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Review

Spinal cord injury, immunodepression, and antigenic challenge

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ABSTRACT

The inability to effectively control microbial infection is a leading cause of morbidity and mortality in individuals affected by spinal cord injury (SCI). Available evidence from clinical studies as well as animal models of SCI demonstrate that increased susceptibility to infection is derived from disruption of central nervous system (CNS) communication with the host immune system that ultimately leads to immunodepression. Understanding the molecular and cellular mechanisms governing muted cellular and humoral responses that occur post-injury resulting in impaired host defense following infection is critical for improving the overall quality of life of individuals with SCI. This review focuses on studies performed using preclinical animal models of SCI to evaluate how injury impacts T and B lymphocyte responses following either viral infection or antigenic challenge.

1. Introduction

Spinal cord injury (SCI) is a dramatic and devastating condition affecting approximately 1.3 million people within the United States [1,2]. Aside from the varying severity of motor skill impairment, SCI results in numerous metabolic and immune problems that can last the lifetime of the injured individual. With regards to the latter, SCI-induced immunodeficiency leads to increased susceptibility to infection resulting in elevated morbidity and mortality. For over 40 years, researchers have made efforts to characterize the molecular and cellular interactions between the nervous, endocrine and immune systems which facilitate immune regulation and physiological homeostasis. Early findings have elucidated the mechanisms controlling the important interplay between these systems related to cause and effect relationships of inflammation and physiological changes such as observed in fever. More recently, researchers have described suppression of immune responses in response to external factors that disrupt neuroendocrine-mediated regulation. The interactions between the neural and immune systems is a complex process involving bidirectional communication of neurotransmitters, hormones, and immune cells/lymphoid tissues which highlights the lack of autonomy between these two organ systems [3–7]. Understanding the multifactorial balance of immune regulation continues to be a growing interest especially in the field of neurotrauma research.

Many factors, including stroke, traumatic brain injury (TBI), and SCI are known to have detrimental effects to the immune system [8] and this is collectively referred to as CNS injury-induced immunodepression (CIDS) [9]. Following stroke, TBI or SCI, patients exhibit an increased rate of infection and mortality [9]. Complications from infection are the leading cause of re-hospitalization and death in the post-acute phase following SCI [10,11], and immune dysfunction can impede neurologic recovery in stroke patients [12,13]. Evidence supporting neuroendocrine involvement in immune dysfunction was shown in 2000 by Cruse and colleagues in clinical studies that correlated suppression of immune functions with increased cortisol levels in patients with SCI [5,14,15]. Therefore, understanding the mechanisms underlying immunodepression following SCI have been the focus of many clinicians and researchers for the purpose of improving therapeutic intervention and the quality of life for those with SCI. This brief review article will focus on SCI-induced deregulation of neuroimmune pathways and provide perspective on how the severity of immunodepression may be influenced by the level of SCI. Specifically, we will focus on how primary adaptive immune responses and immunological memory are impacted following SCI within the context of both viral infection and responses to defined chemical antigens.

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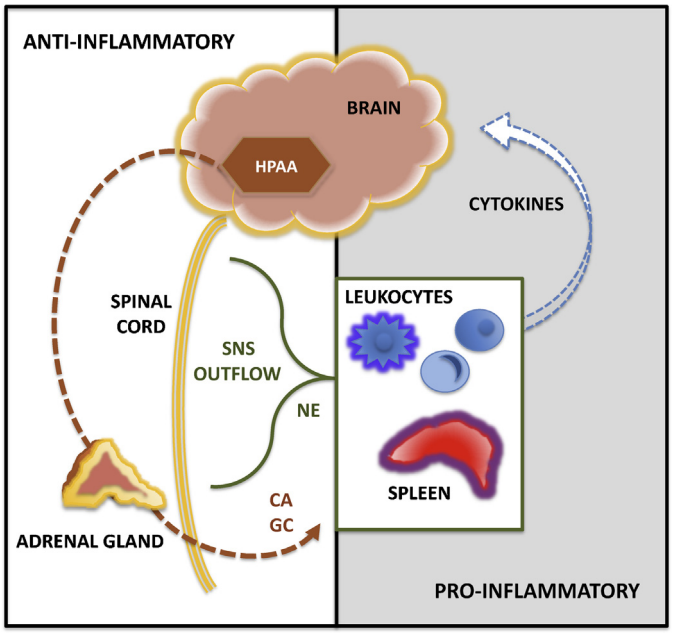

Fig. 1. Neuroimmune connection and modulation of immune responses. The CNS and immune system interact to balance inflammatory responses. Pro-inflammatory cytokines released during an immune response are processed by the CNS resulting in anti-inflammatory signals from the HPAA and SNS. Activation of the HPAA results in production of glucocorticoid hormones (GCs) and catecholamines (CAs), which have systemic effects on leukocytes and lymphoid tissues. Activation of the SNS results in production of norepinephrine (NE), which reach leukocytes via hardwire connection to lymphoid tissues. The counter anti-inflammatory response from the CNS and interactions between these systems helps to maintain homeostasis.

2. Neuroimmune connection and modulation of immune responses

The CNS provides a network of pathways to regulate inflammation, resolve infection and maintain homeostasis. The immune system can be modulated by the CNS via the hypothalomo-pituitary-adrenal axis (HPAA), the sympathetic nervous system (SNS) and the parasympathetic nervous system. In general, these components maintain homeostasis via anti-inflammatory mediators that counterbalance inflammation at both systemic and cellular levels (Fig. 1). Among the various effects on the immune system, the HPAA and autonomic regulation via glucocorticoid, catecholamine and cholinergic signals, respectively, target leukocytes and have been implicated in modulating circulating and lymphoid tissue cell numbers. In addition, numerous biological functions critical in host defense in response to microbial infection including migration, proliferation, phagocytosis, and cytokine secretion are controlled by these pathways [4,16–18]. Cells of the immune system express receptors for these transmitters, which reach their cellular targets via circulating blood or by proximal nerve terminal-cell interaction. While increasing evidence supports a vagus nerve based anti-inflammatory pathway [17], the majority of data indicate neuroimmune interaction is dominated by sympathetic modulation via norepinephrine (NE) [3]. Anatomical studies mapping neuroimmune pathways reveal the majority of primary and secondary lymphoid organ innervation is sympathetic [19,20]. Furthermore, leukocytes express adrenergic receptors and the influence of NE on immune cell functions and been studied in detail [3].

Proinflammatory cytokines such as IL-1β, TNF-α and IL-6 are produced by the immune system in response to stress, injury or infection, and these factors signal to the CNS resulting in immune modulation; activation of the HPAA leads to the release of the humoral immunosuppressive glucocorticoids [6], and increased NE turnover rate in the spleen correlates with suppression of immune cells [21]. Meltzer and colleagues show that the SNS is primarily responsible for the immunosuppressive effects of stress rather than HPAA, using combinations of experimental splenic nerve cuts, adrenalectomies and adrenual demedullations [22]. Interestingly, activation of the SNS can inhibit or enhance lymphocyte immune function, yet inhibits the function of innate immunity [19]. NE signaling contributes to CD4+ T cell development to Th1 subtype and balance of Th1/Th2 associated immune responses [23,24]. The duration and timing of catecholoamine exposure to lymphocytes relative to their maturation phase may influence the effector function, indicating additional complexity to neuroimmune regulation [19,24]. Furthermore, the negative-feedback paradigm of neuroimmune interaction may be over simplified and Nance and Metlzer argue CNS outputs are delayed relative to ongoing immune reactions, and thus may instead provide a greater influence to delimit the duration of an immune response [16]. Nonetheless, the CNS and immune system share a counter-balance relationship that is disrupted following CNS-injury. As a result, injury to the CNS presents a unique situation in which there is a defined period of elevated inflammation within the CNS exacerbating neuropathology, yet there is a long-lasting impairment with regards to controlling peripheral microbial infection that relies on inflammation in order to eliminate the invading pathogen. This scenario ultimately leads to immunodepression and emphasizes the importance of the SNS and HPAA pathways in contributing to regulating immune responses to infection [9]. Understanding the underpinnings involved in immune deregulation following SCI has been the focus of ongoing research by many investigators.

3. Disruption of neuroimmune regulation following SCI

SCI and the resulting physiological changes have been studied extensively in both experimental and clinical settings. The severity and location of injury to the spinal cord influences the outcome of paralysis, muscle atrophy, loss of sensory, bowel, bladder and sexual function and may influence the degree of immune suppression. Importantly, complications from infections are a leading cause of re-hospitalization and death in the post-acute phase of SCI [10,11]. The normally well-balanced neuroimmune interactions are disrupted following SCI, resulting in immune suppression and increase susceptibility to infection. Despite the immune suppressive effects of methylprednisolone acute SCI-therapy, immunodepression and increased sensitivity to infection can occur in the absence of treatment [9,25,26]. Therefore, SCI itself is a primary factor in dictating the severity of immune suppression.

SCI can interrupt neural pathways involved in neuroimmune balance, most notably, central autonomic pathways that descend via the spinal cord. Output signals by preganglionic sympathetic axons that innervate lymphoid organs and the adrenal gland are modulated post-SCI [27,28]. Although the peripheral nerves are intact following SCI, the output to these peripheral tissues would no longer be regulated by supraspinal control. The majority of meaningful SNS activity evolves from thoracic level T6 and above, and innervation to key lymphoid tissues such as the spleen and the adrenal medulla arise from the mid-thoracic and lumbar spinal cord [29,30]. Therefore, SCI at or above T6 level may damage SNS pathways resulting in greater loss of neuroimmune regulation compared to lower level injury which would conserve normal central connectivity. Other physiological processes normally influenced by the SNS, such as blood pressure regulation, also experience level-dependent changes following SCI. Reduced sympathetic activity, morphological changes in sympathetic preganaglionic neurons and peripheral alpha-adrenoceptor hyperresponsiveness are observed