Stress: Brain yields clues about why some succumb while others prevail

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Results of a new study may one day help scientists learn how to enhance a naturally occurring mechanism in the brain that promotes resilience to psychological stress. Researchers funded by the National Institutes of Health's National Institute of Mental Health (NIMH) found that, in a mouse model, the ability to adapt to stress is driven by a distinctly different molecular mechanism than is the tendency to be overwhelmed by stress. The researchers mapped out the mechanisms – components of which also are present in the human brain – that govern both kinds of responses.

In humans, stress can play a major role in the development of several mental illnesses, including post-traumatic stress disorder and depression. A key question in mental health research is: Why are some people resilient to stress, while others are not? This research indicates that resistance is not simply a passive absence of vulnerability mechanisms, as was previously thought; it is a biologically active process that results in specific adaptations in the brain's response to stress.

Results of the study were published online in *Cell*, on October 18, by Vaishnav Krishnan, Ming-Hu Han, PhD, Eric J. Nestler, MD, PhD, and colleagues from the University of Texas Southwestern Medical Center, Harvard University, and Cornell University.

Vulnerability was measured through behaviors such as social withdrawal after stress was induced in mice by putting them in cages with bigger, more aggressive mice. Even a month after the encounter, some mice

were still avoiding social interactions with other mice – an indication that stress had overwhelmed them – but most adapted and continued to interact, giving researchers the opportunity to examine the biological underpinnings of the protective adaptations.

“We now know that the mammalian brain can launch molecular machinery that promotes resilience to stress, and we know what several major components are. This is an excellent indicator that there are similar mechanisms in the human brain,” said NIMH Director Thomas R. Insel, MD.

Looking at a specific part of the brain, the researchers found differences in the rate of impulse-firing by cells that make the chemical messenger dopamine. Vulnerable mice had excessive rates of impulse-firing during stressful situations. But adaptive mice maintained normal rates of firing because of a protective mechanism – a boost in activity of channels that allow the mineral potassium to flow into the cells, dampening their firing rates.

Higher rates of impulse-firing in the vulnerable mice led to more activity of a protein called BDNF, which had been linked to vulnerability in previous studies by the same researchers. With their comparatively lower rates of impulse-firing, the resistant mice did not have this increase in BDNF activity, another factor that contributed to resistance.

The scientists found that these mechanisms occurred in the reward area of the brain, which promotes repetition of acts that ensure survival. The areas involved were the VTA (ventral tegmental area) and the NAc (nucleus accumbens).

In a series of experiments, the scientists extended their findings to provide a progressively larger picture of the vulnerability and resistance mechanisms. They used a variety of approaches to test the findings,

strengthening their validity.

“The extensiveness and thoroughness of their research enabled these investigators to make a very strong case for their hypothesis,” Insel said.

For example, the researchers showed that the excess BDNF protein in vulnerable mice originated in the VTA, rather than in the NAc. Chemical signals the protein sent from the VTA to the NAc played an essential role in making the mice vulnerable. Blocking the signals with experimental compounds turned vulnerable mice into resistant mice.

The scientists also conducted a genetic experiment which showed that, in resistant mice, many more genes in the VTA than in the NAc went into action in stressful situations, compared with vulnerable mice. Gene activity governs a host of biochemical events in the brain, and the results of this experiment suggest that genes in the VTA of resilient mice are working hard to offset mechanisms that promote vulnerability.

Another component of the study revealed that mice with a naturally occurring variation in part of the gene that produces the BDNF protein are resistant to stress. The variation results in lower production of BDNF, consistent with the finding that low BDNF activity promotes resilience.

The scientists also examined brain tissue of deceased people with a history of depression, and compared it with brain tissue of mice that showed vulnerability to stress. In both cases, the researchers found higher-than-average BDNF protein in the brain’s reward areas, offering a potential biological explanation of the link between stress and depression.

“The fact that we could increase these animals’ ability to adapt to stress by blocking BDNF and its signals means that it may be possible to

develop compounds that improve resilience. This is a great opportunity to explore potential ways of increasing stress-resistance in people faced with situations that might otherwise result in post-traumatic stress disorder, for example," said Nestler.

"But it doesn't happen in a vacuum. Blocking BDNF at certain stages in the process could perturb other systems in negative ways. The key is to identify safe ways of enhancing this protective resilience machinery," Nestler added.

Source: National Institute of Mental Health