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Commentary

Toshio Narahashi: Life and legacy of the founding father of cellular neuropharmacology

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1. Introduction

This special issue of the journal Neurotoxicology – Ion Channels in Pain, Pleasure, Death and Disease – is dedicated to the memory of the late Toshio Narahashi, an internationally known pharmacologist who is considered the founding father of cellular neuropharmacology – the study of the actions of drugs and toxins on nerve cells. In his long academic career, Professor Narahashi trained close to 140 graduate students, postdoctoral fellows and visiting scientists in his laboratory and as chairman coached and mentored the faculty of the Department of Pharmacology of Northwestern University Medical School to be among the best in their fields. These and many other scientists are indebted to this brilliant, dedicated, kind and caring man for teaching them how to be better scientists and better people, VLS was a postdoc in the Narahashi lab from 1981 to 1984 and XZ was a postdoc and research assistant professor there from 1997 to 2006.

2. Pioneer

Narahashi bolted to prominence in the scientific world with his landmark 1964 paper showing that the puffer fish poison tetrodotoxin blocked nerve conduction by selectively blocking the sodium current, while leaving the potassium current untouched (Narahashi et al., 1964). Today the discovery of the mode of action of a selective neurotoxin is commonplace, largely because of the work of Narahashi and the legions of scientists either trained directly by him or influenced by his work. Like many pioneers in science, his success began with the application of a new method to gain insight into a difficult problem. After graduating with a degree in veterinary medicine from the University of Tokyo in 1948, he joined the Laboratory of Applied Entomology there, where he spent the next twelve years studying the effects of insecticides on nerves with the techniques available at the time – extracellular and intracellular microelectrodes. As he recounts in his citation classic article (Narahashi, 1984), he became convinced in the early 1950s after reading the series of publications by Hodgkin, Huxley and Katz on the use of the newly-developed voltage clamp technique to establish the ionic theory of nerve excitation, that this technique was the key to clearly understanding the actions of drugs and toxins on nerve membranes.

He finally got the chance to realize this radical idea when he joined the Department of Physiology and Pharmacology at Duke University in 1963, where he teamed up with biophysicist John Moore, one of a handful of scientists in the world who understood the voltage clamp technique, to do the experiments on tetrodotoxin, which he had already postulated three years earlier to be a selective inhibitor of sodium channels (Narahashi et al., 1960). The clear demonstration by Narahashi et al. (1964) that tetrodotoxin selectively and potently blocked sodium channels was a bombshell for several reasons. First, it was a landmark in physiology by providing pharmacological support for the theory proposed 12 years earlier by Hodgkin and Huxley that the sodium and potassium conductances needed to explain the action potential were indeed conducted through distinct physical channels; second, it introduced tetrodotoxin as one of the key tools that was essential to much subsequent work in neuroscience; and third, it established the use of the voltage clamp technique as the key tool for ion channel neuropharmacology and was therefore the starting point of modern cellular neuropharmacology, a field that has led to huge advances in our understanding of the actions of drugs, alcohol, neurotoxins and insecticides, and the role of ion channels in pain, pleasure, death and disease.

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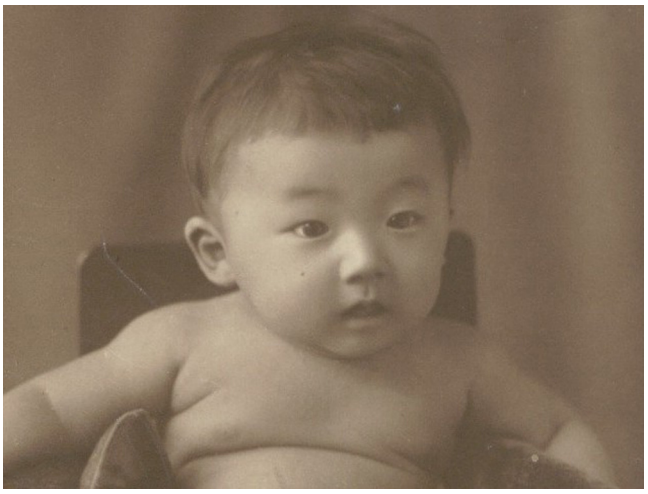

Fig. 1. Toshio Ishii as a baby.

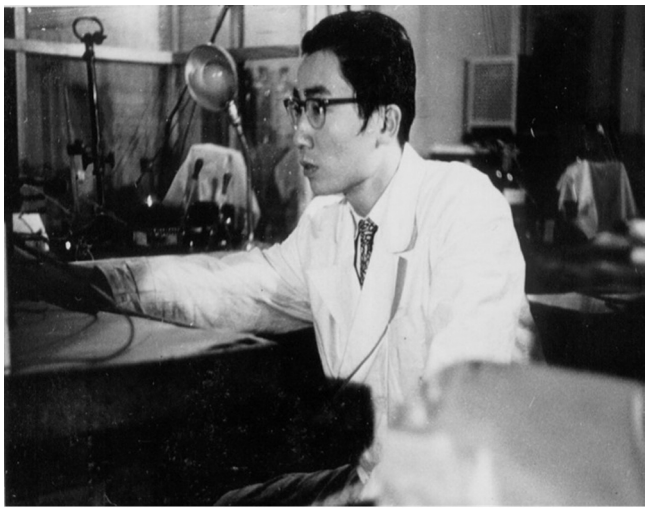

Fig. 3. Toshio Narahashi in his laboratory in Tokyo, 1960.

3. Biographical

Toshio Narahashi was born Toshio Ishii on January 30, 1927 in Fukuoka, Japan (Fig. 1). He received a degree in veterinary medicine from the University of Tokyo in 1948 and began his insecticide mode of action research there, also working as an instructor (Fig. 2). On the basis of 26 published papers on the effects of insecticides and tetrodotoxin on nerves, he was awarded a doctorate from the University of Tokyo in 1960 (Fig. 3). During this time, he married Kyoko Narahashi. Because his wife's family had no male heirs, Toshio Ishii was adopted into the Narahashi family and took the Narahashi surname according to the age-old tradition of Mukoyoshi or adopted son-in-law. The Narahashis had a daughter Keiko (1959) and a son Taro (1962).

In 1961, Narahashi moved to the University of Chicago to work as a postdoctoral research associate, and, in 1963, was recruited to Duke University as an assistant professor. Based on his success as a researcher and teacher, and his legendary capacity for hard work, he attained the rank of full Professor within the unusually short time of six years and was appointed vice chairman in 1973. In 1977, he was recruited by the Department of Pharmacology at Northwestern University's Feinberg School of Medicine to be its chairman, a post he held for 17 years until stepping down in 1994. Still he remained at Northwestern as the John Evans Professor of Pharmacology, focusing on research and teaching until his death on April 21, 2013 at the age of 86, from complications of liver cancer. An obituary with more details has been published (Cranmer, 2013) and is reprinted at the end of this special issue.

Fig. 2. Toshio Ishii at Imperial Tokyo University in 1949.

4. Research

Narahashi led a research laboratory throughout his career, even while department chairman. He published 324 papers and 148 chapters and reviews, and edited 11 books. He also continued teaching during his time as chairman, and after stepping down, even after being diagnosed with cancer. In the winter of 2012, he taught the course “Molecular Basis of Drug Action,” a treatise on excitable cell physiology, biophysics and pharmacology.

Narahashi began his research career with his pioneering studies on the mode of action of insecticides, identifying the voltage-gated sodium channel as the target of DDT and pyrethroids, and he continued to make important contributions to the field throughout his long career. His prominence in this field is what attracted the authors to his lab.

In addition to his work on insecticides and tetrodotoxin, Narahashi also described ion channel modulation by other toxins, including batrachotoxin, grayanotoxin and sea anemone toxins, popularizing their use as highly specific chemical tools to study ion channel function. In defining the highly selective mechanism of action of TTX, he elevated the study of toxins and the associated science of toxinology from one of mere biological curiosity to one of such prominence that biological toxins are now mainstays of experimental studies of excitable cells and signaling processes, and have even become accepted therapeutic agents for treatment of intractable neuropathic pain (omega conotoxin GVIA – Ziconide®) and muscle spasticity (Botulinum toxin A).

Narahashi also made seminal contributions to our understanding of the role that ion channels play in therapeutics. He demonstrated that local anesthetics act from the inside of the axon after first crossing the membrane in the uncharged form. Additionally, his work laid the foundation for the potassium