



## Obituary

## A memorial to Toshio Narahashi, PhD: An international leader of neurotoxicology and the Father of Cellular Neuropharmacology



**Toshio Narahashi, 1927-2013**

Dr. Toshio Narahashi graduated from the University of Tokyo, Faculty of Agriculture, in 1948. He started his scientific career in the Laboratory of Applied Entomology in 1949 where he began a lifetime of study of the mechanism of action of insecticides. Using primarily home-made electrophysiological equipment, he established four seminal principles:

1. Ion channels as a basis for insecticidal actions;
2. Nerve sensitivity as a basis for the negative temperature dependence of insecticidal action of DDT;
3. Nerve sensitivity as a major mechanism explaining insecticide resistance leading eventually to the current concept of *kdr* and *super-kdr*;
4. Tetrodotoxin (TTX), the puffer fish poison, blocks sodium channels selectively and potently.

These four findings had a great impact on their respective fields and launched Dr. Narahashi's remarkable scientific career. In 1955, he was selected as the second recipient of the newly created Society of Entomology and Zoology Award for his studies of the mechanism of action of insecticides, and was conferred a PhD in 1960 (the old European system, after publishing 26 full papers).

Dr. Narahashi came to the University of Chicago in 1961 to work in the Department of Physiology as a Postdoctoral Research Associate. In 1963 he was recruited to Duke University Medical Center as an Assistant Professor in the Department of Physiology and Pharmacology. In order to stay in the US permanently, he had to go back to Japan to get an immigrant visa. He came back to Duke in 1965, and was promoted to Associate Professor in 1967. He was then quickly promoted to Professor in 1969 and appointed as Head of the Physiology Division of the Department, and then as Head of the Pharmacology Division. In 1973 he was appointed Vice Chairman of the Department.

Dr. Narahashi made seminal contributions to the field of cellular neuropharmacology and neurotoxicology during his 12 years at Duke. These include, but are not limited to:

1. Voltage clamp experiments demonstrating that TTX selectively and potently blocks the sodium channel. This discovery led to the use of TTX as a very popular chemical tool. This indeed constitutes the dawn of ion channel pharmacology, and the stories behind the TTX study are cited in neuroscience textbooks.
2. Discovery of action potential generation in the absence of resting potential when squid giant axons were perfused internally with low potassium solutions substituted with sucrose. This astonishing discovery led to the importance of surface potentials for maintaining excitability.
3. Discovery of the mechanism of action of local anesthetics on sodium and potassium channels. He discovered that local anesthetics act from inside the nerve membrane in the charged cationic form after having penetrated the membrane in the uncharged form. This theory is widely cited in pharmacology and anesthesiology textbooks.
4. Demonstration of ion channel modulation by various natural toxins such as batrachotoxin, grayanotoxins, and sea anemone toxins. This led to the popular usage of these toxins as chemical tools.
5. Establishment of the ion channel basis of insecticidal actions, including that of DDT, pyrethroids, dieldrin, and others, making him a world leader of insecticide toxicology. Through his

research at Duke, he established himself as an international leader of neurotoxicology and is regarded as the Father of Cellular Neuropharmacology.

In 1977 Dr. Narahashi accepted the chairmanship of Northwestern University's Feinberg School of Medicine Department of Pharmacology in Chicago. While serving as chair he maintained a large laboratory and actively pursued ion channel research. He applied patch clamp techniques to the study of therapeutic agents, insecticides, and heavy metals. Examples include:

1. Development of a method to count the number of sodium channels modified by pyrethroids. This concept has had a great impact on insecticide research and neuropharmacology in general.
2. Elucidation of the mechanism underlying the negative temperature dependence of action of pyrethroids on sodium channels. This phenomenon remained a mystery for half a century.
3. Ethanol modulation of nicotinic acetylcholine receptors (nAChRs). This action has a broad impact on the systemic effects of ethanol as nAChRs modulate the activity of other receptor systems.
4. Ionic basis of general anesthetic action including that on nAChRs. Role of membrane lipid in general anesthetic action, a hypothesis that prevailed over 90 years, cannot account for the mechanism.
5. Modulation of ion channel activity by heavy metals such as mercury and lead, a new aspect of action.
6. Ionic basis for the action of psychotropic drugs such as chlorpromazine and nicotine. The study of nicotine led to the concept of dual action, an important factor for the toxic action of nicotine. More recently he was actively involved in the study of microglia.

During his 17-year tenure as chair, the Department of Pharmacology at Northwestern ranked among the top tier in the US. While serving as chair, he pursued additional research in neuropharmacology including work on alcoholism, general anesthetics, drugs for Alzheimer's, and neuroprotective drugs. After stepping down as chair, he was appointed as the John Evans Professor of Pharmacology, the most distinguished position appointed directly by the University President.

During his 12 years at Duke and 36 years at Northwestern, Dr. Narahashi published hundreds of scientific papers and trained 140 professionals, postdoctoral fellows and graduate students.

With his discovery of the nerve blocking action of tetrodotoxin, the puffer fish poison, Dr. Narahashi established the scientific field of modern pharmacology of ion channels. In addition, he was a pioneer scientist of insecticide toxicology. Owing to his extensive and influential studies, Dr. Narahashi received numerous society awards. These include the: Society Award from the Society of Entomology and Zoology (1955); Cole Award from the Biophysical Society; Javets Neuroscience Investigator Award from the National Institutes of Health (1986–1993); Burdick & Jackson International Award from the American Chemical Society (1989); Merit Award from the Society of Toxicology (1991); Otto Kraye Award from the American Society for Pharmacology and Experimental Therapeutics (2000); First Distinguished Investigator Lifetime Achievement Award in Neurotoxicology from the Society of Toxicology Neurotoxicology Specialty Section (2001); Honorary Member of the Japanese Pharmacology Society (2002); and the Distinguished Toxicology Scholar Award from the Society of Toxicology (2008).

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