Neuropharmacology

Sometimes science needs a stubborn mind: the discovery of dopamine

Often great discoveries are born out of serendipity, sometimes aided by a touch of stubbornness. This was the case for the discovery of dopamine by the neuropharmacologist Arvid Carlsson.

While Carlsson was a junior postdoc in the group of Bernard B. Brodie, the lab made a breakthrough discovery demonstrating that reserpine, an antipsychotic and antihypertension drug, caused akinesia, eyelid ptosis and depletion of brain serotonin in the mouse. Intrigued by these results, Carlsson proposed to explore the effect of reserpine on catecholamines, such as dopamine and noradrenaline, as he was aware of their chemical similarity to serotonin. Although Brodie reportedly considered Carlsson's idea a "waste of time," because serotonin seemed a more promising molecule to study, Carlsson decided to follow his intuition and, in a later collaboration with the catecholamine expert Nils-Åke Hillarp, proved that reserpine depletes the catecholamine pool.

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These findings prompted Carlsson to wonder which of these neurotransmitters underlay the effects of reserpine; in a seminal paper published in *Nature* in 1957, he provided the answer. In this study, Carlsson and colleagues separately administered the precursor of either serotonin or catecholamines to reserpine-treated mice, as he knew that the neurotransmitters per se cannot pass the blood brain barrier. Surprisingly, only the catecholamine precursor 3,4-dihydroxyphenylalanine (DOPA) was able to rescue the akinetic phenotype and the eyelid ptosis induced by reserpine treatment. Moreover, if the animals were treated with an inhibitor of monoamine oxidase, an enzyme involved in the catabolism of catecholamines, the dose of DOPA required to revert the reserpine phenotypes was considerably reduced. This suggested that the observed effect was caused by a molecule derived from DOPA. Carlsson considered that this molecule was likely to be noradrenaline, as dopamine was considered mainly to be a precursor of noradrenaline with limited physiological function. However, DOPA treatment failed to restore noradrenaline levels as predicted. These observations led Carlsson to reconsider the catecholamine pathway, eventually paying closer attention to the so-far disregarded molecule dopamine.

This was a moment of epiphany. However, at that time, no technique was available to measure dopamine. Therefore, Carlsson developed a method to detect dopamine and, in a follow-up publication in *Science* in 1958, reported that DOPA administration rescued dopamine content after reserpine treatment, supporting the hypothesis that the reserpine phenotypes were due to dopamine depletion.

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Carlsson's 1957 paper laid the groundwork for later demonstrations that dopamine is highly enriched in the basal ganglia, the brain region involved in motor control and linked to Parkinson disease. Furthermore, this discovery paved the way for the first medication for the disease, using the precursor DOPA, which is still the most effective symptomatic treatment used in clinics. With these findings, Carlsson showed that dopamine played a crucial role in brain physiology, revolutionizing the foundation of neuropharmacology and showing that, sometimes, it pays to follow your intuition even in the face of the prevailing dogma.

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Competing interests
The author declares no competing interests.

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