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Invited Review

Stress-induced glucocorticoids as a neuroendocrine alarm signal of danger

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ABSTRACT

A considerable number of studies demonstrate that acute and chronic stressors prime CNS innate immune responses to subsequent pro-inflammatory challenges and that glucocorticoids mediate, in part, stress-induced sensitization of pro-inflammatory immune responses. Here, we explore the notion that GCs produce a persisting sensitization of CNS innate immune effectors (e.g. microglia) so that they will generate a potentiated pro-inflammatory response after the GC rise has dissipated, thereby enhancing the sickness response to infection or injury and maximizing the animal's ability to neutralize danger. The stress-induced GC response is conceptualized here as an neuroendocrine warning signal or alarmin to the innate immune system, which prepares or sensitizes the innate immune response to potential danger. Thus, a new understanding of the stress response and its function (priming CNS innate immune responses to infection or injury during a fight/flight emergency) would be suggested.

1. Introduction

> To answer some of these questions, I proposed the Danger model, which suggests that the immune system is more concerned with damage than with foreignness, and is called into action by alarm signals from injured tissues, rather than by the recognition of nonself (Matzinger, 2002).

Stress and glucocorticoids (GCs) are almost universally regarded to be anti-inflammatory, and this concept has been a bedrock principle (Boumpas et al., 1993; Munck et al., 1984; Webster Marketon and Glaser, 2008). This has been the view since Selye's pioneering work on the general adaptation syndrome, which included findings that stress (a) produces thymic and lymph node involution, effects blocked by adrenalectomy, and (b) decreases the inflammation produced by challenges such as egg white, with the decrease also blocked by adrenalectomy (Selye, 1946). Consistent with this principle, a considerable body of evidence indicates that (1) GCs ameliorate stress-induced defense mechanisms (e.g. pro-inflammatory cytokines) (Munck and Naray-Fejes-Toth, 1994) and (2) GCs directly suppress innate inflammatory immune mediators such as the pro-inflammatory transcription factor NF-κB (De Bosscher et al., 2003). However, it has never been clear how inhibition of peripheral and brain innate immune inflammatory responses by GCs would be adaptive during a fight/flight emergency as these are periods of increased risk for infection and injury. This paradox has provoked numerous theoretical attempts at a resolution that generally focus on the idea that the anti-inflammatory actions of stress and GCs function to restrain stress-activated defense mechanisms from overshooting, and thus protect the organism from deleterious bystander effects of an uncontrolled defense response (Munck et al., 1984). In addition, it has been argued that immune responses are energy intensive, and that perhaps this energy would be better spent in the service of fighting and fleeing. Notably, GCs also display a spectrum of permissive effects on host defense mechanisms (Ingle, 1952; Munck and Naray-Fejes-Toth, 1994; Sorrells and Sapolsky, 2007). However, it is unclear how the suppressive and permissive effects of GCs on host defense mechanisms functionally integrate to prepare an organism for the increased risk of infection and injury, which can occur during a fight/flight emergency.

Perhaps this paradox can be resolved by separately considering processes that might occur **while** fight/flight is actually occurring (GCs are elevated), and the period immediately **after** the emergency is past (GC elevations dissipate). Many years ago, Bolles and Fanselow proposed a behavioral model, called the perceptual-defensive-recuperative (PDR) model, to try and understand how organisms behave in response to a threat. First, threats perceived at a distance produce certain types of behavior (e.g., freezing), while threats that are physically present instead produce defensive behaviors (e.g., fleeing and fighting), followed by recuperative behaviors (e.g., licking wounds) once the threat is gone

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(Bolles and Fanselow, 1980). The PDR model differed from prior conceptions in suggesting that after a threat is past, the organism does not simply go back to baseline, but instead enters an active recuperative state. This model might also apply to stress-induced immune defenses. We propose that **after** the organism survives the fight/flight emergency, immune defenses in the periphery and brain should be vigilant or **primed** beyond basal levels. Of note, throughout this review, we will use the terms priming and sensitization interchangeably. These terms refer to the general notion that exposure of an organism to a prior stimulus amplifies the immune response to a subsequent stimulus. Innate immune responses in the periphery directly fight infection and promote repair (Turvey and Broide, 2010), while innate immune responses in the brain do so indirectly by initiating and orchestrating adaptive sickness behaviors (Dantzer et al., 2008); that is, recuperative behaviors. We propose that GCs produce this vigilant or primed innate immune state, which is a heightened state of immunological sensitivity to exogenous (pathogens) or endogenous (sterile injury) danger. Dhabhar and his colleagues have long suggested that GCs mobilize immune defenses and facilitate immune responding to damage and infection that can occur during fight/flight emergencies (Dhabhar et al., 2012). Here, we propose a similar view for innate immunity in the CNS.

If stress and GCs can actually prime inflammatory responses in the brain to subsequent inflammatory challenges (e.g., infection, injury), a new role for stress and GCs would be suggested. It is, therefore, time to re-examine the traditional wisdom concerning the anti-inflammatory role ascribed to stress and GCs, as has been done in several other reviews (Munck and Naray-Fejes-Toth, 1994; Pace et al., 2007). There is no question that GCs are predominately anti-inflammatory while they are elevated, as they are **during** a fight/flight emergency. After all, the transcription factor NF-κB, which is crucial for the induction of an array of inflammatory genes, is inhibited by high levels of GCs (De Bosscher et al., 2003). Moreover, the activated GC receptor can rapidly inhibit NF-kB signaling by directly interfering with NF-kB transcriptional activity (Hayashi et al., 2004). Indeed, the GC rise that occurs **during** a stressor inhibits or restrains inflammatory reactions to the stressor, rather than being responsible for them (Munck and Naray-Fejes-Toth, 1994). Thus, for example, adrenalectomy **increases** the elevations in brain IL-1β produced by a stressor (Nguyen et al., 1998).

However, here we are proposing the novel idea that during a fight/flight emergency, in addition to the well known anti-inflammatory effects just described, stress-induced GCs also function to alert peripheral and central innate immune cells to potential inflammatory threats such as infection or injury. The stress-induced GC response is conceptualized here as a neuroendocrine warning signal to the innate immune system, which prepares or primes the innate immune response to potential danger. Thus, after the emergency is over and GC levels have diminished, innate immune responses will be enhanced to any persisting injury or infection that would have occurred. As noted above, innate immune responses occur both in the periphery and the central nervous system (Dantzer et al., 2008; Turvey and Broide, 2010). Because much of the recent evidence concerns innate immune responses in the CNS, the present review will be restricted to central effects of stress and GCs, although a considerable literature also shows that stress can potentiate peripheral immune responses as well (Avitsur et al., 2009).

The argument will be that GCs produce a persisting sensitization of CNS innate immune effectors (e.g. microglia) so that they will generate a potentiated pro-inflammatory response after the GC rise has dissipated, thereby enhancing the sickness response to infection or injury and maximizing the animal's ability to neutralize danger. Thus, a new understanding of the stress response and its function (priming CNS innate immune responses to infection or injury during a fight/flight emergency) would be suggested.

CNS innate immunity and its primary immune effector cell, microglia, are key immunologic substrates for understanding how stress and GCs potentiate neuroinflammatory responses to pro-inflammatory challenges. Here, we will develop the thesis that stress-induced priming of neuroinflammatory processes is mediated by a 2 step process: (1) stress-induced GCs modulate the immunophenotype of microglia (priming phase) and (2) upon exposure to a later pro-inflammatory insult (e.g., bacterial infection, injury), endogenous danger signals are released within the CNS, which precipitate exaggerated neuroinflammatory responses and behavioral sequelae (e.g. sickness responses). As we consider microglia to be key, a brief orientation on microglia will be provided along with an elaboration on potential GC-modulated innate effector mechanisms.

2. CNS innate immunity and GCs

2.1. Microglia

Innate immunity is the first line of defense against infection. Within the CNS, microglia, as part of the myeloid lineage, constitute the predominant innate immune cell in the brain parenchyma and serve many functions including immunosurveillance for pathogens, cellular debris, apoptotic cells, and alterations in neuronal phenotype (Ransohoff and Cardona, 2010). It is important to note that other mononuclear phagocytes including meningeal, choroid plexus, and perivascular macrophages, which reside outside the brain parenchyma, are also of myeloid origin. These macrophage subtypes also serve a critical role in the brain's innate immune response (Schiltz and Sawchenko, 2003) and may contribute to the processes under discussion.

In the healthy CNS, microglia send out processes that sample the local environment at a rate of several times per second (Nimmerjahn et al., 2005) and have been termed surveillant (Ransohoff and Cardona, 2010). If a microorganism or danger signal (below) is encountered, the cell undergoes rapid morphological and functional changes that include the synthesis and secretion of inflammatory mediators including pro-inflammatory cytokines (e.g., interleukin-1beta (IL-1β)), chemokines, nitric oxide, prostaglandins, and reactive oxygen species (Colton, 2009). This response induces neuroinflammation. Microglia are a heterogeneous cell type and cannot be regarded as being in only inactive or activated states and it is common to consider whether these cells are activated classically or alternatively, each of which produces cells with different properties (Colton, 2009). However, recent views (Ransohoff and Perry, 2009) suggest that microglia can enter a spectrum of activation states, producing varying blends of pro- and anti-inflammatory products. Of particular relevance to the present discussion, these cells can enter a state called primed (Perry, 2004). Here, microglia undergo a morphological transformation from ramified to activated and show up-regulation of myeloid markers (e.g. major histocompatibility complex II; MHCII) (Perry, 2004). Though activated, these primed microglia do not constitutively produce inflammatory or anti-inflammatory products, but, if further stimulated, produce exaggerated levels of inflammatory products (Perry et al., 2007). Notably, GCs are sufficient to sensitize the neuroinflammatory and microglial response to pro-inflammatory stimuli (see Section 4). Moreover, GCs modulate innate immune signaling pathways (i.e., Toll-like receptors and inflammasome formation) that are pivotal to generating a pro-inflammatory immune response. Below we explore this topic of GC immunomodulation, which will serve as the basis for shaping our understanding of