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The influence of acute stress on the regulation of conditioned fear

Candace M. Raio [a], Elizabeth A. Phelps [a, b, c, *]

[a] Department of Psychology, New York University, 6 Washington Place, New York, NY 10003, USA
[b] Center for Neural Science, New York University, 4 Washington Place, New York, NY 10003, USA
[c] Nathan Kline Institute for Psychiatric Research, 140 Old Orangeburg Road, Orangeburg, NY 10962, USA

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ABSTRACT

Fear learning and regulation is a prominent model for describing the pathogenesis of anxiety disorders and stress-related psychopathology. Fear expression can be modulated using a number of regulatory strategies, including extinction, cognitive emotion regulation, avoidance strategies and reconsolidation. In this review, we examine research investigating the effects of acute stress and stress hormones on these regulatory techniques. We focus on what is known about the impact of stress on the ability to flexibly regulate fear responses that are acquired through Pavlovian fear conditioning. Our primary aim is to explore the impact of stress on fear regulation in humans. Given this, we focus on techniques where stress has been linked to alterations of fear regulation in humans (extinction and emotion regulation), and briefly discuss other techniques (avoidance and reconsolidation) where the impact of stress or stress hormones have been mainly explored in animal models. These investigations reveal that acute stress may impair the persistent inhibition of fear, presumably by altering prefrontal cortex function. Characterizing the effects of stress on fear regulation is critical for understanding the boundaries within which existing regulation strategies are viable in everyday life and can better inform treatment options for those who suffer from anxiety and stress-related psychopathology.

1. Introduction

Experiencing stress is an inevitable part of daily life that serves a critical role in shaping adaptive behavior. Brief exposure to stress can be a powerful motivating force in both the pursuit of rewards and avoidance of punishment, and can rapidly boost energy stores in times of homeostatic disruption to ensure safety and survival. However, stress exposure and the concomitant neurophysiological response it elicits can also exert detrimental effects on brain regions that facilitate the control and regulation of behavior. These effects are especially relevant for the regulation of fear expression, where top-down regulatory mechanisms are engaged to control emotional responses to threatening stimuli. This process—broadly referred to as 'emotion regulation'—allows an individual to tailor emotional responses and behavior to a dynamic environment (Gross and Thompson, 2007). The capacity to regulate fear responses to threatening cues once the value or significance of such cues change is critical to emotional resilience and health, while deficits in fear regulation capacity strongly predict vulnerability to an array of affective psychopathology, such as anxiety disorders and depression (Cisler et al., 2010; Johnstone et al., 2007).

Fear responses can be flexibly changed through a broad range of processes that include learning that an aversive stimulus no longer poses a threat, or adopting a strategy to deliberately change the nature of an emotional response. These techniques have been repeatedly shown to inhibit or alter fear expression in the service of generating more adaptive responses that are better aligned with the current state of the environment. Importantly, the adaptive benefits afforded by fear regulation are widely known to rely on intact functioning of the prefrontal cortex (PFC), which supports the inhibition and flexible control of fear (see Hartley and Phelps, 2010 for review). The PFC, however, is also a major target of stress hormones that a growing body of research suggests can markedly impair its function (see Arnsten, 2009 or Holmes and Wellman, 2009; for reviews). This suggests that the flexible control of fear responses to aversive stimuli may be compromised when accompanied or preceded by exposure to stress. Despite the significance of this possibility, stress has remained largely unexplored within the fear regulation literature.

In this review, we examine research investigating the effects of stress and stress hormones on regulatory techniques used to

* Corresponding author. Department of Psychology, New York University, 6 Washington Place, New York, New York 10003, USA.

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flexibly control fear responses in humans. Before doing so, it is important to recognize that the constructs of fear and stress are often conflated in the literature due to their behavioral, neural and neurochemical similarities. To clearly differentiate fear expression from that of a stress response in the context of this review, we refer to fear expression as discrete emotional or behavioral responses that occur when an organism detects a threat in its environment, or when it encounters a cue that has predicted danger in the past. In rodents, fear expression is typically measured through defensive behaviors such as freezing, whereas in humans fear is often assessed by recording transient sympathetic nervous system arousal responses (i.e., skin conductance, pupil dilation) in the presence of a threatening stimulus (Critchley et al., 2002, 2013). In contrast, a stress response is operationalized as a more pervasive response that unfolds over a longer timescale and recruits a range of neuromodulatory systems. Unlike transient fear arousal, stressors produce more intense and prolonged response to homeostatic disruptions, eliciting both autonomic and neuroendocrine systems that can exert a broad range of effects on brain function and behavior.

Fear expression can be modulated using a number of regulatory strategies, including extinction learning and retention, cognitive emotion regulation, avoidance strategies and reconsolidation. Extinction learning and retention is the most commonly explored form of fear inhibition and occurs by learning through experience that a stimulus is no longer associated with a threatening outcome. Cognitive emotion regulation refers to a broad range of regulatory strategies that can be used to deliberately alter the nature of an emotional response. Avoidance strategies entail performing certain behaviors in order to prevent the occurrence of an aversive outcome. Finally, interfering with the reconsolidation of fear memories can lead to reductions in fear expression by persistently modifying aversive associations. The neural circuitry underlying each of these forms of fear regulation overlaps with the neural systems that orchestrate both the response to and recovery from stress exposure, rendering these techniques especially sensitive to the effects of stress. Despite the pervasive use of these strategies in research and real-world settings, relatively little is known regarding their efficacy when accompanied or preceded by exposure to stress. Understanding how stress affects these regulatory processes has broad implications both for adaptive daily functioning and for how stress-induced regulatory impairments may lead to or exacerbate affective psychopathology.

Below we discuss what is known about the impact of stress on the ability to flexibly regulate fear responses that are acquired using standard Pavlovian fear conditioning, a fundamental form of associative learning that imbues biologically insignificant cues with aversive value. Given that our primary aim is to explore the impact of stress on fear regulation in humans, we primarily discuss techniques where stress has been linked to alterations of fear regulation in humans (extinction and emotion regulation), although we also briefly mention other techniques (avoidance and reconsolidation) where the impact of stress or stress hormones have been mainly explored in animal models.

We begin by providing a brief overview of the neurobiological mechanisms of acute responses to stress. We then review the behavioral and neural mechanisms underlying Pavlovian fear acquisition and extinction. Our focus in this review is placed primarily on the learning and regulation of cued fear associations, which rely on the amygdala and surrounding brain regions. In the interest of space, we do not cover contextual fear learning and regulation processes, which are known to instead rely on the hippocampus. However, we do mention specific findings from other fear learning procedures when relevant. Since stress may differentially impact different phases of fear conditioning, we discuss the effects of stress and stress hormones on the phases (i.e., learning, consolidation, retrieval) of fear acquisition and extinction by surveying research that has induced stress or administered stress hormones before or concurrently with these phases. We then review the mechanisms of cognitive emotion regulation and the impact of stress in humans. Finally, we briefly review other fear regulation techniques (avoidance and reconsolidation) where the impact of stress and stress hormones have mainly been explored in animal models.

2. The neurobiology of an acute stress response

Stress is induced when real or perceived threats are detected in the environment (Joels et al., 2012). Stressors can emerge from a number of sources that can be generally categorized as physical or psychological in nature. Physical stressors comprise threats to survival such as predatory threats that signal imminent danger, or disruptions to homeostasis such as hunger, sickness or pain. Psychogenic stressors constitute emotional or social threats that may occur through negative social evaluation or severe emotional distress (Dickerson and Kemeny, 2004). Irrespective of their source, stressors are typically characterized by the perception of being novel, unpredictable and, importantly, outside of one's control (Lupien et al., 2007).

The detection of a stressor promotes a broad range of hormonal and neurotransmitter responses that can exert a powerful influence on brain function and behavior (McEwen, 2003). Acute stress exposure rapidly activates the autonomic nervous system through its sympathetic branch that triggers peripheral responses, such as increased respiration, heart rate and blood pressure and allocates metabolic resources to promote defensive behavior (Goldstein, 2003; Ulrich-Lai and Herman, 2009). This response also triggers catecholamine release by way of sympathetic nerves that activate noradrenergic terminals throughout the body, as well as the adrenal medulla that releases adrenaline directly into the bloodstream.

In contrast, the hypothalamic-pituitary-adrenal (HPA) axis elicits neuroendocrine effects that peak at a longer timescale after stress exposure. Activation of the HPA-axis triggers the systemic release of glucocorticoids (cortisol in humans) that can work in a synergistic manner with catecholamines to potentiate their short-lived effects (Ulrich-Lai and Herman, 2009). This is especially so for the effects of stress on modulating emotional learning and memory, as noradrenergic signaling is critical to the enhancing effects of glucocorticoids on memory consolidation and retrieval (Quirarte et al., 1997; Roozendaal et al., 2009). Stressors activate the HPA-axis through the release of corticotropin-releasing hormone (CRH) from the paraventricular nucleus (PVN) of the hypothalamus. When CRH reaches the anterior pituitary gland, it elicits adrenocorticotropic hormone (ACTH) release, which prompts glucocorticoid synthesis in the adrenal glands. Finally, glucocorticoids are released into the bloodstream where they travel and bind to receptors throughout the body and brain (McEwen et al., 1986; DeKloet, 2004; Sapolsky et al., 2000). Glucocorticoid release follows a slower time course than rapidly released catecholamines, peaking 10–20 min after the onset of stress exposure (Sapolsky et al., 2000). Glucocorticoids are often characterized as a recovery hormone that adapts an organism to the neurophysiological changes that occur during stress (Lupien et al., 2007). Collectively, these two systems interact and function in a complementary manner to mobilize energy and help an organism cope with stressful experiences.

Despite the inability of peripheral catecholamines to cross the blood–brain barrier, noradrenaline is projected throughout the brain by way of the locus coeruleus (LC). The LC serves as the brain's