MedicalXpress

Gene linked to anxious behavior in mice

February 19 2009

(PhysOrg.com) -- To measure anxiety in a mouse and suggest it's similar to anxiety in a person may seem like a stretch, but the metrics sound uncannily familiar. Paralyzed by fear, afraid to leave the house or socialize with others, scared of new places, preferring the dark to the light of day.

Researchers at The Rockefeller University report this week that mice missing a particular gene show a big increase in these symptomatic behaviors. The scientists also show how the gene, *Lynx2*, alters the way brain cells communicate and say a similar process may underlie anxiety disorders in humans.

"I'd be surprised if these findings are not relevant to humans," says Nathaniel Heintz, head of the Laboratory of Molecular Biology at Rockefeller, who led the research. "With structures relating to basic functions as evolutionarily ancient as fear and anxiety, I think you can learn a great deal from cross-species studies."

Lynx2 produces molecules that influence communication between neurons in brain areas associated with anxiety. In prior work, the researchers showed that the gene generates a molecule called a mammalian prototoxin, an evolutionary precursor to snake venom toxins. The prototoxins target the same cells as snake venom but regulate their activity instead of inactivating them completely. To investigate exactly what *Lynx2* does, Heintz and colleagues knocked out the gene in a line of mice and compared their behavior — and biochemistry — to that of a normal cohort. The bottom line: Mice lacking Lynx2 had no glaring

defects, apart from being a very nervous breed.

Compared to regular mice, the jittery creatures spent less time in brightly illuminated spaces, preferring to hide in the dark. They were slower to explore a mysterious new space when presented the option. They chose to isolate themselves in an empty cage rather than socialize with a companion next door.

To study the brain-based cause of the odd behavior, Heintz, who is also a Howard Hughes Medical Institute investigator, collaborated with Paul Greengard, head of the Laboratory of Molecular and Cellular Neuroscience to perform a series of biochemical tests and single-cell electrical recordings. The results showed that a particular group of neurons in the genetically modified mice became more sensitive to nicotine. These neurons were in a key part of the medial prefrontal cortex, which projects to the amygdala, both brain structures known to be active in anxious people. The researchers speculate that this excitability may cause the anxious behavior in the mice lacking the Lynx2 gene, and that variation in this gene — which humans share — could play a role in human anxiety.

Now the scientists will knock out the gene in certain parts of the complex anxiety circuit in hopes of zeroing in on a single cell-type responsible for the behaviors in mice. “If we can find exactly what part of the circuit is responsible for the generalized anxiety we see here, in-depth studies of those cells might provide new avenues for development of effective treatments for common anxieties or social phobias,” Heintz says.

More information: *Proceedings of the National Academy of Sciences* online, A role for LYNX2 in anxiety-related behavior, Ayse B. Tekinay, Yi Nong, Julie M. Miwa, Ivo Lieberam, Ines Ibanez-Tallon, Henry A. Lester, Paul Greengard and Nathaniel Heintz