Current Topics in Puffer Fish Accumulation of Tetrodotoxin

Yuji Nagashima a) and Takuya Matsumoto b)
a) Tokyo University of Marine Science and Technology, Graduate School of marine Science and Technology
4-5-7 Konan, Minato-ku, Tokyo 108-8477, Japan
b) Department of Environmental Sciences, Faculty of Life and Environmental Sciences, Prefectural University of Hiroshima
562 Nanatsuka-cho, Shohara-shi, Hiroshima 727-0023, Japan

Summary
Marine puffer fish belonging to the family Tetraodontidae feature a potent neurotoxin, tetrodotoxin (TTX), found mainly in the liver and ovaries. The toxin is thought to be derived through the food web, starting from marine and gastrointestinal bacteria, and feeding experiments have demonstrated that innocuous cultured puffer fish Takifugu rubripes and Takifugu niphobles become toxic and accumulate TTX primarily in the liver when fed TTX-containing diets. Since these results indicate that TTX in puffer fish is exogenous and effectively transferred to the liver, pharmacokinetic studies on uptake mechanism of TTX in T. rubripes were performed with in vivo administration. After a single bolus injection of TTX into the hepatic portal vein, the blood concentration-time course profiles of TTX showed multiple distinct phases, suggesting TTX disposition in T. rubripes involves multiple compartments and the presence of peripheral tissues that do not rapidly achieve concentration equilibrium of TTX with the central compartment. Furthermore, after gastrointestinal administration of 0.25 mg TTX/kg body weight, the blood concentration-time profiles of TTX showed a typical absorption curve with a first-order absorption process and a high bioavailability of 62%. Most TTX administrated was detected in the liver 300 min after injection, regardless of the injection route. These in vivo experiments verified that TTX is well absorbed into the systemic circulation with high gastrointestinal absorption and accumulation in the liver. As a next step, in vitro incubation assays of liver with TTX were performed to investigate transmembrane transport processes. Liver slices of puffer fish T. rubripes demonstrated increase in TTX accumulation with incubation time and TTX concentration in the culture media, while those of other fish, parrot-bass Oplegnathus fasciatus, filefish Thamnaconus modestus and threadsail filefish Stephanolepis cirrhifer, did not. These results confirmed that the T. rubripes liver specifically and actively accumulates TTX even under in vitro conditions, suggesting the involvement of a carrier-mediated transport system. TTX-binding proteins were therefore isolated from plasma of T. niphobles and Takifugu pardalis. PSTBP (puffer fish saxitoxin and tetrodotoxin binding protein) was well characterized: a wide distribution in plasma of puffer fish in the genus Takifugu, and ubiquitous presence in tissues of T. pardalis. Finally, we have focused attention on the role and significance of TTX in puffer fish, with likely involvement in immunopotentiating and physiological functions.