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Novel mechanism regulating stress identified

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Neuroscience researchers from Tufts have demonstrated, for the first time, that the physiological response to stress depends on neurosteroids acting on specific receptors in the brain, and they have been able to block that response in mice. This breakthrough suggests that these critical receptors may be drug therapy targets for control of the stress-response pathway. This finding may pave the way for new approaches to manage a wide range of neurological disorders involving stress.

The stress-control pathway, more technically known as the Hypothalamus-Pituitary-Adrenal (HPA) axis, determines the levels of cortisol and other stress hormones in the human body. In addition to being implicated in the types of emotional and psychological stress that can lead to major depression, disorders of the stress-control pathway are also associated with obesity, premenstrual syndrome, postpartum depression, Cushing's syndrome (hypercortisolism) and diseases including epilepsy and osteoporosis.

"We have identified a novel mechanism regulating the body's response to stress by determining that neurosteroids are required to mount the physiological response to stress. Moreover, we were able to completely block the physiological response to stress as well as prevent stress-induced anxiety," said author Jamie Maguire, PhD, assistant professor in the department of neuroscience at Tufts University School of Medicine and a member of the Neuroscience and Pharmacology & Experimental Therapeutics program faculties at the Sackler School of Graduate Biomedical Sciences at Tufts.

Using the brain tissues of adult mice, the research team identified mechanisms controlling the activity of Corticotrophin Releasing Hormone (CRH) neurons involved in the control of the stress pathway. By monitoring the activity of CRH neurons following stress and measuring levels of corticosterone in the blood, they found that the production of stress hormones required the action of neurosteroids on specific receptors on CRH neurons.

Apart from the finding that stress causes a neurosteroid-induced increase in blood corticosterone levels, the researchers also found that blocking the synthesis of neurosteroids is sufficient to block the stress-induced elevations in corticosterone and prevent stress-induced, anxiety-like behavior in mice. Previous research had identified the presence of specialized CRH-nerve-cell receptors in the HPA axis, but the findings had been controversial because of limited studies showing any connection between these receptors and the regulation of the CRH nerve cells.

"We have found a definite role of neurosteroids on the receptors regulating CRH nerve cells and the stress response. The data suggest that these receptors may be novel targets for control of the stress-control pathway. Our next work will focus on modulating these receptors to treat disorders associated with stress, including epilepsy and depression-like behaviors," said Maguire.

The first author on the study is Jhimly Sarkar, PhD, formerly a postdoctoral associate in the neuroscience department at TUSM. Additional authors are Seth Wakefield, BS, a neuroscience graduate student at the Sackler School; Georgina MacKenzie, PhD, a postdoctoral associate in neuroscience at TUSM; and Stephen Moss, PhD, professor of neuroscience at TUSM and a member of the neuroscience program faculty at the Sackler School.

More information: Sarkar J, Wakefield S, MacKenzie G, Moss SJ, Maguire J. *The Journal of Neuroscience*. "Neurosteroidogenesis is required for the physiological response to stress: role of neurosteroid-sensitive GABAA receptors." Published December 14, 2011, doi:10.1523/JNEUROSCI.2560-11.2011

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