This Week's Citation Classic

Kostrzewa R M & Jacobowitz D M. Pharmacological actions of 6-hydroxydopamine. *Pharmacol. Rev.* 26:199-288. 1974.
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This paper was the first extensive review on the selective catecholaminergic neurotoxins, 6-hydroxydopamine and 6-hydroxydopa. The paper summarized their mechanisms and selectivities of action and gave detailed descriptions of their histochemical, neurochemical, and behavioral effects in animals. [The *SCI*® indicates that this paper has been cited in more than 590 publications.]

Pharmacology of 6-Hydroxydopamine

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By determining functional impairment when a nerve is destroyed, one can begin to realize the normal role of that nerve.[1] In the 1950s the Nobel laureate, R. Levi-Montalcini, established that anti-nerve growth factor (anti-NGF) destroyed sympathetic nerves, and she used this means to study changes in nerve function.[2] An inherent limitation was that anti-NGF had to be administered during ontogeny. Then, in 1967, J.P. Tranzer and H. Thoenen made the remarkable discovery that 6-hydroxydopamine (6-OHDA) produced overt destruction of sympathetic nerves in adult animals.[3] Soon, 6-OHDA was shown to have this effect on catecholamine nerves in brain.

In 1970, as a graduate student in the Department of Pharmacology at the University of Pennsylvania, I chose David Jacobowitz as my thesis advisor. My dissertation project was the pharmacology of 6-hydroxydopa, a pro-toxin that would cross the blood-brain barrier and be converted in vivo to 6-OHDA.[4]

I completed my thesis research in spring 1971 and then spent most of that summer writing the thesis in my bedroom. Somehow my wife managed to keep the four children at a less-than-shouting level. The historical review comprised 90 pages, and we thought this would be an ideal topic for a review journal. As is typical, when I assumed an appointment as a research pharmacologist at the VA Medical Center in New Orleans in the fall, I had to spend my time setting up a new laboratory. I wrote updates of the review article with a sawtooth approach—some days in the lab and some days in the library. Dave, now chief of histopharmacology at the National Institute of Mental Health, corrected newer versions of the paper. We seemed to be getting close to the end, but the finish line was elusive. Then, in 1973, Dave was invited for a lecture by the Tulane Medical Student Association. As the time of his visit approached, we both worked more frantically on the article. Finally, with his being in town we managed to put aside one night to complete the article. After dinner, about 9 p.m., we went directly to his hotel room and spent an "all-nighter" just working on the still incomplete portions of the paper. By 6 a.m. the next morning we finished. Dave immediately left for the airport, and I headed home to get ready to be at work by 8 a.m.

The popularity of the review article is probably due to several events. The paper has several tables showing how different 6-OHDA doses affected levels of catecholamines in the brain and in peripheral organs, at different intervals from injection. This made the article a handy reference. The article made its appearance just after L-DOPA proved to be effective in Parkinsonism. S. Matthysse soon proposed the dopamine hypothesis of schizophrenia.[5] U. Ungerstedt snowed how unilateral 6-OHDA lesions were useful in studying dopamine receptor supersensitivity,[6] while R. Heikkila and G. Cohen showed that peroxide and free radicals were intermediates in the destructive action of 6-OHDA.[7] All of these areas of investigation, and many others not mentioned here, made 6-OHDA an indispensable tool to study new areas of neuroscience.

1. **Cannon W B & Rosenblueth A.** *Aulonomic neuroeffecior systems.* New York: Macmillan. 1937. 229 p. (Cited 185 times since 1945.)
2. **Levi-Montalcini R & Booker B.** Destruction of the sympathetic ganglia in mammals by an anliserum to the nerve growth promoting factor. *Proc. Nat. Acad. Sci. USA* 46:384-91. 1960. (Cited 345 times.)
3. **Tranzer J P & Thoenen H.** Ultra-morphologische Verandeningen der sympatischen Nervendigunden der Katze nach Vorbehandlung mit 5- und 6-hydroxy-dopamin (Ultra-morphological changes in sympathetic nerve endings of the cat after preliminary treatment with 5- and 6-hydroxydopamine). *Naunyn-Sclunied. Arch. Pharmacol.* 257:343-4. 1967. (Cited 165 times.)
4. **Jacobowitz D** & **Kostrzewa R.** Selective action of 6-hydroxydopa on noradrenergic terminals: mapping of pretermmal axons of the brain. *Life Sci.* 10:1329-41. 1971.
5. **Matthysse** S. Dopamine and the pharmacology of schizophrenia: the state of the evidence. *J. Psychiai. Res.* 11:107-13. 1974.
6. **Ungerstedt** U. Postsynaptic supeniensitivity after 6-hydroxydopamine induced degeneration *of* the nigro-striatal dopamine system. *Ada Physiol. Scand.* 367(Supp.):69-73. 1971. (Cited 1.145 times.)
7. **Heikkila R** & **Cohen** G. In vivo generation of hydrogen peroxide from 6-hydroxydopamine. *Experiemia* 28:1197-8. 1972.

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