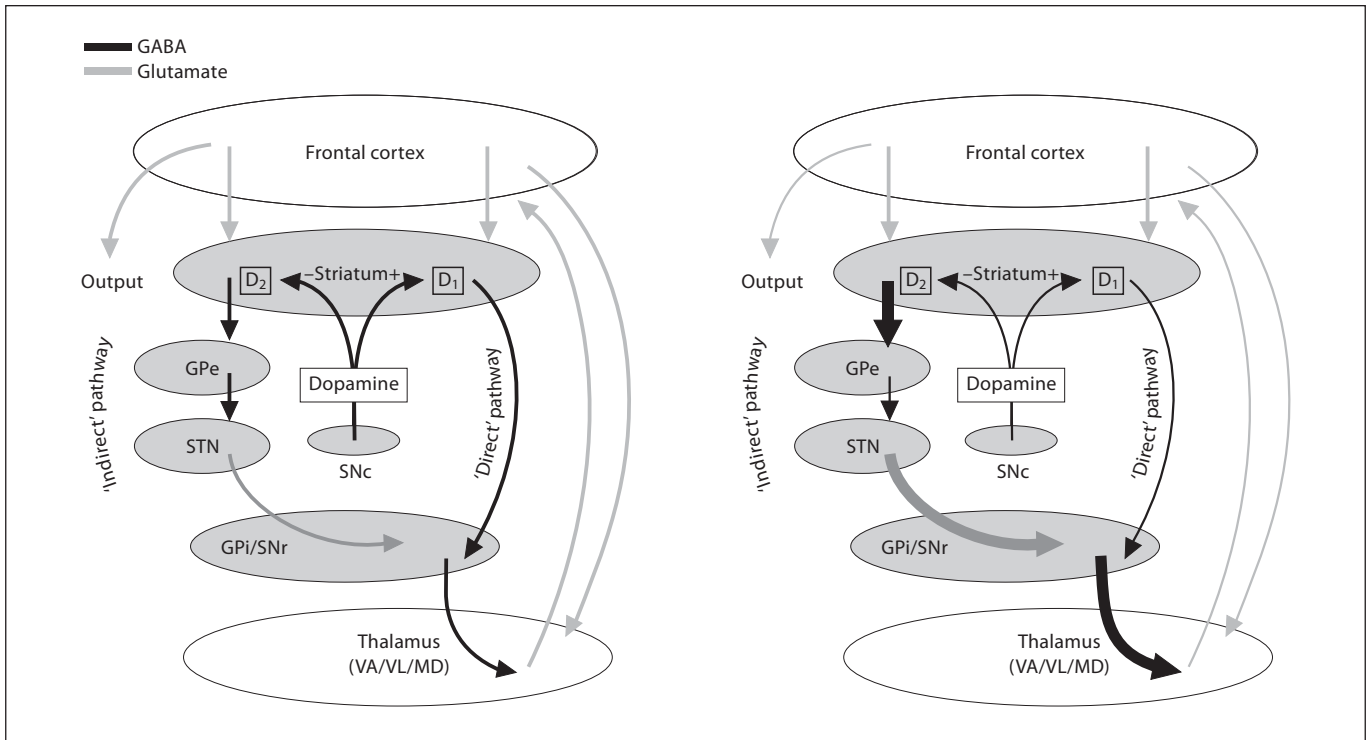
Levodopa has been the mainstay of treatment for Parkinson's disease (PD) for more than 40 years. During this time, researchers have strived to optimize levodopa formulations to minimize side effects, enhance central nervous system (CNS) bioavailability, and achieve stable therapeutic plasma levels. Current strategies include concomitant treatment with inhibitors of dopa decarboxylase (DDC) and catechol-*O*-methyltransferase (COMT) to prolong the peripheral levodopa half-life and increase CNS bioavailability. Levodopa combined with DDC inhibition is the current standard method of delivering levodopa for symptomatic treatment of PD. Recent research suggests that continuous dopaminergic stimulation that more closely approximates physiological stimulation may delay or prevent the development of motor fluctuations ('wearing off') and dyskinesias. Strategies currently being used to achieve more continuous dopaminergic stimulation include the combination of an oral levodopa/DDC inhibitor with a COMT inhibitor and the enteral infusion of a levodopa gel formulation. Attempts are underway to develop oral and transdermal very long-acting levodopa preparations.

Copyright © 2009 S. Karger AG, Basel

## Introduction

Parkinson's disease (PD) is a multisystem disorder characterized by the loss of nigrostriatal dopaminergic neurons [1–3]. The cardinal motor features of PD – tremor, rigidity, and bradykinesia – emerge when a significant proportion of substantia nigra dopamine neurons have been lost and striatal dopamine has been reduced by 60 to 80% (fig. 1) [4–6].

The goal of medical management of PD is to control signs and symptoms for as long as possible while minimizing adverse events (AEs). Levodopa, combined with a dopa decarboxylase (DDC) inhibitor such as carbidopa or benserazide, is the current standard treatment for motor signs. In addition to levodopa, dopamine agonists (e.g., pramipexole, ropinirole), centrally acting antimuscarinic drugs (e.g., trihexyphenidyl, benztropine, orphenadrine), monoamine oxidase-B (MAO-B) inhibitors (e.g., selegiline, rasagiline), and amantadine are used in the treatment of PD [7–9]. The choice of agents depends on a number of factors, including age of the patient, stage of disease, level of functional disability, cognitive status, and AEs associated with the drug. However, a detailed discussion of these agents is beyond the scope of this review which focuses on levodopa.



**Fig. 1.** Schematic representation of the main basal ganglia-thalamocortical circuits (left). Normal status: the two output routes ('indirect' and 'direct') are in balance at the level of the output structures (the GPi and the SNr) (right). Presumed disturbance in PD: depletion of dopamine in the striatum leads to imbalance in the two output routes and suppression of thalamocortical activity. The thickness of the arrows indicates the level of activity in the

pathways. D = Dopamine; GABA =  $\gamma$ -aminobutyric acid; GPe = external segment of globus pallidus; GPi = internal segment of globus pallidus; MD = mediodorsal nucleus; SNr = reticular part of the substantia nigra; SNc = pars compacta of the substantia nigra; STN = subthalamic nucleus; VA/VL = ventral anterior/ventral lateral thalamic nuclei (used with permission from Bonnet [79]).

## Historical Perspective

### *Development of Levodopa Treatment in PD*

The development of levodopa formulations is summarized in table 1. In 1911, D,L-dopa was first synthesized in the laboratory by Casimir Funk [10]. Two years later, Marcus Guggenheim was the first to isolate L-dopa from *Vicia faba* seedlings [10]. Both Funk and Guggenheim believed dopa to be a possible precursor of adrenaline [10]. Guggenheim's early investigations into the pharmacology of levodopa suggested that the compound was inactive; however, he became ill and vomited after ingesting 2.5 g. In the late 1920s and early 1930s, investigators found that levodopa was biologically active, causing hyperglycemia and hypotension in rabbits [10]. The discovery of DDC in mammalian tissue in 1938 focused levodopa research on the elucidation of the role of levodopa as a precursor to biological catecholamines, including dopa-

mine, noradrenaline, and adrenaline [10]. Dopamine was identified in the brains or brainstems of several species in the late 1950s [11, 12], and Carlsson et al. [13] reported an L-dopa-induced increase in the central stimulatory action in the rabbit. In the late 1950s and early 1960s, Isamu Sano and colleagues [14] published the first of a series of important papers on the distribution of catecholamines in the human brain; this research and subsequent work were extensively reviewed by Foley [15]. In the first report, Sano et al. [14] showed that dopamine was localized in the lentiform and caudate nuclei and the thalamus and hypothalamus.

Two important achievements followed: the recognition in 1960 that the predominant neurochemical impairment in PD is a dopamine deficiency in brain regions involved in movement control [16], and the subsequent success of single intravenous injections of levodopa in controlling PD symptoms (i.e., transient reversal of aki-

**Table 1.** Landmarks in the history of levodopa in PD (adapted from Hornykiewicz [10] and Tolosa et al. [39])

1911	D,L-Dopa synthesized in laboratory
1913	Levodopa isolated from <i>Vicia faba</i> (fava bean) seedlings
1927	Levodopa found to be biologically active
1938	L-Dopa decarboxylase enzyme identified
1960	Striatal dopamine deficiency in PD patients described [13]
1961	First reported trial of intravenous levodopa in PD [14]
1967	Levodopa activity enhanced with peripheral dopa decarboxylase inhibitor (benserazide)
1967	Effectiveness of oral levodopa demonstrated in patients with parkinsonism [16]
1969	First double-blind, placebo-controlled study showing efficacy of levodopa but with development of choreiform movements [17]
1969	Combined levodopa-decarboxylase inhibitor RO4-4602 (benserazide) proves more effective than levodopa alone
1974	Clinical use of carbidopa-levodopa reported [34]
1975	Continuous levodopa administration tried for preventing complications
1975	Levodopa-benserazide (Madopar) commercialized
1975	Carbidopa-levodopa (Sinemet) commercialized
1989	Sustained-release carbidopa-levodopa (Sinemet CR) reduces 'off' time and improves clinical disability better than standard carbidopa-levodopa (Sinemet), but effects are variable [36]
1989	Two COMT inhibitors found to be orally active [40]
1991	Sustained-release carbidopa-levodopa commercially available
1993	First clinical trial of enteral carbidopa-levodopa infusion [65, 72]
1998	First COMT inhibitor became commercially available (tolcapone; Tasmar)
2003	Combination carbidopa-levodopa-entacapone tablets (Stalevo) become commercially available

PD = Parkinson disease; COMT = catechol-*O*-methyltransferase.

nesia) in a small ( $n = 20$ ) open-label trial reported in 1961 by Birkmayer and Hornykiewicz [17]. The injections resulted in marked resolution of akinesia within 2–3 h and the effects persisted for up to 24 h [17]. However, in 1964, McGeer and Zeldowicz [18] reported that D,L-dopa had 'little to offer as a therapeutic agent in the treatment of parkinsonism'. Subsequently, Bertler and Rosengren [19] suggested that dopamine in the central nervous system (CNS) was probably a neurotransmitter, and that it might be a response modifier when other agents induce polarization of the nerve cell.

Following early evidence of the activity of levodopa in the symptomatic control of PD [16], Cotzias et al. [20] treated 16 PD patients with oral D,L-dopa 3–16 g/day and reported marked improvements in akinesia, tremor, and rigidity. However, 4 patients developed agranulocytopenia. Cotzias [21, 22] subsequently found that the use of L-dopa (8 g/day) rather than the racemic D,L-dopa resulted in symptomatic improvement with less toxicity.

In 1969, Yahr et al. [23] reported results of the first double-blind, placebo-controlled study to demonstrate the efficacy of levodopa in improving akinesia, tremor, and rigidity in patients with PD. AEs included involuntary choreiform and athetotic movements at higher dosages (up to 8 g/day was permitted) or after administration for about 6 months [23]. These involuntary movements were reported to resolve after dose reduction [23]. Soon thereafter, Bernheimer et al. [1] noted morphological and neurochemical correlations with brain dopamine levels in PD.

The US Food and Drug Administration approved levodopa as a treatment for PD in 1970. In 1975, Lloyd et al. [24] analyzed postmortem brain tissue from levodopa-treated and untreated PD patients and controls, and demonstrated that the effectiveness of levodopa is related to its metabolism to dopamine in the brain. Dopamine concentrations in the putamen and caudate nucleus were up to 15 times higher in treated than untreated patients and within the range of that found in control subjects. Dopamine concentrations correlated with the time between the last levodopa dose and death. Furthermore, higher striatal concentrations of levodopa were found in patients who had responded well to treatment [24].

#### *Complications of Levodopa Therapy*

Although treatment with levodopa was shown to improve the symptoms of PD, it became apparent in the late 1960s that many patients who responded to levodopa also developed motor fluctuations and dyskinesias [23, 25]. Between 40 and 75% of patients developed these complications after 4–6 years of levodopa therapy [26, 27]. More recently, it has been recognized that both motor and non-motor symptoms can fluctuate in association with the clinical duration of benefit of levodopa [28, 29].

The mechanism by which a patient's response to levodopa changes during long-term therapy is not fully understood. The shortening of the clinical response may be related to both pre- and postsynaptic events. Carbidopa/levodopa immediate-release (IR) can be administered initially on a TID or QID schedule and will last from dose to dose despite the short half-life of levodopa (90 min

when given in combination with carbidopa) [7]. Presumably, levodopa is taken up into remaining dopamine neurons and converted to dopamine, which is stored and slowly released into the synapse over time. However, as the loss of dopamine neurons progresses, this conversion, storage, and release mechanism is compromised [30]. Eventually, dopamine levels in the synapse begin to reflect levels of levodopa in the peripheral circulation, and patients become dependent on a constant influx of levodopa into the brain to achieve a clinical response [30, 31]. Postsynaptic mechanisms also may be involved in the reduced duration of benefit of levodopa as long-term administration of dopamine agonists in animal models of PD leads to a shortened duration of response [32], even though these agents act independently of presynaptic dopamine neurons.

The development of dyskinesias is also hypothesized to relate in large measure to postsynaptic mechanisms. In healthy individuals, dopamine receptors in the striatum are generally tonically innervated, and pulsatile stimulation from levodopa-derived dopamine may induce downstream changes that alter the function of basal ganglionic neurons [31, 33]. Pulsatile administration of short-acting dopamine agonists induces more dyskinesia than administration of the same agonist in a continuous fashion [34]. Similarly, continuous administration of levodopa has been associated with a reduction in dyskinesia [33]. Following elucidation of the continuous dopaminergic stimulation concept, research has focused on attempting to provide more sustained dopamine concentrations in the CNS.

#### *Effect of Dopa Decarboxylase Inhibition*

Unlike dopamine, which cannot cross the blood-brain barrier, the transport of levodopa into the brain is facilitated by the large neutral amino acid transport system [35]. However, only 1% of an orally administered dose of levodopa enters the brain because of extensive first-pass metabolism and rapid plasma clearance by decarboxylation to dopamine [35, 36]. The addition of a DDC inhibitor, as first performed by Walter Birkmayer, was found to provide a better therapeutic profile of levodopa, including prolonged efficacy and better tolerability [37]. Concomitant administration of a DDC inhibitor was demonstrated to increase levodopa CNS availability 10-fold [38]. The mechanism behind this increase in levodopa CNS availability was subsequently discovered by DaPrada et al. [37]. DDC inhibitors such as benserazide and carbidopa do not cross the blood-brain barrier. Therefore, they primarily block levodopa metabolism in

the periphery, thereby reducing the rate of the first-pass metabolism and slowing the plasma clearance of levodopa. An additional benefit of this reduced peripheral decarboxylation of levodopa to dopamine is the amelioration of the characteristic peripheral side effects of dopamine (i.e., nausea, vomiting, anorexia). When administered with a DDC inhibitor, the peripheral half-life of levodopa is prolonged to about 90 min and the required levodopa dose is reduced by 60–80% [35, 38]. Combinations of levodopa with benserazide or carbidopa became commercially available in 1975 [39].

Early clinical studies comparing carbidopa/levodopa with levodopa monotherapy showed that the addition of carbidopa markedly decreased nausea and vomiting [40, 41], with some improvement in the signs and symptoms of PD [40, 41]. However, more than 75% of patients treated with carbidopa/levodopa experienced marked dyskinesias after 4–6 months of treatment and, after 2 years of treatment, the benefits were sustained in only 20% of patients due to the progression of PD [41].

Carbidopa/levodopa controlled-release (CR) formulations were developed in the hope that they would further prolong the half-life of levodopa and stabilize serum levels, thereby decreasing the development of motor complications [42–44]. Carbidopa/levodopa CR became commercially available in the USA in 1991. In a 5-year study comparing carbidopa/levodopa IR with carbidopa/levodopa CR, scores on the Unified Parkinson's Disease Rating Scale Activities of Daily Living (UPDRS-ADL) scale were significantly better with carbidopa/levodopa CR than with carbidopa/levodopa IR at annual assessments [45]. In both groups, most improvement over baseline occurred in year 1, followed by deterioration. The rate of deterioration was somewhat slower in the CR group, but the incidences of motor fluctuations and dyskinesias were not significantly different between the two groups [45]. Thus, carbidopa/levodopa CR was not shown to lower the risk of levodopa-related motor complications [45]. However, the trial may have been flawed in that carbidopa/levodopa CR was administered on a BID schedule [45] and this may not have been frequent enough to establish continuous dopamine receptor stimulation.

Clinical experience also reflected pharmacokinetic data and suggested that although carbidopa/levodopa CR maintained levodopa levels longer than carbidopa/levodopa IR, the time to onset of clinical benefit was delayed owing to slower absorption [44]. Because of this, carbidopa/levodopa CR is commonly administered with carbidopa/levodopa IR in patients with motor fluctua-

tions to maintain optimal control of PD symptoms, particularly for the first dose in the morning [42].

#### *Effect of Catechol-O-Methyltransferase Inhibition*

The combination of carbidopa and levodopa allowed substantial reductions in the effective dosage of levodopa and reduced many of the peripheral AEs. However, only 5–10% of an oral dose of levodopa administered in combination with carbidopa crosses the blood-brain barrier [46]. Inhibition of the decarboxylation pathway with carbidopa shifts the metabolism of levodopa to the catechol-O-methyltransferase (COMT) metabolic pathway, causing an increase in the peripheral metabolite 3-O-methyl-dopa (3-OMD) [35], which is a competitive inhibitor of the active transport of levodopa through the intestinal mucosa and across the blood-brain barrier [35, 46]. It may also compete with levodopa in the synthesis, transport, and uptake of dopamine in the CNS [47]. The discovery that inhibition of COMT leads to both an increase in the amount of levodopa in the CNS and a reduced formation of 3-OMD prompted research into inhibitors of COMT [46]. Early efforts were initially unsuccessful, but two compounds did prove orally active [46].

In multiple clinical trials, the addition of the COMT inhibitors entacapone and tolcapone to levodopa/DDC inhibitor in fluctuating patients has been shown to improve clinical outcomes. Specifically, the addition of either compound increases ‘on’ time and decreases ‘off’ time, improves parkinsonian motor status, and decreases average levodopa daily dose [48–58]. Tolcapone became commercially available in 1998, and entacapone in 1999. Tolcapone has a greater effect on levodopa metabolism [59], although some studies of patients with motor fluctuations have shown entacapone and tolcapone to have somewhat similar clinical effects [60]. The recognition that tolcapone could rarely cause fatal hepatotoxicity generally limited its use to patients who do not respond to other medications [61], although this limitation recently has been called into question [62]. An evidence-based review by the American Academy of Neurology recommended that while both entacapone (Level A) and tolcapone (Level B) reduce ‘off’ time, tolcapone should be used with caution and requires liver function monitoring [9].

In four randomized, placebo-controlled trials in patients with ‘wearing off’ motor fluctuations, adding entacapone to levodopa/DDC inhibitor has been demonstrated to increase ‘on’ time, decrease ‘off’ time, and prolong the duration of response to levodopa [63–66]. In the MPTP marmoset model of PD, the administration of en-

tacapone with carbidopa/levodopa on a QID schedule reduced ‘off’ time and was associated with less dyskinesia than the same regimen of carbidopa/levodopa administered without entacapone [67]. More recently, carbidopa/levodopa was combined with the COMT inhibitor entacapone in a single tablet (carbidopa/levodopa/entacapone, Stalevo) [68].

A recent double-blind clinical trial in early PD patients found that carbidopa/levodopa/entacapone 25/100/200 TID improved PD signs and symptoms significantly more than carbidopa/levodopa 25/100 TID without an increase in the development of motor complications [69]. Another large, double-blind clinical trial is now underway to determine whether carbidopa/levodopa/entacapone delays the onset of dyskinesia compared with carbidopa/levodopa in patients with early PD [33, 70, 71].

#### **Future Directions**

Several new levodopa formulations that may provide more continuous dopamine stimulation are being investigated. These include oral long-acting, once-daily pills, transdermal formulations, and continuous infusion.

A carbidopa/levodopa gel formulation for enteral infusion has been shown to provide more consistent clinical effects and reduce motor complications in advanced patients [72]. The levodopa gel is contained in a pump cartridge that delivers levodopa continuously via a cannula to the duodenum. In a series of open-label studies reviewed by Nyholm [72], a total of 80 patients received enteral infusions of carbidopa/levodopa gel for periods of up to 7 years. Motor function was improved in all studies, with patients in one study showing little or no disease progression over 4–7 years of treatment [72]. In a small study (n = 9), after 12 months’ treatment with levodopa infusion, ‘off’ time was reduced by 89% and time with dyskinesia was reduced by 74% [73]. The main limitations regarding levodopa infusion include the need for a trans-abdominal tube with the tip placed in the duodenum [74] and the expense. However, this therapy may offer an important alternative to deep brain stimulation, as it avoids major CNS morbidity and mortality as well as subtle cognitive and behavioral changes.

The primary technical challenge involved in creating an oral once-daily formulation of levodopa is in delivering sufficient quantities of levodopa to the proximal small bowel over time. One approach is the use of sustained-release floating minitables that increase the mean resi-

dence time of levodopa in the gastrointestinal tract, thereby increasing the opportunity for absorption. In vitro studies have shown that minitables coated with an insoluble acrylic polymer can remain buoyant for >13 h and provide sustained release of levodopa for >20 h [75]. In vivo testing is planned in the near future.

Another approach involves administration of a CR formulation of a levodopa prodrug that can be absorbed along longer portions of the intestinal tract. A recent press release regarding the levodopa prodrug XP21279 (<http://phx.corporate-ir.net/phoenix.zhtml?c=187883&p=irol-newsArticle&ID=1117889&highlight=>) reported that in a Phase 1 pharmacokinetic study in healthy fed controls, for carbidopa/levodopa IR, the mean time to peak concentration ( $T_{max}$ ) for levodopa was 2.1 h and the ratio of the maximum concentration ( $C_{max}$ ) to the mean concentration at 12 h ( $C_{12}$ ) was 39.7. In contrast, for XP21279, the mean  $T_{max}$  was 4.3 h and the ratio of  $C_{max}$  to  $C_{12}$  was 4.2, suggesting relatively continuous levodopa levels. Additional levodopa prodrugs are in development [76], but as yet, no clinical results have been reported.

The primary technical challenge in developing a levodopa transdermal patch is overcoming the poor solubility and stability of levodopa [77, 78]. It has been suggested that the stability of levodopa can be improved by use of ion-exchange fibers and transdermal iontophoresis [78], but further research is required. A transdermal patch is being developed with a grant from the Michael J. Fox Foundation for Parkinson's Disease (<http://www.michaeljfox.org/research.cfm>) using the ethyl ester of levodopa (<http://www.neuroderm.co.il/rdip.html> and <http://www.neuroderm.co.il/overview.html>). A press release ([http://www.businesswire.com/portal/site/google/?ndmViewId=news\\_view&newsId=20070131005754&newsLang=en](http://www.businesswire.com/portal/site/google/?ndmViewId=news_view&newsId=20070131005754&newsLang=en)) reporting the completion of a pharmacokinetic study showed that levodopa blood levels were maintained.

## Summary

Parkinson's disease is a progressive neurodegenerative disease associated with the loss of dopamine-producing neurons. Levodopa is the gold standard for PD therapy, and numerous studies have established its efficacy in reducing the cardinal motor signs of rest tremor, bradykinesia, and rigidity. Advances in levodopa therapy include extending its half-life and improving efficacy by concomitant dosing with DDC inhibitors and COMT inhibitors. Recent research is focused on providing more continuous

dopaminergic stimulation by using novel levodopa preparations in an effort to minimize the motor complications associated with current levodopa therapy.

## Additional Readings

Barbeau A, Murphy GF, Sourkes TL: Les catécholamines dans la maladie de Parkinson; in De Ajuriaguerra J (ed): *Monoamines et système nerveux central* (in French). Paris, Masson, 1962, pp 247–262.

Birkmayer W, Hornykiewicz O: The L-dihydroxyphenylalanine (L-dopa) effect in Parkinson's syndrome in man: on the pathogenesis and treatment of Parkinson akinesia (in German). *Arch Psychiatr Nervenkr Z Gesamte Neurol Psychiatr* 1962;203:560–574.

Birkmayer W, Hornykiewicz O: The L-3,4-dioxyphenylalanine (dopa) effect in Parkinson-akinesia (in German, translated in Birkmayer, 1998 [17]). *Wien Klin Wochenschr* 1961;73:787–788.

Birkmayer W, Mentasti M: Further experimental studies on the catecholamine metabolism in extrapyramidal diseases (Parkinson and chorea syndromes) (in German). *Arch Psychiatr Nervenkr* 1967;210:29–35.

Degkwitz R, Frowein R, Kulenkampff C, Mohs U: On the effects of L-dopa in man and their modification by reserpine, chlorpromazine, iproniazid and vitamin B<sub>6</sub> (in German). *Klin Wochenschr* 1960;38:120–123.

Ehringer H, Hornykiewicz O: Distribution of noradrenaline and dopamine (3-hydroxytyramine) in the human brain and their behavior in diseases of the extrapyramidal system (in German, translated in Ehringer, 1998 [16]). *Klin Wochenschr* 1960;38:1236–1239.

## Acknowledgments

The contents expressed in this review are the views of the author. The author wishes to thank Patricia Bichler (Embryon) and the staff at Embryon for their editorial support.

## Disclosures

Funding for editorial support was provided by Novartis Pharmaceuticals Corp. Dr. Hauser did not receive any compensation for his work on this review. Dr. Hauser has received honoraria and/or consulting fees from Novartis, Orion Pharma, Valeant Pharmaceuticals, Impax Laboratories, and Solvay Pharmaceuticals. Dr. Hauser's institution has received funds for research from Novartis, Valeant, and Solvay.

## References

- Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, Seitelberger F: Brain dopamine and the syndromes of Parkinson and Huntington. Clinical, morphological and neurochemical correlations. *J Neurol Sci* 1973;20:415–455.
- Lloyd KG, Hornykiewicz O: Parkinson's disease: activity of L-dopa decarboxylase in discrete brain regions. *Science* 1970;170:1213.
- Fahn S, Lipsch LR, Cutler RW: Monoamines in the human neostriatum: topographic distribution in normals and in Parkinson's disease and their role in akinesia, rigidity, chorea, and tremor. *J Neurol Sci* 1971;14:427–455.
- Lang AE: The progression of Parkinson disease: a hypothesis. *Neurology* 2007;68:948–952.
- Hornykiewicz O: Biochemical aspects of Parkinson's disease. *Neurology* 1998;51:S2–S9.
- Kish SJ, Shannak K, Hornykiewicz O: Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications. *N Engl J Med* 1988;318:876–880.
- Deleu D, Northway MG, Hanssens Y: Clinical pharmacokinetic and pharmacodynamic properties of drugs used in the treatment of Parkinson's disease. *Clin Pharmacokinet* 2002;41:261–309.
- Oldfield V, Keating GM, Perry CM: Rasagiline: a review of its use in the management of Parkinson's disease. *Drugs* 2007;67:1725–1747.
- Pahwa R, Factor SA, Lyons KE, Ondo WG, Gronseth G, Bronte-Stewart H, Hallett M, Miyasaki J, Stevens J, Weiner WJ: Practice parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006;66:983–995.
- Hornykiewicz O: L-Dopa: from a biologically inactive amino acid to a successful therapeutic agent. *Amino Acids* 2002;23:65–70.
- Montagu KA: Catechol compounds in rat tissues and in brains of different animals. *Nature* 1957;180:244–245.
- Weil-Malherbe H, Bone AD: Intracellular distribution of catecholamines in the brain. *Nature* 1957;180:1050–1051.
- Carlsson A, Lindqvist M, Magnusson T: 3,4-Dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. *Nature* 1957;180:1200.
- Sano I, Gamo T, Kakimoto Y, Taniguchi K, Takegada M, Nishinuma K: Distribution of catechol compounds in human brain. *Biochim Biophys Acta* 1959;32:586–587.
- Foley P: The L-dopa story revisited. Further surprises to be expected? *J Neural Transm Suppl* 2000;60:1–20.
- Ehringer H, Hornykiewicz O: Distribution of noradrenaline and dopamine (3-hydroxytyramine) in the human brain and their behavior in diseases of the extrapyramidal system. *Parkinsonism Relat Disord* 1998;4:53–57.
- Birkmayer W, Hornykiewicz O: The effect of L-3,4-dihydroxyphenylalanine (L-dopa) on akinesia in parkinsonism. *Parkinsonism Relat Disord* 1998;4:59–60.
- McGeer PL, Zeldowicz LR: Administration of dihydroxyphenylalanine to parkinsonian patients. *Can Med Assoc J* 1964;90:463–466.
- Bertler A, Rosengren E: Possible role of brain dopamine. *Pharmacol Rev* 1966;18:769–773.
- Cotzias GC, Van Woert MH, Schiffer LM: Aromatic amino acids and modification of parkinsonism. *N Engl J Med* 1967;276:374–379.
- Cotzias GC: L-Dopa for Parkinsonism. *N Engl J Med* 1968;278:630.
- Cotzias GC, Papavasiliou PS, Vanwoert MH, Sakamoto A: Melanogenesis and extrapyramidal diseases. *Fed Proc* 1964;23:713–718.
- Yahr MD, Duvoisin RC, Schear MJ, Barrett RE, Hoehn MM: Treatment of parkinsonism with levodopa. *Arch Neurol* 1969;21:343–354.
- Lloyd KG, Davidson L, Hornykiewicz O: The neurochemistry of Parkinson's disease: effect of L-dopa therapy. *J Pharmacol Exp Ther* 1975;195:453–464.
- Cotzias GC, Papavasiliou PS, Gellene R: Modification of Parkinsonism – chronic treatment with L-dopa. *N Engl J Med* 1969;280:337–345.
- Ahlskog JE, Muentner MD: Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Mov Disord* 2001;16:448–458.
- Fahn S: Parkinson disease, the effect of levodopa, and the ELLDOPA trial. Earlier vs. later L-dopa. *Arch Neurol* 1999;56:529–535.
- Witjas T, Kaphan E, Azulay JP, Blin O, Ceccaldi M, Pouget J, Poncet M, Cherif AA: Nonmotor fluctuations in Parkinson's disease: frequent and disabling. *Neurology* 2002;59:408–413.
- Gunal DI, Nurichalichi K, Tuncer N, Bekiroglu N, Aktan S: The clinical profile of non-motor fluctuations in Parkinson's disease patients. *Can J Neurol Sci* 2002;29:61–64.
- Olanow CW, Obeso JA, Stocchi F: Drug insight: continuous dopaminergic stimulation in the treatment of Parkinson's disease. *Nat Clin Pract Neurol* 2006;2:382–392.
- Obeso JA, Rodriguez-Oroz MC, Chana P, Lera G, Rodriguez M, Olanow CW: The evolution and origin of motor complications in Parkinson's disease. *Neurology* 2000;55:S13–S20.
- Blanchet PJ, Grondin R, Bedard PJ, Shiosaki K, Britton DR: Dopamine D<sub>1</sub> receptor desensitization profile in MPTP-lesioned primates. *Eur J Pharmacol* 1996;309:13–20.
- Olanow CW, Obeso JA, Stocchi F: Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications. *Lancet Neurol* 2006;5:677–687.
- Stocchi F, Ruggieri S, Vacca L, Olanow CW: Prospective randomized trial of lisuride infusion versus oral levodopa in patients with Parkinson's disease. *Brain* 2002;125:2058–2066.
- Nutt JG, Fellman JH: Pharmacokinetics of levodopa. *Clin Neuropharmacol* 1984;7:35–49.
- Jankovic J: Levodopa strengths and weaknesses. *Neurology* 2002;58:S19–S32.
- Pletscher A, DaPrada M: Pharmacotherapy of Parkinson's disease: research from 1960 to 1991. *Acta Neurol Scand Suppl* 1993;146:26–31.
- Cedarbaum JM: Clinical pharmacokinetics of anti-parkinsonian drugs. *Clin Pharmacokinet* 1987;13:141–178.
- Tolosa E, Marti MJ, Valdeoriola F, Molinuevo JL: History of levodopa and dopamine agonists in Parkinson's disease treatment. *Neurology* 1998;50:S2–S10.
- Markham C, Diamond SG, Treciokas LJ: Carbidopa in Parkinson disease and in nausea and vomiting of levodopa. *Arch Neurol* 1974;31:128–133.
- Lieberman A, Goodgold A, Jonas S, Leibowitz M: Comparison of dopa decarboxylase inhibitor (carbidopa) combined with levodopa and levodopa alone in Parkinson's disease. *Neurology* 1975;25:911–916.
- LeWitt PA, Nelson MV, Berchou RC, Galloway MP, Kesaree N, Kareti D, Schlick P: Controlled-release carbidopa/levodopa (Sinemet 50/200 CR4): clinical and pharmacokinetic studies. *Neurology* 1989;39:45–53.
- Koller WC, Hutton JT, Tolosa E, Capilldeo R: Immediate-release and controlled-release carbidopa/levodopa in PD: a 5-year randomized multicenter study. *Carbidopa/Levodopa Study Group. Neurology* 1999;53:1012–1019.
- Hammerstad JP, Woodward WR, Nutt JG, Gancher ST, Block GA, Cyhan G: Controlled release levodopa/carbidopa 25/100 (Sinemet CR 25/100): pharmacokinetics and clinical efficacy in untreated parkinsonian patients. *Clin Neuropharmacol* 1994;17:429–434.
- Block G, Liss C, Reines S, Irr J, Nibbelink D: Comparison of immediate-release and controlled release carbidopa/levodopa in Parkinson's disease. A multicenter 5-year study. The CR First Study Group. *Eur Neurol* 1997;37:23–27.

- 46 Mannisto PT, Kaakkola S: New selective COMT inhibitors: useful adjuncts for Parkinson's disease? *Trends Pharmacol Sci* 1989; 10:54–56.
- 47 Lee ES, Chen H, King J, Charlton C: The role of 3-O-methyldopa in the side effects of L-dopa. *Neurochem Res* 2008;33:401–411.
- 48 Dupont E, Burgunder JM, Findley LJ, Olsson JE, Dorflinger E: Tolcapone added to levodopa in stable parkinsonian patients: a double-blind placebo-controlled study. Tolcapone in Parkinson's Disease Study Group II (TIPS II). *Mov Disord* 1997;12:928–934.
- 49 Baas H, Beiske AG, Ghika J, Jackson M, Oertel WH, Poewe W, Ransmayr G: Catechol-O-methyltransferase inhibition with tolcapone reduces the 'wearing off' phenomenon and levodopa requirements in fluctuating parkinsonian patients. *J Neurol Neurosurg Psychiatry* 1997;63:421–428.
- 50 Adler CH, Singer C, O'Brien C, Hauser RA, Lew MF, Marek KL, Dorflinger E, Pedder S, Deptula D, Yoo K: Randomized, placebo-controlled study of tolcapone in patients with fluctuating Parkinson disease treated with levodopa-carbidopa. Tolcapone Fluctuator Study Group III. *Arch Neurol* 1998;55:1089–1095.
- 51 Fenelon G, Gimenez-Roldan S, Montastruc JL, Bermejo F, Durif F, Bourdeix I, Pere JJ, Galiano L, Schadrack J: Efficacy and tolerability of entacapone in patients with Parkinson's disease treated with levodopa plus a dopamine agonist and experiencing wearing-off motor fluctuations. A randomized, double-blind, multicentre study. *J Neural Transm* 2003;110:239–251.
- 52 Mizuno Y, Kanazawa I, Kuno S, Yanagisawa N, Yamamoto M, Kondo T: Placebo-controlled, double-blind dose-finding study of entacapone in fluctuating parkinsonian patients. *Mov Disord* 2007;22:75–80.
- 53 Grandas F, Hernandez B: Long-term effectiveness and quality of life improvement in entacapone-treated Parkinson's disease patients: the effects of an early therapeutic intervention. *Eur J Neurol* 2007;14:282–289.
- 54 Larsen JP, Worm-Petersen J, Siden A, Gordin A, Reinikainen K, Leinonen M; NOMESAFE Study Group: The tolerability and efficacy of entacapone over 3 years in patients with Parkinson's disease. *Eur J Neurol* 2003;10:137–146.
- 55 Gershanik O, Emre M, Bernhard G, Sauer D: Efficacy and safety of levodopa with entacapone in Parkinson's disease patients suboptimally controlled with levodopa alone, in daily clinical practice: an international, multicentre, open-label study. *Prog Neuropsychopharmacol Biol Psychiatry* 2003;27:963–971.
- 56 Durif F, Devaux I, Pere JJ, Delumeau JC, Bourdeix I: Efficacy and tolerability of entacapone as adjunctive therapy to levodopa in patients with Parkinson's disease and end-of-dose deterioration in daily medical practice: an open, multicenter study. *Eur Neurol* 2001;45:111–118.
- 57 Roberts JW, Cora-Locatelli G, Bravi D, Amantea MA, Mouradian MM, Chase TN: Catechol-O-methyltransferase inhibitor tolcapone prolongs levodopa/carbidopa action in parkinsonian patients. *Neurology* 1993; 43:2685–2688.
- 58 Limousin P, Pollak P, Gervason-Tournier CL, Hommel M, Perret JE: Ro 40-7592, a COMT inhibitor, plus levodopa in Parkinson's disease. *Lancet* 1993;341:1605.
- 59 Nutt JG, Woodward WR, Beckner RM, Stone CK, Berggren K, Carter JH, Gancher ST, Hammerstad JP, Gordin A: Effect of peripheral catechol-O-methyltransferase inhibition on the pharmacokinetics and pharmacodynamics of levodopa in parkinsonian patients. *Neurology* 1994;44:913–919.
- 60 Entacapone to Tolcapone Switch Study Investigators: Entacapone to tolcapone switch: multicenter double-blind, randomized, active-controlled trial in advanced Parkinson's disease. *Mov Disord* 2007;22:14–19.
- 61 Borges N: Tolcapone in Parkinson's disease: liver toxicity and clinical efficacy. *Expert Opin Drug Saf* 2005;4:69–73.
- 62 Olanow CW, Watkins PB: Tolcapone: an efficacy and safety review. *Clin Neuropharmacol* 2007;30:287–294.
- 63 Parkinson Study Group: Entacapone improves motor fluctuations in levodopa-treated Parkinson's disease patients. *Ann Neurol* 1997;42:747–755.
- 64 Rinne UK, Larsen JP, Siden A, Worm-Petersen J; Nomescomt Study Group: Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. *Neurology* 1998;51:1309–1314.
- 65 Poewe WH, Deuschl G, Gordin A, Kultalahti ER, Leinonen M: Efficacy and safety of entacapone in Parkinson's disease patients with suboptimal levodopa response: a 6-month randomized placebo-controlled double-blind study in Germany and Austria (Celomen Study). *Acta Neurol Scand* 2002;105: 245–255.
- 66 Brooks DJ, Sagar H: Entacapone is beneficial in both fluctuating and non-fluctuating patients with Parkinson's disease: a randomised, placebo-controlled, double-blind, six-month study. *J Neurol Neurosurg Psychiatry* 2003;74:1071–1079.
- 67 Smith LA, Jackson MJ, Al Barghouthy G, Rose S, Kuoppamäki M, Olanow W, Jenner P: Multiple small doses of levodopa plus entacapone produce continuous dopaminergic stimulation and reduce dyskinesia induction in MPTP-treated drug-naive primates. *Mov Disord* 2005;20:306–314.
- 68 Hauser RA: Levodopa/carbidopa/entacapone (Stalevo). *Neurology* 2004;62:S64–S71.
- 69 Hauser RA, Panisset M, Abbruzzese G, Mancione L, Dronamraju N, Kakarietka A: Double-blind trial of levodopa/carbidopa/entacapone versus levodopa/carbidopa in early Parkinson's disease. *Mov Disord* 2008. [Epub ahead of print].
- 70 Schrag A: Entacapone in the treatment of Parkinson's disease. *Lancet Neurol* 2005;4: 366–370.
- 71 Stocchi F: Optimising levodopa therapy for the management of Parkinson's disease. *J Neurol* 2005;252(suppl 4):IV43–IV48.
- 72 Nyholm D: Enteral levodopa/carbidopa gel infusion for the treatment of motor fluctuations and dyskinesias in advanced Parkinson's disease. *Expert Rev Neurother* 2006;6: 1403–1411.
- 73 Antonini A, Isaias IU, Canesi M, Zibetti M, Mancini F, Manfredi L, Dal FM, Lopiano L, Pezzoli G: Duodenal levodopa infusion for advanced Parkinson's disease: 12-month treatment outcome. *Mov Disord* 2007;22: 1145–1149.
- 74 Syed N, Murphy J, Zimmerman T Jr, Mark MH, Sage JI: Ten years' experience with enteral levodopa infusions for motor fluctuations in Parkinson's disease. *Mov Disord* 1998;13:336–338.
- 75 Goole J, Deleuze P, Vanderbist F, Amighi K: New levodopa sustained-release floating minitables coated with insoluble acrylic polymer. *Eur J Pharm Biopharm* 2008;68: 310–318.
- 76 Di Stefano A, Sozio P, Cerasa LS: Antiparkinson prodrugs. *Molecules* 2008;13:46–68.
- 77 Priano L, Gasco MR, Mauro A: Transdermal treatment options for neurological disorders: impact on the elderly. *Drugs Aging* 2006;23:357–375.
- 78 Kankkunen T, Huupponen I, Lahtinen K, Sundell M, Ekman K, Kontturi K, Hirvonen J: Improved stability and release control of levodopa and metaraminol using ion-exchange fibers and transdermal iontophoresis. *Eur J Pharm Sci* 2002;16:273–280.
- 79 Bonnet AM: Involvement of non-dopaminergic pathways in Parkinson's disease: pathophysiology and therapeutic implications. *CNS Drugs* 2000;13:351–364.