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## Mice Show How to Calm Anxiety

Scientists have found a genetic switch that helps calm anxiety in "stressed out" mice.

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— **Michael G. Rosenfeld**

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In three articles published in the April 2000 issue of the journal *Nature Genetics*, three independent groups of researchers report that *Crhr2* (corticotropin-releasing hormone receptor-2), which is found in pituitary gland tissue and in other areas of the brain, actually quells the stress response in mice.

One of the leaders of the research efforts, Michael G. Rosenfeld, an HHMI investigator at the University of California, San Diego (UCSD), cautioned that the discoveries represent only a beginning in understanding the complexities of the stress response.

"It has long been known that many severe psychiatric disturbances show a heightening of the anxiety response," Rosenfeld said. "With these findings, we provide an initial motivation for further dissecting two distinct receptor systems in terms of potential drug discovery programs."

Rosenfeld's research group included his former UCSD colleague Toshimitsu Kishimoto, who is now at Yoshitomi Pharmaceuticals in Japan, and Jelena Radulovic and Joachim Spiess at the Max Planck Institute for Experimental Medicine in Germany. The other groups were from the Oregon Health Sciences University and The Salk Institute.

When a human or animal is stressed, the hypothalamus secretes the hormone, corticotropin-releasing hormone (Crh), which stimulates the pituitary gland to release additional hormones. These hormones from the pituitary gland cause the adrenal gland to secrete hormones that stoke the stress response,

increasing anxiety, energy and blood pressure, and suppressing immune responses.

According to Rosenfeld, previous studies by his group and by other researchers revealed the existence of two distinct receptors for Crh Crhr1 and Crhr2 in the pituitary and in other brain regions involved in emotional and autonomic functions, as well as in the periphery.

"These two receptors had overlapping but clearly distinct anatomical patterns of expression in the brain," said Rosenfeld. "Also, previous research had found that Crhr2 also responds to a different chemical trigger, called eucortin.

"So, we set out to differentiate the potential distinct roles of the Crhr2 receptor by creating a mouse in which the gene for the Crhr2 receptor was functionally deleted," said Rosenfeld.

Once the researchers produced mice that lacked a functional *Crhr2* gene, they measured the animals' anxiety by observing the animals' response to stress-inducing situations such as bright light and heights.

They discovered that male mice lacking *Crhr2* showed a higher level of anxious behavior than did normal mice. They also found that male mice that lacked a single copy of the *Crhr2* gene showed anxiety levels that fell somewhere between those seen in normal mice and those in mice that lacked two copies of *Crhr2*. In additional experiments, the researchers showed that they could also induce anxiety in mice by feeding them a drug that selectively blocked the Crhr2 receptor.

Further tests, in which the researchers used drugs to turn the Crhr1 receptor on or off, ruled out the Crhr1 receptor as a cause of anxiety-producing activity.

And, in an intriguing finding, the researchers discovered that female *Crhr2*-deficient mice did not show increased anxiety, perhaps due to some compensating effect in those mice, speculated Rosenfeld.

The scientists also found evidence that anxiety caused by *Crhr2*- deficiency did not appear to be related to changes in the receptor's function in the "hypothalamic-pituitary-adrenal" response to stress. They believe the anxiety could be caused by a lack of Crhr2 in specific areas of the brain that govern emotional and autonomic functions. The scientists have begun to identify how anxiety is triggered in those brain regions, where they have found markedly lower levels of phosphorylation of the gene-regulatory transcription factor CREB, in the absence of Crhr2 activity.

"Basically, we have found that the Crhr2 receptor in some areas of the brain responds to Crh and acts to oppose the anxiety response," says Rosenfeld. "One might think of this activity of Crhr2 as a focusing of the anxiety response. Thus, instead of having the animal exhibit a full anxiety response to a stressful situation with many areas of the brain mediating a Crhr1-dependent anxiety effect other areas may exert specific anxiolytic actions on the activity of the Crhr2 receptor."