Levodopa: History and Therapeutic Applications

Sujith Ovallath, Bahiya Sulthana

James Parkinson's Movement Disorder Research Centre, Kannur Medical College, Kannur, Kerala, India

Abstract

Levodopa – the aromatic amino acid L-3,4–dihydroxy phenylalanine has held the attention of neurologists and pharmacologists alike for more than half a century. Even though extensive research has been done across the globe in treatment of Parkinson's disease, with different molecules, none could replace the gold standard treatment or provide complete relief for the debilitated. Although research brought us better tips and tricks to modulate the dopamine blood levels to balance between the desired and deleterious effects, it could never replace the basic substrate. From simple oral preparation to more advanced treatment like duodenal dopa administration for better efficacy and compliance, L-dopa has sure undergone scrutiny and stayed strong as the fundamental neurotransmitter replacement therapy to pave path for many more new therapeutic strategies. So as a token of gratitude to the revolutionary agent and pioneers behind it, a trip down the memory lane is in order.

Keywords: Dopamine, history of levodopa, levodopa, newer levodopa

Introduction

Introduction of levodopa therapy in Parkinson's disease almost half a century back has revolutionized the therapeutic outcome of this challenging disease. Although several other agents have been subsequently added to the therapeutic armamentarium, levodopa remains the gold standard till date. The levodopa era began in 1967, when Cotzias *et al*. showed that orally administered levodopa had a dramatic and sustained effect on the symptoms of severely disabled Parkinsonian patients.[1,2]

The basic research that lead to the introduction of this wonder drug was the discovery of dopamine – a neurotransmitter that could control movements – by the Swedish pharmacologist Arvid Carlsson, who shared the Nobel prize in physiology and medicine in the year 2000.[3] Another major landmark in the development of levodopa therapy was the introduction of carbidopa the peripheral decarboxylase inhibitor. The success of levodopa therapy for Parkinson's disease also was the key factor in creating a new subspecialty of neurology, namely, movement disorders.[4]

Although the modern history of levodopa unfolds from the 19th century, it would be interesting to note that ancient Indian ayurvedic physicians used the seeds of Mucuna pruriens, which later proved to contain 4%–6% of levodopa, to treat symptoms of Parkinson's disease, as early as 300BC.[5-8]

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History of Levodopa

L-Dopa, the naturally occurring isomer of the amino acid 3,4-dihydroxyphenylalanine, was first isolated in 1913 from legumes (seedlings of Vicia faba) by Marcus Guggenheim.[9] Casimir Funk had synthesized D, L-dopa in the laboratory two years prior to this at the Welcome labs in London, England [10] Almost 40 years later, Dale suggested its current name, dopamine for the compound synthesized earlier.[11] Both funk and Guggenheim considered the amino acid as a possible parent compound of adrenaline.

The discovery by Peter *et al*.[12]of an enzyme, DOPA decarboxylase, in mammalian tissue (kidney) extracts that converted L-dopa to the corresponding – biologically active amine, in 1938, represented a turning point in catecholamine research. This has led to the postulation of the possible pathway of catecholamine synthesis in the body by Blaschko and Holtz in 1939, which still holds good, and proceeds from L-tyrosine to L-dopa which get converted to dopamine, and this in turn get converted into catecholamines.[13] The discovery of the enzyme aromatic-L-amino-acid decarboxylase (also called dopa

Address for correspondence: Dr. Sujith Ovallath, James Parkinson's Movement Disorder Research Centre, Kannur Medical College, Kannur, Kerala, India. E-mail: sujithok@gmail.com

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decarboxylase), provided a mechanism for the formation of dopamine in the brain from an exogenous source since L-dopa, unlike dopamine itself, can cross the blood–brain barrier.

Guggenheim, in addition to isolating L-dopa, was also the first to perform a self-experiment, by ingesting 2.5 g of L-dopa and demonstrated its emetic action which was however interpreted by him as a an unspecific irritation of the gastric mucosa but was later proved to be due to its conversion to dopamine which acts on the emetic centre in the medulla oblongata. Guggenheim believed L-dopa was biologically inactive but, in 1927, nearly 15 years later, it was disproved by Hirai and Gondo, who found that D, L-dopa caused hyperglycemia in rabbit (200–300 mg s. c.).[14] In 1930, Hasama demonstrated that in the rabbit D, L-dopa, in contrast to the vasopressor effect of adrenaline, produced a clear fall in arterial blood pressure, the lowest effective dose, given intravenously.[15]

In 1942, Holtz demonstrated that the administration of L-dopa in laboratory animals and humans results in excretion of dopamine in the urine.[16] He noticed that in humans, 50 mg L-dopa intravenous (IV) caused tachycardia. Dopamine was isolated first in the adrenal medulla by Goodall, 1950.[17] Raab and Gigee discovered the occurrence of a catecholamine-(adrenaline-) like substance in the brain of many species, including humans in 1951.[18] From then onward, reports of isolation of dopamine from body tissues started pouring in, from tumor tissue of phaeochromocytoma,[19] in the human brain,[20] in the iris and choroidal layer of the calf eye.[21]

Indisputably, the first researchers to study the effect of systemically administered dopa on brain catecholamines were Raab and Gigee in 1951. They injected, in rats, a great number of biologically active substances and found that only dopa increased the brain concentration of a catecholamine-(adrenaline-) like substance. Following these results, early dopamine and L-dopa trials[22] were started.

In 1956, Hornykiewicz working in Blaschko's laboratory, now located in Oxford, was assigned the task of determining whether blood pressure was directly affected by dopamine or if some other product of dopamine was responsible. Hornykiewicz showed that, indeed, dopamine did lower blood pressure and that L-dopa had a similar effect.[23]

Carlsson's Discovery of Dopamine

Arvid Carlsson, a Swedish postdoctoral fellow in Bernard Brodie's cardiac pharmacology laboratory at NIH, was investigating the mechanism whereby reserpine lowers blood pressure and slows heart rate. Brodie's laboratory had shown that reserpine lowered serotonin levels[24] and had proposed that loss of serotonin was responsible for reserpine's cardiovascular effect and also for its neurologic effect of "tranquilization" (now recognized as akinesia). Carlsson, however, wondered if perhaps it was not serotonin, but rather a catecholamine. At about the same time, L-dopa was found to cause central, behavioral as well as EEG activation and to antagonize reserpine's "tranquilizing" effects[25] responsible for lowering blood pressure and for the akinetic effect of reserpine. In 1957, he observed that norepinephrine and epinephrine disappeared more or less completely from tissues, including brain, after reserpine treatment[26] the same effect that Brodie and coworkers had shown for serotonin. After returning to Sweden, Carlson established his own laboratory at the University of Lund, he showed that D, L-dopa, not 5-hydroxytryptophan (the precursor of serotonin), reversed the akinetic effect of reserpine in rabbits[3] In dramatic fashion, reserpinized rabbits, after receiving D, L-dopa, went from being totally unresponsive to alert, with their drooping ears popping up almost immediately. During its initial phases, the Carlsson experiments were viewed with skepticism by the scientific community but mooted interest in several researchers to experiment on dopamine. Although a bit delayed, the revolutionary discovery of Carlson was honored by the Nobel committee in 2000 by awarding him the Nobel Prize in physiology and medicine.

Almost during the same period, Hornykiewicz, who returned back to Vienna from being a postdoc in Blaschco's lab in Oxford, began to measure postmortem brain dopamine in people with PD, postencephalitic parkinsonism, Huntington's disease, and in other extrapyramidal disorders, as well as in control brains, and in 1960, published a landmark paper showing for the first time a marked depletion of dopamine in the caudate and putamen of patients only in the PD and postencephalitic parkinsonian brains.[27] Six years later, Hornykiewicz published a major review article in Pharmacological Reviews positing

Table 1: Levodopa the journey so far

YEAR	MILESTONE
1911	Synthesized in the laboratory
1913	Isolated from seed of *Vicia faba*
1916-1939	Effect on blood sugar and arterial blood pressure studied in rabbits
1939	Inactive precursor to catecholamine
1940-1957	Found in adrenals and brains
1950-1960	Catecholamine depletion reversal
1957-1959	Reversal of resperidone-induced extrapyramidal side effects
1960-1962	Depleted dopamine in cadaveric brains
	Decreased dopamine in basal ganglia of parkinsonism patients
1961	L-dopa tried in parkinsonism patients
1967	Used with peripheral dopa decarboxylase inhibitor
1973	Sustained release formulations of L-dopa
1975	L-dopa intravenous administration
1975	Combination with carbidopa emerged
1982	Dopamine agonist adjunct with L-dopa for better results
1989	Motor fluctuation minimized with controlled release
1990	On and off fluctuations with continuous L-dopa administration
1993	Intermittent oral preparations for motor fluctuations
1994	L-dopa potency rises in combination with COMT inhibitors
1997	Controlled release combinations proved to be more effective

COMT = Catechol-O-methyltransferase

that striatal dopamine deficiency is correlated with most of the motor symptoms of PD.[28]

Levodopa and Human Experiments

In view of the existing evidences for use of L-dopa in Humans, in 1961 Hornykiewicz together with the neurologist Birkmayer performed a trial with i. v. L-dopa in a group of twenty patients[29] and first time reported the dramatic improvement of all motor deficits related to the symptom of akinesia, lasting for several hours. At the same time, and independently, over the next several years, some investigators around the world showed similar benefits using higher doses of L-dopa[29-35] while other investigators reported no benefits with similar doses.[35-39]

The first person to use really high doses of DOPA was Patrick McGeer in Vancouver, British Columbia. Even with 5 g of D, L-dopa per day, McGeer failed to show a benefit.

The breakthrough for L-dopa as a therapeutic agent in PD came 6 years after the initial studies, in 1967, when George Cotzias in New York introduced, with great success, the high-dose oral L-dopa regimen, still used, in principle, today (Cotzias *et al*., 1967). George Cotzias developed a new approach, in which he used levodopa in gradually incremental dosages, eventually giving up to 16 g/day. Patients with PD tolerated this very slow, gradual build-up of dosage and then began to achieve dramatic, revolutionary benefit as therapeutic doses were reached. This was associated with less gastrointestinal side effects.

Soon after that, in 1969, Melvin Yahr in New York published the very first double-blind L-dopa study, establishing objectively the amino acids superior effectiveness as an Antiparkinsonian agent[40] [Table 1].

There have been several papers questioning the usefulness of levodopa, but none could disprove its usefulness.[41-43] Most of the criticism waned off when 1975 Ken Lloyd in Toronto published a study conclusively demonstrated that in the striatum of PD patients treated with L-dopa, showed nine to fifteen-fold higher levels of dopamine than in nondopa-treated patients.[44]

Theraputic Applications of Levodopa

The major therapeutic application of levodopa is still revolves around its use in Parkinsonism, Parkinsons plus syndrome and dopa-responsive dystonias. Clinical efficacy of levodopa varies in different subsets of symptoms. The classical motor symptoms of PD, bradykinesia, and rigidity, usually respond well to levodopa.

Response of tremor is less pronounced. Uniform poor response is the rule for other motor symptoms, such as speech and swallowing disorders, postural instability, and freezing gait. The response to nonmotor symptoms is poor with levodopa therapy, for example, cognitive disorders, dementia, depression psychosis autonomic dysfunction, and sleep disorders. Nocturnal treatment with levodopa may improve sleep in some patients. Chronic levodopa treatment is associated with Dyskinesia and motor fluctuations. Dyskinesias are involuntary movements that are mainly divided into peak-dose and biphasic dyskinesia. It is estimated that ~30%–50% of patients on levodopa therapy for more than 5-year experience dyskinesia.[45] Although duodopa has been developed to achieve continuous dopaminergic stimulation, the treatment remains unaffordable to most of our patients.

Newer Formulations and Future of Levodopa Formulations

Recent research has highlighted newer pharmacological properties of levodopa other than its actions on the dopaminergic system. For example, levodopa undergoes nonenzymatic conversion to form 2, 4, 5–trihydroxyphenylalanine (TOPA), a compound that reacts to form TOPA-quinone.[46] *In vitro* research using both TOPA and TOPA-quinone has found that these compounds are excitotoxic at glutamate receptors. These experiments showed additional properties of levodopa administration that is independent of dopaminergic receptor signaling, including alteration in neuronal firing rates, membrane depolarization, and inward current flux.[47] These responses occurred faster than the subsequent neurotransmission by dopamine at its receptors.

Nonenzymatic reactions in a physiological environment also yield a levodopa conjugate with cysteine, 5-S-cysteinyldopa. When it is decarboxylated *in vivo*, the resulting compound (5-S-cysteinyldopamine) produces pharmacological effects that differ from those of dopamine.[48]

The newer long-acting preparations, which have given promising result, include the latest extended-release levodopa-carbidopa product IPX066. This levodopa-carbidopa formulation utilizes microspheres created with coatings that govern the rate of drug release. By mixing a population of slower and more rapid release microspheres, the intended goal is a pharmacokinetic profile of drug release with greater constancy than that achieved with immediate-release levodopa-carbidopa. The results of clinical investigation with IPX066 show that its therapeutic-range plasma concentration of levodopa lasts 4 h or longer.[49]

Two products are under development for improving levodopa uptake are utilizing gastric retention strategies. One is DM-1992 (DepoMed), a gastric retentive formulation of levodopa and carbidopa. This product when exposed to gastric juices swells to an expanded size incapable of passing through the pylorus until it eventually dissolves up to 8 to9 h later.[50] Another gastro retentive product under development uses a proprietary drug delivery system that has been termed the accordion pill (AP). The AP is composed of layered polymer sheets folded into a capsule, that, when released, extend to exceed the size of the pylorus aperture. Consequently, the polymer sheets have several hours for the controlled

gastric leaching of imbedded carbidopa and levodopa. This biodegradable drug platform remains in the stomach for up to 12 h before it dissolution.[51] Other modes of drug delivery, such as inhaled form of levodopa and subcutaneous delivery of levodopa are also under development.[52,53]

Conclusion

The story of levodopa probably dates back from its use in ancient India as Atmagupta, the powdered form of mucuna pruriens for the treatment of tremor disorders. The revolutionary discovery of dopamine by Carlsson was probably the turning point in using this marvelous agent in modern therapeutics. However, the contributions from other scientists and researchers who have paved the way to the development of "Levodopa-the molecule of the century" cannot be undermined.

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Conflicts of interest

There are no conflicts of interest.

References

1. Cotzias GC, Papavasiliou PS. Therapeutic studies of Parkinsonian patients: long term effects of D, L, and L Dopa. Brookhaven National Lab., Upton, NY; 1967 Jan 1.
2. Cotzias GC, Van Woert MH, Schiffer LM. Aromatic amino acids and modification of parkinsonism. N Engl J Med 1967;276:374-9.
3. Carlsson A, Lindqvist M, Magnusson TO. 3, 4-Dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. Nature. 1957;180:1200.
4. Fahn S. The history of dopamine and levodopa in the treatment of Parkinson's disease. Mov Disord 2008;23 Suppl 3:S497-508.
5. Bell EA, Janzen DH. Medical and ecological considerations of L-dopa and 5-HTP in seeds. Nature 1971;229:136-7.
6. Chaudhri RD. Herbal drugs industry, a practical approach to industrial pharmacognosy. New Delhi: Eastern Publishers xii; 1996.
7. Gourie-Devi M, Ramu MG, Venkataram BS. Treatment of Parkinson's disease in 'Ayurveda' (ancient Indian system of medicine): Discussion paper. J R Soc Med 1991;84:491-2.
8. Ovallath S, Deepa P. The history of parkinsonism: Descriptions in ancient Indian medical literature. Mov Disord 2013;28:566-8.
9. Guggenheim M. Dioxyphenilalanin, a new amino acid Vicia faba. Trübner; 1913.
10. Casimir F. LXV-Synthesis of dl-3:4-dihydroxyphenylalanine. J Chem Soc Trans 1911;99:554-7.
11. Barger G, Dale HH. Chemical structure and sympathomimetic action of amines. J Physiol 1910;41:19-59.
12. Holtz P, Heise R, Lüdtke K. Fermentative degradation of l-dioxyphenylalanine (dopa) by kidney. Naunyn-Schmiedeberg's Archives of Pharmacology. 1938;191:87-118.
13. Hugh B. The specific action of L-dopa decarboxylase. J Physiol 1939;96:50P-1P.
14. Hirai K, Gondo K. About DOPA-hyperglycemia. Biochem Z 1927;189:92-100.
15. Hasama BI. Contributions to the investigation of the importance of the chemical configuration for the pharmacological effects of the adrenaline-like substances. Naunyn-Schmiedeberg's Archive for Experimental Pathology and Pharmacology. 1930;153:161-86.
16. Holtz P, Credner K, Koepp W. The enzymatic formation of oxytyramine in the organism and the physiological significance of dopadecarboxylase. Naunyn-Schmiedeberg's Archives of Pharmacology. 1942 ;200:356-88.
17. Goodall McC. Dihydroxyphenylalanine and hydroxytyramine in mammalian suprarenals. Acta Chem Scand 1950;4:550.
18. Raab W, Gigee W. Concentration and distribution of "encephalin" in the brain of humans and animals. Proc Soc Exp Biol Med 1951;76:97-100.
19. Weil-Malherbe H. Phaeochromocytoma catechols in urine and tumour tissue. Lancet 1956;271:282-4.
20. Montagu KA. Catechol compounds in rat tissues and in brains of different animals. Nature 1957;180:244-5.
21. Bernheimer H. On the presence of catecholamines and 3,4-dihydroxyphenylalanine (Dopa) in the eye. Naunyn Schmiedebergs Arch Exp Pathol Pharmakol 1964;247:202-13.
22. Van Arman CG. Amino acids and amines as precursors of epinephrine. Am J Physiol 1951;164:476-9.
23. Hornykiewicz O. The action of dopamine on the arterial blood pressure of the guinea-pig. Br J Pharmacol Chemother 1958;13:91-4.
24. Pletscher A, Shore PA, Brodie BB. Serotonin release as a possible mechanism of reserpine action. Science 1955;122:374-5.
25. Monnier M, Tissot R. Action of reserpine and its mediators (5-hydroxytryptophan and serotonin-noradrenaline-dopa) on behavior and brain of the rabbit. Helv Physiol Pharmacol Acta 1958;16:225-67.
26. Carlsson A. Morphologic and dynamic aspects of dopamine in the nervous system. Biochemistry and pharmacology of basal ganglia, ed. E. Casta, J. Cote, & MD Yahr. 1965:107-13.
27. Hornykiewicz E, Hornykiewicz O. Verteilung von noradrenalin und dopamin (3-Hydroxytyramin) im gehirn des menschen und ihr verhalten bei erkrankungen des extrapyramidalen systems. J Mol Med 1960;38:1236-9.
28. Hornykiewicz O. Dopamine (3-hydroxytyramine) and brain function. Pharmacol Rev 1966;18:925-64.
29. Birkmayer W, Hornykiewicz O. The 1-dioxyphenylalanine (1-Dopa) effect in Parkinson's akinesia. Wien Klin Wochenschrift. 1961: 77-88.
30. Barbeau A, Sourkes TL, Murphy GF. Catecholamines in Parkinson's disease. Monoamines and central nervous system. 1962: 247-62.
31. Friedhoff AJ, Hekimian L, Alpert M, Tobach E. Dihydroxyphenylalanine in extrapyramidal disease. JAMA 1963;184:285-6.
32. Umbach W, Baumann D. The efficacy of L-dopa in Parkinson's patients with and without stereotactic brain attack. European Archives of Psychiatry and Clinical Neuroscience. 1964;205: 281-92.
33. Hirschmann J, Mayer K. On the control of akinesia and other extrapyramidal motor disorders with L-dopa (L-dihydroxyphenylalanine). Dtsch Med Wochenschr 1964;89:1877-80.
34. Pazzagli A, Amaducci L. The Dopa clinical trial in parkinsonian syndromes. Rev Neurobiol. 1966;12: 138-45.
35. A Bruno, Bruno SC. Effects of L-2, 4-dihydossifenilalanina (L-Dopa) in parkinsonian patients. Riv Sper Freniat. 1966; 90: 39.
36. Greer M, Williams CM. Dopamine metabolism in Parkinson's disease. Neurology 1963;13:73-6.
37. Aebert K. What is l-dopa in the treatment of Parkinson's akinesis ?. DMW-German Medical Weekly. 1967;92: 483-7.
38. Clas F. Treatment of Parkinson's syndrome with Levodopa. A Double blinded study. Acta Neurol Scand 1966;42:367-72.
39. Rinne UK, Bracco F, Chouza C, Dupont E, Gershanik O, Marti Masso JF, *et al.* Early treatment of Parkinson's disease with cabergoline delays the onset of motor complications. Results of a double-blind levodopa controlled trial. The PKDS009 Study Group. Drugs 1998;55 Suppl 1:23-30.
40. Yahr MD, Duvoisin RC, Schear MJ, Barrett RE, Hoehn MM. Treatment of parkinsonism with levodopa. Arch Neurol 1969;21:343-54.
41. Bertler A, Rosengren E. Possible role of brain dopamine. Pharmacol Rev 1966;18:769-73.
42. Jasper HH. Neurophysiological mechanisms in parkinsonism. L-Dopa and Parkinsonism. Philadelphia: FA Davis; 1970. p. 408-11.
43. Vogt M. Functional aspects of the role of catecholamines in the central nervous system. Br Med Bull 1973;29:168-72.
44. Lloyd KG, Davidson L, Hornykiewicz O. The neurochemistry of Parkinson's disease: Effect of L-dopa therapy. J Pharmacol Exp Ther 1975;195:453-64.
45. Schrag A, Quinn N. Dyskinesias and motor fluctuations in Parkinson's disease. A community-based study. Brain 2000;123(Pt 11):2297-305.
46. Newcomer TA, Rosenberg PA, Aizenman E. Iron-mediated oxidation of 3,4-dihydroxyphenylalanine to an excitotoxin. J Neurochem 1995;64:1742-8.

47. Guatteo E, Yee A, McKearney J, Cucchiaroni ML, Armogida M, Berretta N, *et al.* Dual effects of L-DOPA on nigral dopaminergic neurons. Exp Neurol 2013;247:582-94.
48. Aureli C, Cassano T, Masci A, Francioso A, Martire S, Cocciolo A, *et al.* 5-S-cysteinyldopamine neurotoxicity: Influence on the expression of a-synuclein and ERp57 in cellular and animal models of Parkinson's disease. J Neurosci Res 2014;92:347-58.
49. Hsu A, Yao HM, Gupta S, Modi NB. Comparison of the pharmacokinetics of an oral extended-release capsule formulation of carbidopa-levodopa (IPX066) with immediate-release carbidopa-levodopa (Sinemet(®)), sustained-release carbidopa-levodopa (Sinemet(®) CR), and carbidopa-levodopa-entacapone (Stalevo(®)). J Clin Pharmacol 2015;55:995-1003.
50. Verhagen Metman L, Stover N, Chen C, Cowles VE, Sweeney M. Gastroretentive carbidopa/levodopa, DM-1992, for the treatment of advanced Parkinson's disease. Mov Disord 2015;30:1222-8.
51. LeWitt PA, Giladi N, Gurevich T, Shabtai H, Djaldetti R, Roizen N, *et al*. Accordion pill carbidopa/levodopa (ap-cd/ld) for treatment of advanced Pd. Mov Disord 2014;29:248.
52. LeWitt PA, Saint-Hilaire MH, Grosset DG, Hauser R, Stocchi F, Freed MI, *et al*. Inhaled levodopa (CVT-301) provides rapid motor improvements after administration to Parkinson's disease patients when OFF. Mov Disord 2015;30:1996.
53. Giladi N, Caraco Y, Gurevich T, Djaldetti R, Cohen Y, Yacobi-Zeevi O, *et al*. Pharmacokinetic profile of Nd0612l (levodopa/carbidopa for subcutaneous infusion) in patients with moderate to severe Parkinson's disease. Mov Disord 2015;30:S87-8.