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| **Generalized fear after acute stress is caused by a change in neuronal cotransmitter identity** |
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| Presenter: Wei-Jie Chen | Date/Time: 2024/04/10, 15:20 -16:10 |
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**Background:**

Overgeneralization of fear in harmless situations is a core feature of anxiety disorders resulting from acute stress, yet the mechanisms by which fear becomes generalized are poorly understood. The behavioral correlates of generalized fear are regulated by the activity of neurotransmitters within neural circuits that involve the ventrolateral periaqueductal gray (vlPAG) and the dorsal raphe nucleus (DRN). The vlPAG and DRN overlap in the lateral wings subnucleus of the dorsal raphe nucleus (lwDR). Activity in the 5-HTlwDR serotonergic neurons has been linked to panic-like fear responses. The ability of 5-HTlwDR neurons to corelease GABA, glutamate, and serotonin complicates the study of the behavior of this population of neurons in neural circuits.

**Objective:**

Previous studies have shown that the fear and anxiety network is related to the ventrolateral periaqueductal gray (vlPAG) and the lateral parabrachial nucleus dorsalis (lpDR), with 5-HT-lpDR neurons implicated in regulating panic-like fear responses. These neurons are known to release multiple neurotransmitters, including gamma-aminobutyric acid (GABA), glutamate, and serotonin. Therefore, the authors aimed to investigate the neurotransmitter mechanisms through which 5-HTlwDR neurons regulate generalized fear.

**Results:**

Through the induction of fear response using foot shock and placing it in the original environment (conditioned fear) and similar environments (generalized fear), it was found that only intense foot shock stimulation caused generalized fear. Glutamate decarboxylase 67 (GAD67) and vesicular glutamate transporter 3 (VGLUT3) expression changes occurred after day 7, including an increase in the number of 5-HTlwDR GAD67 neurons and a decrease in the number of 5-HTlwDR VGLUT3 neurons. These changes did not occur in conditioned fear. Using shRNA knockdown and stimulating generalized fear further confirmed that GAD67 plays a significant role. 5-HTlwDR neurons project to various brain regions. After generalized fear occurs,) The vesicular GABA transporter (VGAT) or VGLUT3 in the central amygdala (CeA) and lateral hypothalamus (LH) is significantly increased. This stress stimulation causes a VGLUT3-to-GAD67 switch, which is mediated through the hypothalamic-pituitary-adrenal (HPA) axis downstream response. Previous studies have shown that selective serotonin reuptake inhibitors (SSRIs) can reduce conditioned fear induced by stress. However, in generalized fear, it was found that early administration of SSRI drugs is necessary. Delayed treatment only improved conditioned fear and could not eliminate the effects of generalized fear responses.

**Conclusion:**

This study demonstrates that the release of corticosterone and the activation of glucocorticoid receptors mediate the VGLUT3-to-GAD67 switch, and prompt antidepressant treatment can block this cotransmitter switch and generalized fear.