

Birkmayer W & Hornykiewicz O. Der L-3, 4-Dioxyphenylalanin (= DOPA)-Effekt bei der Parkinson-Akinese. *Wien. Klin. Wochenschr.* 73:787-8, 1961.
[Pharmakologische Institut der Universität Wien, and Neurologische Abteilung des Krankenhauses der Stadt Wien-Lainz, Austria]

This paper shows the beneficial antiakinetik effect of L-DOPA medication. Further, the improvement by combined administration of L-DOPA plus benseracid (inhibitor of the peripheral decarboxylase) and an advantage by additive treatment of deprenil (specific inhibitor of MAO-Type B) are shown. [The SC¹ indicates that this paper has been cited over 260 times since 1961.]

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February 12, 1982

"During World War II, Birkmayer observed certain disturbances in the function of the autonomous system. One soldier (42 years old) with a splinter in the hypothalamus began to grow again in size by 13 cm and the circumference of his skull increased from 56 to 63 cm. Another patient with a splinter in the right part of the midbrain developed severe obesity on the contralateral side. A variety of other cases led him to assume that the brain stem is the central region responsible for regulation of autonomous functions for affective-emotional behaviour and for motoric instinct reactions.

"As director of the neurological department of the city hospital, Vienna-Lainz, Birkmayer had the opportunity to see a great number of parkinsonian patients. In many of these, he observed crises in their autonomous functions, in addition to the hitherto known defects in kinetic activity. These crises manifested themselves in sweatbursts which lasted 30-60 minutes and disappeared spontaneously without any treatment. In addition they exhibited flushes, phases of continuous sleep and gluttony, depressive crises, and phases of social and sexual slips. These decompensations were, in Birkmayer's opinion, caused by an uncontrolled release of certain

neurotransmitters, some of which were enriched in the brain stem. Birkmayer insisted on his theory and asked a pharmacologist (Hornykiewicz) to look for 5-OH-tryptamine and for norepinephrine in the brain of parkinsonian patients. Hornykiewicz detected that dopamine was also reduced considerably in the striatum of parkinsonian patients, whereas norepinephrine and 5-OH-tryptamine were much less reduced. Consequently, we tried to supplement parkinsonian patients with L-DOPA, the physiological precursor of dopamine. The first patient, hitherto unable to move his arms and legs, suddenly stood up and walked around for several hours. This was an overwhelming experience. Birkmayer thought it was a new principle comparable to that of Archimedes. As a consequence, input of dopamine will cause the release of its antagonist (5-OH-tryptamine), and nonphysiological concentrations of neurotransmitters will cause side effects.

"We modified our therapeutic concept by adding a decarboxylase inhibitor (benseracid) to L-DOPA. This inhibitor blocks the conversion of L-DOPA to dopamine in all areas of the body, except the brain. It cannot pass the blood-brain barrier. It causes a sixfold increase of L-DOPA in the dopaminergic neurons of the brain stem.¹ This yielded a considerable improvement of the kinetic effect. However, the increase of L-DOPA in the brain leads to a variety of cerebral interactions. Some patients developed a toxic delirium. In these patients, we found 5-OH-indoleacetic acid to be five times higher than in controls. We treated these patients with L-tryptophan, and the psychotic symptoms disappeared within ten days. We deduced from these findings that the equilibrium of neurotransmitters is essential for a balanced behaviour. A decisive improvement in the kinetic activity of parkinsonian patients could be achieved by adding a specific MAO-inhibitor (deprenil) to the drug L-DOPA.²

"The results of these investigations have been published in the book *Die Parkinson Krankheit (Biochemie, Klinik, Therapie)*.³

"This work has been highly cited because it shows that an existing lack of neurotransmitters in Parkinson's disease can be substituted by specific precursors, thus yielding unique success."

- 1 Birkmayer W & Meztastl M. Weitere experimentelle Untersuchungen über den Catecholaminstoffwechsel bei extrapyramidalen Erkrankungen. *Arch Psychol Z Neurol* 210 29-35, 1967
- 2 Birkmayer W, Riederer P, Youdim M B H & Linauer W. The potentiation of the antiakinetik effect after L-DOPA treatment by an inhibitor of MAO-B, deprenil. *J Neural Transm* 36 303-26, 1975
- 3 Birkmayer W & Riederer P. *Die Parkinson Krankheit (Biochemie, Klinik, Therapie)*
Vienna: Springer-Verlag, 1980.