Preventing Disorders Caused by Early-Life Stress

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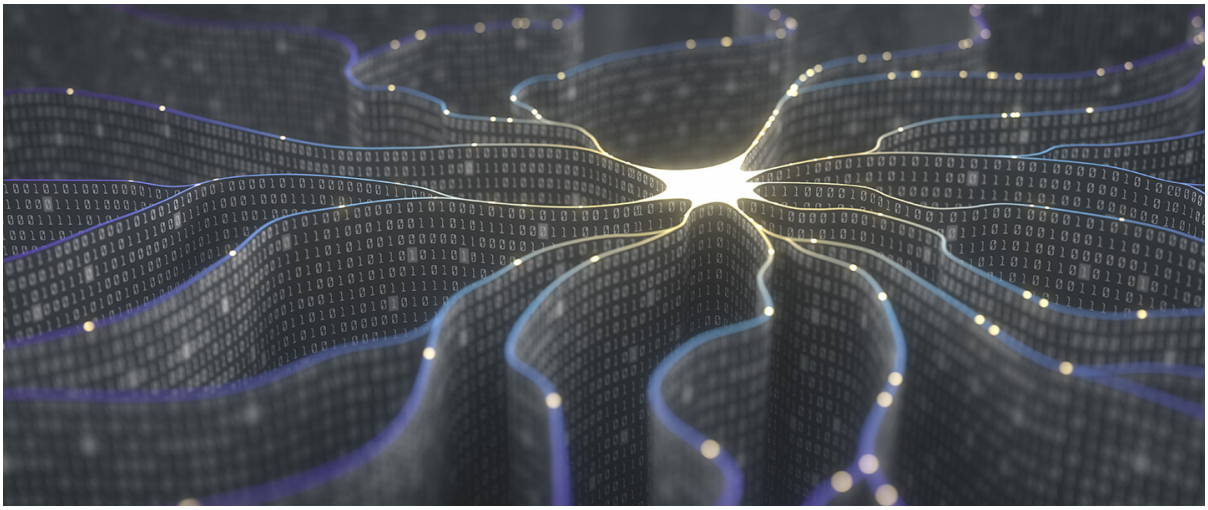

New Clues for Medications to Prevent Disorders Caused by Early-Life Stress

For several decades researchers have known that acute stress experienced early in life can harm the brain and can lead immediately or in later years to a variety of disorders, from depression and anxiety to panic disorder and PTSD.

These observations have launched many research projects, aimed at identifying the underlying brain areas harmed by early-life stress and seeking to untangle the

intertwined and overlapping neural circuits that are in various ways modified, leading to emotional and behavioral problems.

Now, a team led by Fereshteh S. Nugent, Ph.D., a 2013 BBRF Young Investigator at the Uniformed Services University of the Health Sciences in Maryland, has published in *Science Signaling* the results of their study of one brain area impacted by early-life stress, and the role of a protein called CRF in the pathology that it can cause. In so doing, the team has revealed new targets for future drugs designed to lessen the impact of early-life stress.

The researchers, who included Foundation Scientific Council member and 2004 BBRF Distinguished Investigator Irwin Lucki, Ph.D., focused on the lateral habenula (LHb), a small "nucleus" of nerve cells in the brain that plays a large role whenever we make value-based decisions or seek to evade the impact of stress. Increased activity in the LHb is known to inhibit reward circuits activated by the neurotransmitter dopamine. This inhibition has been implicated in addiction, depression, schizophrenia and other behavior disorders.

In part through their study of rats that had been subjected to a severe early-life stress – deprivation of maternal care – the researchers were able to dissect some of the relevant circuits in the LHb, paying particular attention to the way they were affected by CRF, or corticotropin-releasing factor. A stress hormone, CRF has various roles in the body. In this research, its role as a mediator of the stress response in the brain was in focus, specifically its impact on neurons in the LHb.

The team confirmed that the introduction of CRF increases the intrinsic excitability of neurons in the LHb and at the same time reduces the ability of a neurotransmitter called GABA to inhibit these same neurons. After maternal deprivation, neurons in the LHb in young rats exhibit the same tendencies – they are more excitable and less sensitive to inhibition by GABA.

By determining how stress can alter the biology of receptors for CRF on nerve cells in the LHb, the team was able to suggest various ways in which pathologies caused by stress might potentially be attenuated or even prevented by future drugs. The team suggests that such drugs might be designed to block one of the two CRF receptor types, or tiny pores called ion channels that help regulate whether a nerve cell fires or not; or, they might disrupt signals between nerve cells that would prevent CRF from increasing the excitability of LHb neurons.

Meantime, the team will continue its study of the LHb and how stress causes it to malfunction, work that will continue to inform the potential of developing new treatments.

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