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Review article

Glucocorticoids and resilience☆

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ABSTRACT

All organisms endure frequent challenges to homeostasis, or stressors, that require adaptation. Depending on the individual, the context, and the magnitude of stress, this active adaptation can lead to behavioral susceptibility or resilience. The latter is an under-appreciated consequence of stress, as the damaging effects of chronic stress and chronically elevated glucocorticoids have received much more attention. We suggest here that neural pathways promoting resilience are initiated at the time of stress, and that they involve glucocorticoid signaling. By focusing on the neurobiology of resilience induction and the identification of vulnerable individuals, we may be able to intervene in the future at the time of stress to promote positive adaptation.

Stress is the foundation of evolution. All organisms undergo stressors, defined as internal or external challenges to homeostasis that require adaptation (Karatsoreos et al., 2013). Organisms that adapt positively to stress will survive; thus, evolution has selected for resilience promoting traits. The classic idea of allostasis, or stability through change, argues that an organism can handle a certain amount of stress or allostatic load, adapting well to it in order to return to equilibrium (McEwen, 1998). Thus, in allostasis, individuals who recover successfully are resilient, generally not exhibiting negative physiological or behavioral effects after stress. However, beyond a certain level, the homeostatic compensation to accumulated stress breaks down, and this allostatic overload results in negative health effects and increased vulnerability to subsequent stressors (McEwen et al., 2015).

As implied in the concept of allostasis, the maintenance of biological stability in the face of change is an active process associated with distinct changes in gene expression, neuroanatomy, and neurogenesis involving many of the same brain regions that mediate stress susceptibility (Anacker et al., 2018, 2016; Bagot et al., 2017; Gray et al., 2014). Moreover, individuals are not only resilient *in spite of* stress; rather, the inevitable stressors of life can promote positive adaptation, termed "good" stress (McEwen et al., 2015).

As the attention to resilience has recently increased, most studies have focused on what a resilient organism versus a susceptible one looks like based on specific behavioral criteria at a distal time point to a particular stress paradigm. This line of investigation has yielded fruitful insights into individual differences in neurobiological adaptation, including how genetic predisposition and early developmental events can bias an organism toward greater vulnerability or resilience (Aydin et al., 2015; Clinton et al., 2013; Meaney, 2001; Rana et al., 2016).

However, by only studying downstream resilient and vulnerable phenotypes, we miss information about resilience-promoting mechanisms. For example, gene expression changes in the brain of stress-recovered animals have very little overlap with the changes seen immediately following stress (Gray et al., 2014). Therefore, the mechanisms of resilience are distinct and not necessarily discoverable by studying a resilient organism in recovery. Here we argue for a renewed focus on the acute neurobiological adaptations to stress. We suggest that acute stress activates resilience-promoting pathways in part via glucocorticoids. Studying the mechanisms by which these resilience-promoting pathways are initiated in the brain in response to acute stress will yield critical insights into the neurobiology of adaptation that will have strong translational potential.

1. Glucocorticoids in short- and long-term adaptation to stress

Two concepts in the field, while important, have overshadowed the notion that glucocorticoids may promote positive neurobiological adaptation to stress. One is the idea that elevated glucocorticoids during acute stress serve mostly to promote physiologic mechanisms important for survival, such as increased vascular tone, alteration of metabolism, and a balanced enhancement and suppression of inflammation (Dhabhar, 2018; Hamrahian et al., 2017). While glucocorticoids do support these processes, very high levels of glucocorticoid are not clearly required for an organism to adequately withstand

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Table 1
Studies showing a role for glucocorticoids during acute stress in behavioral resilience.

Study	Organism	Challenge	Measurement/intervention	Follow-up	Findings
Delahanty et al., 2000	Human	Motor vehicle accident	Post-trauma urinary cortisol (15 h)	1 month	Lower urinary cortisol predicted higher PTSD symptoms
Schelling et al., 2001	Human	Septic shock	Hydrocortisone during illness (observational)	31 months (mean)	Hydrocortisone was associated with lower PTSD incidence
Schelling et al., 2004	Human	Cardiac surgery	Perioperative hydrocortisone (randomized)	6 months	Hydrocortisone decreased PTSD symptoms
Weis et al., 2006	Human	Cardiac surgery	Hydrocortisone after surgery	6 months	Hydrocortisone decreased PTSD symptoms and increased HRQoL
Zohar et al., 2011	Human	Traumatic event	Hydrocortisone or placebo injection after trauma	Up to 3 months	Hydrocortisone decreased all symptoms
Bienvenu et al., 2013	Human	ARDS	ICU corticosteroid treatment days	2 years	More steroid days predicted fewer PTSD symptoms
Spencer-Segal et al., 2017	Human	ARDS	ICU corticosteroid treatment days	6 months	More steroid days predicted lower anxiety
Zohar et al., 2011	Rat	Predator scent	Corticosterone injection 1 h after exposure	7 days	Corticosterone decreased anxiety and startle, and prevented dentate dendritic retraction
Cohen et al., 2006	Rat	Predator scent	Corticosterone response to predator scent/Pre-exposure corticosterone injection	7 days	Lower corticosterone predicted greater anxiety and startle, prevented with corticosterone
Cohen et al., 2008	Rat	Predator scent	Corticosterone injection 1 h after exposure	30 days	High dose corticosterone decreased anxiety, startle, and freezing
Rao et al., 2012	Rat	Acute restraint	ADX/corticosterone treatment pre-restraint	10 days	ADX exacerbated and corticosterone prevented anxiety and BLA dendritic spine increase

Abbreviations: PTSD, Post-traumatic stress disorder; ARDS, Acute Respiratory Distress Syndrome; HRQoL, Health-related quality of life; BLA, basolateral amygdala; ASD, acute stress disorder.

significant physical stressors (Udelsman et al., 1986). The second concept underscores the damaging effects of sustained high levels of glucocorticoids. A key notion of allostasis and allostatic load is that chronic elevation of glucocorticoids, which occurs in chronic stress and other situations, results in structural and functional alterations in the hippocampus and other brain regions leading to significant affective, cognitive, and metabolic problems (McEwen, 2008; Starkman et al., 1992). However, as discussed below, acute and chronic glucocorticoids may activate distinct and often opposing neurobiological processes. The focus on the damaging effects of chronic glucocorticoids has unfortunately detracted attention from their short-term role in resilience.

Several human studies support the notion that glucocorticoids promote resilience via their actions in the brain during acute stress (Table 1). In humans, corticosteroid treatment during critical illness is associated with lower symptoms of PTSD and anxiety in survivors, suggesting a possible protective effect (Bienvenu et al., 2013; Schelling et al., 1999; Spencer-Segal et al., 2017). Indeed, in a few small trials hydrocortisone treatment improved mental health outcomes after sepsis or cardiac surgery (Schelling et al., 2001, 2004; Weis et al., 2006). The association between high cortisol and lower PTSD symptoms has also been seen after other traumatic experiences such as a motor vehicle accident (Delahanty et al., 2000). Finally, in one small trial, treatment with high doses of hydrocortisone after a traumatic experience attenuated PTSD development in patients exhibiting acute stress reactions (Zohar et al., 2011).

The putative protective effect of glucocorticoids in acute stress has also been investigated in rats (Table 1). Compared with other strains, Lewis rats showed a blunted corticosterone response to predator odor stress along with greater anxiety- and PTSD-like behaviors later on, which were attenuated by corticosterone treatment immediately following the stressor (Cohen et al., 2006). Similarly, treatment with high-dose corticosterone during or immediately following restraint or predator odor stress prevented the later emergence of anxiety- and PTSD-like behavior (Cohen et al., 2008; Rao et al., 2012; Zohar et al., 2011). Thus, in both humans and rats undergoing varied acute stressors, glucocorticoids seem to prevent the development of the anxiety- and PTSD-like behaviors. The conservation of this effect between species suggests evolutionary importance to this phenomenon and implies that rodent studies may help elucidate the mechanism.

2. Neural mechanisms of acute and chronic glucocorticoid action

Acute and chronic glucocorticoids may promote resilience or vulnerability through direct actions on brain regions important for emotional behavior. Glucocorticoid receptors (GR) are expressed in neurons throughout the brain, while mineralocorticoid receptors (MR) are found in limbic areas, especially the hippocampus, commonly implicated in stress neurobiology (Reul and De Kloet, 1985). Due to the higher affinity of MR relative to GR for the main adrenal glucocorticoids, corticosterone (in rodents) and cortisol (in humans) (Reul and De Kloet, 1985), GR is considered a likely candidate to mediate the acute effects of stress levels of hormone. Rapid nongenomic actions via membrane MR are likely important, as well (ter Heegde et al., 2015). Acting through MR and GR, glucocorticoids alter many processes including dendritic branching, spine formation, apoptosis, neurogenesis, and memory formation (ter Heegde et al., 2015; McEwen, 2008; Schoenfeld and Gould, 2012).

Acute and chronic glucocorticoids may have different and even opposite effects on neural processes. For example, chronic stress and glucocorticoids cause decreased dendritic branching and dendritic spine density in hippocampal and prefrontal cortical pyramidal cells (Anderson et al., 2016; Gourley et al., 2013; Woolley et al., 1990). In general, these changes are linked to negative behavioral adaptations such as impaired cognitive processing and anhedonia (Gourley et al., 2013; Liston et al., 2006). In contrast, during acute stress,

corticosterone seems to prevent detrimental changes in neural architecture. For example, endogenous and exogenous corticosterone prevent specific changes to dendritic branching in the rat hippocampal dentate gyrus and basolateral amygdala after acute stress (Rao et al., 2012; Zohar et al., 2011). In both of those cases, corticosterone at the time of stress prevented not only the changes to dendritic architecture but also the increase in anxiety-like behavior. This evidence suggests that glucocorticoids during acute stress promote behavioral resilience in part via the preservation of limbic dendritic architecture.

A better understanding of the different effects of acute and chronic glucocorticoids on neural processes will be an important step toward identifying the mechanisms by which acute glucocorticoids may promote resilience. In regard to dendritic spine density, acute and chronic corticosterone were reported to have different effects on spine turnover (Liston and Gan, 2011). In that study, acute corticosterone increased turnover of new spines, while chronic corticosterone increased elimination of both old and new spines without affecting rates of spine formation. It is possible that rapid nongenomic mechanisms dominate the acute effects while genomic actions are more prominent chronically. Additionally, MR and GR can have opposing cellular effects; for example, GR seems to increase cell death in several paradigms while MR has the opposite effect (ter Heegde et al., 2015). Therefore, changes in receptor expression level, the ratio of MR to GR, or receptor sensitivity could alter the effect of glucocorticoids. In some cases, acute and chronic glucocorticoids may have similar outcomes that are perceived as adaptive in the short term but detrimental in the long term. For example, glucocorticoids may prevent PTSD by interfering with the formation or consolidation of traumatic memories (Roozendaal, 2003), but in the long term this impairment in cognitive processing would be undesirable.

Importantly, the downstream effects of acute glucocorticoids depend on context. For example, in the absence of stress, acute corticosterone treatment can actually promote long-term anxiety and dendritic hypertrophy in the amygdala, the opposite of its effect when paired with acute stress (Mitra and Sapolsky, 2008). Moreover, more “positively” viewed stimuli that activate the hypothalamic-pituitary-adrenal (HPA) axis such as environmental enrichment and exercise can stimulate neurogenesis, while more aversive stressors have the opposite effect (Schoenfeld and Gould, 2012). Furthermore, dose is crucial, as the effects of glucocorticoids often follow a U-shaped curve. For example, in one study, lower doses of acute corticosterone actually exacerbated the anxiety-like and startle behavior seen after predator odor stress, while high doses prevented these responses (Cohen et al., 2008). Of course, glucocorticoids will interact with other systems such as adrenergic, endocannabinoid, and estrogen signaling (Lorsch et al., 2018). All these factors need to be accounted for when considering the mechanisms by which glucocorticoids may promote resilience after acute stress.

3. Harnessing biology to promote resilience

Despite decades of studying glucocorticoid signaling and stress biology, no glucocorticoid-directed treatments are currently available for stress-susceptible individuals. Reasons for this likely include the complexity of acute and chronic glucocorticoid actions in stressed individuals, and individual variation in glucocorticoid signaling and stress susceptibility. More effective development and implementation of endocrine treatments could result from a renewed focus on the role of glucocorticoids in promoting resilience to acute stress. Genetic polymorphisms and epigenetic modifications of HPA axis components have been associated with PTSD and mood disorders, and they could influence vulnerability in part by affecting glucocorticoid signaling during stress (Bogdan et al., 2012; Davydow et al., 2014; Griffiths and Hunter, 2014; van Zuiden et al., 2012; Vogel et al., 2014; Yehuda et al., 2014). The identification of glucocorticoid-based markers of vulnerability and implementation of a mechanistically appropriate intervention to enhance resilience would be a major success for precision mental health.

4. Conclusion

We suggest that when faced with a stressor, circulating endocrine and other signals initiate resilience-promoting pathways in the brain to protect against detrimental behavioral outcomes and to prepare for future challenges. Glucocorticoids in particular appear to be crucial components of resilience induction in the brain, subject to nuances of context, dose, and timing. In this way the acutely stressed brain is like a sore muscle, with glucocorticoids the physical activity which can, if calibrated correctly, trigger mechanisms that are beneficial to short-term healing (Søgaard and Sjøgaard, 2017). On the other hand, just as chronic overuse of any muscle or joint can be damaging, natural mechanisms of resilience may break down in the long term because they are unsustainable or have damaging side effects. Though intrinsic to the original allostasis model, the benefits of short-term stress and the stress response are often overshadowed by the attention paid to damaging effects of chronic stress and stress hormones. We therefore propose a renewed focus on short-term adaptation, or the initiation of resilience-promoting pathways by acute stress and glucocorticoids. In the future, we envision that individuals vulnerable to maladaptation to acute or chronic stress may be identified by their genetic, epigenetic, or phenotypic (e.g., neuroendocrine) signatures. Real-time interventions that promote natural mechanisms of resilience programming during stress could then be designed to promote positive adaptation.

Conflict of interest

The authors have no conflicts of interest to disclose.

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