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RESEARCH HIGHLIGHT

"Corting" stress: post-stress corticosterone administration prevents delayed-onset biobehavioral consequences

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We live in stressful times. It is estimated that about 50% of adults experience a traumatic event at least once in their lifetime [1]. Severe or prolonged stress can cause long-term physiological alteration in the brain, and in some cases results in the development of anxiety disorders and post-traumatic stress disorder (PTSD). When faced with a stressful situation, activation of the hypothalamic–pituitary–adrenal (HPA) axis results in release of adrenal glucocorticoids (GC), cortisol in humans, and corticosterone (CORT) in rodents, which primarily acts through mineralocorticoid and glucocorticoid receptors (MR and GR) in the mammalian brain. Both stress and exogenous application of CORT result in hyperactivity in the basolateral amygdala (BLA), a brain area critical for regulating emotional behavior [2]. It does so by altering excitation–inhibition balance to favor heightened excitability and triggers dendritic hypertrophy in BLA neurons [2]. Stress-induced plasticity in the BLA has been shown to positively correlate with enhancement of anxiety across multiple studies, and to severity of symptoms in stress-related disorders [2]. This has led to the apparent conclusion that CORT orchestrates the detrimental effects of stress, with BLA hyperactivity being one of the key effectors. However, there also exists evidence of CORT conferring protection against adverse consequences of stress. For instance, exogenous application of cortisol in ICU patients lowers the incidence of PTSD symptoms [3]. Opposing effects of CORT have also been observed in slice recordings of BLA neurons where an initial surge in CORT results in MR-dependent increase in glutamate release, but a subsequent presentation of CORT surprisingly reduces glutamate release through mechanisms involving GRs [4]. These observations support the need for continued investigation into the potentially opposing effects of CORT on the physiological and behavioral sequelae of stress exposure.

Work from Chattarji and colleagues has previously shown that a single exposure to 2 h of immobilization stress leads to a significant increase in spine density in principal neurons of the BLA that is evident 10 days, but not 1 day, after stress exposure [5]. A delayed-onset increase in anxiety-like behavior is also observed at the 10-day time point [5]. Furthermore, inspired by clinical reports of potential protective effects of GCs against gradual development of stress-related disorders, these authors also found that exogenous CORT administration prior to stress exposure prevents the aforementioned delayed onset of stress-induced increase in anxiety-like behavior and dendritic spinogenesis in the BLA [6]. These data highlight the complexity and potentially bidirectional effects of CORT on stress-induced long-term biobehavioral adaptations, and suggest that a deeper insight into the temporal dynamics of this interaction could have significant translational implications.

In this issue of *Neuropsychopharmacology*, Chakraborty et al. [7] capitalize on the fact that the structural and behavioral consequences of immobilization stress in rats start to emerge at a delayed time point and not immediately after stress exposure. They use this "symptom-free" window to explore whether GC administration could be effective in preventing long-term negative consequences even if delivered after stress exposure. The authors show that administering CORT in the drinking water of rats for a duration of 12 h, starting 24 h after stress exposure, prevented stress-induced delayed enhancement of anxiety-like behavior, measured as the amount of time spent in, and the number of entries made into, the open arm of an elevated plus maze (Fig. 1). Post-stress CORT also prevented stress-induced reductions in sociability measured using the juvenile social-interaction test. These effects were accompanied by a concomitant prevention of stress-induced delayed spinogenesis in BLA principal neurons (Fig. 1). Since exogenous CORT has been shown to elevate the levels of endogenous cannabinoids in the amygdala [8], and pharmacological augmentation of endocannabinoid levels during acute stress mitigates the onset of glutamatergic hyperactivity and spinogenesis in the amygdala [9], the authors suggest the intriguing possibility that CORT-induced endocannabinoid activation could underlie the protective effects of CORT observed here. This proposal is further strengthened by previous observations of corticosterone metaplasticity being dependent on GR-mediated activation of endocannabinoid signaling [4]. Future studies will be required to test these hypotheses.

To begin to understand the mechanisms by which post-stress exogenous CORT administration could affect long-term stress-induced behavioral and anatomical changes, the authors examined CORT levels at distinct time points. The authors report stressed rats that received exogenous post-stress CORT showed lower levels of plasma CORT 48 h post stress (at hour 60, H60), relative to vehicle treatment (Fig. 1). In addition, they show that CORT administration for 12 h results in stress-like levels in control rats (H48), which returns to baseline 12 h later (H60). In future studies, it will be important to examine systemic CORT concentrations in stressed rats receiving exogenous post-stress CORT, and to determine critical time windows required to show the beneficial effects of this intervention. As endogenous CORT concentrations are high 48 h after stress exposure (H60), they presumably were also high at hour 36, when exogenous CORT was initially administered in the drinking water. It would be of interest to

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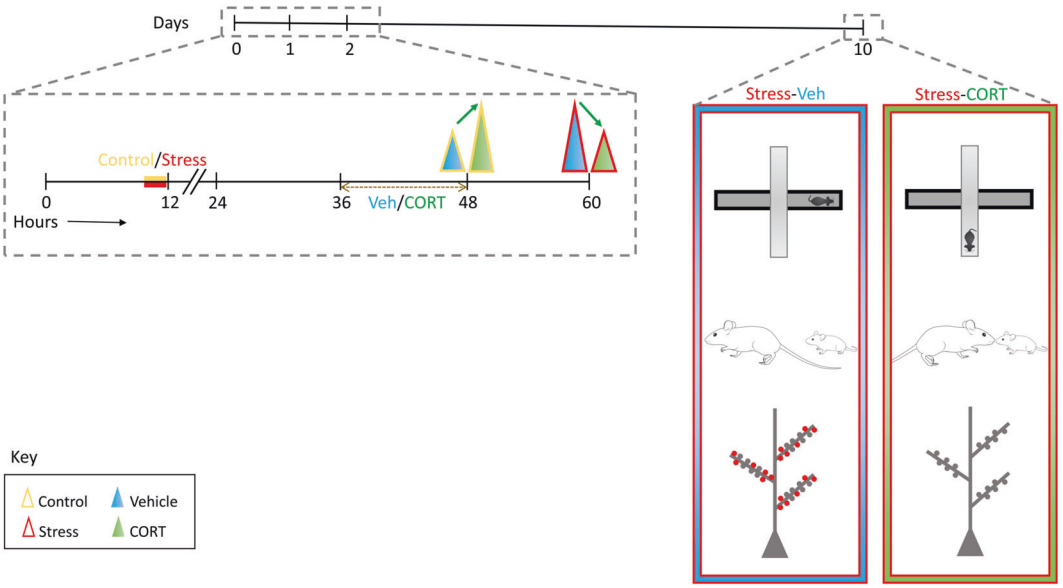

Fig. 1 Schematic depicting the experimental timeline and key findings from Chakraborty et al. Two hours of immobilization stress increases anxiety-like behavior, reduces social interaction, and triggers formation of new spines in BLA principal neurons 10 days later. Administration of CORT via drinking water 24 h after stress (H36–48) reduces stress-induced increase in systemic CORT concentrations measured 24 h later (H60), and prevents stress-induced behavioral consequences and BLA spinogenesis. In nonstressed mice, the CORT administration paradigm increases CORT to levels comparable to those observed after stress, relative to vehicle-treated nonstressed mice (H48). Triangles depict systemic CORT concentrations.

examine if and how the two sources of CORT (endogenous vs. exogenous) interact. For example, does exogenous CORT work additively or synergistically with endogenous CORT release to modulate negative feedback mechanisms that could then contribute to the reduced CORT levels observed at hour 60 in stressed rats?

An interesting observation in this study is that CORT on its own did not have stress-like effects as measured by changes in anxiety-like behavior or dendritic hypertrophy [7]. These data suggest that CORT alone, not unexpectedly, is not sufficient to recapitulate the complex effects of stress on anxiety-like behaviors and amygdala hypertrophy. Indeed, these data highlight the complex interactions between stress hormones and other stress-responsive neurotransmitter systems, such as glutamate and norepinephrine, that are likely required for the full expression of stress-related biobehavioral adaptations. Moving forward, a more comprehensive understanding of how the magnitude and temporal dynamics of CORT levels interact with the internal state of an organism, and how CORT interacts with other stress-responsive neuromodulatory systems, could provide insight into the utility of CORT-based interventions (such as GCs) as potential treatments for stress- and trauma-related psychiatric disorders.

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AUTHOR CONTRIBUTIONS

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ADDITIONAL INFORMATION

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