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Review

Glucocorticoids and macrophage migration inhibitory factor (MIF) are neuroendocrine modulators of inflammation and neuropathic pain after spinal cord injury

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ABSTRACT

Traumatic spinal cord injury (SCI) activates the hypothalamic–pituitary–adrenal (HPA) axis, a potent neuroendocrine regulator of stress and inflammation. SCI also elicits a profound and sustained intraspinal and systemic inflammatory response. Together, stress hormones and inflammatory mediators will affect the growth and survival of neural and non-neural cells and ultimately neurologic recovery after SCI. Glucocorticoids (GCs) are endogenous anti-inflammatory steroids that are synthesized in response to stress or injury, in part to regulate inflammation. Exogenous synthetic GCs are often used for similar purposes in various diseases; however, their safety and efficacy in pre-clinical and clinical SCI is controversial. The relatively recent discovery that macrophage migration inhibitory factor (MIF) is produced throughout the body and can override the anti-inflammatory effects of GCs may provide unique insight to the importance of endogenous and exogenous GCs after SCI. Here, we review both GCs and MIF and discuss the potential relevance of their interactions after SCI, especially their role in regulating maladaptive mechanisms of plasticity and repair that may contribute to the onset and maintenance of neuropathic pain.

1. Introduction

Improvements in clinical care and rehabilitation have dramatically increased life expectancy for people living with spinal cord injury (SCI). However, the mechanisms that are responsible for causing various secondary complications, most notably chronic neuropathic pain (NP), remain poorly defined or incompletely understood. Inflammation is a pivotal component of tissue injury and is believed to contribute to the onset and maintenance of NP. In response to inflammation, the body orchestrates a complex but tightly integrated neuroendocrine response that involves activation of the hypothalamic–pituitary–adrenal (HPA) axis. Once activated, the HPA axis enhances the synthesis and release of glucocorticoids (GCs). GCs are potent steroid hormones with pleotropic effects in the body but are best known for their anti-inflammatory and metabolic (i.e., gluconeogenesis) functions; however, aberrant release or regulation of GCs can have pathological consequences. Here, we review what is known about GCs, inflammation and the novel interaction between GCs and macrophage migration inhibitory factor (MIF), a unique cytokine that is produced in parallel with GCs and can counteract their effects in vitro and in vivo. A role for GC/MIF interactions in post-SCI pathophysiology is likely and is discussed here in the context of maladaptive plasticity and NP.

2. Glucocorticoids and spinal cord injury

Glucocorticoids (GCs) are hormones produced by the adrenal cortex in response to psychological or physical stressors. GCs bind to mineralocorticoid and glucocorticoid receptors (GR), which are nuclear receptors found in all cells throughout the body. When unoccupied, GRs exist in the cytoplasm; when bound by GCs they translocate to the nucleus where they bind to GR responsive elements (GREs), which are short segments of DNA present in the promoters of target genes, and initiate gene transcription [1]. GRs also are present on plasma membranes, where they can influence cellular function without affecting gene transcription [2,3].

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A PubMed search using the terms "*glucocorticoid*" and "*spinal cord injury*" returned 859 articles, many devoted to an ongoing debate about the safety and efficacy of using the synthetic GC, methylprednisolone (MP), as a treatment for acute human SCI (reviewed in Ref. [4]). Much less is known about how the HPA axis and endogenous GC synthesis are affected by SCI or how these natural mechanisms of stress response affect post-injury sequelae.

Circulating levels of corticosterone (rodents) or cortisol (humans), i.e., endogenous GCs, do increase after SCI [5,6] and these hormones undoubtedly affect various GR-dependent cellular functions but the remarkable diversity and complexity of GC/GR signaling is not well-defined, especially in the context of CNS injury. It is estimated that 25% of the genome is responsive to GC/GRs [2] which helps explain why GC/GR signaling is essential for cellular metabolism, cell survival and neural development [7,8]. It is well known that GCs inhibit inflammation. Recent data indicate that this occurs by "tethering" and "transrepression" of transcription factors (e.g., AP-1, NFkB), rather than direct binding of GC/GR complexes to DNA [9]. The transrepression of transcription factor binding blocks expression of genes that encode inflammatory mediators [10]. GCs also can enhance innate immunity [9] and can exacerbate neuroinflammatory damage in the CNS [11,12]. GRs regulate other processes that may affect tissue damage and recovery after SCI. For example, in zebrafish, GR regulates neurogenesis [13] and in lymphocytes, GRs regulate miRNAs that control apoptosis [14].

Recent data indicate that GCs, via a GR-dependent mechanism, also regulate the formation and signaling of G-protein coupled receptors (GPCR), which are the largest class of cell surface receptors [15]. GPCRs control cellular responses to various ligands including biogenic amines (e.g., 5-HT, norepinephrine), neurotransmitters (e.g., metabotropic glutamate receptors), peptides, proteins and lipids. These diverse effects of GCs may differ by cell type, CNS region or time post injury [11,12].

3. Glucocorticoids and neuropathic pain after SCI

Neuropathic pain is experienced by 50–90% of people living with SCI [16–18]. Since individuals with SCI often experience enhanced psychological stress [19,20] and clinical data indicate that stress increases susceptibility to develop pain and exacerbates existing pain [21–26], stress and subsequent activation of the HPA axis with enhanced GC release are likely to be critical therapeutic targets for modifying the development and severity of NP after SCI.

Synthetics GCs (e.g., dexamethasone, methylprednisolone) are used to treat pain caused by inflammation or complex regional pain syndrome [27,28]. However, even though synthetic GCs can suppress select inflammatory cascades and associated sequelae (e.g., edema), any salutary effects on pain are indirect and transient. Moreover, recent data indicate that GCs, both endogenous cortisol/corticosterone and synthetics, may exacerbate the severity or duration of neuropathic pain. In both rats and mice, the neuropathic pain cause by peripheral nerve injury can be inhibited using the GR antagonist, RU486, or antisense mediated knockdown of GR [21,29]. Similarly, loss of naturally occurring GCs via adrenalectomy blunts the NP response caused by chronic nerve constriction injury; pain is restored following replacement of endogenous GCs with dexamethasone [21].

There are several mechanisms by which GCs can modulate NP. GRs directly or indirectly regulate the expression of many genes implicated in NP including brain derived neurotrophic factor (BDNF), N-methyl-D-aspartate (NMDA) receptors, calcitonin gene-related polypeptide alpha (CGRP), interleukin-6 (IL-6), protein kinase C-gamma (PKCγ), N–type calcium channels, the spinal glutamate transporter EAAC1, kalirin (a Rho-guanine nucleotide exchange factor) and cannabinoid-1 (Fig. 1) [30–32]. Most of these proteins or receptors have been implicated in the development and maintenance of NP and all are affected by GR antagonism or GR knockdown [21,29,33–36].

Using a mouse model of spared nerve injury, we recently showed that stress and associated spikes in circulating GCs exacerbate neuropathic pain (NP) caused by nerve injury [36]. Specifically, acute restraint stress (60 min) increases circulating GCs that, when bound to GRs, increase phosphorylated extracellular signal-regulated kinase (pERK) in spinal cord dorsal horn neurons. Because an increase in pERK is indicative of enhanced glutamatergic signaling, mice were treated prior to nerve injury and stress with memantine, an NMDA receptor antagonist. Memantine prevented the enhanced NP caused by stress. Together, these data indicate that stress-induced activation of the HPA axis with enhanced GC/GR signaling causes "central sensitization" and exacerbates NP caused by nerve injury.

Additional research is needed to clarify how GCs affect the onset, maintenance and severity of NP caused by traumatic SCI. Indeed, even though SCI, like peripheral nerve injury, increases the expression of GRs and circulating GCs [6,37,38], there are no empirical data directly linking GC/GR signaling to enhanced pain-like behaviors after SCI. Future experiments should determine whether GCs act on neurons or other cell types (e.g., glia, leukocytes) through genomic or non-genomic mechanisms (Fig. 1). Also, since neurons in the periphery (e.g., dorsal root ganglia), the spinal cord (e.g., dorsal horn neurons) and brain (e.g., thalamic neurons) are needed to sense and process pain, it will be important to know whether GCs exert similar effects in all neuron subtypes. This will refine efforts to target GR signaling to modulate pain. One way to understand these differences would be to profile gene expression in these distinct neuronal populations under different experimental conditions.

4. Macrophage migration inhibitory factor (MIF)

MIF is a 12.5 kDa protein with homologues in plants, nematodes and vertebrates. In mammals, MIF was the first cytokine to be identified and is produced by every cell type in the body, with relatively high concentrations (ng/ml) expressed by cells in liver, kidney, central nervous system (CNS) and immune system [39,40]. Given its evolutionary conservation and ubiquity, MIF is expected to be physiologically essential. However, genetic deletion of MIF produces no overt pathology or functional deficits in healthy adult mice suggesting that MIF may be more important in the context of disease or pathology [41,42]. This notion is supported by various studies showing that genetic or pharmacological deletion or inhibition of MIF is therapeutic, presumably because pathological levels of MIF exacerbate inflammation, metabolic dysfunction and oxidative stress. Indeed, MIF can act as an inflammatory cytokine, a hormone (as described below), and a redox-sensitive enzyme that influences cell growth and survival [43–45].

MIF is stored in intracellular pools so cells can rapidly release MIF without the need for gene transcription [46,47]. However, polymorphisms in the promoter region of the MIF gene can influence the susceptibility or severity of inflammatory diseases [46,47]. Specifically, a guanine-to-cytosine transition at position −173 is associated with activation of MIF transcription and juvenile arthritis [47], while the CATT-tetranucleotide repeat at position −794 is associated with reduced transcription and reduced risk of arthritis [46].

MIF elicits effects by receptor dependent and independent mechanisms (Fig. 1). MIF has three known receptors: the major histocompatibility complex class II antigen-associated invariant chain (CD74), and the chemokine C-X-C motif receptor 2 and 4 (CXCR2, CXCR4) [48,49]. MIF directly binds to CD74, but also