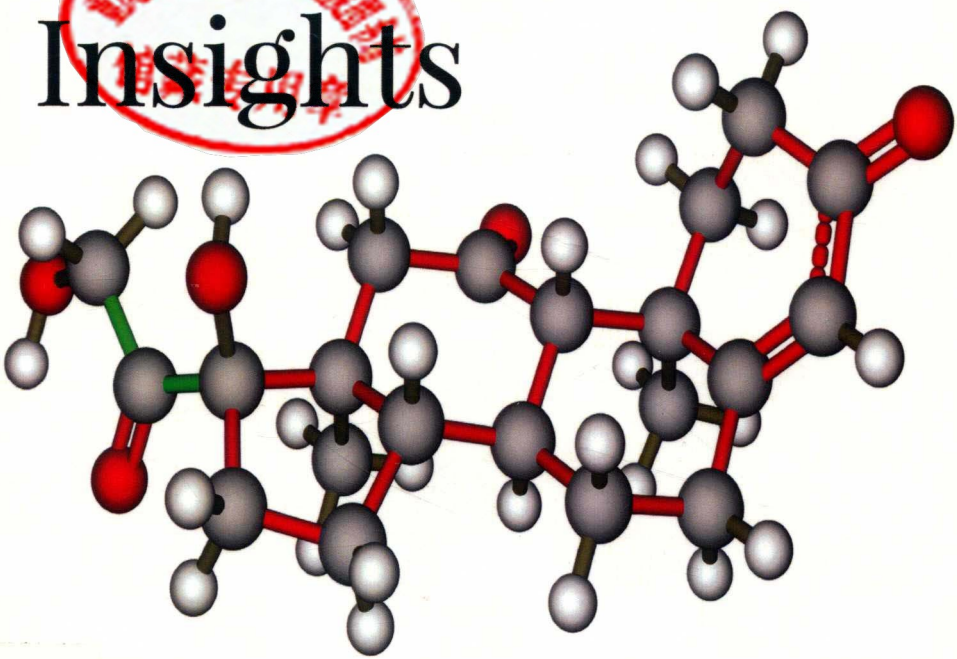
Corticosterone

Roles, Research and Insights



Jonathan Simmons
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CORTICOSTERONE:

ROLES, RESEARCH AND INSIGHTS

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PREFACE

This book discusses the roles and provides new research and insights on the glucocorticoid known as corticosterone. Chapter One presents and discusses the mechanisms underlying the harmful effects of glucocorticoids in the pathophysiology of major depressive disorder. Chapter Two focuses on alterations of the brain serotonergic system induced by dysfunctions of the adrenal gland. Chapter Three highlights wild animal studies on glucocorticoids and discusses how they inform biomedical research. Chapter Four summarizes present knowledge about corticosterone regulation in rodents with special emphasis to stressor differences.

Chapter 1 - Major depressive disorder (MDD) is a chronic, recurrent, and potentially life-threatening psychiatric disorder. It is the leading cause of disability worldwide and the third contributor to the worldwide burden of disease. According to projections from the World Health Organization, by 2030, it is expected to be the main contributor of burden of disease. Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis is one of the most consistent biological alterations found in MDD. The HPA axis regulates the production of glucocorticoids by the adrenal glands. Cortisol (humans) and corticosterone (rodents) are glucocorticoids mainly released under confronting stressful situations. However, when oversecreted, glucocorticoids are deleterious to the brain by inducing dendritic atrophy and apoptotic neuronal cell death, key structural changes observed in preclinical models of MDD. Also, it has been hypothesized that a loss of hippocampal volume may explain the long lasting mood disturbance that occurs in MDD patients. In this chapter, the mechanisms underlying the harmful effects of glucocorticoids in the pathophysiology of MDD are presented and discussed. In particular, the authors provide cellular,

molecular and behavioral evidence regarding the deleterious effects of glucocorticoids in clinical and preclinical models of MDD.

Chapter 2 - Major depression is often associated with elevated and flat glucocorticoid hormone levels, probably due to a diminished negative feed-back regulation of corticotropin releasing hormone (CRH). Moreover, the pathologic increase in glucocorticoid hormone secretion (Cushing's disease) is associated with major depression, which improves after the successful treatment of the endocrine disorder. The excess of glucocorticoid hormone secretion alters the activity of the brain's serotonergic (5-HT) system. Thus, clinical studies reported that depressed patients present a decreased binding capacity of 5-HT1A receptors, whereas various experimental studies reported a diminished function of 5-HT1A autoreceptors upon chronic administration of glucocorticoids. However, other experimental studies reported an inverse effect of chronic glucocorticoids, i.e., the increase in sensitivity of 5-HT1A autoreceptors.

Nicotine produces antidepressant effects in both humans and animal models of depression, through the release of endogenous antidepressants such as noradrenaline, dopamine and serotonin. The prevalence of smoking in depressed patients is significantly higher than in the normal population, and various investigators consider smoking to be a form of auto medication in depression. Experiments performed in the authors' laboratory indicated that nicotine, administrated in midbrain slices, increases the firing rate of 70-80% 5-HT dorsal raphe nucleus (DRN) neurons, as well as 5-HT release inside the DRN. Approximately 20-30% DRN 5-HT neurons responded to nicotine administration with inhibition of the firing rate. The stimulatory effect of nicotine results from its direct, postsynaptic effects, as well as from its indirect, presynaptic effects (glutamate and noradrenaline release). The inhibitory effects of nicotine were due to an increased intra-raphe serotonin release.

In order to determine if nicotine or analogs can serve as therapeutic tools for treating the depression induced by elevated glucocorticoid hormone levels, experiments were performed on Wistar rats that were adrenalectomized and implanted subcutaneously with a 70 mg corticosterone capsule each. This experimental model ensures high and stable levels of blood corticosterone levels. After two weeks of exposure to corticosterone, midbrain slices were obtained and the responses of 5-HT DRN neurons to nicotine were studied. In most 5-HT DRN neurons the responses to nicotine were inhibitory, due to an increased function of the 5-HT1A autoreceptors and/or an increased nicotine-induced 5-HT release. These results contradict previous ones obtained from non-adrenalectomized rats, and may be explained by a diminished transport of tryptophan across the blood-brain barrier in adrenalectomized rats.

Chapter 3 - Biomedical laboratory research has yielded much of what the authors know about the physiology of stress. However, this approach can have limitations. For example, laboratory studies can inflate the relative importance of hormones, as researchers often experimentally control many "confounding" variables. Research on wild animals often examines the relative importance of the actions of such variables and of glucocorticoids on the expression of physiological and behavioral traits. Wild animal models also can provide opportunities to explore glucocorticoid-trait relationships because of unusual reproductive or physiological features. Because many elements of the hypothalamic-pituitary-adrenal (HPA) axis are evolutionarily conserved across vertebrates, wild species can be ideal models for studying physiological relationships among pathways. Glucocorticoids are well-known to play a key role in energy regulation, especially during periods of both predictable and unpredictable exposures to stressors, and hormonal stress responses can alter animals in adaptive manners. Changes in sexual behavior, memory, and foraging are examples of key fitness traits enhanced by short-term glucocorticoid responses to stressors. Glucocorticoid elevation also can enhance immune function, including leukocyte migration and antibody production. Finally, exposure to stressors of the previous generations can alter the phenotype via epigenetics, and some such effects are linked to alterations in the HPA axis.

Chapter 4 - Corticosterone is the main glucocorticoid hormone in rodents with adrenal cortex origin. According to textbook knowledge its secretion is under the control of the hypothalamic-pituitary-adrenocortical axis. More specifically, adrenocorticotropin (ACTH), secreted from the corticotroph cells of the anterior pituitary is the primary secretagogue of corticosterone secretion. However, numerous studies indicated dissociation between ACTH and corticosterone secretion. Several other factors were shown to release corticosterone from the adrenal cortex both in *vitro* and in *vivo*. Among others, catecholamines from the adrenal medulla or from splanchnic nerve activation stimulate glucocorticoid secretion. Here the authors aim to summarise the present knowledge about the corticosterone regulation in rodents with special emphasis to stressor differences.

CONTENTS

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Chapter 1

ROLES OF GLUCOCORTICOIDS IN THE PATHOPHYSIOLOGY OF MAJOR DEPRESSION

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ABSTRACT

Major depressive disorder (MDD) is a chronic, recurrent, and potentially life-threatening psychiatric disorder. It is the leading cause of disability worldwide and the third contributor to the worldwide burden of disease. According to projections from the World Health Organization, by 2030, it is expected to be the main contributor of burden of disease. Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis is one of the most consistent biological alterations found in MDD. The HPA axis regulates the production of glucocorticoids by the adrenal glands. Cortisol (humans) and corticosterone (rodents) are glucocorticoids mainly released under confronting stressful situations. However, when oversecreted, glucocorticoids are deleterious to the brain by inducing dendritic atrophy and apoptotic neuronal cell death, key structural changes observed in preclinical models of MDD. Also, it has been hypothesized that a loss of hippocampal volume may explain the long lasting mood disturbance that occurs in MDD patients. In this chapter, the mechanisms underlying the

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harmful effects of glucocorticoids in the pathophysiology of MDD are presented and discussed. In particular, we provide cellular, molecular and behavioral evidence regarding the deleterious effects of glucocorticoids in clinical and preclinical models of MDD.

Keywords: glucocorticoids, HPA axis, major depression, stress

INTRODUCTION

Major depressive disorder (MDD) is a serious, debilitating and high prevalent medical condition. It is characterized by abnormalities on affect and mood, neurovegetative functions (such as appetite and sleep disturbances), cognition (such as difficulty in focusing/concentration, inappropriate guilt and feelings of worthlessness and suicidal ideation), and psychomotor activity (such as agitation or retardation). Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is one of the most robust neurobiological findings in MDD pathophysiology over the last 40 years. The HPA axis is the primary regulator of stress response and participates in the control of the entire body homeostasis. Glucocorticoids are the final effectors of the HPA axis, and the excess of glucocorticoids is deleterious to the brain by inducing abnormalities in limbic areas and depressive symptoms. In this context, this chapter presents information on the discovery of glucocorticoids, its uses in the clinical practice; the structure and function of the glucocorticoid receptors; physiological mechanisms involved in HPA activation; and finally the glucocorticoid-induced neurochemical abnormalities and their mood effects.

GLUCOCORTICOIDS: FROM THE DISCOVERY TO CLINICAL PRACTICE

The American physician Solis-Cohen [1] was the first scientist to study the effects of adrenal extracts. Solis-Cohen discovered in 1900 that the oral administration of adrenal substance pills produced positives effects on asthma [1]. Besides the fact that these effects had been produced by the steroids presented in the adrenal gland, it encouraged the development of adrenaline (epinephrine) and sympathomimetics as bronchodilators. Nowadays, it is well known that adrenaline is poorly absorbed through the gastrointestinal tract. Years later, in 1950, the American physician Hench along with his American

colleague Kendall and the Polish-Swiss chemist Reichstein were awarded the Nobel Prize for Physiology and Medicine "for their discoveries related to adrenal cortical hormones, their structure and biological effects" [2]. In the study published in 1950, Hench et al. [3] described the effects of cortisone acetate and pituitary adrenocorticotropic hormone (ACTH) on rheumatoid arthritis, rheumatic fever and certain other conditions. Subsequently, prednisone and prednisolone were developed in 1954 at the Schering Corporation (USA) having three to five times the potency of cortisone, and less mineralocorticoid effects [4]. Positive effects of cortisone acetate on status asthmaticus were also shown by the English Medical Research Council in 1956 [5]. Four years later, the Joint Committee published a study demonstrating that prednisolone are more effective than aspirin in the treatment of defined cases of rheumatoid arthritis [6]. Brown et al. [7] described in 1972 the positive effects of beclomethasone dipropionate aerosol in many cases of chronic perennial asthma with no evidence of systemic absorption or side effects. Nowadays, inhaled corticosteroids are the most effective therapy available for the control of asthma [8]. Since the first biological properties of glucocorticoids were reported in 1900, corticosteroids and corticosteroid derivatives have emerged as therapies in broad-spectrum conditions in clinical practice, as described following.

Intranasal steroid are indicated in both adults and children suffering with allergic rhinitis [9], steroid ear drops can be used in the treatment of acute otitis externa or eczematous otitis externa improving erythema, swelling and discharge [10]. Corticosteroids produce beneficial effects on gastrointestinal conditions such as active ulcerative colitis, distal colitis and left side colitis; Crohn's disease; and hepatitis B, C, autoimmune and alcoholic disorders [11-14]. Injections of corticosteroids are recommended for rotator cuff tendonitis, adhesive capsulitis, epicondylitis, carpal tunnel syndrome, trigger finger, thumb and osteoarthritis [15]. Corticosteroids are also indicated for the management of rheumatological conditions such as arthritis, gout, and synovitis [16]. Inhaled steroids are the first choice treatment for patients with asthma symptoms at all levels of severity [17]. The following respiratory disorders may also require corticosteroid therapy: allergic bronchopulmonary aspergillosis, alveolar hemorrhage syndromes, eosinophilic pneumonia, interstitial lung disease, post-radiation pneumonitis, pulmonary vasculitis, and sarcoidosis [18]. Combined inhaled corticosteroids with long-acting bronchodilators should be considered in severe chronic obstructive pulmonary disease (COPD) [19]. Topical corticosteroids are indicated for the treatment of atopic eczema, psoriasis, dermatomyosistis, and systemic lupus erythematosus [20-23]. In elderly patients and children, topical corticosteroids should only be used for short time periods

[24]. Steroid eye drops are used for the management of ophthalmic diseases such as acute red eyes, and conjunctivitis [25, 26]. In children, corticosteroids are recommended for the treatment of laryngotracheobronchitis, mild croup, asthma, and eczema [27, 28]. The use of corticosteroids in children requires particular attention and monitoring especially because they may produce side effects such as growth retardation and reduction of bone markers [29, 30].

THE GLUCOCORTICOID RECEPTOR: STRUCTURE AND FUNCTION

Glucocorticoids are key regulators of several biological processes, such as metabolic homeostasis, cell proliferation, inflammation, immune responses, development, and reproduction [24, 31]. The physiologic and pharmacologic functions of glucocorticoids (cortisol in humans and corticosterone in rodents) are mediated by the glucocorticoid receptor (GR). The GR is a three-domain structure comprising: 1) an N-terminal transactivation domain (NTD), which directs gene regulation; 2) a DNA-binding domain (DBD), which binds to target DNA sequences – the glucocorticoid response elements, and 3) a carboxy-terminal ligand-binding domain (LBD), representing the specific binding sites for glucocorticoids and contains a binding region for heat shock proteins [31]. The NTD contains a variable domain, which differs significantly in size and sequence between receptors. A strong transcriptional activating function (AF1) motif is typically found in the NTD [32]. AF-1 is rich in acidic amino acids and is required for maximal transcriptional activation of GR, being responsible for binding cofactors and components of the basal transcription machinery [33]. Close to the AF-1 region is the DBD characterized by eight cysteine residues tetrahedrally organized about two zinc atoms [34]. These two highly conserved zinc fingers motifs tetrahedrally coordinate a zinc atom held by four cysteine residues and create a three dimensional configuration that permits the binding of the receptor to DNA [32]. More specifically, the amino terminal zinc finger discriminates DNA response elements and the carboxyl terminal zinc finger is necessary for receptor dimerization [33]. DBD also plays a role in GR interaction with cofactors or other transcription factors, such as c-Jun [35], factor nuclear kappa B (NF-κB), activator protein 1 (AP-1) and cAMP response element binding (CREB) [36]. Finally, the highly conserved LBD is located at the carboxyl-terminal consisting of twelve α-helices and four β-sheets [37]. LBD forms a hydrophobic pocket for binding glucocorticoids and also contains

an activation function (AF-2) that interacts with co-regulators in a ligand-dependent manner [38].

Cytoplasmic GRs are normally bound to a protein complex that includes two subunits of the heat shock protein-90 (Hsp90), which act as molecular chaperones. These chaperones prevent the nuclear localization by covering the sites on the receptor that are needed for transport across the nuclear membrane into the nucleus [39]. Upon ligand binding, changes in receptor structure result in dissociation of Hsp90-GR complex, allowing the translocation of the activated GR-corticosteroid complex into the nucleus, where it binds to DNA at specific sequences in the promoter region of corticosteroid-responsive genes, namely glucocorticoid response elements (GREs) [40]. The GRE mediates the glucocorticoid-dependent activation of many genes, and therefore is known as an activator or positive GRE [41]. Conversely, recent genome-wide analyses have revealed that GR occupancy of the canonical GREs can also lead to the repression of target genes (see Surjit et al. [42] for details). Most of the effects of glucocorticoids on the immune system may be mediated by the interaction between GR and NFκB, AP-1, and STATs [signal transducer and activator of transcription) [36, 43, 44], which lead to subsequent transcriptional repression of many genes. Suppression of transactivation of other transcription factors through protein-protein interactions may be particularly important in suppression of immune function and inflammation by glucocorticoids [36]. In addition, the anti-inflammatory effects of glucocorticoids implicate induction of genes encoding anti-inflammatory proteins, such as Tsc22d3 (encoding GILZ) and Dusp1 (encoding MKP-1) [45]. Thus, the predominant effect of glucocorticoids is the modulation of multiple inflammatory genes (encoding cytokines, chemokines, adhesion molecules, inflammatory enzymes, receptors and proteins) that have been activated during the chronic inflammatory process [46].

The GR-encoding gene (NR3C1) is a member of the nuclear receptor superfamily that is located on chromosome 5 [37]. Besides the fact that a single gene encodes human GR, several variants emerged as result of alternative transcript splicing and alternative translation initiation [47]. The GR gene was cloned and sequenced in 1985, revealing the expression of GRα and GRβ [48]. The main GR isoforms, GRα and GRβ, were generated by an alternative splicing at exon 9 of primary GR transcript, which produced two highly homologous mRNA transcripts [49]. GRα, the predominant form of GR, is composed of an additional 50 amino acid residues, while GRβ encodes an additional 15 nonhomologous amino acid residues in the C-terminus [50]. GRα, the classic

glucocorticoid receptor, is ubiquitously expressed and mediates most of the known actions of glucocorticoids. GRα binds corticosteroids, whereas GRβ is an alternatively spliced form that binds to DNA, however it is not activated by corticosteroids [50]. GRβ is expressed at low levels as compared to GRα. The GRβ isoform is still capable of forming heterodimers with GRα, but the complex has substantially diminished transcriptional activity compared with the GRα-GRα homodimer [51]. Therefore, GRβ acts as a dominant negative inhibitor of GRα transcriptional activities and provides enhanced resistance to the biological and pharmacological effects of glucocorticoids. A great amount of clinical evidence suggests that GRβ is responsible for the development of tissue-specific insensitivity to glucocorticoids in different disorders, most of them associated with dysregulation of immune function [50]. They include glucocorticoid-resistant asthma, rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, chronic lymphocytic leukemia, and nasal polyps [52]. Although GRβ does not bind glucocorticoids, it actively binds GR antagonist mifepristone (RU 486), and the GRβ endogenous ligand is still unknown [53].

It is worth noting that glucocorticoid receptors are susceptible to post-translational modifications. These modifications might alter the response to corticosteroids by affecting ligand binding, cofactors recruitment, translocation to the nucleus, efficacy of trans-activating or protein-protein interactions [54, 55]. Like other steroid hormone receptors, GR are phosphoproteins, and alterations in their phosphorylation status may modulate their activity. Receptor phosphorylation may influence the interactions of GR with other transcription factors required for transactivation [56]. Evidence from the literature has shown that the mitogen-activated protein kinases (MAPK) and the cyclin-dependent kinases (CDK) are main kinase families which mediate GR N-terminal phosphorylation [54]. The MAPKs consists of three main members: the extracellular signal-regulated protein kinases (ERKs), the c-Jun N-terminal kinases (JNKs), and the p38 family of kinases. Phosphorylation of GR by JNK directly, and by ERK indirectly, have been reported to inhibit GR-dependent gene transcription [57]. Finally, GR can be also regulated by ubiquitination, acetylation or sumoylation [58].

Considering the relevance of glucocorticoids for the cellular and physiological processes, it is reasonable to understand that it plays important roles in the cerebral neuroplasticity and machinery, and more specifically, *in the pathophysiology of MDD, as explained in the following sections.*

MAJOR DEPRESSIVE DISORDER (MDD)

Depressive disorders are frequent and debilitating conditions characterized by affective manifestations, disturbed mood, loss of interest and pleasure in daily activities [59]. Depressive disorders are classified into different subtypes according to patient's symptomatology: dysthymic disorder currently known as persistent depressive disorder (PDD) characterized by all features of depressive disorder that persists at least 2 years continuously with incomplete remission between episodes; postpartum depressive disorder that committees 10-15% of pregnant women, affects babies' development and are associated with impaired maternal care, engagement and also shorter breastfeeding duration; and seasonal depressive disorder (SAD), a subtype of depressive disorder with onset in the fall/winter months and remission in spring/summer months connected to annual variations in suicidality [60-62]. Moreover, premenstrual dysphoric disorder (PMDD) affects 2-5% of women before menses causing cognitive-mood prejudice in addition to physical symptoms [63].

The most common and studied subtype of depressive disorders is MDD, a serious medical illness considered a long-lasting and recurrent type of depression that affects and debilitates millions of people around the world [64, 65]. Until now, diagnostic criteria and standard classification for mental health in MDD have been performed based on criteria established by Diagnostic and Statistical Manual of Mental Disorders V (DSM-V), which characterizes MDD by the presence of at least 5 from 9 following symptoms for at least 2 weeks: depressed mood and/or anhedonia (main symptoms reported by patients), as well as changes in appetite, weight and sleep, psychomotor activation or retardation, fatigue and loss of energy, feelings of hopelessness, worthlessness or guilt, diminished ability to think and concentrate, suicide ideation [64, 66, 67].

There are multiple risk factors associated with the development of MDD, including genetic predictors, life style, endocrine abnormalities, presence of other diseases and exposure to environmental challenges and adversities [59, 68, 69]. Depressive episodes are associated with several comorbidities like chronic conditions presenting an inflammatory profile and pain [70], cardiovascular diseases [71, 72], diabetes, and obesity [73, 74]. Moreover, disturbed sleep is associated with MDD and suicidal attempt and ideation in adolescents and older adults [75, 76]. Preventing depression development involves a healthy life style, and many detrimental habits can be modified by the subject, such as substance use, dieting, negative coping strategies and obesity [77].

The prevalence of MDD in the population is estimated around 16% being the adults more affected [78-80]. In 1990, MDD was ranked as the fourth major cause of burden. A considerable epidemiological concern remains because MDD is expected to affect a huge percentage of the world population until 2020, being the crucial contributor to the years lived with disability (YLD) in developed and developing countries. Therefore, MDD is considered the leading cause of YLD in 56 countries, the second leading cause in 56 countries, and the third in 34 countries [80, 81].

The economic impact of MDD on society involves the "direct costs" which take into account the costs generated to treat MDD, and "indirect costs" which consider the impact caused by MDD, such as decrease in work productivity and in other activities [82]. Therefore, the general economic impact caused by MDD is extremely high and of public interest. In the United States by the year of 2000, MDD was considered to reach 83 billion dollars and in 2010 this value increased to 210.5 billion dollars [83, 84].

Besides the economic concern, MDD causes a negative social impact to the individuals, leading to poor social functioning [85], and negative impacts to their family [86]. Therefore, great efforts have been done to better elucidate the mechanisms underlying the depressive symptoms in order to improve diagnosis and treatment and ameliorate patient's quality of life.

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