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Mechanistic insights into corticosteroids in multiple sclerosis: War horse or chameleon?

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ABSTRACT

Objectives: Relapse management is a crucial component of multiple sclerosis (MS) care. High-dose corticosteroids (CSs) are used to dampen inflammation, which is thought to hasten the recovery of MS relapse. A diversity of mechanisms drive the heterogeneous clinical response to exogenous CSs in patients with MS. Preclinical research is beginning to provide important insights into how CSs work, both in terms of intended and unintended effects. In this article we discuss cellular, systemic, and clinical characteristics that might contribute to intended and unintended CS effects when utilizing supraphysiological doses in clinical practice. The goal of this article is to consider recent insights about CS mechanisms of action in the context of MS.
Methods: We reviewed relevant preclinical and clinical studies on the desirable and undesirable effects of high-dose corticosteroids used in MS care.
Results: Preclinical studies reviewed suggest that corticosteroids may act in unpredictable ways in the context of autoimmune conditions. The precise timing, dosage, duration, cellular exposure, and background CS milieu likely contribute to their clinical heterogeneity.
Conclusion: It is difficult to predict when patients will respond favorably to CSs, both in terms of therapeutic response and tolerability profile. There are specific cellular, systemic, and clinical characteristics that might merit further consideration when utilizing CSs in clinical practice, and these should be explored in a translational setting.

1. Introduction

High-dose steroids have been the "war horse" therapy in the treatment of autoimmune diseases and the standard of care for decades [1]. Indeed, much benefit has been realized for patient care since the introduction of steroids into clinical practice in the 1940s [2]. However, preclinical findings over the last several years suggest a re-evaluation of the therapeutic benefits and adverse effects of steroid therapy, in particular the use of high-dose steroids for the treatment of relapses in multiple sclerosis (MS), may be warranted. In some cases standard practice of care persists, despite advances in preclinical research that might suggest alternative approaches to optimal patient care. The relationship between MS and various comorbid conditions, including psychiatric illnesses with likely endocrine-immune pathophysiological underpinnings, further encourage a re-examination of the use of high-dose steroids for MS. Such a critical look at steroids may not only be beneficial for understanding when steroids may be most effective for MS and other autoimmune disorders, but also when other therapies should be considered. The goal of the current article is to offer a "fresh" perspective for clinical neurologists and clinician scientists on the convergence of recent preclinical science and mainstream medicine related to the use of corticosteroids (CSs) in MS care. Our hope is that this opinion piece will foster further preclinical and clinical research on the use of high-dose steroids for treatment of MS. Synthetic CS analogs have been developed to harness the anti-inflammatory properties of endogenous cortisol, and we first

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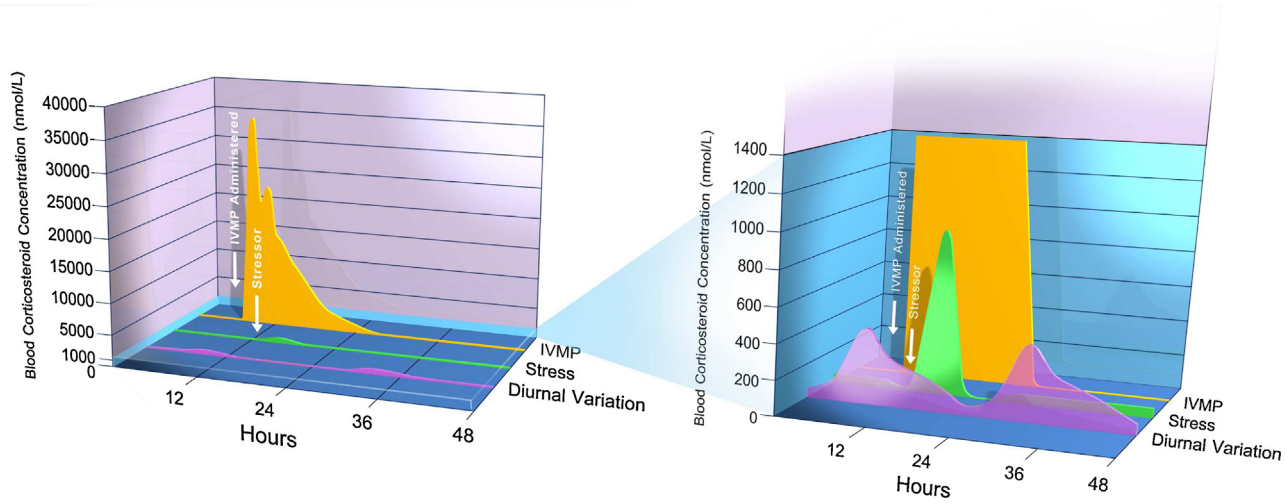

Fig. 1. Circulating corticosteroid (CS) concentrations over the normal diurnal cycle, in response to acute psychological stress, and after a single 1 g intravenous methylprednisolone (IVMP) treatment (depicted over a 48-h period). Measurements from original sources converted to nmol/L for comparison. The panel on the right is a magnification of the lower section of the graph on the left. Diurnal variations of CS concentrations were assessed in healthy volunteers by immunoassay of serum cortisol levels at various timepoints to create a daily physiological profile of cortisol (purple) [17]. A maximal CS response to stress was measured in serum samples taken from individuals during acute military exercises and measured by radioimmunoassay (green) [18]. Stress-induced circulating CS concentrations do not always reach this level, and can be substantially lower than the values represented here depending on the stressor. More moderate stressors such as a laboratory psychosocial stress challenge elicit an acute stress response of approximately 350 nmol/L [19]. Supraphysiological concentrations of CSs are seen following treatment with a single dose of 1 g IVMP. Plasma MP was measured by reverse phase high-performance liquid chromatography (yellow) [20]. Of note, others have found even higher circulating concentrations of MP [21], and MP is known to exert greater bioactivity compared to endogenous CSs [22]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

consider how they are believed to work in MS. We then discuss relevant preclinical and clinical reports that reveal important information regarding CS treatment in MS, including potential limitations of treating patients with CSs. Finally, possible lessons from the overlap of MS and major depression will be explored.

2. Relapse treatment

Acute relapses in MS are defined by newly-emerging neurologic deficits that last for longer than 24 h [3]. Characteristics of these relapses (also referred to as "attacks" or exacerbations) include optic neuritis, limb weakness, numbness, or brainstem episodes, including imbalance, vertigo, diplopia, and loss of facial strength or sensation. Relapses typically develop over a day or days, persist at their symptomatic peak for days to weeks, and self-resolve over a period of weeks to months. Approximately 50% of relapses leave behind residual loss of neurologic function [4], contributing to the step-wise accrual of disability in MS. Various chronic symptoms, including fatigue, depression, and cognitive difficulties, are common in MS, particularly in the progressive stage of the illness. These symptoms are less common in the context of acute relapses, but greater awareness has led to their recognition as acute manifestations of MS in some instances.

On a pathophysiological level, acute relapses are considered to be a clinical manifestation of new inflammatory activity in the central nervous system (CNS). Multiple sclerosis lesions generally occur around small venous vessels, and are thought to be driven by autoreactive T-cells that cross the blood brain barrier (BBB) and orchestrate an attack on myelin [5]. In many patients, the disease progresses to a neurodegenerative phase and the immune response to the acute injury progresses to a more chronic inflammatory state that includes activated immune responses from local immune cells, T-cells, B-cells, macrophages, and microglia [5–8]. As our understanding of the specific immunopathology that contributes to MS lesions has expanded, so has our appreciation for active inflammatory lesions being associated with axonal transection and loss [9]. Incomplete recovery from early relapses is common [10] and has been associated with a worse prognosis [11]. This suggests that neuronal vulnerability after a relapse has important clinical implications.

The clinical management of MS includes interventions that are intended to: (1) prevent relapses and the accumulation of disability; (2) hasten resolution of acute relapses (i.e., "abortive" therapy); and (3) manage MS-related symptoms. Preclinical and clinical research of MS therapies has focused primarily on the first of these through the development of disease-modifying therapies (DMTs). While DMTs are the standard of care in MS for chronic treatment to prevent relapses, none do so completely [12], making the prompt recognition and treatment of relapse a primary challenge in MS therapy. Abortive treatment of acute relapses is used to bring about a faster resolution of relapse symptoms than would be expected to occur naturally.

Corticosteroids, which include the stress hormone cortisol, have robust anti-inflammatory properties and have been a mainstay of treatment in MS ever since the discovery in the 1940s that their therapeutic effect in the context of autoimmune conditions was beneficial. High-dose CSs are currently the mainstay treatment for acute MS relapses [13–15]. The current standard treatment for acute relapses in MS is a supraphysiological dose of intravenous (IV) methylprednisolone (MP) 1 g/day for 3–5 days, which was derived from the Optic Neuritis Treatment Trial [16]. This dose of MP is much greater than the amount of endogenous CS produced during normal circadian cycles or in response to stress (Fig. 1) [17–22]. A few key studies have examined the tolerability and efficacy of high-dose steroids versus placebo in MS relapse (Table 1; Durelli [23], Milligan [24], Beck [16], Barnes [25], Sellebjerg [26]; for more detailed reviews of relapse treatments and high-dose steroids, see Berkovich 2012 [27], Filipini [28], Miller [29], Burton [30]). Less widely employed treatments for MS relapses include plasmapheresis, IVIg, and Acthar Gel. These treatments are well beyond the scope of the current discussion, and are reviewed elsewhere [12,31].

It is widely known that CS treatments can lead to both desirable and undesirable effects depending on the type of steroid and the situation in which it is used. Although CSs are frequently effective for shortening relapses in MS, they also often exhibit