Neuroscience 289 (2015) 429–442

NEUROSCIENCE FOREFRONT REVIEW

PERIPHERAL AND CENTRAL EFFECTS OF REPEATED SOCIAL DEFEAT STRESS: MONOCYTE TRAFFICKING, MICROGLIAL ACTIVATION, AND ANXIETY

B. F. READER, [a†‡] **B. L. JARRETT,** [a†] **D. B. MCKIM,** [a] **E. S. WOHLEB,** [e§] **J. P. GODBOUT** [a,c,d] **AND J. F. SHERIDAN** [a,b,d*]

[a] *Institute for Behavioral Medicine Research, The Ohio State University Wexner Medical Center, 460 Medical Center Drive, Columbus, OH 43210, USA*

[b] *Division of Biosciences, The Ohio State University College of Dentistry, 305 West 12th Avenue, Columbus, OH 43210, USA*

[c] *Department of Neuroscience, The Ohio State University Wexner Medical Center, 333 West 10th Avenue, Columbus, OH 43210, USA*

[d] *Center for Brain and Spinal Cord Repair, The Ohio State University Wexner Medical Center, 460 West 12th Avenue, Columbus, OH 43210, USA*

[e] *Department of Psychiatry, Yale University School of Medicine, 34 Park Street, New Haven, CT 06519, USA*

Abstract—The development and exacerbation of depression and anxiety are associated with exposure to repeated psychosocial stress. Stress is known to affect the bidirectional communication between the nervous and immune systems leading to elevated levels of stress mediators including glucocorticoids (GCs) and catecholamines and increased trafficking of proinflammatory immune cells. Animal models, like the repeated social defeat (RSD) paradigm, were developed to explore this connection between stress and affective disorders. RSD induces activation of the sympathetic nervous system (SNS) and hypothalamic–pituitary–adrenal (HPA) axis activation, increases bone marrow production and egress of primed, GC-insensitive monocytes, and stimulates the trafficking of these cells to tissues including the spleen, lung, and brain. Recently, the observation that these monocytes have the ability to traffic to the brain perivascular spaces and parenchyma have provided mechanisms by which these peripheral cells may contribute to the prolonged anxiety-like behavior associated with RSD. The data that have been amassed from the RSD paradigm and others recapitulate many of the behavioral and immunological phenotypes associated with human anxiety disorders and may serve to elucidate potential avenues of treatment for these disorders. Here, we will discuss novel and key data that will present an overview of the neuroendocrine, immunological and behavioral responses to social stressors.

Key words: repeated social defeat, macrophages, cell trafficking, inflammation, microglia, anxiety-like behavior.

Contents

*Correspondence to: J. F. Sheridan, 223 IBMR Building, 460 Medical Center Drive, Columbus, OH 43210, USA.
E-mail address: john.sheridan@osumc.edu (J. F. Sheridan).
† Co-first authors.
‡ Present address: Pulmonary, Allergy, Critical Care, and Sleep Medicine, The Ohio State University Wexner Medical Center, 473 W. 12th Avenue, Columbus, OH 43210, USA.
§ Present address.

Abbreviations: ACTH, adrenocorticotropic hormone; AMYG, amygdala; βAR, β adrenergic receptor; BNST, bed nucleus of the stria terminalis; CAM, cell adhesion molecule; CCL2, chemokine (C–C motif) ligand 2; CCR2, chemokine (C–C motif) receptor 2; CD11b, cluster of differentiation molecule 11b; CD19, cluster of differentiation 19; CD45, cluster of differentiation 45; CD86, cluster of differentiation 86; CNS, central nervous system; CX_3CL1, chemokine (C–X_3–C motif) ligand 1; CX_3CR1, chemokine (C–X_3–C motif) receptor 1; eIL-1R1kd, endothelial-specific knock down; GC, glucocorticoid; GM-CSF, granulocyte macrophage-colony-stimulating factor; HPA, hypothalamic–pituitary–adrenal; Iba1, ionized calcium-binding adapter molecule 1; ICAM-1, intracellular adhesion molecule-1; IL-1, interleukin 1; IL-1R1, interleukin-1 receptor type 1; IL-1α, interleukin-1 alpha; IL-1β, interleukin-1 beta; IL-6, interleukin-6; KO, knockout; LPS, lipopolysaccharide; LS, lateral septum; LsyM, lysozyme M; Ly6C, lymphocyte antigen 6C; GFP, green fluorescent protein; M-CSF, macrophage-colony-stimulating factor; NFκB, nuclear factor κ B; PFC, prefrontal cortex; PTSD, post-traumatic stress disorder; PVN, paraventricular nucleus; RSD, repeated social defeat; SNS, sympathetic nervous system; TLR2, Toll like receptor 2; TLR4, Toll like receptor 4; TLRs, Toll-like receptors; TNF-α, tumor necrosis factor alpha; VCAM-1, vascular cell adhesion molecule-1.

http://dx.doi.org/10.1016/j.neuroscience.2015.01.001
0306-4522/

INTRODUCTION

Although the biological mechanisms are not fully understood, the individual response to prolonged or severe stressors contributes to the development and exacerbation of depression and anxiety (Maes et al., 1998; Kalynchuk et al., 2004; Raison et al., 2006; Norman et al., 2010; Capuron and Miller, 2011; Gilman et al., 2013). One potential contributor to the etiology of stress-related mental health disorders involves the bidirectional communication between the immune system and the central nervous system (CNS) (Miller et al., 2009). In humans, the experience of chronic stress is associated with proinflammatory leukocytic phenotypes that are unresponsive to the anti-inflammatory actions of glucocorticoids (GCs) (Cohen et al., 2012) and a transcriptional profile that is consistent with the expansion and priming of myeloid-derived cells (Miller et al., 2008; Powell et al., 2013). The mechanistic association between inflammation and depression is particularly well-established (Raison et al., 2006; Dantzer et al., 2008; Miller et al., 2009; Norman et al., 2010; Capuron and Miller, 2011), while the case continues to build for the mechanistic association between inflammation and anxiety (Maes et al., 1998; Pitsavos et al., 2006; O'Donovan et al., 2010; Pace and Heim, 2012).

The murine repeated social defeat (RSD) paradigm recapitulates many key immunological and behavioral features associated with psychosocial stress in humans. In the bone marrow, RSD increases production, egress, and trafficking of proinflammatory immune cells that are insensitive to GCs (Avitsur et al., 2002; Engler et al., 2004, 2005; Kinsey et al., 2007; Hanke et al., 2012; Wohleb et al., 2012) (Fig. 1a) and traffic to the spleen (Engler et al., 2004), lung (Curry et al., 2010), and brain (Wohleb et al., 2013) (Fig. 1b). Furthermore, data from the RSD paradigm support a conserved inflammatory transcriptional response in leukocytes that is comparable to that of chronically stressed human populations (Powell et al., 2013).

RSD not only precipitates a proinflammatory environment within the periphery, but also activates brain regions associated with fear, anxiety, and threat appraisal that appear to contribute to behavioral changes. In many of these stress-responsive brain regions, neuronal activation co-occurs with neuroinflammatory events like microglial activation and recruitment of primed monocytes from the periphery (Wohleb et al., 2013). Studies suggest a connection between monocyte trafficking to the brain and RSD-induced anxiety-like behavior (Wohleb et al., 2013, 2014a). Moreover, RSD induces long-term stress-sensitization that is related to monocyte trafficking from the spleen to the brain (Wohleb et al., 2014a). In this review, we will introduce the concept of social defeat stress and provide an overview of studies that have used the RSD paradigm to elucidate the peripheral and central effects of social stress. Finally, we will discuss monocyte trafficking to the CNS and its relationship to anxiety-like behavior.

Stress and inflammation

Inflammation is an adaptive biological response to tissue injury and other immune challenges and is a key indicator of mental and physical disease. Inflammation is characterized, in part, by an increase in primed and activated immune cells and the subsequent release of proinflammatory immune products (Black and Garbutt, 2002). In particular, stress majorly impacts the expression of cytokine and chemokine genes that are instrumental in mobilizing immune cells to aid in the resolution of an insult and restoration of tissue function (Black and Garbutt, 2002). In response to stress, a milieu of hormones, peptides, and neurotransmitters are released by the nervous and endocrine systems that pleiotropically function to modulate the immune system. Specifically, the response to stress activates the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system (SNS) subsequently releasing GCs and catecholamines, respectively. Depending on the nature, intensity, and duration of the stressor and the type of immune challenge, stress effects on the immune system differ. On the one hand, chronic, unrelenting stress (e.g., prolonged restraint stress) is able to induce immunosuppression and cause a skew toward an anti-inflammatory immune cell phenotype that increases susceptibility to disease (Cohen et al., 2012). On the other hand, bouts of repeated defeat stress (e.g., RSD) can induce immunoenhancement and cause a skew toward a proinflammatory phenotype by inducing a state of GC-insensitivity to occur in innate immune cells; this insensitivity prevents the GC-induced suppression of inflammation through immune cell apoptosis and inhibition of nuclear factor κ B (NFκB) pathways (Chrousos et al., 1996; Barnes and Adcock, 2009). This enhanced inflammation can be described as a double-edged sword. In the short-term, inflammation beneficially eradicates the immune challenge, but, over time, inflammation can worsen tissue damage and negatively impact disease outcome. Associated with the experience of social stress, it is this prolonged inflammatory state that has the potential to contribute to the etiology of depression and anxiety (Meduri and Yates, 2004; Barnes and Adcock, 2009).

Social stressors

Numerous studies indicate that social status modulates the immunological and physiological responses to stress. Some of the first studies in this field examined subordinate non-human primates, who, in response to social reorganization (i.e., a shift in social hierarchy) had reduced body weights, higher levels of circulating GCs (i.e., cortisol), and increased susceptibility to upper respiratory infections (Cohen et al., 1997; Sapolsky,