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The discovery of dopamine's physiological importance

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The discovery of neurotransmitters is one of the great achievements of 20th century neuroscience. Dopamine is among the most well-researched neurotransmitters. For the first half of this century, however, interest in dopamine was minimal, and only a few scattered groups of researchers studied it. It was their research that stimulated current interest and laid the foundations for our present understanding of this important substance. By the late 1950s, it was clear to these individuals that dopamine served an important physiological role in mammalian brains, and that its role was most likely that of a central nervous system agonist.

Until 1958, dopamine was thought only to be a precursor in the biosynthesis of noradrenaline, and not a neurotransmitter in its own right. In this year, however, Carlsson, Lindqvist, Magnusson, and Waldeck discovered that dopamine is present in the brains of rabbits in an amount of about 0.4 μg/g, a quantity much higher than what would be expected if dopamine were merely noradrenaline's precursor [1]. Carlsson et al. provided further evidence for an independent role for dopamine when they found that intravenous injection of reserpine made dopamine almost completely disappear from the brain, while intravenous injection of the precursor L-DOPA caused a more than fourfold increase in the amount of dopamine present in the brain. Moreover, increases in the amount of noradrenaline following administration of L-DOPA were much less pronounced, if present at all.

Soon thereafter, Bertler and Rosengren (who were students of Carlsson at this time) began investigating the regional distribution of dopamine in the brain and other tissues. Dopamine was found in the brains of all species examined, which included the cow, sheep, pig, dog, cat, rabbit, guinea-pig, and rat [2]. Bertler and Rosengren also observed that dopamine was most prevalent in the caudate nucleus. In fact, in the dog, the caudate nucleus contains about 80% of the total amount of brain dopamine. Later that year, this finding was extended to humans [3]. It soon became apparent that the sites with the highest dopamine content in the brain are typically the sites that contain the smallest amounts of noradrenaline. These findings, along with Carlsson et al.'s findings, provided compelling evidence that dopamine is a neurotransmitter its own right (Fig. 1).

Soon after these events, the depletion of dopamine was clearly implicated in Parkinson's disease. Bertler and Rosengren's and

FIG. 1. From left to right, Arvid Carlsson, Oleh Hornykiewicz, and Theodore Sourkes (photographs provided by Drs. Carlsson, Hornykiewicz, and Sourkes).

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Sano et al.'s work stimulated Oleh Hornykiewicz to make arrangements for the acquisition of human autopsy material from normal patients and patients who had suffered from Parkinson's disease [4]. Hornykiewicz submitted tissue from the corpus striatum of these brains to the von Euler and Hamberg iodine reaction. His finding was that the control samples were pink in color, indicating the presence of dopamine, but that this color was absent in the Parkinson's samples [5]. A group of researchers led by Theodore Sourkes soon followed up on this finding by reporting that there was a reduced excretion of dopamine in the urine of patients with Parkinson's disease [6].

Late in 1960, the possibility of giving Parkinson's patients dopamine's precursor, L-DOPA, occurred to Hornykiewicz and Ehringer [4]. Their work coincided with that of Sourkes and Murphy, who asked Barbeau to administer L-DOPA orally to Parkinsonian patients [7]. Both groups found a reduction in Parkinsonian symptoms, including a reduction of rigidity hypokinesia, but nausea and vomiting proved to be rather troublesome.

In 1967, Cotzias, Van Woert, and Schiffer largely overcame these side effects by adopting a regimen of gradually increasing oral doses of DOPA [8]. Cotzias et al. reported that 8 of their 16 patients showed either complete recovery or sustained amelioration of their symptoms, and L-DOPA remains a staple in the treatment of Parkinson's Disease to this day.

For more information on this topic, see [9].

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