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"Cousin" of Snake Venom Toxin Found in Mice

Snake venoms produce devastating effects on the nervous system, so it comes as somewhat of a surprise that the brain of a mouse would harbor a molecule similar to a major component of the deadly toxins. Howard Hughes Medical Institute (HHMI) researchers at The Rockefeller University have found that this is indeed the case, and they believe that the molecule they discovered, called lynx1, may be involved in pathways that are linked to memory and muscle function.

Nathaniel Heintz, an HHMI investigator at The Rockefeller University, emphasized that at this time the discovery by his group, which is reported in the May 28, 1999, issue of the journal *Neuron*, pertains only to cultured mouse cells. "The presence of lynx1 in the brain is really provocative because parts of the protein bear a striking resemblance to certain snake toxins," said Heintz.

When a poisonous snake bites a person, alpha-neurotoxins in the venom block acetylcholine receptors on the tips of muscle nerves. Acetylcholine is a neurotransmitter that helps to activate muscles and causes them to contract. Most who are killed by venomous snakes die of respiratory failure because the alpha-neurotoxins shut down the diaphragm muscles, causing suffocation.

While searching for genes that regulate brain development, Heintz and postdoctoral associate Julie Miwa found lynx1. The investigators decided to continue studying lynx1 when experiments indicated that the gene is expressed in the mouse brain two to three weeks after birth time during which the wiring of the mouse's nervous system is fine-tuned. Further experiments showed that expression of the newly found gene was restricted to certain classes of neurons in the brain, suggesting a specialized and perhaps unique role for the protein.

Heintz and Miwa, however, did not realize the full impact of their discovery until they identified the family to which the gene belonged. "Nat and I sat down at the computer one day and tried to match lynx1's sequence of amino acids with those of known proteins. We did an exhaustive search of the

database utilizing several different algorithms, then suddenly we got a hit," Miwa said. Relatively small but critically important sections within lynx1 matched the amino acid sequence of a snake toxin called alpha-bungarotoxin. This venom is a member of a large family of proteins called Ly-6. With that in mind, Heintz and Miwa named their gene "lynx," for Ly -6 n euroto x in.

"At that point we realized the potential significance of lynx1," Miwa said. "Bungarotoxin was known to bind to acetylcholine receptors, so if lynx1 could bind to these receptors too, it might be important for brain signaling."

Ines Ibanez-Tallon, an HHMI associate in Heintz's lab, localized the nerve cell receptors with which lynx1 interacts, and showed that the distribution of these receptors is similar to that of acetylcholine receptors in the cerebellum, a region of the brain involved in controlling motion and motor learning.

Additional collaborators in Lorna Role's laboratory at Columbia University tested lynx1's effect on frog eggs (or oocytes) that had been injected with these receptors. Miwa said the eggs' acetylcholine response was 30 percent larger after bathing them with lynx1, suggesting that lynx1 might enhance the action of acetylcholine. By contrast, its cousin, alpha-bungarotoxin, interferes with acetylcholines activity. But many drugs that affect the brain have been found to generate effects opposite to those of similar substances produced by brain tissue, Heintz said.

Acetylcholine receptors are thought to be involved in memory and in the pathogenesis of Alzheimer's disease, where loss of inputs from acetylcholine neurons is a hallmark of the disease. "If lynx1 acts in the whole animal like it does in cells, then the structure of the protein could be a good start in designing rational therapy for human conditions," Heintz said.