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Synaptic plasticity and context-dependent behavioral responses expand the repertoire of stress reactivity (retrospective on DOI 10.1002/bies.201300178)

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Adaptation requires effective learning and behavioral modifications based on stressful experiences. This process necessitates mechanisms whereby stress can influence behavior, and processes through which the stress response can be modified. Recent studies have begun to elucidate the mechanisms whereby the stress response can be rapidly modified for an optimal response to stress in a context-dependent manner. A series of studies from the laboratory of Dr. Jaideep Bains has uncovered bidirectional plasticity at GABAergic synapses on parvocellular neuroendocrine cells (PNCs) in the paraventricular nucleus (PVN) of the hypothalamus, which govern the body's physiological response to stress. The activity of PNCs and, thus, the HPA axis, is tightly regulated by GABAergic inhibition. Under non-stress conditions, GABA exerts inhibitory control over PNCs. However, following stress, the GABAergic constraint on corticotropin-releasing hormone (CRH) neurons is compromised due to a collapse of the chloride gradient. This collapse of the gradient results from Cl^- accumulation due to the dephosphorylation and downregulation of the K^+/Cl^- co-transporter, KCC2 [1]. Thus, rapid alterations in the nature of GABAergic signaling facilitate the physiological response to stress. In addition, plasticity at GABAergic synapses also impacts the capacity for GABAergic control of PNCs. For example, previous stress experience unmasks the capacity for long-term potentiation (LTP) at GABAergic synapses on PNCs [2] whereas glucocorticoids have the capability to induce long-term depression (LTD) [3]. These opposing mechanisms provide temporal dynamics in the plasticity of PNCs where the stress response can be initially enhanced and then subsequently diminished [4]. LTP at GABAergic synapses on PNCs favors chloride accumulation intracellularly and promotes depolarizing and/or excitatory actions of GABA immediately following stress. In contrast, LTD at GABAergic synapses will aid in reducing chloride accumulation intracellularly and may help restore the inhibitory actions of GABA after a stressor. Plasticity at GABAergic synapses on CRH neurons is likely to impact both the synaptic and neuroendocrine functions of CRH neurons and may contribute to stress adaptation.

The traditional view holds that CRH neurons in the PVN govern the physiological response to stress through their classical endocrine functions, releasing CRH into the bloodstream and initiating the cascade leading to glucocorticoid release from the adrenal cortex. Recent developments suggest that activation of CRH neurons in the PVN may induce more rapid effects on stress-related behaviors involving local synaptic circuitry rather than signaling

through the hypophyseal portal system. In addition to the neuroendocrine-mediated responses, CRH neurons also send afferents into the brain which play a role in mediating stress-related behaviors independent of corticosterone [5]. Recently, a novel synaptic CRH-specific circuit arising from the PVN and projecting to the lateral hypothalamus has been identified [5]. CRH neurons in the PVN send direct glutamatergic projections to a sub-population of neurons in the lateral hypothalamus with a distinct electrophysiological profile [5], thereby identifying a novel circuit which plays a role in the presentation of stress-related behaviors.

The environment also modulates the nature of the behaviors elicited following stress. When placed back into their homecage following a stressor, mice engage in increased grooming behaviors. In the stress environment, on the other hand, there is initial freezing behavior followed by an increase in walking/exploring and less grooming compared to the homecage group. These data demonstrate that the environment can modify the behavioral repertoire following stress. The more familiar the environment, the more likely mice are to increase grooming, perhaps as a means to cope with the previous stressor. In contrast, when placed in a stressful environment, mice respond with behavioral responses which might indicate that the animals are continuing to assess the threat. Activation of CRH neurons in the PVN which project to the lateral hypothalamus can override the contextual cues that impact the behavioral response to stress [5]. Thus, there is an intersection between environmental cues and activity of CRH neurons in the PVN controlling the presentation of specific behaviors following stress. It remains to be determined whether the environment alters the plasticity at GABAergic synapses on PNCs which modulate stress reactivity. These studies are beginning to unravel the mechanisms mediating the spectrum of behavioral responses to stress, shedding light on the mechanisms of stress adaptation.

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