

Scientists find genetic factor in stress response variability

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Inherited variations in the amount of an innate anxiety-reducing molecule help explain why some people can withstand stress better than others, according to a new study led by researchers at the National Institute on Alcohol Abuse and Alcoholism (NIAAA), part of the National Institutes of Health (NIH).

“Stress response is an important variable in vulnerability to alcohol dependence and other addictions, as well as other psychiatric disorders,” noted NIAAA Director Ting-Kai Li, M.D. “This finding could help us understand individuals’ initial vulnerability to these disorders.”

Scientists led by David Goldman, M. D., chief of the NIAAA Laboratory of Neurogenetics, identified gene variants that affect the expression of a signaling molecule called neuropeptide Y (NPY). Found in brain and many other tissues, NPY regulates diverse functions, including appetite, weight, and emotional responses.

“NPY is induced by stress and its release reduces anxiety,” said Dr. Goldman. “Previous studies have shown that genetic factors play an important role in mood and anxiety disorders. In this study, we sought to determine if genetic variants of NPY might contribute to the maladaptive stress responses that often underlie these disorders.” A report of the findings appears online today in *Nature*.

Analyses of human tissue samples led by researchers at NIAAA identified several NPY gene variants. Collaborations with NIH-

supported scientists at the University of Michigan, University of Pittsburgh, University of Helsinki, University of Miami, University of Maryland, the University of California at San Diego, and Yale University, showed that these variants result in a range of different effects including altered levels of NPY in brain and other tissues, and differences in emotion and emotion-induced responses of the brain.

The researchers evaluated the NPY gene variants' effects on brain responses to stress and emotion. Using functional brain imaging, they found that individuals with the variant that yielded the lowest level of NPY reacted with heightened emotionality to images of threatening facial expressions. "Metabolic activity in brain regions involved in emotional processing increased when these individuals were presented with the threatening images," explained Dr. Goldman.

In another brain imaging experiment, people with the low level NPY variant were found to have a diminished ability to tolerate moderate levels of sustained muscular pain. Previous studies had shown that NPY's behavioral effects are mediated through interactions with opioid compounds produced by the body to help suppress pain, stress, and anxiety. "As shown by brain imaging of opioid function, these individuals released less opioid neurotransmitter in response to muscle discomfort than did individuals with higher levels of NPY," said Dr. Goldman. "Their emotional response to pain was also higher, showing the close tie between emotionality and resilience to pain and other negative stimuli."

In a preliminary finding, the low level NPY gene variant was found to be more common than other variants among a small sample of individuals with anxiety disorders. The researchers also found that low level NPY expression was linked to high levels of trait anxiety. "Trait anxiety is an indication of an individual's level of emotionality or worry under ordinary circumstances," explained Dr. Goldman.

The researchers conclude that these converging findings are consistent with NPY's role as an anxiety-reducing peptide and help explain inter-individual variation in resiliency to stress. "This inherited functional variation could also open up new avenues of research for other human characteristics, such as appetite and metabolism, which are also modulated by NPY," said Dr. Goldman.

Source: National Institute on Alcohol Abuse and Alcoholism

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