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This Week's Citation Classic™

Narahashi T, Moore J W & Scott W R. Tetrodotoxin blockage of sodium conductance increase in lobster giant axons. *J. Gen. Physiol.* 47:965-74, 1964.
[Dept. Physiology, Duke Univ. Medical Center, Durham, NC]

The highly specific and potent action of tetrodotoxin, a puffer fish poison, in blocking nerve membrane sodium channels was demonstrated for the first time using the voltage clamp technique. This finding triggered a widespread use of this and other toxins as tools for the study of ionic channels. [The *SCI*® indicates that this paper has been cited in over 630 publications since 1964.]

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"Whereas the experiments were performed in only two months, the above study was a result of my long-term dream and planning. In the early 1950s, I was an instructor at the University of Tokyo and was shocked, to say the least, by reading a series of publications by Hodgkin, Huxley, and Katz,[1] who used the voltage clamp technique to establish the ionic theory of nerve excitation. I clearly foresaw the applicability of this powerful technique to my study of drug action on nerve membranes, but the idea was too provocative to pursue at that time. The technique was difficult, and believe it or not, the use of chemicals as tools was almost unthinkable in neurophysiology.

"In 1959, I came across a truly fascinating action of tetrodotoxin (TTX), a toxic component contained in the puffer fish. Based on intracellular microelectrode experiments with frog skeletal muscle fibers, we proposed that TTX blocks the excitation through a selective inhibition of sodium channels.[2] On the day of my departure for the US, in January 1961, Norimoto Urakawa, a collaborator in the TTX study, slipped a small vial containing TTX into my pocket. We were hoping that some day we would be able to demonstrate our hypothesis by using the voltage clamp technique.

"It was not until December 1962 that I had a chance to do the long-awaited experiment. I was then an assistant professor at Duke University, and decided to stay in the US permanently. However, the situation forced me to go back to Japan temporarily to obtain an immigrant visa, and I had only two more months to work there before my departure. John W. Moore, an expert in the voltage clamp technique, and I thought that the TTX project could be carried out during that short period of time. Voltage clamp experiments with lobster giant axons were then conducted literally day and night throughout the Christmas holiday with the help of William Scott (then a medical student) using a double sucrose-gap technique.[3] The technique was far from satisfactory at that time, and countless experimental results had to be discarded because of poor membrane current records. Nevertheless, we were jubilant at finding that TTX blocked the sodium current without any effect on the potassium current. I took the films of oscilloscope records, which had barely dried, to Japan for analysis in January 1963. After submitting the above paper, I received the first request for a sample of TTX which was jotted down with the signature at the end of the referee's comments!

"Because of the highly specific and potent action, TTX has since become an extremely popular tool for the study of excitable membrane ionic channels. It has been used to estimate the sodium channel density, to identify and characterize sodium and other ionic channels, to study synaptic transmission, and to isolate and purify the sodium channels, to mention a few. I believe that this is the very reason for frequent citation of this paper which represents the first, clear-cut demonstration of the TTX action by voltage clamp. The paper has made another equally important contribution—it opened up the avenue to the use of specific toxins and chemicals as tools for the study of excitable membrane,[4-6] an enthusiasm generated only after that study. My ten-year-old dream had finally materialized. A series of studies initiated by this paper led Moore and me to receive, in 1981, the Cole Award in Membrane Biophysics, the most prestigious in the field."

1. **Hodgkin A L, Huxley A F & Katz B.** Measurement of current-voltage relations in the membrane of the giant axon of *Loligo*. *J. Physiol.—London* 116:424-48, 1952. (Cited 555 times.)
2. **Narahashi T, Deguchi T, Urakawa N & Ohkubo Y.** Stabilization and rectification of muscle fiber membrane by tetrodotoxin. *Amer. J. Physiol.* 198:934-8, 1960. (Cited 175 times since 1960.)
3. **Julian F J, Moore J W & Goldman D E.** Current-voltage relations in the lobster giant axon membrane under voltage clamp conditions. *J. Gen. Physiol.* 45:1217-38, 1962. (Cited 135 times.)
4. **Narahashi T.** Chemicals as tools in the study of excitable membranes. *Physiol. Rev.* 54:813-89, 1974. (Cited 425 times.)
5. **Catterall W A.** Neurotoxins that act on voltage-sensitive sodium channels in excitable membranes. *Annu. Rev. Pharmacol. Toxicol.* 20:15-43, 1980.
6. **Ritchie J M.** A pharmacological approach to the structure of sodium channels in myelinated axons. *Annu. Rev. Neurosci.* 2:341-62, 1979.