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Mice offer clues to the roots of human resilience

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When faced with adversity, some people succumb to debilitating psychological diseases including posttraumatic stress disorder and depression, while others are able to remain remarkably optimistic.

Now, a new mouse study in the October 19 issue of the journal *Cell* reveals that the difference may depend in part on the chemistry of the brains' reward circuits. The findings could point to new psychiatric drugs, and perhaps even new ways to encourage resilience for people in high-stress circumstances, including soldiers in combat, disaster relief workers, and disaster victims, according to the researchers.

They found that mice who are more susceptible to social defeat show increased levels of a growth factor known as brain-derived neurotrophic factor (BDNF) in a portion of the brain integral to reward- and emotion-related behaviors. Mice that seem to cope better with the same stressful circumstances don't show the same chemical rise. BDNF promotes plasticity in the brain, presumably enabling new connections between neurons, the researchers explained, a process which is considered the cellular basis for learning and memory.

"The increase in BDNF may have an adaptive role normally, allowing an animal to learn that a situation is bad and avoid it in the future," said Eric Nestler of The University of Texas Southwestern Medical Center. "But under conditions of extreme social stress, susceptible animals may be 'over-learning' this principle and generalizing it to other situations. They avoid their aggressors, but they also avoid all mice and even other

fun things like sugar or sex."

The observed distinction in the animals' susceptibility to stress was despite the fact that they were all virtually identical genetically and were raised in the same carefully controlled environment, Nestler noted. "There may still be environmental influences that affect the animals' ability to cope with stress later on, such as the dominance hierarchies within a litter," he said. "But it's just as likely that random or stochastic events during development may play a role."

An individual's emotional response to acute stresses, such as terrorist acts, or to more prolonged chronic stress, such as a divorce, is determined by genetic and environmental elements that interact in complex and poorly understood ways, Nestler said. While a vast literature describes the effects of several kinds of acute and chronic stress on an individual's physiology and behavior, much less has been known about the biological basis of individual differences in stress responses.

To shed some light on the issue in the current study, the researchers repeatedly forced small mice into aggressive interactions with larger mice. Nestler's group had earlier shown that, after suffering ten defeats in ten days, the small mice show a lasting tendency to avoid social interaction. Now, they reveal that the mice actually show a wide variation in that response. While all of the defeated animals had signs of anxiety, "some of the mice show a syndrome with features that are similar to PTSD or depression. Others don't," Nestler said.

In addition to their lonely lifestyle, the susceptible mice showed significant weight loss and less interest in sugar, both of which are consistent with a depression-like state, they reported. The more vulnerable mice also showed greater sensitivity to a low dose of cocaine, among other abnormalities. They traced the differences in stress

response to BDNF, revealing that the susceptible animals had a 90 percent greater concentration of the growth factor in the brain's reward circuits than normal mice did. Levels of BDNF in more resilient mice remained steady.

Further examination of the animals' brains found that stress-resistant mice exhibited increased activity in genes expected to make neurons less excitable. Indeed, they found evidence that dopamine neurons of animals susceptible to social stress fire at a faster rate than those of more resilient animals do. They also report that a less active form of BDNF lends mice greater toughness following socially stressful conditions.

Finally, they found, the postmortem brain tissue of patients who had been depressed showed a 40 percent increase in BDNF compared to unaffected individuals, suggesting that the results in mice may have clinical relevance. Nestler said that any of the genes found to differ in activity between the brains of susceptible and resilient mice could be drug targets for those suffering the affects of acute stress. "We may even find ways to help humans adapt better to chronic stress," he added.

Source: Cell Press