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A brief history of levodopa

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Abstract This article highlights some landmarks in the history of levodopa, beginning with its isolation in 1910–13 from seedlings of Vicia faba to the demonstration, in 1961, of its "miraculous" effect in patients with Parkinson's disease (PD). Midway between these two time points, in 1938, L-dopa decarboxylase was discovered, the enzyme that produces dopamine (DA) from levodopa. In 1957, DA was shown to occur in the brain, and in 1959 it was found to be enriched in the basal ganglia. At that time the striatal localization of DA, together with studies done in 1957–58 in naive and reserpine-treated animals regarding DA in the brain and the central effects of levodopa, suggested its possible involvement in "extrapyramidal control" and "reserpine parkinsonism". Following these discoveries, a study of (postmortem) brains of patients with basal ganglia disorders, including PD, was started, demonstrating, in 1960, a severe striatal DA deficit specifically in PD, thus furnishing a rational basis for the concept of "DA replacement therapy" with levodopa. Accordingly, in 1961, the first highly successful clinical trial with i.v. levodopa was carried out. In 1963, the DA deficit in the PD substantia nigra was found, indicative of a nigrostriatal DA pathway in the human brain, subsequently established in animal studies in 1964–65. In 1967, the chronic, high dose oral levodopa regimen was introduced in treatment of PD. Besides the above highlights in the history of levodopa, the article also cites critical opinions of world authorities in brain research of the time, harmful to the cause of DA, levodopa and PD. Today, the concept of DA replacement with levodopa is uncontested, with levodopa being the "gold standard" of modern drug treatment of PD.

Keywords History of Parkinson's disease · Levodopa therapy · Striatal and nigral dopamine deficit

Levodopa (L-dopa) is the naturally occurring L-isomer of the amino acid D, L-dihydroxyphenylalanine. It was first isolated from the bean of Vicia faba in 1910–11 by Torquato Torquati [1]. In 1913, the chemical structure of the isolated substance was established by Markus Guggenheim [2]. A turning point in the early history of levodopa was the discovery, in 1938 by Peter Holtz [3], of the enzyme L-dopa decarboxylase which, through decarboxylation, converted the biologically inert levodopa to the biologically active catecholamine dopamine (DA). This discovery also gave both levodopa and DA their first (rather modest) biochemical role in the body as metabolic intermediates in the biosynthetic chain of the - at that time more prominent and biologically highly active–catecholamines noradrenaline and adrenaline [4, 5]. Generally speaking, however, both levodopa and DA played, for a long period of time, only a marginal role in biological research. (For a more detailed levodopa history of the early period, see [6]).

The biological importance of levodopa and DA dramatically changed with the publication, in August 1957 by Kathleen Montagu [7] soon followed by Weil-Malherbe and Bone [8] from the same laboratory, about the occurrence of DA in the mammalian, including human, brain.

A month or so later, Holtz reported, for the first time, on the central excitatory effect of levodopa (in rodents), and suggested DA as the active levodopa metabolite in the brain [9]. This report was followed by (a) the observation, made in November 1957 by Carlsson [10], showing that in

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laboratory animals levodopa antagonized the "tranquilizing" action of reserpine (whose side-effects were known to include, in humans, a parkinson-like syndrome); and (b) Pletscher demonstrating, in December 1957, that levodopa in fact increased the brain levels of "catecholamines" assayed as a whole [11]. In actual fact, in early 1958, shortly after Pletscher's publication, two at that time prominent research groups—Weil-Malhorbe and Bone and Carlsson and his colleagues—independently showed that in the brains of reserpine-treated animals depleted of all three catecholamines, levodopa preferentially restored the levels of DA, with only a slight effect on noradrenaline and adrenaline [12, 13].

The above observations, made in a very short span of time, set the stage for the step from studies in animals to work in the human (postmortem) brain and, eventually, the patient. Thus, when in early 1959, both Bertler and Rosengren [14] and Sano and collaborators [15] showed that, in the dog and human respectively, the bulk of brain DA was localized in the caudate nucleus and putamen, suggesting DA's possible involvement in parkinsonism produced by reserpine [14], and, more generally, in the control of striatal (extrapyramidal) motor functions [14, 15], Hornykiewicz went directly to the brains of patients with basal ganglia disorders, including Parkinson's disease (PD), to see whether there actually was an abnormality of striatal DA or not. The results of this study [16], published in 1960, were clear: brains of patients with PD had a profound loss of DA in the caudate nucleus and the putamen. This biochemical abnormality was specific for PD, as other basal ganglia disorders, including Huntington's disease (analyzed in addition to PD brains) did not have significantly changed striatal DA levels. This discovery radically changed our research approach to, and understanding of, the pathophysiology and pharmacotherapy of PD; it has since stood the test of time, becoming common textbook knowledge.

Following this discovery, the final step "from brain homogenate to treatment" was taken by Hornykiewicz, who initiated a clinical trial with (i.v.) levodopa, with the aim of restoring function by replacing the missing DA in the live patient. The dramatic acute therapeutic, especially anti-akinesia, levodopa effect observed in this study [17] was published, together with the neurologist Birkmayer in 1961, only one year after the demonstration of the striatal DA deficit. A placebo effect of levodopa (always a possibility in clinical trials) was excluded in a consecutive study [18] demonstrating ineffectiveness of compounds chemically related to levodopa (such as D-dopa, DA, 3-*O*-methyldopa and others), applied to the patients in the same manner as levodopa. Six years after this first clinical levodopa trial, the use of levodopa in clinical routine as a drug superior in efficacy to any other known antiparkinson drug became definitely established in 1967, when Cotzias [19] introduced the chronic, high dose oral levodopa regimen, which is basically still practiced today.

At the time these fundamental observations were made, nothing was known about the cellular elements in the striatum (intrinsic neurons, glia cells, afferent terminals, blood vessels?) in which the DA—so severely reduced in PD and functionally so successfully replaced by levodopa—was localized. The answer to this question, eminently important for the understanding of the DA/PD pathophysiology, came soon from a study, published in 1963, about the behavior of DA in the substantia nigra, a brain region known to regularly degenerate in PD. In this study, Hornykiewicz observed severe loss of nigral DA, similar in magnitude to the striatal DA loss and suggested that "the celi loss in the substantia nigra could well be the cause of the DA deficit in the striatum" [20]. This observation triggered intense experimental studies by other research groups regarding the nigral DA in laboratory animals, resulting in the demonstration of a nigrostriatal DA pathway [21–23].

Considering the pathophysiological and clinical-therapeutic significance of the discovery of the DA deficit in the PD striatum, so dramatically underscored by the "miraculous" levodopa effect in the patient, one would have expected unanimous support and unreserved applause from all quarters of the basic and clinical neuroscience community. This was indeed the case with the vast majority of clinical neurologists, but not at all the rule among the basic brain scientists. Among those strongly critical of DA and levodopa were the best minds of the contemporary neuroscience; they included top experts on the anatomy, pathology and pathophysiology of the basal ganglia, as well as notable DA researchers, paradoxically some of the latter being previously instrumental in important brain DA discoveries. The examples given in Table 1 convey an idea of what it took in those pioneer years of DA research to remain a DA/levodopa/PD "believer".

Considering the weight carried by the statements of such world authorities in brain research of that time, in retrospect the possibility appears real that, if it were not for the "levodopa miracle" in the patient, the brain DA/PD story may have been laid quietly to rest right then and there.

The critical, caustic views quoted in Table 1, and many similar voices, were eventually silenced by the overwhelming clinical evidence in favor of the levodopa-DA connection, as well as the wealth of experimental evidence coming from top laboratories specifically focusing on these questions. To quote a few such studies, in 1970 Robert Moore established beyond doubt the existence of the nigrostriatal DA tract (in the cat) by rigorous morphological criteria [35]. In 1973, Ken Lloyd demonstrated that patients receiving levodopa had, indeed, higher DA levels in their

Table 1 Some critical statements from brain research authorities of the time about brain dopamine, levodopa, substantia nigra and parkinsonism

A. On the wrong track toward the substantia nigra, parkinsonism, and nigrostriatal dopamine pathway:
Denny-Brown (1962): "We have presented reasons against the common assumption that lesions of the substantia nigra are responsible for parkinsonism" [24]
Mettler (1964): "The attribution of such a complex clinical syndrome [Parkinson's disease] to a rather small and homogeneous structure [substantia nigra] has not appeared logical" [25]
Carpenter (1966): "Numerous recent studies based upon excellent selective lesions of the substantia nigra failed to demonstrate nigrostriatal fibres. This casts considerable doubt upon [their] existence" [26]
Hassler (1967): "The interpretation of your [Hornykiewicz's] observations does not agree with many known facts about the direction of the nigrostriatal connection… all your observations can be equally well, if not better, explained by the striatonigral direction [of the dopamine fibres]" [27]
B. Stabs in the back of dopamine, levodopa and parkinsonism, coming from unexpected quarters:
Seiden and Carlsson (1964): "Dopamine… in the high concentrations observed [in brain after L-dopa] may be able to function as noradrenaline" [28]
Hanson (1965): "Dopamine [formed in brain from L-dopa] may possibly take over some of the transmitter functions of noradrenaline" [29]
Carlsson (1965): "…not possible to draw any conclusions about the relative importance of dopamine and noradrenaline for the central effects [incl. parkinsonism?] of reserpine" [30]
Bertler and Rosengren (1966): "The effect of L-dopa is too complex to permit a conclusion about disturbances of the striatal dopaminergic system in Parkinson's disease" [31]
Vogt (1973): "[because L-dopa causes] 'flooding' of the brain with DA … it is possible that even the therapeutic effects in parkinsonism result from actions of DA at sites …from which DA is normally absent… To relate these [L-dopa] effects to the normal function of dopaminergic neurons may be erroneous" [32]
Jasper (1970): "[L-dopa is] the right therapy for the wrong reason" [33] (The same statement also made by Ward [34])

striata than untreated patients [36]; and in 1974, Donald Calne showed that the direct DA receptor agonist bromocriptine had levodopa-like antiparkinson activity in the patient [37], removing all possible doubts about levodopa being a true DA replacing drug in PD. Today, levodopa is the "gold standard" in the drug treatment of PD, with the DA/levodopa/PD story being generally recognized as one of the greatest success stories of modern neuroscience.

Conflicts of interest None.

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