

Dopamine, Levodopa and Parkinson's Disease

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Our first report, from Vienna's University Institute of Pharmacology, about the brain dopamine (DA) deficit in Parkinson's Disease (PD) came out in print in December 1960.¹ Eleven months later, in November 1961, we published the results of our first clinical levodopa trials in PD patients.² Both articles were written in German; they were re-published in English translations, in 1974 in a book³ and in 1998 in a neurological journal.^{1,2}

How did all this come about? What was the status at that time of DA as a substance of biological importance? When in August 1957 Kathleen Mongatu, in England, reported the discovery that DA occurred in the mammalian brain,⁴ DA was generally regarded as being merely a metabolic intermediate in the formation of the catecholamines noradrenaline and adrenaline in the body. However, already in the autumn of 1956, Hermann Blaschko of Oxford's pharmacology department, had proposed that DA, in addition to being a metabolic intermediate, may have "some regulatory functions of its own which are not yet known".⁵ At that time, I was working as a visiting scientist in Blaschko's laboratory, trying to define the nature of DA's action on the guinea-pig blood pressure. The results of my study confirmed Blaschko's idea, indicating that DA had indeed its own biological activity; levodopa, DA's immediate precursor substance, had the same effects as DA.⁶

I finished my experiments shortly before the publication, between October 1957 and May 1958, of a cluster of animal studies related to levodopa's central effects, showing that, in chronological order, levodopa caused central excitation and abolished the 'hypnotic' effect of hexobarbital (Peter Holtz, Germany); abolished the 'tranquillising' effect of reserpine (Arvid Carlsson, Sweden); increased the brain catecholamine levels (Alfred Pletscher, Switzerland); and increased the brain DA levels reduced by reserpine (Arvid Carlsson, Sweden; Hans Weil-Malherbe, England). Interestingly, of the researchers involved in these studies, only Holtz came forward with the conclusion that the amine responsible for levodopa's central actions must be "the hydroxytyramine [DA] formed from dopa in the brain".⁷

For me, now back in Vienna, the idea of DA having central effects appeared quite exciting. I switched my research from the periphery to the brain, and in 1958 examined in the rat, together with Georg Holzer, the effect on brain DA of centrally acting drugs, among them chlorpromazine – the first drug to produce a reversible neurological syndrome in humans very much like PD. To do the study, I had to develop a chemical DA assay applicable to brain tissue. This proved very useful when, early in 1959, Bertler and Rosengren, in Sweden, and Sano, in Japan, discovered that DA was highly concentrated in the striatal/basal ganglia nuclei – in particular the caudate and putamen.^{8,9} In a flash, I saw the connection between the striatal localisation of DA, its central stimulant effect, the DA depleting effect of reserpine (like chlorpromazine a parkinsonism-inducing agent) and human PD, a well-known disorder of striatal function. And rather than trying to use animal models of the disease, like many others did, I felt that the best way to test my idea was to go directly to the human brain and see whether in PD there was a DA deficit or not. After arriving at this conclusion, what remained to be done was simple: to arrange, together with my collaborator in training Herbert Ehringer, for the collection and dissection of freshly autopsied human brains; then process the tissue samples and analyse them for DA – with the chemical DA assay already in my hands.

We started the work in February/March 1959 and published the full paper in December 1960.¹ We included a total of 20 adult controls; six PD brains; six cases with extrapyramidal (basal ganglia) symptoms of unknown aetiology; and two Huntington's disease brains. Of the fourteen cases with basal ganglia symptomatology, only the six PD cases had a severe DA deficit in the caudate and putamen. The results of the study, remarkable for its completeness, were immediately accepted and never put in doubt. They have become common textbook knowledge. For the first time, a specific chemical abnormality was found in a specific brain region in a specif-



ic degenerative brain disorder – a model for all current research into the causes and treatments of neurodegenerative diseases.

The most important immediate consequence of the DA work was the step "from brain homogenate to DA replacement".¹⁰ In November 1960, I proposed to the neurologist Walter Birkmayer a clinical trial with slow i.v. injections of levodopa. Being aware of the literature about levodopa, including my 1957 Oxford study,

replacement of the missing DA with levodopa appeared to me the most rational thing to do. We started the first trials in July 1961 and published the results in November 1961. In most of the 20 patients studied, the antiparkinson effect of levodopa was spectacular. As stated in our report, "for short periods of time, the patients were able to perform motor activities which could not be prompted to any comparable degree by any other known drug".²

However, our observations were received with some reservations. Many neurologists suspected a placebo effect of the i.v. injections, ignoring the fact that we also had shown, using the same patients, the ineffectiveness of i.v. injected substances related to levodopa.¹¹ Finally, in 1967 George Cotzias, in New York, gave D,L-dopa orally in large, gradually increasing doses chronically and showed that the effect was not only dramatic but also sustained.¹² Nonetheless, some – among them rather prominent¹⁰ – brain scientists were reluctant to admit that the 'miraculous' therapeutic effect of levodopa was actually due to the DA formed from it, thereby undermining the whole DA replacement concept as the rational basis on which our first levodopa trials had hinged. The doubts were eventually silenced in 1974 by Donald Calne, in England, who demonstrated that the direct DA receptor agonist bromocriptine had a clinical antiparkinson effect qualitatively identical with that of levodopa.¹³ At present levodopa remains the single most potent drug for PD and the reference standard for any new approaches to the treatment of this common debilitating movement disorder.

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