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L-DOPA: From a biologically inactive amino acid to a successful therapeutic agent

Historical review article

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Summary. The article traces the development of research on the naturally occurring amino acid L-3,4-dihydroxyphenylalanine (L-dopa), from the first synthesis of its D,L racemate in 1911, and the isolation of its L-isomer from seedling of *Vicia faba* beans to the amino acid's successful application, from 1961 onward, as the most efficacious drug treatment of Parkinson's disease (PD). Upon its isolation from legumes in 1913, L-dopa was declared to be biologically inactive. However, two early pharmacological studies, published in 1927 and 1930 respectively, proved (in the rabbit) that D,L-dopa exerted significant effects on glucose metabolism (causing marked hyperglycemia) and on arterial blood pressure. Interest in L-dopa's biological activity increased considerably following the discovery, in 1938, of the enzyme L-dopa decarboxylase and the demonstration that in the animal and human body L-dopa was enzymatically converted to dopamine (DA), the first biologically active amine in the biosynthetic chain of tissue catecholamines. This prompted, in the 1940s, many studies, both in animals and in humans, especially concerned with the vasopressor potential of L-dopa/DA. In the 1950s, the focus of L-dopa research shifted to its potential for replenishing the experimentally depleted (by insulin or reserpine) peripheral and brain catecholamine stores and the concomitant restoration of normal function. During that period, of special interest were the observations that L-dopa reversed the reserpine-induced state of "tranquilisation" and that its decarboxylation product DA occurred in high amounts in animal and human brain, with a preferential localization in the basal ganglia. These observations set the stage for the beginning of DA studies in PD brain. In 1960, the severe brain DA deficit, confined to patients with PD was discovered, and a year later L-dopa's strong therapeutic effect in patients with PD was demonstrated. In 1967, the chronic high-dose oral L-dopa regimen was successfully introduced into clinical practice. Despite some initial doubts about L-dopa's mechanism of action in PD, it is now generally recognized that L-dopa use in PD is a classic example of a brain neurotransmitter replacement therapy. However, the DA replacement potential of L-dopa may not be its sole action of interest, as suggested by recent evidence that L-dopa may also have its own biological activity in the CNS, independent of DA.

Keywords: L-Dopa history – L-Dopa pharmacology – Dopamine – Dopamine replacement – L-Dopa therapy – Parkinson's disease

Introduction

The aromatic amino acid L-3,4-dihydroxyphenylalanine (L-dopa) offers an instructive example – not completely unknown in the history of drug research – of a compound that, after having been regarded for a long time as biologically inactive, unexpectedly turns out to be an effective therapeutic agent. In the following article, some of the more prominent stages (see Table 1) in the development of L-dopa as a pharmacological agent will be reviewed – from a mere precursor role in the biosynthesis of the catecholamine neurotransmitters to the most efficacious drug in the treatment of Parkinson's disease (PD). It will be pointed out that by being converted to dopamine (DA) in the DA-deficient PD striatum, L-dopa represents a classic (and so far singular) example of a brain neurotransmitter replacement therapy. Finally, attention will be drawn to the possibility of L-dopa having, in the CNS, a physiological neurotransmitter/modulator function of its own, independent of its role as the parent compound of tissue catecholamines.

The first four decades

L-Dopa, the naturally occurring isomer of the amino acid 3,4-dihydroxyphenylalanine, was first isolated in

Table 1. L-Dopa's "historical profile"*

1911	Synthesized as D,L racemate in the laboratory
1913	Isolated from seedlings of *Vicia faba* as L-isomer, biologically "inactive"
1916	Postulated as parent substance of skin melanin
1927	Causes hyperglycemia in the rabbit
1930	Lowers blood pressure in the rabbit
1938	Converted by kidney homogenates to DA; discovery of L-dopa decarboxylase
1939	Postulated as an intermediate in the formation of the physiologically active catecholamines
1941–42	Decarboxylated to DA in animal and human body
1941–45	Vasoactive in normal and hypertensive animals and humans
1950–57	Occurrence in periphery (adrenals) and brain
1950–60	Replenishes catecholamine transmitter depleted by insulin (adrenals) and reserpine (adrenergic neurons; brain)
1957–60	Antagonizes reserpine "sedation" ("tranquilisation") and causes central nervous system and EEG activation
1957–59	Its decarboxylation product DA occurs in animal and human brain, and is concentrated in the basal ganglia
1960–62	DA greatly reduced in basal ganglia and urine specifically in PD patients
1961–67	L-dopa the most efficacious drug treatment of PD
~1990–	Own physiological (CNS) role, independent of DA?

* For references to the original literature, see text

1913 from legumes (seedlings of *Vicia faba*) by Marcus Guggenheim (1913). Already two years earlier, Casimir Funk (1911) had synthesized D,L-dopa in the laboratory. Both he and Guggenheim considered the amino acid as a possible parent compound of adrenaline. The discovery by Peter Holtz et al. (1938) of an enzyme, DOPA decarboxylase, in mammalian tissue (kidney) extracts that converted L-dopa to the corresponding – biologically active (Barger and Dale, 1910) – amine, that is DA (3,4-dihydroxyphenylethylamine), represented a turning point in catecholamine research; it permitted both Blaschko (1939) and Holtz (1939) to postulate the still valid pathway of catecholamine synthesis in the body (L-tyrosine → L-dopa → DA → noradrenaline → adrenaline).

Guggenheim, in addition to isolating L-dopa, was also the first to perform, with the isolated material, some simple pharmacology. In a self-experiment, Guggenheim ingested 2.5 g of L-dopa and noticed its emetic action which, however, he interpreted as an unspecific irritation of the gastric mucosa; now we know that L-dopa's emetic action is due to its conversion to DA acting on the emetic centre in the medulla oblongata. In Guggenheim's hands, L-dopa was essentially ineffective, be it on the rabbit blood pressure (20 mg i.v.), on the isolated rabbit uterus and intestine, or on the conscious rabbit's general behaviour (1 g L-dopa orally). The view that L-dopa was essentially devoid of biological activity seems to have prevailed for many years. However, in 1927, nearly fifteen years after Guggenheim's negative observations, Hirai and Gondo (1927) found that D,L-dopa caused a strong hyperglycemia in the rabbit (200–300 mg s.c.). 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 i.v., being 0.5 mg/kg (Hasama, 1930). This disproved Guggenheim's negative result which he had obtained in the same species, using similar i.v. L-dopa doses. Hasama did not try to explain the qualitatively different effect (specifically in the rabbit) of L-dopa (vasodepressor) versus adrenaline (vasopressor) (see below).

The demonstration that L-dopa was decarboxylated by tissue extracts to yield DA (Holtz et al., 1938), prompted a new approach to L-dopa's pharmacology, now mainly aimed at bringing out the biological role of the amino acid as the precursor substance of the catecholamines in the body. In the early 1940s, several research groups (Holtz and Credner, 1942; Schroeder, 1942; Page and Reed, 1945), but not all (Bing, 1941; Oster and Sorkin, 1942), observed a pressor response to i.v. L-dopa in the normal experimental animal. In 1941, Bing found that injection of L-dopa into the circulation of the ischemic kidney of the cat (in situ) produced acute (renal) hypertension (Bing and Zucker, 1941; see also Oster and Sorkin, 1942). Bing, in addition, showed that the isolated, perfused (ischemic) cat kidney converted L-dopa to DA (Bing, 1941). In 1942, Holtz showed that administration of L-dopa in laboratory animals and in humans was followed by excretion of DA in the urine (Holtz and Credner, 1942). He noticed that in humans, 50 mg L-dopa i.v. caused some tachycadia; 150 mg taken orally

remained without any noteworthy effects. In the same year Oster and Sorkin (1942) studied the effect of L-dopa in humans with essential hypertension showing that in these subjects 120 to 450 mg L-dopa i.v. produced larger rises in blood pressure than in healthy controls. The larger L-dopa doses caused tachycardia, sweating, nausea, retching and vomiting. Confirming, although unknowingly, Hasama's 1930 study, twelve years later Holtz and Credner (1942) also reported that in the rabbit, unlike in the cat, L-dopa produced, in contrast to adrenaline, a fall in the arterial blood pressure. Since in their study, Holtz and Credner (1942) made the discovery that in the rabbit also DA had a vasodepressor effect (Holtz and Credner, 1942), Hasama's earlier observation could now be logically explained as being due to the amine (DA) formed from L-dopa in the body. In the guinea-pig, as in the rabbit, L-dopa as well as DA, also produce a characteristic fall in the blood pressure (Holtz and Credner, 1942; Hornykiewicz, 1958).

L-Dopa is a normal constituent of animal tissues

Following the discovery of the dopa decarboxylase, small amounts of L-dopa could be expected to occur in many tissues. (As early as 1916, Bruno Bloch, a dermatologist, had postulated that L-dopa may be the parent compound of skin melanin, thus implying its presence in the skin [Bloch, 1916]). From 1951 on, reports on the occurrence of small amounts of dopa started to appear in the literature, first in the adrenal medulla (Goodall, 1950) and phaeochromocytoma (Weil-Malherbe, 1956) and in 1957 in the human brain (Montague, 1957; Sano et al., 1959). Larger amounts of L-dopa were later reported for the iris and choroidal layer of the calf eye (Bernheimer, 1964). Although the occurrence of dopa, and its decarboxylation product DA, in the brain of various species, including man, was first demonstrated in 1957 by Montagu (1957) and Weil-Malherbe and Bone (1957), already six years earlier, in 1951, Raab and Gigee discovered the occurrence of a catecholamine-(adrenalin-)like substance in the brain of many species, including humans (Raab and Gigee, 1951) (see below).

The catecholamine-replenishing potential of L-dopa

After the discovery of dopa's occurrence in the body, many biochemical studies with L-dopa were performed in an attempt to provide experimental support for the proposed biosynthesis of the catecholamines, mainly DA, from the amino acid. Demis et al. (1956) and Hagen and Welch (1956) incubated dopa-α-C^{14} with adrenal homogenates and recovered most of the radioactivity as DA and only a small amount as radioactive noradrenaline. Important for the later experiments with L-dopa in the catecholamine depleted brain, is an early study, performed in 1951, by Van Arman who depleted the adrenals of rats with insulin and showed that of various possible catecholamine precursors only dopa restored the adrenal catecholamine (adrenaline) levels (Van Arman, 1951). L-dopa also restored (in part) the functioning of the postganglionic adrenergic neurons abolished by reserpine (Burn and Rand, 1960), indicating a partial replenishment of the neuronal transmitter stores depleted by reserpine. Similarly, in human subjects treated with reserpine, L-dopa antagonized the central reserpine "sedation" (Degkwitz et al., 1960).

Indisputably the first researchers to study the effect of systemically administered dopa on brain catecholamines were Raab and Gigee (1951). They injected, in rats, a great number of biologically active substances i.p. and found that only dopa increased the brain concentration of a catecholamine-(adrenaline-) like substance, just then discovered by them, with a time course of the increase that, as we now know, is identical with the accumulation of brain DA after L-dopa administration. In view of these early "DA" and L-dopa studies, including the study by Van Arman (1951) in rats with adrenals depleted by insulin (see above), it was not surprizing that in reserpine-treated animals (rabbits), Carlsson, in 1958, found that D,L-dopa injections restored depleted brain DA (with a much smaller effect on the likewise depleted brain noradrenaline) (Carlsson et al., 1958). At about the same time, L-dopa was found to cause central, behavioural as well as EEG activation and to antagonize reserpine's "tranquilizing" effects (Carlsson et al., 1957; Monnier and Tissot, 1958; see also above, Degkwitz et al., 1960). When, a little later, Bertler and Rosengren (1959) as well as Sano et al. (1959) demonstrated that (in the dog and the human, respectively) the bulk of brain DA was concentrated in the corpus striatum (basal ganglia), for the first time it became clear that brain (striatal) DA may be involved in regulation of central motor functions and the parkinsonism-like condition produced by reserpine in laboratory animals and in humans (Sano et al., 1959; Bertler and Rosengren, 1959; Carlsson, 1959). As a matter of his-

torical fact, eight years earlier Raab and Gigee had already discovered the preferential occurrence of their catecholamine-(adrenaline-)like substance (in large part consisting of DA; see above) in the basal ganglia (caudate nucleus) of several larger domestic animals (dog, cow, bull, hog), as well as in monkeys and humans (adults, infants) (Raab and Gigee, 1951). Here it is interesting to note that throughout the 1950s, Raab's brain studies were well-known and referred to by notable researchers (e.g., Holtz, 1950; Vogt, 1954; Montagu, 1957; Rothballer, 1959).

L-Dopa as a therapeutic agent – Parkinson's disease

Probably the most decisive observation in the history of L-dopa was the discovery of the DA deficit in the striatum specifically in patients with PD, providing a strictly rational basis for L-dopa's use in this disorder. In 1960 Ehringer and Hornykiewicz measured DA and noradrenaline in 17 human control brains obtained at autopsy, 2 Huntington's disease brains, 6 brains of patients with extrapyramidal disorders of unknown etiology, and 6 PD brains. They found that of the 14 patients with extrapyramidal disease, only the 6 PD patients had a severe DA loss in the caudate nucleus and putamen (Ehringer and Hornykiewicz, 1960). At about the same time, Barbeau et al. (1961) published their observation on reduced urinary excretion of DA in PD.

Together with the relationship previously demonstrated in laboratory animals, between reserpine-induced tranquilizing action and L-dopa and brain DA (Carlsson et al., 1957; 1958), the striatal DA deficit, limited specifically to the brain of patients with PD, immediately suggested the step "from brain homogenate to treatment", that is the rational use of L-dopa in order to replenish the missing striatal DA in the brain of patients suffering of PD (see Hornykiewicz, 1992; 1994; 2001). In view of the fact that there existed since the early 1940s ample experience with the use of intravenously injected L-dopa in humans (and the accompanying side-effects, including the recent study by Degkwitz et al., 1960), in 1961 Hornykiewicz together with the neurologist Birkmayer performed a trial with i.v. L-dopa in a group of 20 patients (Birkmayer and Hornykiewicz, 1961). They for the first time reported on a dramatic improvement of all motor deficits related to the symptom of akinesia, lasting for several hours. At the same time, and independently, Theodore (Ted) Sourkes and Gerald Murphy induced the neurologist Andre Barbeau (all in Montreal) to give L-dopa orally to PD patients, and observed a beneficial effect on the Parkinsonian symptom of rigidity (Barbeau et al., 1962). (It should be noted here that Ted Sourkes already in the 1950s had made important contributions to the field of dopa decarboxylase, its inhibitors, and L-dopa metabolism in vitro and in vivo, including DA [Sourkes et al., 1952; Sourkes, 1961]). 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). Soon after that, in 1969, Melvin Yahr in New York published the very first double-blind L-dopa study, establishing objectively the amino acid's superior effectiveness as an antiparkinson agent (Yahr et al., 1969).

It is interesting that despite the unprecendented therapeutic success, doubts about the "miraculous" effect, and the rational basis, of L-dopa use persisted for more than a decade. In 1966, Bertler and Rosengren, Carlsson's collaborators for many years who also were among the first to describe (in the dog) the striatal localization of DA (and the first to suggest a causal connection between the brain DA depleting action of reserpine and its parkinsonism-like effects in laboratory animals; see above) expressed doubts about DA and L-dopa in PD; they stated, in an important review article on brain DA, that "the effect of L-dopa was too complex to permit a conclusion about disturbances of the DA system in PD" (Bertler and Rosengren, 1966). In a similar vein, Herbert Jasper of the Montreal Neurological Institute and Arthur Ward of the Neurosurgery department in Seattle, both highly respected neuroscientists, suggested in 1969 that L-dopa "was the right therapy for the wrong reason" (Jasper, 1970; Ward, 1970). Even as late as 1973, Marthe Vogt, a distinguished brain scientist in Cambridge (England) had doubts about the rational basis of L-dopa's therapeutic use; she felt that "since L-dopa floods the brain with DA, to relate its [antiparkinson] effects to the natural function of DA neurones may be erroneous" (Vogt, 1973). These and many other similar doubts could be dispelled when in 1975 Ken Lloyd in Toronto published a study conclusively showing that in the striatum of PD patients treated with L-dopa, the levels of DA (1) were nine-to-fifteen fold higher than those in non-dopa treated patients; (2) were related to the time before death of

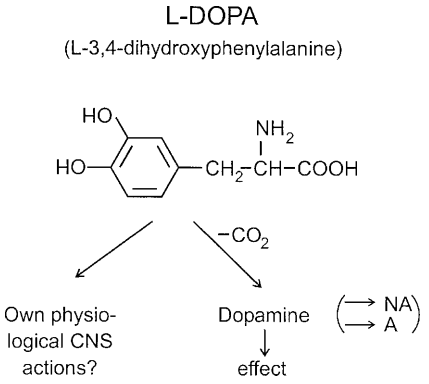

Fig. 1. Two distinct mechanisms for L-dopa's physiological/pharmacological actions in the CNS: by the amino acid's decarboxylation to DA (the established, major, mechanism); and, in an as yet to be defined way, through a neurotransmitter/modulator activity of its own (still under investigation)

the last L-dopa dose; and (3) were greater in the striatum of patients with good response to L-dopa than in poor responders (Lloyd et al., 1975). The final proof of L-dopa's DA replenishing mechanism of action was provided in 1973 by Donald Calne in London, by the demonstration that bromocriptine, a direct acting DA agonist, had qualitatively the same therapeutic anti-parkinson action as L-dopa (Calne et al., 1974).

Is brain L-dopa a neurotransmitter/modulator in its own right?

It appears that the first indication of L-dopa having a biological activity different from that of DA was provided by Krnjevic and Phillis who made the intriguing observation, in 1963, that L-dopa, topically (iontophoretically) applied onto cortical neurons of the cat had an excitatory effect on their discharge activity, whereas DA inhibited it (Krnjevic and Phillis, 1963). In the last decade, especially Japanese researchers (see Misu and Goshima, 1993; Misu et al., 1995) adduced evidence, from both in vitro and in vivo experiments, for the possibility that L-dopa may indeed have biological activity independent of the DA formed from it. Thus, they propose that in the striatum, L-dopa may be a modulator substance, acting as a potentiator for presynaptic β-adrenoceptors to facilitate DA release as well as a potentiator at the postsynaptic D-2 DA receptors (see also Fisher et al., 1999). They further postulate from their experiments that L-dopa may be a neurotransmitter in primary baroreceptor afferents terminating in the nucleus tractus solitarii, thus playing a major physiological role in the medulla oblongata for baroreceptor reflexes and central regulation of blood pressure.

Thus, it would appear that exactly 90 years after the first synthesis of its racemic mixture by Casimir Funk, L-dopa has become not only the most successful therapeutic amino acid, highly effective in a chronic, progressive, neurodegenerative brain disorder, i.e. PD, but is about to start a new career as a brain neurotransmitter substance in its own right (Fig. 1).

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