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Thoenen H & Tranzer J P. Chemical sympathectomy by selective destruction of adrenergic nerve endings with 6-hydroxydopamine.
Naunyn-Schmied. Arch. Pharmakol. Exp. Pathol. **261**:271-88, 1968.
[Dept. Experimental Medicine, F. Hoffmann-La Roche & Co. Ltd., Basle, Switzerland]

This paper describes the use of 6-hydroxydopamine (6-OHDA) as a tool for the selective and extensive destruction of sympathetic nerve terminals in rats and cats. The specificity of the destructive action is based on the fact that 6-OHDA is selectively accumulated in sympathetic nerve terminals with high efficiency and that the highly reactive oxidation products of 6-OHDA undergo covalent binding with nucleophilic groups of macromolecules leading to the destruction of the nerve terminals. [The *SCI*® indicates that this paper has been cited in over 645 publications since 1968, probably the most-cited paper published in this journal.]

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"In the context of a project designed to replace the physiological transmitter norepinephrine (NE) by 'false transmitters,' the late Jean-Pierre Tranzer and I investigated the ultramorphological manifestations of this transmitter exchange. By test-tube experiments, we could to some extent predict whether this replacement would result in apparent 'empty' or 'dense core' vesicles. Dense core vesicles were to be expected if the false transmitter substance, after reacting with glutaraldehyde, still reduced osmium tetroxide. Thus, the replacement of NE by 5-hydroxydopamine (5-OHDA) and 6-hydroxydopamine (6-OHDA) was predicted to result in dense core vesicles in adrenergic nerve terminals. This indeed was the case for 5-OHDA. This substance became a valuable tool for the unambiguous identification of catecholaminergic nerve terminals, i.e., after treatment with 5-OHDA all the vesicles contained an intense dense core.[1]

"The effect of 6-OHDA was quite different. Dense core vesicles could be demonstrated only at a very early stage of NE depletion, i.e., a few hours after administration of 6-OHDA.[2] However, this replacement of the physiological transmitter was very soon followed by signs of degeneration and finally destruction of the adrenergic nerve terminals. This explained the very long lasting NE depletion.[2] In adult animals, the destroyed nerve terminals regenerated, and a complete morphological, biochemical, and functional restoration occurred. In newborn animals, however, 6-OHDA resulted in a complete destruction of the peripheral sympathetic nervous system in a manner identical to administration of anti-nerve growth factor (NGF) antibodies.[3] After demonstrating that NGF acts as a retrograde messenger between effector organs and innervating sympathetic neurons, it became evident that the destruction of the sympathetic neurons in newborn animals by 6-OHDA resulted in an interruption of the supply of endogenous NGF from the periphery and that chemical sympathectomy with 6-OHDA and immunosympathectomy with antibodies to NGF both result from the abolition of the supply of NGF from the periphery to the sympathetic cell bodies.[4]

"6-OHDA became a standard experimental tool for general or local destruction of peripheral and central catecholaminergic nerve terminals.[2] Moreover, experiments with 6-OHDA led also to the detection of the transsynaptic induction of tyrosine hydroxylase, the first demonstration that nerve impulses regulate the synthesis of specific neuronal macromolecules.[4,5]

"When we submitted the first observation on the destruction of adrenergic nerve terminals by 6-OHDA to *Nature*, the paper was rejected because a reviewer came to the conclusion that our observation was an artifact. We also obtained the fatherly advice that we learn how to process tissue samples appropriately for electron microscopy in order to avoid future artifacts.

"After publication of the initial morphological observation,[6] we published this more extensive paper, in which the treatment schedule for as complete as possible a destruction of sympathetic nerve terminals was given. I think that this was the major reason for the frequent citation. Moreover, we also offered a first explanation for the mechanism of action of 6-OHDA, namely, that the oxidation product(s) of 6-OHDA underwent covalent binding with nucleophilic groups of neuronal macromolecules resulting in their denaturation and, consequently, in degeneration of the nerve terminals. The reaction as such is nonspecific, but the specificity of the destruction results from the efficient accumulation of 6-OHDA by the transport system for biogenic amines localized in the plasma membrane of sympathetic nerve terminals."

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3. **Angeletti P U & Levi-Montalcini R.** Sympathetic nerve cell destruction in newborn mammals by 6-hydroxydopamine. *Proc. Nat. Acad. Sci. US* 65:114-21, 1970. (Cited 145 times.)
4. **Thoenen H, Otten U & Schwab M E.** Orthograde and retrograde signals for the regulation of neuronal gene expressions: the peripheral sympathetic nervous system as a model. (Schmitt F O & Worden F G, eds.) *The neurosciences: fourth study program*. Cambridge, MA: MIT Press, 1979. p. 911-28.
5. **Mueller R A, Thoenen H & Axelrod J.** Adrenal tyrosine hydroxylase: compensatory increase in activity after chemical sympathectomy. *Science* **163**:468-9, 1969. (Cited 125 times.)
6. **Tranzer J P & Thoenen H.** An electron microscopic study of selective, acute degeneration of sympathetic nerve terminals after administration of 6-hydroxydopamine. *Experientia* **24**:155-256, 1968. (Cited 360 times.)