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Review Article

Endocannabinoids: Effectors of glucocorticoid signaling

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ABSTRACT

For decades, there has been speculation regarding the interaction of cannabinoids with glucocorticoid systems. Given the functional redundancy between many of the physiological effects of glucocorticoids and cannabinoids, it was originally speculated that the biological mechanisms of cannabinoids were mediated by direct interactions with glucocorticoid systems. With the discovery of the endocannabinoid system, additional research demonstrated that it was actually the opposite; glucocorticoids recruit endocannabinoid signaling, and that the engagement of endocannabinoid signaling mediated many of the neurobiological and physiological effects of glucocorticoids. With the development of advances in pharmacology and genetics, significant advances in this area have been made, and it is now clear that functional interactions between these systems are critical for a wide array of physiological processes. The current review acts a comprehensive summary of the contemporary state of knowledge regarding the biological interactions between glucocorticoids and endocannabinoids, and their potential role in health and disease.

1. Introduction

There is unequivocal evidence for an interaction between glucocorticoid and endocannabinoid signaling pathways. Firstly, the cannabinoid receptor (CB1 receptor) is highly expressed in biological tissues, and within the brain, neuroanatomical regions that are implicated in glucocorticoid function (Herkenham et al., 1991; Marsicano and Lutz, 1999). Secondly, it has been shown that glucocorticoids are able to mobilize the endocannabinoid system (Di et al., 2003; Hill et al., 2005a, 2010a). Finally, at a functional level there are several lines of evidence revealing the prerequisite of intact endocannabinoid signaling for many glucocorticoid-mediated outcomes (Bowles et al., 2015; Campolongo et al., 2009; Coddington et al., 2007; Evanson et al., 2010; Hill et al., 2011). Following is a review of the literature describing a role for endocannabinoid signaling in glucocorticoid-mediated behaviours, physiological processes and neuroendocrine outputs.

2. Glucocorticoid signaling

Glucocorticoids (GCs) are cholesterol-derived steroid hormones that are essential for life, exhibiting widespread effects on multiple organ systems to regulate broad physiological functions for the maintenance of basal and stress-related homeostasis (Chrousos et al., 2004). An important role of GCs is the regulation of glucose metabolism. In fact, GCs were so named according to their ability to increase circulating glucose concentrations to fuel biological processes (in the brain, muscle, etc.) in order to adequately respond to changes in the physical environment (Sapolsky et al., 2000) Furthermore, GCs are key regulators of vascular tone, immune function, bone mineralization, and central nervous system function. Consequently, glucocorticoid function and dysfunction have significant clinical implications (Kadmiel and Cidlowski, 2013). For example, synthetic GCs are commonly used in the treatment of several chronic and acute illnesses including certain malignancies, asthma, allergic rhinitis, rheumatoid arthritis, eczema, and psychiatric disorders. Furthermore, dysregulation of glucocorticoid production leads to severe health complications, exemplified by Cushing's disease and Addison's disease, characterized as the overproduction of GCs and diminished production of GCs, respectively. In this context, it is important to understand the biological and physiological actions of GC hormones and the underlying signal transduction mechanisms mediating these effects.

GCs are synthesized in response to stress (de Kloet et al., 2005). A stressor is defined as a physical or psychological threat to homeostasis, such as a shift in the internal physiological environment (including changes in pH, osmolarity or elevations in inflammatory mediators) or external stimuli that may represent a threat (such as the presence of a predator or uncertainty due to novel environmental circumstances; Brown et al., 2007; Chrousos, 1998; de Kloet et al., 2005; Droste et al.,

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2007; Leuner et al., 2010). When a situation is perceived as stressful, the body mounts a response aimed at reinstating homeostasis, which largely comprises the concerted actions of the autonomic nervous system (ANS) and the hypothalamic-pituitaryadrenal (HPA) axis, and involves the reallocation of energy stores to be able to meet the energetic demands imposed by the challenge and enhance the likelihood of survival. Importantly however, GCs are also released in response to non-threatening, and even rewarding stimuli, such as sexual activity or physical exercise, which similarly require alterations in energy allocation to maintain appropriate function. Activation of the HPA axis governs the neuroendocrine response to a stressor, which culminates in the release of GCs. Specifically, in response to a stressor, corticotropin releasing hormone (CRH) is released into the median eminence from parvocellular neuronal projections originating within the hypothalamic paraventricular nucleus (PVN). From here, CRH enters the hypophyseal portal circulation to reach the anterior pituitary, where it acts to stimulate adrenocorticotropic hormone (ACTH) production and release into general circulation. ACTH in turn stimulates the synthesis of GCs in the adrenal cortex. Elevated levels of circulating GCs subsequently coordinate a series of biological processes that allow the organism to cope with the demands of the stressor. In addition, GCs are involved in a negative feedback loop at the level of the pituitary, hypothalamus, and higher brain centers, in order to terminate HPA axis activation and the stress response. With respect to extrahypothalamic regulation of the HPA axis, the amygdala has been identified as a primary limbic structure whose activation can drive the HPA axis in response to a stressor (Ulrich-Lai and Herman, 2009). By contrast, the hippocampus and the prefrontal cortex (PFC) are recognized as the primary extrahypothalamic mediators of GC feedback inhibition of the HPA axis. In the absence of a stressor, the HPA axis maintains a dynamic oscillatory activation pattern. Specifically, the HPA axis presents a distinctive circadian rhythm of GC release, in which the peak and nadir of GC diurnal secretion coincide with the onset and termination of the active period, respectively (Spiga et al., 2014). In addition to circadian variations, GC secretion is also characterized by a rapid, ultradian pulsatility with a periodicity of approximately 1 h (Lightman and Conway-Campbell, 2010). Taken together, GCs are dynamically regulated, which in turn is an important feature of their physiological function.

In the traditional view, GCs exert their effects through genomic mechanisms, involving gene transcription and requiring a time delay (hours to days). More recently, mounting evidence points to non-genomic actions of GCs. Non-genomic GC action underlie the rapid effects (within minutes) of GCs, which often require membrane-associated GC receptors. Here we review both the classical, delayed actions of GCs as well as the rapid actions of GCs.

2.1. Classical delayed actions of glucocorticoids

Classical GC signaling refers to the genomic actions of GCs, which depend on gene transcription and de novo protein synthesis, and thus reflect the delayed effects of GC signaling. These genomic effects are mediated by two distinct classes of corticosteroid receptors: type I mineralocorticoid receptors (MRs) and type II glucocorticoid receptors (GRs) (de Kloet, 2013). MR and GR are both members of the nuclear receptor superfamily, which act as transcription factors (Mangelsdorf et al., 1995). In the absence of GCs, both MR and GR reside in the cytoplasm as a large inactive heteromeric complex comprised of molecular chaperone and co-chaperone proteins. Lipophilic GCs readily cross the phospholipid bilayer of the cell membrane. Upon ligand binding, GR and MR undergo conformational changes and translocate to the nucleus (Ricketson et al., 2007). Within the nucleus, homodimer steroid receptors are able to transcriptionally activate genes harboring a glucocorticoid response element (GRE) either in their promoter region or intragenic regions. Moreover, activated GR and MR interact with other transcription factors including activator protein 1 (AP-1) and nuclear factor κB (NFκB), to form heterodimers within the nucleus, in order to inhibit their transcriptional activity in a process referred to as transrepression (Pascual and Glass, 2006).

Although both MRs and GRs bind the same hormone (cortisol in humans and corticosterone in rodents), they have distinct binding affinities (Reul and de Kloet, 1985) and are discretely distributed (Reul and de Kloet, 1986), which contribute to differences in their biological function. In rodents, MRs have a tenfold higher affinity for corticosterone than GRs, which ultimately leads to differences in receptor occupancy throughout the diurnal rhythm and in response to stress. MRs are widely occupied during the nadir of the diurnal cycle, whereas GRs only become saturated in response to stress or at the circadian peak (de Kloet et al., 2005). In regards to receptor localization, GRs show a widespread distribution across many tissues and cell types. Within the central nervous system, GRs are localized to both neurons and glia, with especially high concentrations in the limbic system, PVN, and in ascending monoaminergic neurons. By contrast, MRs show a much more restricted expression profile, but nevertheless are highly concentrated in limbic structures. Based on such differences between MRs and GRs, it is thought that MR signaling is largely involved in the maintenance of stress-related neural circuits and the onset of the stress response, whereas GR signaling is only activated by high concentrations of GCs, and thus has been implicated in stress reactivity, facilitating the mobilization of energy stores and the termination of the stress response through inhibition of the HPA axis (de Kloet et al., 2005).

Genomic effects of GCs within the central nervous system are well documented. The best studied examples of GC action in the brain have focused on the GC negative feedback of the HPA axis. In particular, slow, transcription-dependent GC actions regulate the expression of ACTH and CRH receptors at the level of the pituitary (Birnberg et al., 1983; Makino et al., 1995) as well as the expression of CRH in the hypothalamus (Sawchenko and Swanson, 1985). In addition, extrahypothalamic regions, including the hippocampus and PFC, facilitate negative feedback inhibition on the HPA axis through indirect projections to the PVN (Ulrich-Lai and Herman, 2009). Indeed GCs exert strong genomic effects in both the hippocampus (Kim and Diamond, 2002; McEwen, 2001) and the PFC (Arnsten, 2009; Holmes and Wellman, 2009). Nevertheless, it is clear that additional fast-acting mechanisms underlie the rapidly-induced negative-feedback inhibition of the HPA axis, which manifests within minutes.

2.2. Rapid actions of glucocorticoids

GCs induce a wide range of rapid effects on behavioral and endocrine outputs within seconds to minutes of exposure, precluding the involvement of gene transcription in mediating these effects (Groeneweg et al., 2011; Haller et al., 2008). Such rapid GC-mediated effects have been attributed to non-genomic actions of GCs, which are characterized as effects with short onset latencies and which are insensitive to inhibitors of DNA transcription and protein synthesis (Haller et al., 2008). In addition, GC hormone action persists with the application of cell-impermeable hormone conjugates. Importantly, the non-genomic effects of GCs require high concentrations of GCs, suggesting that the physiological significance of such non-genomic effects is related to stress (Jiang et al., 2014). In fact, it is speculated that the non-genomic effects of GCs are integral to the early phase of acute stress and the termination of the stress response via the feedback inhibition of the HPA axis. This is supported by experimental evidence which demonstrates that rapid non-genomic mechanisms govern the acute effects of GCs through the suppression of CRH-induced ACTH secretion at the pituitary (Hinz and Hirschelmann, 2000; Widmaier and Dallman, 1984). Furthermore, using a cell-impermeable GC hormone conjugate (DEX:BSA), it was shown that GC-induced fast feedback inhibition of the HPA axis is mediated by a non-genomic signaling mechanism at the level of the PVN (Evanson et al., 2010). From such findings, it is clear that GCs act through non-genomic and genomic mechanisms to elicit both rapid and delayed effects on physiological and behavioral