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Relative of Snake Venom Toxin May Aid in Understanding Nicotine Addiction

Scientists have found that a protein resembling snake venom neurotoxin modulates the sensitivity of specific receptors in the brain that are targets of nicotine, the primary addictive drug in tobacco. The researchers say that the protein, lynx1, may be a new tool with which to probe how nicotine and other drugs activate “pleasure centers” of the brain.

Although studies of lynx1 and other members of this intriguing “prototoxin” protein family are still in the early stages, the researchers say they may help in understanding nicotine addiction or possibly human genetic diseases caused by defective prototoxins.

Howard Hughes Medical Institute investigator Nathaniel Heintz and his colleagues Inés Ibañez-Tallon and Julie Miwa at The Rockefeller University and colleagues at The Mayo Foundation and Columbia University reported in the March 14, 2002, issue of the journal *Neuron* that lynx1 is an interesting new modulator of nicotinic acetylcholine receptors.

Julie Miwa, a member of Heintz’s laboratory and co-author of the *Neuron* article, first discovered lynx-1 in 1999. The discovery was especially intriguing, said Heintz, because it confirmed that mammals harbored a natural, or “endogenous,” protein resembling snake venom that could affect the nervous system. At the time the discovery was made, such an assumption was scientifically risky, said Heintz.

“It was an appealing hypothesis that there might be an endogenous neurotoxin-like molecule that regulated some sort of receptor in the nervous system,” said Heintz. “But Julie was very, very brave to pursue this gene and its protein product on such a flimsy basis.”

Miwa’s initial work showed that lynx1 was concentrated in the nervous system. Additional studies in collaboration with Ibañez-Tallon showed that lynx-1 altered the function of nicotinic acetylcholine receptors. Acetylcholine is a neurotransmitter that helps to activate muscles and causes them to contract.

The discovery of lynx1 had potential clinical importance since nicotine is known to increase the level of the neurotransmitter dopamine, which in turn produces pleasurable effects in the brain. Following up on Miwa's work, lead author of the *Neuron* paper, Inés Ibañez-Tallon, used antibodies specific to lynx1 to reveal in mice that the protein was closely associated with the nicotinic acetylcholine receptors in neurons.

Ibañez-Tallon then performed more detailed studies of the function of lynx1 by engineering frog eggs, called oocytes, to produce both lynx1 and nicotinic acetylcholine receptors. "By studying the oocytes, Inés found that lynx1 directly modified nicotinic receptors – an important finding because physiologists had told us they weren't really sure that a membrane-bound molecule like lynx-1 could even access the receptor," said Heintz. "That finding really stimulated us to do an in-depth analysis of how lynx1 changed the properties of the receptors. She further showed that lynx1 had a dramatic effect on enhancing desensitization of the receptors to acetylcholine, and it did so by directly binding to the receptors," he said.

Co-author Steven Sine and colleagues at The Mayo Foundation performed electrophysiological studies of the effects of lynx1 in cultured human cells, and discovered that lynx1 affected the electrical conductance of the receptors.

"Steve's findings revealed that lynx1 modulates this receptor in a different way than other known modulators," said Heintz. Since nicotinic acetylcholine receptors are also expressed on immune cells, the prototoxin family that includes lynx1 might have broad regulatory roles in both the immune and nervous systems, he added.

"It will be very interesting to find out if this class of molecules in the nervous system just modulates neurotransmitter receptors, or whether they regulate other cell surface receptors. We really don't know yet," said Heintz.

Heintz and his colleagues are planning additional studies of the prototoxin gene family in mice. They have disrupted the gene for lynx1 and are studying what effects the loss of the protein will have.

"Although we can't say much about these effects at this early stage, clearly this family of proteins is physiologically important," he said. Heintz noted, for example, that more work is needed to determine whether lynx1 or its family members will be useful drug targets in treating nicotine addiction.

But there's hope that further studies of the prototoxins in mice could lead to discovery of genetic disorders caused by mutations in these genes. "Once we understand the basic functional roles of the prototoxins in mice, we can proceed to explore whether prototoxin genes might be mutated in human disease. We will be able to obtain much more functional information in humans, because we can more readily detect any subtle abnormalities in people with mutations in a prototoxin gene," he said.