

The Discovery of Dopamine

Dopamine as an independent neurotransmitter in the nervous system was discovered in Lund by the pharmacologist Arvid Carlsson in 1957, working at the Department of Pharmacology at Sölvegatan 10 in Lund (the current Geocentrum building). This discovery had tremendous impact on modern neuroscience research and – in combination with his later work performed at the University of Göteborg - would render him the Nobel Prize for Physiology and Medicine in 2000.

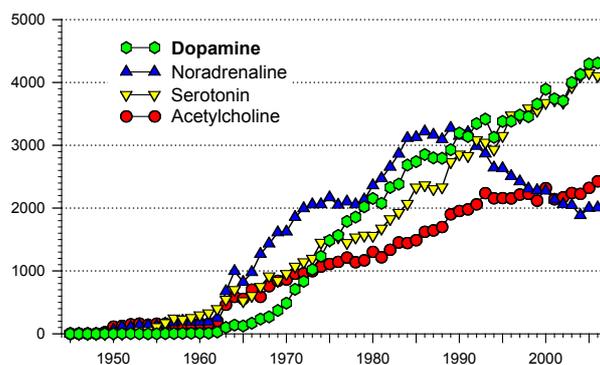
The amine *3-hydroxytyramine* ('dopamine') had earlier been identified as an intermediary in the synthesis of noradrenaline and adrenaline from tyrosine. In 1957, Arvid Carlson, Margit Lindqvist, Tor Magnusson and Bertil Waldeck, made the seminal observations that during the subsequent years would lead to the unravelling of dopamine as a transmitter in the central nervous system, independent of its role as a precursor in noradrenaline and adrenaline synthesis.

In their 1957 and 1958 papers [1,2], ([Carlsson et al 1957](#)) ([Carlsson et al 1958](#)) Carlsson and co-workers made the intriguing observation that the akinetic effects of reserpine could be reversed by an intravenous injection of the dopamine (and noradrenaline) precursor, 3,4-dihydroxyphenylalanine (DOPA). The functional effect was correlated to a recovery of dopamine, but not noradrenaline, content in the brain, suggesting that depletion of dopamine, rather than noradrenaline or serotonin, was the cause of the akinetic state in reserpine-treated animals. The following year, Carlsson's students Åke Bertler and Evald Rosengren [3], and I. Sano and collaborators in Japan [4], reported that the bulk of the brain's dopamine was located in the striatum (a structure containing little noradrenaline), thus providing further support for the idea that this new, putative transmitter may play a central role in the control of motor function [5].

As described by Oleh Hornykiewicz in his review of these early events [6], it was the 1959 paper of Bertler and Rosengren that stimulated him, together with Herbert Ehringer, in Vienna, to embark on a series of studies of the distribution of dopamine in human post-mortem brain, showing that dopamine is markedly and consistently reduced in the caudate and putamen in patients with Parkinson's disease (PD) [7], which in turn led to the first trials of L-DOPA in PD patients by Walther Birkmayer and Oleh Hornykiewicz [8] in Vienna, and by André Barbeau, Ted Sourkes and Gerald Murphy [9] in Montreal. The real break-

through, however, had to wait another 5 years, until 1967, when George Cotzias in New York developed the clinically efficacious, high-dose oral DOPA treatment that is still used today [10]. For the more interested reader, we recommend the reviews by Carlsson [11] and Hornykiewicz [6] for more detailed personal accounts of these early discoveries.

For the first decade after its discovery, interest in dopamine drew remarkably little attention. A search in the PubMed database shows that throughout the 1960s research on this new transmitter lagged behind that given to the other classical neurotransmitters, noradrenaline, serotonin and acetylcholine. As shown in the figure below, the turning point was around 1967, *i.e.* the year of Cotzias' break-through in L-DOPA therapy. The number of papers published on dopamine that year, as listed in PubMed, was 234. Ten years later the publication rate was 10-times greater and quickly approaching that of noradrenaline.



Number of publications per year from 1945 to 2006 on the topics of Dopamine and of related classical neurotransmitters. Method: Pub Med online search criteria for {dopamine OR hydroxytyramine}, {noradrenalin OR noradrenaline OR norepinephrin OR norepinephrine}, {serotonin OR 5-HT OR 5-hydroxytryptamine}, {acetylcholine OR ACh}. Prepared for the 50 year anniversary symposium held in Göteborg in 2007.

This dramatic increase coincides with the introduction of a range of new neurochemical and pharmacological tools for the study of dopamine neurons and their function in the brain, as well as the identification of the dopamine receptors, their pharmacology, and their role in mediating the antipsychotic action of neuroleptics [12,13].

The discovery of dopamine as a neurotransmitter in the brain was one of the seminal events in the development of modern neuroscience. Research on dopaminergic neurotransmission has remained highly dynamic over the years and been extremely important in shaping our understanding of how the brain works in health and disease. Dopamine has turned out to have a fundamental role in almost all aspects of behavior: from motor control to mood

regulation, cognition, addiction, and reward. In addition, dopamine research has been unique within the neurosciences in the way it has bridged basic science and clinical practice.

The demonstration of dopamine's involvement not only in movement disorders of Parkinson's disease, and the parkinsonian side effects of anti-schizophrenic drugs, but also as a central player in cognitive and motivational disorders, including the positive symptoms of schizophrenia, drug addiction, and attention deficit hyperactivity disorder (ADHD), has meant that since the 1970s dopamine has remained at the forefront of psychopharmacological research.

References:

- 1 Carlsson, A. et al. (1957) 3,4-dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. *Nature* 180, 1200
- 2 Carlsson, A. et al. (1958) On the presence of 3-hydroxytyramine in brain. *Science* 127, 471
- 3 Bertler, A. and Rosengren, E. (1959) Occurrence and distribution of dopamine in brain and other tissues. *Experientia* 15, 10-11
- 4 Sano, I. et al. Distribution of catechol compounds in human brain. *Biochim. Biophys. Acta* 32, 586-587
- 5 Carlsson, A. (1959) The occurrence, distribution and physiological role of catecholamines in the nervous system. *Pharmacol. Rev.* 11, 490-493
- 6 Hornykiewicz, O. (2002) Dopamine miracle: from brain homogenate to dopamine replacement. *Mov Disord.* 17, 501-508
- 7 Ehringer, H. and Hornykiewicz, O. (1960) Verteilung von Noradrenalin und Dopamin (3-Hydroxytyramin) im Gehirn des Menschen und ihr Verhalten bei Erkrankungen des Extrapyramidalen Systems. *Klin. Wochenschr.* 38, 1236-1239
- 8 Birkmayer, W. and Hornykiewicz, O. (1961) Der l-Dioxyphenylalanin (l-Dopa)-Effekt bei der Parkinson-Akinese. *Wien. Klin. Wochenschr.* 73, 787-788
- 9 Barbeau, A., Sourkes, T.L. and Murphy, G.F. (1962) Les catecholamines de la maladie de Parkinson. In de Ajuriaguerra, J. (ed), *Monoamines et Système Nerveux Central*. Georg et Cie., Geneva, pp. 247-267
- 10 Cotzias, G.C. et al. (1967) Aromatic amino acids and modification of Parkinsonism. *N. Engl. J. Med.* 282, 31-33
- 11 Carlsson, A. (2002) Treatment of Parkinson's with L-DOPA. The early discovery phase, and a comment on current problems. *J. Neural Transm.* 109, 777-787

- 12 Kebabian, J.W. et al. (1972) Dopamine-sensitive adenylate cyclase in caudate nucleus of rat brain, and its similarity to the "dopamine receptor". *Proc. Natl. Acad. Sci. U. S. A* 69, 2145-2149
- 13 Seeman, P. et al. (1976) Antipsychotic drug doses and neuroleptic/dopamine receptors. *Nature* 261, 717-719
- 15 Iversen, L.L. and Iversen, S.D. (2007) Dopamine: 50 years in perspective. *Trends Neurosci.* 30, 188-193.