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Novel Aspects of Glucocorticoids Actions on Energy Homeostasis and Hydromineral Balance

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1. Introduction

Glucocorticoids can readily diffuse into the cells due to their lipophilic nature and bind to glucocorticoid (GR) and mineralocorticoid (MR) receptors, which, in the inactive form, are associated with other proteins in the cytosol. MR was shown to bind most of the glucocorticoids under basal conditions. However, after an increase in the circulating levels of glucocorticoids (i.e. caused by exposure to stress or during the circadian and ultradian peaks of glucocorticoid secretion) GRs are predominantly activated (de Kloet et al., 2005). The activated receptor undergoes conformational changes followed by the translocation of the ligand-bound complex to the nucleus. Within this subcellular compartment, this complex can form homo or heterodimers and bind to responsive elements (GREs) in the promoter region of target genes, a mechanism known as transactivation, or interact with transcription factors as monomers to modulate the transcription of responsive genes, a mechanism known as transrepression. The main transcriptional factors involved in these responses are the nuclear factor kappa B (NFκB) and the AP-1 protein family.

More recently, it has been suggested that nontranscriptional actions may account for the very rapid effects observed with acute glucocorticoid treatment (Limbourg & Liao, 2003). These actions differ from the classic genomic responses by the targets, type of interaction and period of action, being detected within few minutes after hormone secretion (Mikics et al., 2004; Sandi et al., 1996). The administration of high doses of dexamethasone was shown to protect the myocardial tissue from infarction and stroke through the prompt activation of endothelial nitric oxide (NO) system (Hafezi-Moghadam et al., 2002). During the 1990's, NO has been identified as a potent vasodilatory gas. Its properties in decreasing blood pressure are still clinically explored by the use of NO donors as anti-hypertensive drugs.

More recently, NO has also been implicated in neuromodulation, exerting its actions in an autocrine or paracrine manner in the central nervous system (CNS).

In general, these rapid effects mediated by glucocorticoids seem to modulate signaling (through actions on ion channels, neuromodulators, neurotransmitters and other receptors systems), being very distinctive depending on the brain areas involved. It is generally accepted that glucocorticoids increase the excitability in some areas, like hippocampus and amygdala, and potentially decrease neuronal activity in others, such as the hypothalamus. Since the expression of glucocorticoid receptors vary considerably in the CNS, glucocorticoids are likely to modulate not only the activity of the hypothalamic-pituitary-adrenal (HPA) axis, but also indirectly modify the inputs to hypothalamic neurons, projecting from the limbic system and cerebral cortex.

The classic glucocorticoid receptors GR and MR have already been identified in neuronal and non-neuronal cellular membranes, although their involvement in these nongenomic responses is still controversial (Gametchu et al., 1993; Lipositis & Bohn, 1993). In pituitary-derived cells, the use of a GR antagonist prevented the dexamethasone-induced translocation of annexin-1, which was implicated in the rapid inhibition of adrenocorticotrophic hormone (ACTH) release (Buckingham et al., 2003; Solito et al., 2003; Tierney et al., 2003). Nevertheless, a GR-independent pathway has been also reported in the fast feedback mechanism at the pituitary level *in vivo* (Hinz & Hirschelmann, 2000).

Another line of evidence suggests that most of nongenomic responses are mediated by the glucocorticoid binding to G-coupled protein receptors (Liu & Chen, 1995; Orchinik et al., 1991). In tumor-derived cells, a receptor coupled to an inhibitory G-protein (Gi) has been implicated in the glucocorticoid-induced inhibition of ACTH release (Iwasaki et al., 1997). In the hypothalamus, however, the production and release of neuromodulators (endocannabinoids and NO) seem to be driven by the activation of a membrane receptor associated with a stimulatory G-protein (Gs) (Di et al., 2009). Endocannabinoids were shown to mediate most of the nongenomic actions of the glucocorticoids, including the rapid negative feedback on the HPA axis (Evanson et al., 2010). Accordingly, several signaling pathways have been implicated in the responses induced by glucocorticoids downstream from the putative membrane receptors, mainly including protein kinase A (PKA)- and protein kinase C (PKC)-derived mechanisms (Han et al., 2002, 2005; Lou & Chen, 1998; Qiu et al., 1998, 2003).

2. Glucocorticoids and energy balance

2.1. The control of food intake by glucocorticoids: novel aspects

The motivated behaviour of eating comprises one of the most primordial responses in all species. It is regulated by several factors, including adiposity (leptin and insulin) and satiety signals (such as mechanical and chemical stimulation of stomach and small intestine), as well as hormones [such as cholecystokinin (CCK)] (Schwartz et al., 2000). The adiposity factors are involved in the long-term control of energy balance and act primarily in

hypothalamic neurons expressing orexigenic or anorexigenic neuropeptides (Schwartz et al., 2000). Neuropeptide Y (NPY) and agouti related protein (AgRP) in the arcuate nucleus of the hypothalamus (ARC), and orexins and melanin-concentrating hormone (MCH) in the lateral hypothalamic area (LHA), represent the main hypothalamic orexigenic neuropeptides (Gehlert, 1999; Smith & Ferguson, 2008; Valassi et al., 2008). In contrast, proopiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART) in the ARC, and corticotrophin-releasing factor (CRF) and oxytocin (OT) in the paraventricular nucleus of the hypothalamus (PVN) are the main mediators involved in the inhibition of food intake (Schwartz et al., 2000; Valassi et al., 2008). The localization of the above mentioned neuropeptides in hypothalamic nuclei is summarized in Table 1. The satiety signals, in turn, are implicated in the short-term control of food intake and have their actions mediated by brainstem areas, primarily by the nucleus of the solitary tract (NTS), which is implicated in the control of meal size (Havel, 2001). It is well established that the hypothalamic nuclei involved in the control of food intake have reciprocal connections with the brainstem (Sawchenko & Swanson, 1982; Swanson & Kuypers, 1980). This evidence provides the neuroanatomical basis for the hypothesis that adiposity signals may modulate satiety (Matson & Ritter, 1999; Wang et al., 2000).

Neuropeptides	Localization in the hypothalamus
NPY	ARC
AgRP	ARC
Orexins	LHA and PFA
MCH	LHA
POMC	ARC
CART	ARC, PVN and SON
CRF	PVN
OT	PVN and SON

Table 1. Hypothalamic localization of the neuropeptides involved in the control of food intake. NPY, neuropeptide Y; ARC, arcuate nucleus of the hypothalamus; AgRP, agouti related protein; LHA, lateral hypothalamic area; PFA, perifornical area; MCH, melanin-concentrating hormone; POMC, proopiomelanocortin; CART, cocaine and amphetamine-regulated transcript; PVN, paraventricular nucleus of the hypothalamus; SON, supraoptic nucleus of the hypothalamus; CRF, corticotrophin-releasing factor; OT, oxytocin.

Glucocorticoids play an important role in the control of energy balance (La Fleur, 2006). It is well established that a peak in the concentration of glucocorticoids occurs immediately before or at the onset of the activity period, with a progressive decrease in the HPA axis activity being detected over the remaining period within 24 hours, resulting in the classic circadian rhythm (Moreira & Leal, 1997). In addition, this rhythm occurs due to glucocorticoids release from the adrenal gland in discrete pulses, which results in an ultradian rhythm. Changes in the amplitude of these pulses, and to a lesser extent in their frequency, determine the pattern of the circadian rhythm (Lightman et al., 2008). In fact, it has been also demonstrated that feeding is a major synchronizer of the HPA axis rhythmicity (Leal & Moreira, 1997), being the size of the meal directly related to

glucocorticoid secretion (Honma et al., 1983). At the same time, increased food intake and body weight gain have been observed in humans following glucocorticoid treatment (Tataranni et al., 1996). Stress conditions, characterized by elevated circulating glucocorticoids levels, are also associated with increased food intake, body weight gain and obesity (Dallman et al., 2003; La Fleur, 2006; Spencer & Tilbrook, 2011).

Consistent with the importance of glucocorticoids on energy homeostasis are two very prevalent clinical conditions: 1) Cushing's syndrome, which is characterized by clinical findings that include abnormalities in the HPA axis rhythmicity, insulin resistance and hyperglycaemia secondary to hypercortisolism. The most common cause of Cushing's syndrome is the administration of pharmacological doses of oral, parenteral and, rarely, by topical glucocorticoids. Endogenous glucocorticoid excess may arise from ACTH-secreting pituitary tumors, ectopic (nonpituitary) ACTH production, or adrenal tumors. Hypercortisolaemia is associated with increased glucose production, decreased glucose transport and utilization, decreased protein synthesis, increased protein degradation in muscle and body weight gain (Nieuwenhuizen & Rutters, 2008; Shibli-Rahhal et al., 2006); (2) Addison's disease or primary adrenal insufficiency, first described by Addison in 1855, is characterized by an inability of the adrenal cortex to synthesize and secrete glucocorticoids and mineralocorticoids. Chronically, the main clinical findings observed in patients with Addison's disease include malaise, fatigue, anorexia, weight loss, darkening of the skin, hyponatraemia, hypoglycaemia and hyperkalaemia (Nieman and Chanco Turner, 2006).

It has been shown that the effects of glucocorticoids on food intake can vary according to their concentration in the circulation (Devenport et al., 1989). Low doses of corticosterone administered to adrenalectomized (ADX) rats activate MR and induce a stimulatory effect on fat intake, body weight gain and fat depot, being these effects prevalent at the late phase of the feeding period, the same period in which HPA axis activity is reduced during the circadian variation (Tempel & Leibowitz, 1994, 1989; Tempel et al., 1991). In contrast, GRs are activated by higher doses of circulating corticosterone, being this effect observed just before or at the first hours after the beginning of the feeding period, mimicking the peak of glucocorticoids secretion within the 24 hours of circadian rhythm. Such high levels of circulating glucocorticoids produce an increase in carbohydrate ingestion and metabolism (Goldstein et al., 1993; Kumar & Leibowitz, 1988; Kumar et al., 1988; Tempel & Leibowitz, 1994, 1989; Tempel et al., 1993). In addition, extremely high corticosterone plasma concentrations, such as those observed in response to stress or food restriction, stimulate fat and protein catabolism (mainly from muscular source) and, consequently, body weight loss, which increases the availability of gluconeogenesis substrates and enhances glucose plasma concentrations (Tempel & Leibowitz, 1994; Tomas et al., 1979).

Historically, the brain has been considered the main regulator of hunger and satiety. However, the existence of a unique hypothalamic satiety or hunger center, as proposed a few decades ago, is no longer acceptable. It has been demonstrated that dexamethasone injection into the lateral ventricle not only stimulates food intake but also enhances body weight gain in rats, being these effects accompanied by hyperleptinaemia and hyperinsulinaemia (Cusin et al., 2001; Zakrzewska et al., 1999). These central effects of

glucocorticoids seem to be mediated by their interaction with neurons co-expressing glucocorticoid receptors and neuropeptides involved in the control of energy homeostasis (Aronsson et al., 1988; Hisano et al., 1988). This hypothesis has been evaluated by Zakrzewska and co-workers (1999), who demonstrated that the hypothalamic levels of NPY and CRF were, respectively, increased and decreased in response to the intracerebroventricular administration of dexamethasone. In addition, circulating glucocorticoids were shown to be required for the feeding-induced decrease in the expression of orexigenic neuropeptides in the ARC, as well as for the increased expression of the anorexigenic neuropeptide POMC in the same nucleus (Uchoa et al., 2012). It has been hypothesized by these authors that these effects would occur either by a direct effect of glucocorticoids on ARC neurons or indirectly by the feeding-induced secretion of leptin and insulin.

The removal of endogenous glucocorticoids induced by bilateral ADX surgery is one of the most used experimental models for replicating the human Addison's disease. The food intake and body weight gain are reduced in ADX animals, being these effects reversed by glucocorticoid replacement (Freedman et al., 1985; Uchoa et al., 2009a, 2009b, 2010). Furthermore, ADX is effective in diminishing hyperphagia and obesity under diverse experimental conditions (Bruce et al., 1982; Dubuc and Wilden, 1986; Yukimura et al., 1978). The ADX-induced hypophagia has been associated with a decrease of hypothalamic NPY and AgRP mRNA expression (Strack et al., 1995; Uchoa et al., 2012). Conversely, ADX induces an increase in the expression of CRF and OT in PVN (Uchoa et al., 2009b and 2010). The actions on these two peptides in the control of food intake were confirmed by the central administration of OT and CRF-2 receptor antagonists, which were able to reverse the ADX-induced hypophagic effect (Uchoa et al., 2009b and 2010).

It has been hypothesized that the stimulatory action of glucocorticoids on food intake may involve an increased drive for eating. Accordingly, it is believed that the ADX-induced hypophagia is caused, at least in part, by a reduction of this motivated behaviour. However, there are few evidences concerning the role of glucocorticoids on the satiety-related responses. Recent studies have demonstrated that the hypophagic response induced by ADX is associated with increased activation of satiety-related responses mediated by brainstem and hypothalamic circuits (Uchoa et al., 2009a, 2009b). Accordingly, the activation of NTS neurons, assessed by the increased number of cells expressing the nuclear c-Fos protein, is increased in ADX animals after feeding, indicating that this nucleus may be involved in the increased satiety responses following glucocorticoid deficiency (Uchoa et al., 2009a). Interestingly, the activation of CRF and OT neurons was also enhanced in the PVN of fed ADX rats, indicating that, besides the brainstem, the hypothalamus may be also involved in these satiety-related responses. Furthermore, this increased activation of satiety-related responses in the NTS following ADX is reversed by CRF₂ receptor antagonist, indicating that CRF also plays an important functional neuromodulatory role in the brainstem (Uchoa et al., 2010).

In addition to the reduced drive to eat and the increased satiety observed in ADX animals, a change in both the concentration as well as in the sensitivity to peripheral factors seems to underlie the hypophagic effect of glucocorticoid deficiency. Accordingly, ADX reduces

plasma leptin levels in *ad libitum* rats (Germano et al., 2007; Savontaus et al., 2002), as well as the meal-induced insulin secretion (Germano et al., 2008; Uchoa et al., 2012), whereas glucocorticoid treatment increases leptin secretion and leptin expression in adipocytes (Jahng et al., 2008; Sliker et al., 1996; Zakrzewska et al., 1999). Furthermore, the sensitivity to insulin and leptin seems to be enhanced after ADX (Chavez et al., 1997; Zakrzewska et al., 1997), although CCK administration did not significantly alter food intake in ADX rats (Uchoa et al., 2009a). Another hormone that arises as a candidate for the modulation by glucocorticoids is ghrelin, although the effects of this hormone on food intake may also be produced independently of glucocorticoid action.

The physiological instinct of obtaining energy through food intake is parallel to the equally important development of satiation signals, which may terminate the ingestive behaviour as soon as the organism is replenished. Glucocorticoids have a well established role in both processes, contributing to the enhanced drive to eat as well as to the reduction of satiety-related responses. However, it is believed that, particularly in humans, the initiation of a meal often starts in the absence of any depletion signal, which means that it is possible for other brain areas such as the cortex and the limbic system to overcome the inputs coming from the hypothalamus and the brainstem, turning the organism into an ingestive mode, which actually exceeds its needs. Accordingly, both real and potential challenges that activate the HPA axis and, consequently, alter the secretion of glucocorticoids, may also disrupt this balance.

2.2. Glucocorticoids in the interface of immune challenges and food intake

Under acute immune challenges, the body produces a strong inflammatory response to the pathogens. This generalized reaction, triggered by the organism in order to safeguard the host homeostasis, comprises physiological and behavioural changes (Langhans, 2000). However, in a severe condition in which the overwhelming infection leads to life-threatening low blood pressure and decreased tissue perfusion, a medical emergency known as septic shock may contribute to organ damage and death. Microbial products such as lipopolisaccharides (LPS) from the outer lipid bilayer of gram-negative bacteria cell walls are commonly used to model acute illness, leading to the development of sepsis or endotoxaemia, depending on the dose of the endotoxin (Borges et al., 2007; 2011; Giusti-Paiva et al., 2002).

Hypophagia is part of the acute-phase response to illness. During endotoxaemia, food intake is limited and there is an impairment of energy expenditure. Experimental models have demonstrated that LPS dramatically reduces food consumption (Gautron et al., 2005; Sachot et al., 2004), being this hypophagic effect mainly elicited by the production of proinflammatory cytokines (Johnson, 1998; Wise et al., 2006). Consistent with the contribution of proinflammatory cytokines to this illness-induced hypophagia are the studies showing that their peripheral or central administration restrains eating, and that the acute antagonism of their actions attenuates this anorexic response (Asarian & Langhans, 2010).

The systemic administration of LPS triggers the synthesis and release of interleukin (IL)-1 β , IL-6 and tumor necrosis factor (TNF)- α by monocytes and macrophages. In turn, these cytokines can exert local actions as signaling molecules to activate the immune system and the HPA axis (Turnbull and Rivier, 1999; Turnbull et al., 1998). Accordingly, it has been demonstrated that cytokines induce intense nuclear c-Fos immunoreactivity in CRF parvocellular neurons of the PVN (Matsunaga et al., 2000). Endotoxin also increases CRF synthesis and secretion, stimulating ACTH release from the pituitary corticotrophs and, consequently, the secretion of glucocorticoids from the adrenal cortex (Borges et al., 2007; Turnbull & Rivier, 1999). In turn, glucocorticoids inhibit the induction of proinflammatory cytokines, mostly by interacting with the intracellular GR, which culminates with the activation of NF κ B and AP-1 (Jonat et al., 1990; Munoz et al., 1996). After glucocorticoid binding to the cytosolic GR, the activated complex is translocated to the cell nucleus, where it interacts with the specific transcription factors AP-1 and NF- κ B and prevents the transcription of targeted genes, in a process called transrepression. Glucocorticoids are able to prevent the transcription of many inflammation-associated genes, such as those ones encoding cytokines, including interleukins IL-1B, IL-4, IL-5 and IL-8, chemokines, arachidonic acid metabolites and adhesion molecules. The immunosuppressant action exerted by glucocorticoids may be also evidenced by the increased hypothalamic messenger RNA (mRNA) expression of cytokines and IL-1 β plasma levels observed in response to LPS administration to ADX rats (Goujon et al., 1996).

Within this context, glucocorticoids appear as crucial hormones involved in the mobilization of stored peripheral energy, directing the metabolism to the production of key substrates utilized by the liver to sustain gluconeogenesis. Studies performed in rats show that the search and consumption of palatable foods are stimulated by corticosterone in a dose-related fashion (Dallman et al., 2007). Accordingly, these authors have also demonstrated that ADX rats exhibit poor weight gain, low fat content and increased sympathetic and HPA axis outflow, effects that are, in general, reversed by replacement with corticosterone. The removal of the negative feedback exerted by glucocorticoids in ADX animals has been also implicated in the increased expression of CRF mRNA in the PVN (Herman & Morrison, 1996; Rorato et al., 2008). In addition to its essential function in the control of HPA axis activity, CRF also has a physiological role in the control of food intake, as evidenced by the anorexigenic response induced by central administration of CRF and CRF-related peptides to experimental animals (Kalra et al., 1999; Richard et al., 2002), as previously discussed in this chapter. Furthermore, the use of a CRF receptor antagonist partially reverses the reduction in food intake induced by different stress paradigms (Hotta et al., 1999; Krahn et al., 1986). Accordingly, Borges and coworkers (2007) observed that increased CRF mRNA expression in the PVN precedes LPS-induced anorexia. Hence, an interchange between feeding control and HPA axis activity is conceivable to operate in basal conditions as well as following an immune challenge.

Recently, Saito and Watanabe (2008) have described that dexamethasone treatment attenuates the production of multiple proinflammatory cytokines by the brain and liver, suggesting a potential preventive effect of glucocorticoids on the LPS-induced hypophagia.

Furthermore, Rorato and coworkers (2008) reported that the anorexigenic effect induced by LPS is amplified in ADX rats and that the ADX-induced glucocorticoid deficiency promotes an increased activation of hypothalamic CRF and POMC neurons. It has been already demonstrated that the activation of POMC neurons promotes the release of α -melanocyte stimulating hormone (α -MSH), which, in turn, activates melanocortin 4 receptor (MC4R) (Cone, 2005). Melanocortin has been also implicated in the LPS-induced hypophagia, since the administration of exogenous α -MSH intensified, whereas the antagonism of MC4R attenuated the inhibitory effect of LPS on food intake (Fan et al., 1997; Huang et al., 1999). Within this context, glucocorticoids appear as negative regulators of melanocortin signaling, since ADX was shown not only to reduce AgRP expression in the hypothalamus of wild type mice, but also to reverse obese phenotype and restore hypothalamic melanocortin tone to control levels in leptin-deficient *ob/ob* mice (Makimura et al., 2000).

A growing body of evidence has recently linked obesity to a chronic low-grade inflammatory state (Paternain et al., 2011; Trayhurn & Wood, 2005). In fact, inflammation may contribute to a range of metabolic disturbances related to obesity, such as diabetes mellitus and cardiovascular diseases (Oren et al., 2007). Rats fed with high-fat diet express high levels of TNF- α , IL-6 and IL-1 β in the hypothalamus, which is consistent with the development of an inflammatory process (Milanski et al., 2009). Cani and coworkers (2007) have demonstrated that endotoxaemia dysregulates the inflammatory tone and induces body weight gain and diabetes in mice, showing that a 4-week high-fat diet induced a two to three-fold increase in plasma LPS concentrations. The bacterial endotoxin is normally present in the human intestinal tract (Kelly et al., 2012). Accordingly, LPS is detectable in the circulation of both healthy and obese individuals, but it may transiently raise following energy-rich meals. It has also been shown that the intake of fat-rich diet acts as an inducer of chronic stress, elevating basal glucocorticoid levels and enhancing HPA axis responses to stress (Tannenbaum et al., 1997), suggesting that glucocorticoids are likely to participate in the pathogenesis of metabolic syndrome and obesity (Milagro et al., 2007; Paternain et al., 2011), even though obese individuals and patients with metabolic syndrome do not necessarily show elevated systemic glucocorticoid concentrations (Pereira et al., 2012).

In face of these findings, efforts are now being turned to clarify the significance of glucocorticoids in counteracting the pathophysiology of illness-induced hypophagia. The better understanding of these processes may place glucocorticoids as important pharmacological targets to deal with obesity and metabolic syndrome, in which inflammatory modulators seem to play a key role.

3. Endocannabinoids as potential intermediates of glucocorticoids actions

3.1. Endocannabinoids: general aspects

The pharmacological properties of the plant *Cannabis sativa* are known since ancient times. The first cannabinoid receptor (CB1R) was characterized in 1988 and its predominant distribution through the CNS initially suggested a relationship with the control of cognitive function. However, over the past few years, the number of studies investigating the

participation of CB1R in several areas has increased dramatically. Pioneer studies revealed that the exogenous administration of “cannabis-like” compounds inhibits the activity of diverse neuroendocrine functions (Lomax, 1970; Rettori et al., 1990; Tyrey, 1978). Accordingly, it has been demonstrated that the mRNA for the CB1R is expressed in the hypothalamus and in the external layer of the median eminence of rodents (Herkenham et al., 1991; Wittmann et al., 2007), as well as in both the anterior and intermediate lobes of the human pituitary gland (Pagotto et al., 2001). The evidence of the local production of endocannabinoids provided by this later group further suggested a role for these substances on the direct control of pituitary function.

In this context, the CB1R has been implicated in most, if not all, the actions of endogenously produced cannabinoids in neurotransmission. It has been also demonstrated that hippocampal astrocytes functionally express the CB1R and respond with elevations in intracellular calcium concentrations to the stimulation by neurotransmitters released locally from neuronal sources (Navarrete & Araque, 2008). This evidence suggests that non-neuronal populations can also contribute to the complexity of the responses elicited by endocannabinoids within the CNS. Differently from CB1R, the second cannabinoid receptor (CB2R) was identified in immune cells, being predominantly distributed in the peripheral organs, but not restricted to them. Most of the actions of the endocannabinoid system are mediated by the interaction of endogenous ligands with CB1R or CB2R, although the precise actions of orphan receptors, such as GPR55, still remain to be elucidated.

The identification of this receptor system, as well as the description of well-known effects induced by the consumption or administration of “cannabis-like” substances in humans, suggested the existence of endogenous ligands to be discovered. Anandamide (AEA) was the first one, followed by 2-araquidonoilglycerol (2-AG), the main endocannabinoids studied so far. AEA binds to CB1R with high affinity and regulates the signaling cascade as a partial agonist (Bouaboula et al., 1995). On the other hand, 2-AG, besides being the most abundant endocannabinoid produced by the CNS, has a lower affinity for CB1R when compared to AEA but stimulates the intracellular signaling pathway as a full agonist (Mechoulam et al., 1995). Both AEA and 2-AG are synthesized on demand from membrane phospholipids after the activation of membrane-associated glucocorticoid receptors. AEA and 2-AG are also metabolized by independent enzymatic pathways (Freund et al., 2003). Indeed, AEA acts as a very promiscuous ligand, since it can also bind to type 1 vanilloid (TRPV1) receptors with high affinity (Tóth et al., 2005). Accordingly, some of the effects induced by AEA cannot be mimicked by the administration of the synthetic cannabinoid agonist WIN55,212-2 (Al-Hayani et al., 2001) and the well-known AEA-induced antinociception is still preserved in experimental animals lacking the CB1R gene (Di Marzo et al., 2000).

3.2. Endocannabinoids and the ingestive behaviour

3.2.1. Food intake

It has been demonstrated that glucocorticoids increase endocannabinoid levels in hypothalamic PVN slices, supporting the hypothesis that at least part of the effects induced

by glucocorticoids on food intake are mediated by these lipid-derived mediators (Malcher-Lopes et al., 2006). In this study, Malcher-Lopes and colleagues also demonstrated that the glucocorticoid-mediated activation of a membrane receptor coupled to a $G\alpha_s$ -cAMP-PKA signaling cascade leads to an increase in endocannabinoid synthesis. Accordingly, increased hypothalamic levels of endocannabinoids have been also observed *in vivo* following glucocorticoid treatment (Hill et al., 2010).

Both endocannabinoids and glucocorticoids injected into hypothalamic areas induce similar effects on eating behaviour, increasing food consumption (Jamshidi & Taylor, 2001; Tempel et al., 1992). The synthesis of endocannabinoids in the hypothalamus and the expression of both endocannabinoids and glucocorticoid receptors in synapses and in hypothalamic neurons that synthesize peptides with a key role in food consumption reinforce this assumption (Castelli et al., 2007; Cota et al., 2003; Deli et al. 2009; Di Marzo et al., 2001; Malcher-Lopes et al., 2006). In fact, the neuropeptides CRF, OT and TRH, which have well described anorexigenic properties (Arletti et al., 1989, 1990; Morley et al., 1983; Steward et al., 2003), appear as potential targets for endocannabinoid-mediated actions induced by glucocorticoids. Therefore, the glucocorticoid-mediated blockade of excitatory glutamatergic synapses induced by endocannabinoids via CB1R has been already described in CRF, OT and TRH hypothalamic neurons (Di et al., 2003).

Although feeding is one of the main synchronizers of the HPA axis activity and both the endocannabinoid system and glucocorticoids seem to drive the organism into an increased ingestive behaviour under physiological conditions, several studies reported both stimulatory and inhibitory roles for endocannabinoids in the control of stress responses. In the experiments conducted by Patel and co-workers (2004), mice pretreated with a CB1R antagonist exhibited a robust increase in the restraint-induced glucocorticoid release and c-Fos immunolabeling in the PVN. In addition, the administration of a CB1R agonist, an inhibitor of endocannabinoid transport or a FAAH inhibitor attenuated the restraint-induced increase in glucocorticoid secretion. Although these authors hypothesized that the activation of endogenous CB1R may negatively modulate the HPA axis activity, they also demonstrated that the hypothalamic contents of 2-AG were, respectively, decreased and enhanced after acute and sustained stress. This finding is not consistent with an endocannabinoid-mediated inhibition of the HPA axis activity, but rather indicates that glucocorticoids may centrally inhibit the production of endocannabinoids. Similar results were obtained by Borges and colleagues (2011), who reported decreased hypothalamic 2-AG contents after acute LPS administration. Additionally, increased CRF mRNA expression, glucocorticoid plasma concentrations and hypophagia were found by this group in experimental animals submitted to a single LPS injection, being all these responses completely restored to basal levels following repeated LPS administration.

Conversely, an increase in hypothalamic 2-AG levels after acute restraint stress has also been recently reported (Evanson et al., 2010). According to these findings, these authors proposed that the CB1R-mediated signaling is required for glucocorticoid negative feedback, but not for the initial HPA axis response to restraint. In addition, a down-regulation of CB1R and an impaired glucocorticoid-mediated inhibition of excitatory inputs

to parvocellular PVN neurons were observed in hypothalamic slices from rats submitted to repeated immobilization stress (Wamsteeker et al., 2010). Interestingly, application of a CB1R agonist to the bath did not suppress the excitatory inputs onto PVN neurons, suggesting that the CB1R-mediated signaling may be disrupted after prolonged exposure to stress. It has been recently reported by our group that the pharmacological blockade of the CB1R-mediated signaling during LPS-induced endotoxaemia produces a remarkable increase in the activation of CRF neurons in the parvocellular subdivision of the PVN, which is associated with a pronounced hypophagia (Rorato et al., 2011). Although further studies are needed to clarify the precise actions of endocannabinoids on stress responses, the majority of studies suggest that the endocannabinoid system may mediate the fast negative feedback exerted by glucocorticoids at both hypothalamic and pituitary levels, avoiding the overloading of this system and making it continuously responsive to other potential challenges.

It has been also observed that the peripheral nutrition-related hormone leptin reverses the increases in PVN endocannabinoid levels induced by glucocorticoids, indicating a central crosstalk between glucocorticoids and this satiety signal (Malcher-Lopes et al., 2006). In fact, Obese Zucker rats, which do not express leptin receptors, are hyperphagic and exhibit elevated glucocorticoid plasma levels (Ahima, 2000; Freedman et al., 1985) and increased hypothalamic levels of endocannabinoids (Di Marzo et al., 2001; Kirkham et al., 2002). Within this context, the study of the CB1R-mediated signaling has a great clinical relevance and expectation, since obesity is emerging as a very concerning health problem worldwide, either considered alone or in association with other chronic degenerative diseases. Accordingly, an increasing number of recent studies have focused on the glucocorticoid-related effects mediated by CB1R, such as the central control of food consumption (Di Marzo et al., 2001) and satiety (Matias & Di Marzo, 2007), as well as the peripheral control of adiposity, a predictor of several chronic metabolic disorders (Westerink & Visseren, 2011).

Although the endocannabinoid system has been implicated in several physiological and pathological functions related to the control of food intake and body weight by glucocorticoids (Ameri, 1999; Bisogno et al., 2005; Di Marzo & Matias, 2005; Marco et al., 2011), it has been also demonstrated that these lipid-derived mediators can act independently of the glucocorticoid-mediated signalling (Jamshidi & Taylor, 2001; Kirkham & Williams, 2001; Williams & Kirkham, 1999; Williams et al. 1998). Most of these effects are also mediated by the activation of the CB1R, since the administration of the CB1R antagonist rimonabant reverses the cannabinoid-induced increase in food intake (Jamshidi & Taylor, 2001; Williams & Kirkham, 2002). Consistent with the CB1R-mediated orexigenic effects of endocannabinoids, transgenic mice that lack this receptor subtype or experimental animals treated with the CB1R antagonist exhibit decreased food consumption (Colombo et al. 1998; Di Marzo et al. 2001; Pertwee, 2005).

This rimonabant-induced decrease in food intake is, at least in part, mediated by changes in endocannabinoid signalling within the hypothalamus (Cota et al., 2003; Mailleux & Vanderhaeghen, 1992; Marsicano & Lutz, 1999). It has been already reported that the CB1R is co-expressed with several anorexigenic peptides such as CART and CRF (Asakawa et al.,

2001; Cota et al., 2003; Füzesi et al., 2008; Morley et al., 1983; Vrang et al., 2000). Accordingly, CB1R knockout mice exhibit increased CRF mRNA expression in the PVN (Cota et al., 2003). It has been also demonstrated that acute rimonabant treatment induces an increase in the colocalization of c-Fos with CART in the PVN and ARC and with POMC in the ARC, as well as promotes a decrease in both the protein and the mRNA for NPY in the ARC (Verty et al., 2009a). Conversely, no changes in NPY or POMC mRNA expression were found in the ARC of lean rats treated with rimonabant (Doyon et al., 2006), although the administration of AM251, a selective CB1R antagonist, blocked NPY release from hypothalamic explants (Gamber et al., 2005) and the POMC-expressing neurons were shown to release endocannabinoids under basal conditions (Hentges et al. 2005).

In the brainstem, the CB1R and the enzyme that metabolizes AEA, fatty acid amide hydrolase (FAAH), are expressed in the dorsal vagal complex, which includes the NTS (Van Sickle et al., 2001). In addition, peripheral vagal afferents expressing CB1R and the local production of AEA by the gastrointestinal tract are important food-stimulated signals involved with the control of food intake and meal size (Burdyga et al., 2004, 2010; Gómez et al., 2002; Jelsing et al., 2009a,b). Accordingly, our group has recently demonstrated that the previous CB1R blockade potentiates LPS-induced increase in the number of TH-expressing neurons of the NTS co-localizing c-Fos, suggesting that endocannabinoids may modulate satiety during an immune challenge.

Endocannabinoids can also modulate the hedonistic component of food intake. It has been demonstrated that the cannabinoid agonist THC increases the motivation to eat palatable food (Gallate et al., 1999), whereas the CB1R antagonism reduces this response (Simiand et al., 1998). Changes in content of endocannabinoids in the limbic forebrain regions were shown to be correlated with the nutritional status in experimental animals (Kirkham et al., 2002). Furthermore, the expression of the CB1R in the accumbens shell nucleus (NAcS), a key structure involved with motivation and reward, reinforce this hypothesis (Di Marzo et al., 2009). It is already known that dopamine release within NAcS is associated with rewarding associated with the addictive properties of abuse drugs (Volkow et al., 2007). Interestingly, it was observed that the administration of a CB1R antagonist attenuates the increases in dopamine release within this nucleus induced by a novel high palatable food (Melis et al., 2007), indicating that endocannabinoids may account for the integrated control of feeding-associated motivated behaviour.

In addition to their central effects on the control of hunger and satiety, the endocannabinoid signalling has been also implicated in the peripheral control of body weight through changes in energy storage and expenditure (Silvestri et al., 2011). Interestingly, SV40 immortalised murine white and brown adipocytes treated with rimonabant show increased uncoupling protein 1 (UCP1) expression (Perwitz et al., 2010), which is associated with the preferential production of heat. Furthermore, Quarta and colleagues (2010) have demonstrated that mice lacking CB1R exhibit a lean phenotype due to an increased lipid oxidation and thermogenesis. Accordingly, prolonged rimonabant administration was shown to increase lipolysis and decrease fat storage in white adipose tissue of mice with diet-induced obesity (Jbilo et al., 2005). A recent report from Verty and co-workers (2009b)

has proposed that this response may be mediated by the autonomic nervous system, since the denervation of the sympathetic afferents blocked the effect of rimonabant on body weight.

3.2.2. Fluid intake

Although the endocannabinoid system has a great impact on the regulation of energy homeostasis, its participation in the control of fluid intake remains elusive. A pioneer study has demonstrated that the exogenous administration of compounds derived from the plant *Cannabis sativa* inhibits water intake (Sofia & Knobloch, 1976). On the other hand, the CB1R blockade significantly reduced water intake in the experiments conducted by Gardner & Mallet (2006). Recent studies have also reported that endocannabinoids increase the preference for palatable solutions such as sucrose (Higgs et al., 2003; Jarrett et al., 2005), without altering the drinking of salty solutions or distilled water induced by fluid deprivation (Yoshida et al., 2010). However, these conflicting results could be explained, at least in part, by the parallel effects of the endocannabinoid system in the control of locomotor activity, which could directly interfere with the search for eating and drinking.

The specific appetite for sodium and water is a very important adaptative response recruited to restore body fluid homeostasis. However, the excessive intake of sodium in industrialized food has a great impact in modern society, since it may be directly associated with the impairment of cardiovascular and renal functions. The neuropeptide OT appears as an important negative modulator of salt appetite in rats, being particularly relevant in osmolality- but not in the sodium-dependent inhibition of this ingestive behaviour (Blackburn et al., 1993). Furthermore, OT has been implicated in the central inhibition of water intake induced by water deprivation, hypertonic saline administration and angiotensin II injection (Arletti et al., 1990). More recently, studies developed by Verty and co-workers (2004) revealed that these effects of OT on water intake may be partially mediated by CB1R.

An empirical and very interesting observation is that animals that undergo periods of restricted or no access to water also reduce their food consumption, being this anorexic state as long as the water restriction persists. It is believed that this reduction in food intake is a compensatory mechanism, since a slight change in the osmolality of the gastrointestinal tract circulation may be detected after the beginning of the digestive process. This would contribute to a further increase in the already enhanced plasma osmolality, constituting a very life-threatening situation. Although some studies suggest the participation of central increases in CRF in this anorexic response induced by chronic exposure to osmotic stress (Koob et al., 1993; Krahn et al., 1986; Morley, 1987), it is clear that this decreased food intake occurs earlier than the activation of the HPA axis. Accordingly, no changes in c-Fos/CRF immunoreactivity or CRF mRNA expression were found in the hypothalamus of animals submitted to 24 hours (h) water restriction, despite the fact that the anorexigenic response, as well as the decrease in body weight, had already been observed after this short period (Ruginsk et al., 2011).

Furthermore, it has been also demonstrated by Ruginsk and coworkers (2011) that the number of CART neurons activated to produce c-Fos is increased in the hypothalamus of 24h water-deprived rats. Since CART is a well-known anorexigenic peptide, these results suggest a possible intersection between pathways controlling food and fluid intake. These results further propose the existence of an osmolality-related mechanism in this interface, since the immunoreactivity for c-Fos/CART and the CART mRNA expression in the PVN and supraoptic (SON) nuclei of the hypothalamus were increased after hypertonic but not isotonic extracellular volume expansion (Ruginsk et al., 2011).

4. Endocannabinoids and the control of hydromineral homeostasis

The magnocellular neurosecretory system consists of a group of neurons whose cell bodies are located at the PVN and SON in the hypothalamus and whose terminals, located at the neurohypophysis, release vasopressin (AVP) and OT in response to depolarization. Both neuropeptides act in the kidneys to control the excretion of water and electrolytes. AVP is mostly known for its antidiuretic and vasoconstrictor effects, while OT, together with atrial natriuretic peptide (ANP) produced by the heart, are the two major circulating hormones stimulating natriuresis and diuresis.

Immunohistochemical studies have revealed that GR and MR are co-localized in the parvocellular subdivision of the PVN, but not in magnocellular neurons, which predominantly express MR (Han et al., 2005). Accordingly, it has been demonstrated that high doses of dexamethasone can inhibit OT but not AVP secretion in response to hypertonic extracellular volume expansion (Durló et al., 2004; Ruginsk et al., 2007) and central cholinergic, angiotensinergic and osmotic stimulation (Lauand et al., 2007). These effects were also correlated with immunohistochemical data, showing that the magnocellular neurons of the PVN and SON are inhibited by dexamethasone administration (Ruginsk et al., 2007).

More recently, the activation of membrane-associated glucocorticoid receptors has been proposed using hypothalamic slice preparations. It has been demonstrated that glucocorticoids could activate at least two divergent intracellular pathways mediated by $G_{\alpha s}$ and $G_{\beta\gamma}$ subunits. The local production of endocannabinoids and NO would then result in two synapse-specific mechanisms, respectively: 1) suppression of excitatory (glutamatergic) synaptic inputs and 2) facilitation of inhibitory (GABAergic) synaptic inputs to the hypothalamic magnocellular neurosecretory system (Di et al., 2003, 2005, 2009), consequently decreasing AVP and OT release from neurohypophyseal terminals. These actions on glutamatergic neurotransmission would be dependent on the activation of the CB1R, located mainly at presynaptic terminals. Accordingly, it has been recently demonstrated that the administration of rimonabant potentiates AVP and OT release as well as the number of c-Fos/AVP and c-Fos/OT double immunoreactive neurons in the PVN and SON of experimental animals submitted to hypertonic extracellular volume expansion (Ruginsk et al., 2010). Furthermore, the participation of the CB1R in the glucocorticoid-induced inhibition of the magnocellular neurosecretory system was clearly demonstrated by

the same group, since the previous administration of rimonabant reversed the inhibitory effects of dexamethasone on hormone release (Ruginsk et al., 2012).

Although many brain regions seem to share similar cellular mechanisms triggered by endocannabinoids, their central actions can vary widely within the CNS. Several studies suggest that the endocannabinoid system can mediate not only the central effects of glucocorticoids but also independently modulate the excitability of postsynaptic terminals after the dendritic-mediated release of neuropeptides like OT (Hirasawa et al., 2004; McDonald et al., 2008; Olier et al., 2007). This mechanism is likely to be implicated in the intra-hypothalamic feedback on hormone release and neuroplasticity (de Kock et al., 2003). The CB1R is also expressed in the NTS (Tsou et al., 1998), a key structure involved in the control of cardiovascular function that projects to the hypothalamus. Accordingly, the central administration of CB1R agonists was shown to reduce blood pressure and heart rate (Lake et al., 1997), while the microinjection of a CB1R antagonist into the NTS resulted in prolonged hypotension after activation of the baroreflex in experimental animals (Rademacher et al., 2003).

Besides participating in the central control of cardiovascular function, recent reports also suggest a role for peripherally-synthesized cannabinoids in the control of blood pressure. This hypothesis is supported by the evidence that the CB1R is expressed by human, rat and guinea-pig atria (Bonz et al., 2003; Kurz et al., 2008; Sterin-Borda et al., 2005). Within the heart, the activation of the CB1R induces a negative inotropic response on muscular fibers, thus reducing blood pressure. This is of particular interest for the study of the integrated cardiovascular and neuroendocrine responses to an increase in the circulating volume, since the distension of cardiac chambers (especially the right atria) in response to such experimental condition is the main stimulus for ANP secretion. Indeed, a role for the CB1R in ANP release has been recently proposed (Ruginsk et al., 2012), although further studies are needed to support this hypothesis.

5. Conclusions and perspectives

Besides the well-known effects on energy homeostasis and metabolism, the ability of glucocorticoids to suppress inflammatory responses has been extensively explored in therapeutics during the last fifty years. However, the clinical potential of glucocorticoids has not been fully achieved because of the severe dose-limiting side effects as well as the development of glucocorticoid resistance. More recently, a lot of expectation was put on characterization of non-steroidal dissociated GR agonists and modulators, which try to uncouple the desired and adverse effects of glucocorticoid administration based on the type of GR interaction with the DNA (transactivation and transrepression). However, the difficulty to transpose the effects to *in vivo* set-ups and their still unproved long-term safety have limited the use of these drugs in clinical practice so far.

In this context, different approaches to improve the benefit/risk ratio of glucocorticoids also include the development of drugs that selectively target the activation of membrane-associated GRs and its downstream nongenomic events, without evoking adverse effects,

primarily attributed to the activation of genomic pathways. Therefore, the study of the nongenomic actions of glucocorticoids has introduced a novel player in the complexity of the circuitries regulated by the HPA axis and the integrated control of homeostasis. The endocannabinoid system appears as an important mediator of both central and peripheral effects of glucocorticoids, constituting a possible target by which several aspects of stress-mediated responses and energy acquisition/expenditure could be manipulated under diverse physiological and pathological conditions.

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