Chapter 3

Glucocorticoid-Mediated Regulation of Circadian Rhythms: Interface with Energy Homeostasis and Reproduction

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Abstract

All living organisms have evolved by developing concomitant physiological and behavioral adaptations to environment. Through these processes, biological rhythms, such as reproduction, can be synchronized by environmental cues, which include not only the light/dark cycle itself but also the feeding pattern. These adaptations depend on two highly conserved and interrelated systems: an endogenous timing system and the hypothalamic-pituitary-adrenal (HPA) axis. In mammals, the biological circadian rhythms are controlled by a "master oscillator," the suprachiasmatic nucleus of the hypothalamus (SCN). Through neural signals to paraventricular nucleus of hypothalamus (PVN), the SCN also modulates the activation of the HPA axis, ultimately resulting in the circadian rhythm of glucocorticoid secretion by the adrenal cortex. Glucocorticoids, in turn, are well known for their important role in the regulation of energy homeostasis. Accordingly, obese animals exhibit increased glucocorticoid levels and are more susceptible to glucocorticoid-induced anabolic effects. In parallel, glucocorticoids modulate reproductive function and fertility: at physiological levels, glucocorticoids control the timing of puberty onset and gonadal steroidogenesis, as well modulate the immune system, which determines conception and pregnancy progression. However, stress-induced glucocorticoid secretion may exert a dual effect on reproductive function.

Keywords: glucocorticoids, hypothalamus, energy homeostasis, reproductive function, circadian rhythm

1. Introduction

Glucocorticoids are steroid hormones produced by the intermediate layer of the adrenal gland cortex (fasciculate zone) under the stimulation by the adrenocorticotropic hormone (ACTH), released from the anterior pituitary. ACTH secretion, in turn, is stimulated by corticotrophin-releasing hormone (CRH), produced by hypothalamic neurons and released into the portal pituitary capillary system. CRH, ACTH, and glucocorticoids (mainly cortisol in humans) integrate the hypothalamus-pituitary-adrenal (HPA) axis [1], whose activity influences a broad range of physiological functions such as metabolism, immune and inflammatory responses, as well as central nervous system activity [2].

The intracellular actions of glucocorticoids are mediated by the interaction with glucocorticoid (GR) and mineralocorticoid (MR) nuclear receptors, which hold great structural homology and are both ligand-driven transcription factors. In the cytoplasm of target cells, MRs and GRs exist at their unbound form; upon hormone binding, the receptor-ligand complex then translocates to the nucleus to modulate gene transcription [3]. It has been assumed that GR primarily mediates the reactive feedback during stressful episodes, whereas MR mediates the axis feedback during the nadir phase of the circadian rhythm [4].

MR and GR have also been identified in association with neuronal membranes [5], a signaling mechanism that is apparently shared by other steroid receptors [6]. Supporting this evidence, Evanson and coworkers [7] showed that stress-induced corticosterone secretion in rats is rapidly inhibited by the intrahypothalamic dexamethasone administration and that previous conjugation of dexamethasone to bovine serum albumin did not prevent dexamethasone-induced inhibition of ACTH release in stressed animals. Therefore, besides MR and GR being mostly known for their intracellular, delayed genomic role, these results make increasingly evident that these receptors can also mediate rapid, nongenomic signaling.

Indeed, transmembrane GRs seem to be upstream of a complex network controlling neuronal activity. It has been demonstrated that dexamethasone-induced activation of postsynaptic G-protein coupled receptors produces a rapid suppression of excitatory postsynaptic inputs in neurosecretory hypothalamic neurons [8, 9]. These effects were shown to be dependent upon the activation of nonconventional retrograde neurotransmission, mediated by the production of membrane-derived lipid mediators (endocannabinoids) and a gaseous modulator [nitric oxide (NO)]. These nongenomic glucocorticoid actions would accomplish, within the hypothalamus, for rapid, retrograde inhibition of glutamatergic (by endocannabinoids) and stimulation of GABAergic (by NO) signaling. Therefore, this simultaneous and rapid glucocorticoid-mediated and synapse-specific inhibition potentially impacts all the homeostatic responses initiated within hypothalamic nuclei in response to stress.

2. Glucocorticoids and the circadian rhythm

All living organisms have evolved by developing concomitant physiological and behavioral adaptations to environment. Through these processes, biological rhythms, such as reproduction,

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can be synchronized by environmental cues or "zeitgebers," which include not only the light/dark cycle itself but also the feeding pattern. These adaptations depend on two highly conserved and interrelated systems: an endogenous timing system and the HPA axis [10, 11].

The HPA axis circadian maturation may occur at early ages, influenced by prenatal and postnatal environmental synchronizers [12, 13]. In mammals, the biological circadian rhythms are controlled by a "master clock," the suprachiasmatic nucleus of the hypothalamus (SCN), which receives external information via the retinohypothalamic tract and synchronizes the "peripheral clocks," located in almost all organs and tissues [14].

The interaction between the circadian timing system and the HPA axis occurs at different signaling levels. Through neural signals to paraventricular nucleus of hypothalamus (PVN), the SCN also modulates the secretion of CRH, arginine vasopressin [(AVP), an ACTH secretagogue], and ACTH, ultimately resulting in the circadian rhythm of glucocorticoids secretion by the adrenal cortex [15]. The SCN also influences adrenal sensitivity to ACTH through the autonomic nervous system, in a second level of interaction [16].

The molecular machinery for the cell-autonomous circadian clock depends on transcriptional feedback loops. The two core clock proteins—CLOCK and BMAL1—form a heterodimer that activates the transcription of their target genes, *Period* (*Per*) and *Cryptochrome* (*Cry*). The proteins encoded by the genes *Pers* and *Crys* interact with the heterodimer CLOCK/BMAL1, inhibiting their own transcription. The genes *Rev-erbα* and *Rorα* also modulate this transcriptional loop, creating a repetitive and self-sustainable cycle of almost 24 h [17].

At transcriptional level, glucocorticoids synchronize central oscillators in some areas of the brain [18], influencing the expression of clock genes in response to a series of conditions. Glucocorticoids also modulate the circadian rhythm of peripheral oscillators [19–21], regulating the expression of clock genes through genomic actions mediated by activated GR [22]. *Per1* and *Per2* contain glucocorticoid-responsive elements (GREs), whereas *Rev-erbα* and *Rorα* are negatively regulated by glucocorticoids [23].

Additionally, the transcriptional activity of GR is reduced in response to acetylation of multiple lysine residues mediated by the CLOCK protein [24]. The CLOCK/BMAL1 heterodimer physically interacts with the ligand-binding domain (LBD) of the α-subunit of the glucocorticoid receptor (GRα) and represses the transcription of glucocorticoid-responsive genes [24, 25]. Furthermore, the posttranslational acetylation of GRα by CLOCK appears to repress the activation of genes targeted by GRα [25]. Taken together, these findings suggest that CLOCK/BMAL1 heterodimer behaves as a negative regulator of GRα in peripheral tissues, antagonizing the physiological actions of circulating glucocorticoids [24].

An interesting example of the complex interaction between the HPA axis and peripheral oscillators is provided by the modification of the daily dietary pattern, which is considered a powerful "zeitgeber" for the diurnal rhythm of glucocorticoid secretion [26, 27]. In rats, which are nocturnal animals, the change in dietary schedule to the light period results in the inversion of the circadian rhythm of the HPA axis, producing a corticosterone peak in the morning. This evidence reinforces the hypothesis that HPA axis activity is influenced not only by photic synchronizers such as the light/dark cycle but also by nonphotic clues, such as feeding episodes [28, 29].

Therefore, it is quite reasonable to assume that glucocorticoid signaling might somehow reset peripheral clocks in response to changes in feeding pattern [22]. However, larger phase shifts were observed in adrenalectomized (ADX) mice and rats submitted to daytime feeding, suggesting that glucocorticoids in fact inhibit rather than promote phase adjustments of peripheral oscillators to daytime feeding [20]. Based on this finding, it has been hypothesized that nutrient-sensing molecules, such as sirtuin-1 (SIRT1) and AMP-activated protein kinase (AMPK) may also act as clock-resetting signals in response to altered feeding time [30].

The literature clearly reveals feeding as a potent synchronizer of HPA axis activity in murines and the insight into this relationship for humans is not so clear. A study performed in male volunteers before and during Ramadan, the ninth month of the Muslim calendar, during which food intake is restricted to 9 p.m., showed that serum cortisol levels rose in the afternoon, whereas the morning cortisol rise was delayed, with a higher morning peak and a sharper decline, suggesting mealtime as a synchronizer also in humans [31]. A recent report reinforced this hypothesis, demonstrating profound changes in the diurnal expression of CLOCK in Ramadan practitioners [32]. On the other hand, obese women submitted to hypocaloric diet in different restricted feeding patterns demonstrated no significant changes in the circadian rhythm of cortisol secretion regardless the meal timing [33]. These conflicting results could be related to gender differences as well as the duration of feeding/restriction protocol, possibly indicating that a longer duration of altered feeding pattern could be also necessary to evoke those HPA axis changes.

Another line of evidence that has been recently revisited is the relative importance of environmental light (either natural or artificial) as one important "zeitgeber" for cortisol circadian rhythm in humans. Indeed, occasional or sustained (i.e., shift work, exposure to artificial light from electronic devices, etc.) alterations in the timing of the sleep-wake cycle or light exposure can lead to changes in circadian hormonal organization (including cortisol and melatonin secretion) and may contribute to negative health outcomes, such as obesity [34].

In summary, the endogenous timing system and the HPA axis modulate each other's activity through multilevel interactions, which ultimately coordinate homeostasis with the various environmental challenges. Therefore, uncoupling of these systems alters internal regulatory mechanisms and promotes pathologic changes in virtually all organs and tissues, especially those implicated in energy metabolism. Despite the significant progress that has been made during the past few years on the knowledge of molecular mechanisms underlying this multilevel communication, most of the physiologic and pathophysiologic aspects of this interplay remain to be elucidated.

3. Glucocorticoids and energy homeostasis

Energy homeostasis is basically defined as the balance between energy intake and expenditure, being regulated by central and peripheral factors. Feeding behavior is homeostatically controlled by peripheral factors (such as leptin and insulin, known as adiposity signals), as well as by gut-derived signals, classically known as satiety signals [35]. Leptin and insulin medi-

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ate the long-term control of energy homeostasis, by acting primarily in hypothalamic neurons that express orexigenic or anorexigenic neuropeptides [35]. Neuropeptide Y (NPY) and agouti-related protein (AgRP) in the arcuate nucleus of the hypothalamus (ARC), and orexins and melanin-concentrating hormone in the lateral hypothalamic area, constitute the classical hypothalamic orexigenic pathway. The hypothalamic anorexigenic circuit, in turn, includes proopiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART) in the ARC, and CRH and oxytocin (OT) in the PVN. On the other hand, brainstem areas, mainly the nucleus of the *tractus solitarii* (NTS), receive immediate information about the meal from satiety signals [mechanical and chemical stimulation of stomach and small intestine, as well as hormones released during a meal, as cholecystokinin (CCK)], and thus acutely regulate meal size [36].

Glucocorticoids appear as critical hormones regulating energy balance, given their participation in the metabolism of glucose, lipids, and proteins, as well as in the control of food intake and body weight gain and composition. As evidenced before, feeding also plays a key role as a rhythmicity synchronizer of the HPA axis [37], the amount of food ingested also being related to glucocorticoid secretion [38]. On a reciprocal way, increases in circulating glucocorticoids, in consequence to stress, therapeutic strategy, or Cushing's disease, lead to an enhancement in food intake and body weight gain, in addition to increased glucose production, decreased glucose transport and utilization, decreased protein synthesis, and increased muscular protein degradation [39, 40]. Long-term glucocorticoid treatment in intact rodents also induces the development of obesity, as well as other physiological hallmarks of metabolic syndrome, such as increased plasma leptin and insulin, increased plasma triglycerides, and impaired glucose tolerance [41, 42].

On the other hand, anorexia and body weight loss are typically found in response to chronic glucocorticoid deficiency, as observed in Addison's disease or primary adrenal insufficiency [43]. Similarly, removal of endogenous glucocorticoids by bilateral adrenalectomy (ADX) is a well-established experimental model to investigate the mechanisms underlying the hypophagic effect of human primary adrenal insufficiency [44–46]. An increased expression of the anorexigenic neuropeptides CRH and OT is indeed found in the PVN of ADX rats [45, 46], together with a reduction in the expression of the orexigenic neuropeptides NPY and AgRP in the ARC [47]. Surprisingly, ADX was shown to reduce the expression of POMC and CART in the ARC, suggesting that ADX-induced hypophagia may be somehow dissociated from the expression of these neuropeptides [48].

Interestingly, although serum cortisol levels are not clearly increased in human obesity, circulating corticosterone is enhanced in several murine obesity models, ADX being a very effective way to diminish hyperphagia and obesity under these experimental conditions [49, 50]. Reciprocally, obese animals seem to be more sensitive to the anabolic effects of glucocorticoids, evidenced by a higher response to CRH stimulation, as well as by enhanced basal and stimulated response to stress [51].

It is well established that glucocorticoids stimulate the drive to eat, and thus ADX-induced hypophagia involves, at least in part, a reduction on this stimulatory drive. However, glucocorticoids also seem to participate in the short-term control of food intake, since the anorexigenic effect of ADX is also associated with the increased activation of satiety-related responses in

the brainstem, primarily implicated in the control of meal size [44, 45]. In this context, it has been already demonstrated that the hypothalamus and the brainstem are reciprocally interconnected, and OT axonal projections from the PVN to the NTS were also enhanced following ADX [52]. Furthermore, the intracerebroventricular administration of type 2 CRH receptor and OT receptor antagonists reversed ADX-induced hypophagia and the increased activation of NTS neurons induced by feeding [45, 46, 52]. Actually, OT neurons of the PVN may act as downstream mediators of CRH effects on the enhanced meal-induced satiety induced by ADX [53].

Glucocorticoids are also known for their dual effects on lipid metabolism, which vary from lipogenic to lipolytic. White adipose tissue can be found in different regions of the body: in visceral or central depots (omental and mesenteric), found within the abdominal cavity associated with digestive organs, and in subcutaneous depots, located under the skin. In response to excessive energy intake and limited energy expenditure, energy homeostasis is disturbed and subcutaneous adipose tissue is recruited by acting as a metabolic sink, where excess free fatty acids (FFAs) and glycerol are stored as triglycerides (TGs) in adipocytes. If the storage capacity of subcutaneous adipose tissue is exceeded or its ability to generate new adipocytes is impaired, lipid begins to accumulate in areas outside the subcutaneous tissue, originating as visceral adiposity [54].

Indeed, the net effect of glucocorticoids on lipid storage appears to depend on the physiologic context and the type of fat depot. Glucocorticoids increase lipolysis in mature adipocytes as a result of increased transcription and expression of the adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL). ATGL is predominantly responsible for the first step of the process [conversion of triacylglycerol (TAG) to diacylglycerol, with the consequent release of one FFA], whereas HSL converts diacylglycerol to monoacylglycerol [55]. The lipolytic actions of glucocorticoids occur primarily under fasting conditions, characterized by a low-ratio insulin/glucagon, possibly through a permissive role on growth hormone- and catecholamine-induced lipolysis [56].

On the other hand, the lipogenic action of glucocorticoids is composed of several steps, starting with increases in caloric and dietary lipid intake and followed by an increased storage of lipids in the adipose tissue. Glucocorticoids enhance both adipocyte hyperplasia (through increased differentiation of preadipocytes to mature adipocytes) and hypertrophy (through increased synthesis and storage of lipids) [57].

The glucocorticoid-mediated hypertrophic process is accomplished by the deposition of FFA and TAG, originated either from dietary intake (chylomicrons) or from liver secretion [very low-density lipoproteins (VLDL)] and by the parallel stimulation of lipoprotein lipase (LPL), which in turn hydrolyses circulating TAG and increases the amount of FFA available for ectopic lipid accumulation (liver, muscle, and visceral adipocytes) [58]. Interestingly, insulin seems to be crucial for some of these effects, since it potentiates glucocorticoid-induced effects on LPL. Furthermore, treatment with glucocorticoid decreases glucose uptake and metabolism in the absence of insulin [59].

Additionally, glucocorticoids were also demonstrated to increase the secretion of VLDL by the liver (increasing TAG plasma levels), as well as to enhance *de novo* lipid production

in hepatocytes and adipocytes by stimulation of the key enzymes acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS) [55, 56, 58]. Furthermore, glucocorticoids stimulate the enzymatic routes for nicotinamide adenine dinucleotide phosphate (NADPH) generation, required for *de novo* lipogenesis [60].

Interestingly, these lipogenic effects of glucocorticoids are more effective in visceral than in subcutaneous tissue, since both LPL activity and the expression of GRs and MRs are greater in visceral compared to other adipose depots [61, 62]. In addition, elevated levels of type 1 11-beta-hydroxysteroid dehydrogenase (11b-HSD1), the enzyme that generates active glucocorticoid from inactive metabolites, are found in the adipose depots of obese subjects [63, 64]. Accordingly, higher activity of 11b-HSD1 within visceral *versus* subcutaneous adipose tissue suggests that this enzyme may be another target to mediate the site-specific actions of glucocorticoids in the adipose tissue [65]. Indeed, visceral adipose accumulation was observed in mice overexpressing 11b-HSD1, whereas inhibition of this enzyme improved metabolic parameters and reduced body weight in obese animals [66, 67]. Therefore, these results suggest that elevated 11b-HSD1 activity might be one of the causes rather than one of the consequences of visceral adiposity and obesity.

Furthermore, the glucocorticoid-induced increase in the circulating levels of TAG and FFA, besides producing dyslipidemia, is also known to restrict glucose utilization and leads to insulin resistance [68], resulting in other metabolic outcomes such as increased muscle proteolysis and hepatic gluconeogenesis. This impairment of insulin-stimulated glucose uptake in response to chronic exposure to increased levels of glucocorticoids may also be explained by decreased expression of insulin receptor or the insulin receptor substrate 1 (IRS1), with the consequent decrease in insulin binding, and decreased type 4 glucose transporter (GLUT4) translocation to cell membrane [56].

Therefore, it is suggested that the anabolic actions of glucocorticoids in lipid metabolism occur through their effects on the turnover and uptake of FFAs in adipose tissue. Considering that LPL and 11b-HSD1 activities, as well as GR and MR expressions, are higher in visceral fat than in any other adipose depot, glucocorticoids are likely to contribute to central adiposity. This would be also facilitated by an increased insulin/glucagon ratio, exhibited by individuals under positive energy balance and/or elevated glucocorticoid levels. In summary, glucocorticoids act though parallel prolipolytic, antilipolytic, and lipogenic mechanisms, with some of these mechanisms playing more important roles than the others depending on the physiological condition, targeted adipose tissue, and dose and duration of glucocorticoid exposure.

4. Glucocorticoids and reproductive function

In mammals, the capacity to reproduce is crucial to ensure the species perpetuation and is dependent on a functional hypothalamic-pituitary-gonadal (HPG) axis. In males, there is a regular and continuous pulsatile release of gonadotrophin-releasing hormone (GnRH) from hypothalamic neurons into the portal capillary system. In the anterior pituitary of both males and females, GnRH binds to its receptor in gonadotrophs, promoting the production and

release of the gonadotrophin-luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The systemically secreted gonadotrophins, in turn, act on ovaries and testis to stimulate hormone production and gametogenesis.

In males, the HPG axis is always under a negative feedback loop control. In females with spontaneous ovulation (such as rodents and women), however, the regulation of reproduction involves more complex mechanisms, including a cyclic and pulsatile GnRH secretion and the occurrence of preovulatory surges of gonadotrophins, which trigger ovulation.

During most of the cycle's duration, the female HPG axis is under the influence of the negative feedback mechanism exerted by low and moderate concentrations of estradiol, which inhibit the synthesis and release of GnRH and gonadotrophins. Just prior to ovulation, when a more acute estradiol peak takes place, together with a gradual increase in progesterone, the feedback loop changes from negative to positive, resulting in increased GnRH/LH synthesis and release.

The activity of GnRH neurons as well as of other HPG axis components is regulated by several factors, including the two newly discovered neuropeptides: kisspeptin and RF (Arg-Phe) amide-related peptide (RFRP). In rodents, kisspeptin neurons comprise two main hypothalamic populations: one located in the anteroventral periventricular (AVPV) nucleus of preoptic area (POA), whose function seems to be crucial for GnRH surge generation [69–71], and a second population localized in the ARC [69, 70].

Kisspeptin and RFRP exert opposing effects on GnRH secretion: the former stimulates GnRH release [69, 72], whereas RFRP inhibits it [73]. Kisspeptin binds to its cognate receptor KISS-1R, which is expressed, in a gender-independent manner [74, 75], in approximately 70% of GnRH neurons [74]. RFRP effects on GnRH secretion, in turn, seem to be mediated by a G protein-coupled receptor 147 (GPR147) (also known as NPFF1R). Studies have demonstrated that GPR147 is expressed in 15–33% of mice GnRH neurons, and also in kisspeptidergic neurons of the AVPV (5–16%) and ARC (25%) [76–78]. Furthermore, kisspeptin and RFRP neurons seem to mediate the ER-α-induced effects of estradiol on GnRH release [77, 79, 80]. Taken together, these data support the hypothesis that both kisspeptin and RFRP actively participate as neuroendocrine regulators of reproduction.

As discussed previously in this chapter, the master biological clock in mammals is located in the SCN and regulates the circadian rhythm of most biological functions. Evidence indicates that the SCN also integrates and synchronizes all the neuroendocrine events necessary for the activation of GnRH neurons, thereby controlling the onset of GnRH/LH preovulatory surge [81, 82]. The SCN neural outputs to GnRH neurons would involve two neuropeptides: AVP and vasoactive intestinal peptide (VIP). It has been reported that the VIPergic pathway directly modulates GnRH neurons [81, 83], whereas the circadian signaling of AVP to GnRH neurons would be indirectly mediated by AVPV kisspeptidergic neurons [84, 85]. Moreover, it has been recently suggested that the SCN, through VIPergic signaling, may suppress RFRP activity in the dorsomedial hypothalamus (DMH), allowing a full activation of the LH surge [86]. Therefore, the generation of GnRH/LH surges involves many neuroendocrine events that are dependent upon the positive feedback effects of estradiol (in females) and a circadian neural signal indirectly provided by the SCN [87].

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Glucocorticoids are also among the central mechanisms controlling HPG axis function. It is quite clear that exposure to increased glucocorticoid levels, either induced by stress condition or by exogenous administration, may significantly interfere with reproductive function, with massive impacts on fertility [88–90].

In this regard, it has been demonstrated that glucocorticoids inhibit GnRH secretion [91]. In GT1 cells, which synthesize GnRH, glucocorticoids repress GnRH gene expression and hormone release [92]. Glucocorticoids also induce a decrease in gonadotropin synthesis and secretion; however, this effect may be at least partially mediated by the inhibition of GnRH neurons and their neural inputs to gonadotrophs, since GR expression in the anterior pituitary is still controversial [93-95]. Glucocorticoids also decrease GnRH responsiveness in gonadotrophs, a mechanism that apparently underlies glucocorticoid-mediated inhibition of LH secretion [96].

Recently, evidence has been provided on the role of kisspeptin and RFRP also in the mediation of glucocorticoids' actions on the HPG axis. Both kisspeptidergic [97] and RFRP neurons [98] express GR, suggesting that these neuronal populations are responsive to glucocorticoids. Accordingly, corticosterone decreases hypothalamic kisspeptin gene expression and neuronal activity during the estradiol-induced LH surge [99].

The RFRP system has also been implicated in glucocorticoid-mediated effects [98, 100, 101]. Both acute and chronic stress stimulate the RFRP system activation, evidenced by an increase in RFRP mRNA expression [98, 102], which, in turn, suppresses GnRH mRNA levels [102] and LH secretion [98]. Conversely, RFRP expression induced by both acute and chronic immobilization stress is abolished by ADX [98].

In the testis, GR is expressed in both Leydig and Sertoli cells [103, 104], reinforcing the modulation of steroidogenesis, testosterone release, and spermatogenesis by glucocorticoids. Indeed, at physiological levels, glucocorticoids are required for testis development in the postnatal period [105], for the onset and maintenance of spermatogenesis [104, 105], as well as for sperm maturation [104] and erectile function [106]. High circulating levels of glucocorticoids, however, have been associated with disruption of male fertility, with inhibition of testosterone secretion, spermatogenesis, and libido [107, 108]. Indeed, chronic stress was also shown to induce an important reduction in spermatid number in male rats [109]. The induction of Leydig cell and germ cell apoptosis has also been reported in response to high glucocorticoid circulating levels [110]. Another hypothesis is that the LH receptor may be downregulated in Leydig cells in response to stress, thus suppressing testicular response to gonadotropins [111]. There is also evidence showing that glucocorticoids may induce the inhibition of enzymatic machinery required for testosterone biosynthesis [112–114].

In the ovaries, glucocorticoids can modulate the functions of granulosa, cumulus, and luteal cells [99], reducing ovarian response to gonadotropins through the inhibition of LH-induced steroidogenesis [115]. Similar results were obtained in response to dexamethasone in cultured rat preovulatory follicles [116]. Although glucocorticoids seem to impair oocyte development *in vitro* by increasing apoptosis [117], no alterations in oocyte maturation have been reported in response to high circulating levels of glucocorticoids *in vivo* [118]. However, the same study highlighted a decreased blastocyst formation, suggesting that glucocorticoids may alter the oocyte potential for fertilization rather than oocyte maturation.

5. Concluding remarks

Glucocorticoids exert diverse actions throughout the body and remarkably participate in the maintenance of homeostasis. Their importance for energy homeostasis may be illustrated by the fact that obese animals exhibit increased glucocorticoid levels and are more susceptible to glucocorticoid-induced anabolic effects, such as the increase in visceral fat depots. Increased glucocorticoid levels also directly impact food intake, which is consistent with the experimental evidence that the bilateral removal of adrenal glands (ADX) produces hypophagia and also improves other metabolic parameters in obesity models. At physiological levels, glucocorticoids also seem to be crucial for reproductive function, controlling the timing of puberty onset and gonadal steroidogenesis, as well modulating the immune system, which determines conception and pregnancy progression. This broad range of actions is coordinated by the circadian variation of glucocorticoid secretion and is accomplished by both neural interconnections at SCN level and also by the peripheral clocks, which adapt the central oscillator timing to individual organ requirements. This is particularly important for the essential hormone variation in female reproductive cycle. In the case of energy homeostasis, this circadian variation also receives important feed forward information from food intake, one of the most potent synchronizers of the HPA axis activity. Under a broader point of view, the actions mediated by glucocorticoids may permit environmental clues, such as food availability, or stressors, to match internal metabolic priorities, which determine not only individual but also the species survival.

Conflict of interest

All the authors state that they have no conflict of interest to declare.

Abbreviations

ACC	acetyl-CoA carboxylase
ACTH	adrenocorticotropic hormone
ADX	adrenalectomized
AgRP	agouti-related protein
AMPK	adenosine monophosphate-activated protein kinase
ARC	arcuate nucleus of the hypothalamus
ATGL	adipose triglyceride lipase
AVP	arginine vasopressin
AVPV	anteroventral periventricular nucleus

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CART	cocaine and amphetamine-regulated transcript
CCK	cholecystokinin
CRH	corticotrophin-releasing hormone
CRHr2	type 2 corticotrophin releasing hormone receptor
DMH	dorsomedial hypothalamus
FAS	fatty acid synthase
FFA	free fatty acids
FSH	follicle-stimulating hormone
GABA	gamma-aminobutyric acid
GLUT4	type 4 glucose transporter
GnRH	gonadotrophin-releasing hormone
GR	glucocorticoid receptor
GRE	glucocorticoid-responsive element
GRα	α-subunit of the glucocorticoid receptor
HPA	hypothalamus-pituitary-adrenal
HPG	hypothalamic-pituitary-gonadal
HSL	hormone-sensitive lipase
IRS1	insulin receptor substrate 1
KISS-1R	type 1 kisspeptin receptor
LH	luteinizing hormone
LPL	lipoprotein lipase
MR	mineralocorticoid receptor
NADPH	nicotinamide adenine dinucleotide phosphate
NO	nitric oxide
NPY	neuropeptide Y
NTS	nucleus of the solitary tract
OT	oxytocin
OTr	oxytocin receptor

POA	preoptic area
POMC	proopiomelanocortin
PVN	paraventricular nucleus of hypothalamus
RFRP	RF (Arg-Phe) amide-related peptide
SCN	suprachiasmatic nucleus of the hypothalamus
SIRT1	sirtuin-1
TAG	triacylglycerol
TG	triglyceride
VIP	vasoactive intestinal peptide
VLDL	very low-density lipoproteins

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References

[1] Papadimitriou A, Priftis KN. Regulation of the hypothalamic-pituitary-adrenal axis. Neuroimmunomodulation. 2009;**16**(5):265-271. DOI: 10.1159/000216184

[2] Chrousos GP, Charmandari E, Kino T. Glucocorticoid action networks—An introduction to systems biology. The Journal of Clinical Endocrinology and Metabolism. 2004;**89**(2):563-564. DOI: 10.1210/jc.2003-032026

[3] Beato M, Sánchez-Pacheco A. Interaction of steroid hormone receptors with the transcription initiation complex. Endocrine Reviews. 1996;**17**(6):587-609. DOI: 10.1210/edrv-17-6-587

[4] Uchoa ET, Aguilera G, Herman JP, Fiedler JL, Deak T, de Sousa MB. Novel aspects of glucocorticoid actions. Journal of Neuroendocrinology. 2014;**26**(9):557-572. DOI: 10.1111/jne.12157

[5] Groeneweg FL, Karst H, de Kloet ER, Joëls M. Mineralocorticoid and glucocorticoid receptors at the neuronal membrane, regulators of nongenomic corticosteroid signalling. Molecular and Cellular Endocrinology. 2012;**350**(2):299-309. DOI: 10.1016/j.mce.2011.06.020

[6] Srivastava DP, Evans PD. G-protein oestrogen receptor 1: Trials and tribulations of a membrane oestrogen receptor. Journal of Neuroendocrinology. 2013;**25**(11):1219-1230. DOI: 10.1111/jne.12071

[7] Evanson NK, Tasker JG, Hill MN, Hillard CJ, Herman JP. Fast feedback inhibition of the HPA axis by glucocorticoids is mediated by endocannabinoid signaling. Endocrinology. 2010;**151**(10):4811-4819. DOI: 10.1210/en.2010-0285

[8] Di S, Maxson MM, Franco A, Tasker JG. Glucocorticoids regulate glutamate and GABA synapse-specific retrograde transmission via divergent nongenomic signaling pathways. The Journal of Neuroscience. 2009;**29**(2):393-401. DOI: 10.1523/JNEUROSCI.4546-08.2009

[9] Nahar J, Haam J, Chen C, Jiang Z, Glatzer NR, Muglia LJ, Dohanich GP, Herman JP, Tasker JG. Rapid nongenomic glucocorticoid actions in male mouse hypothalamic neuroendocrine cells are dependent on the nuclear glucocorticoid receptor. Endocrinology. 2015;**156**(8):2831-2842. DOI: 10.1210/en.2015-1273

[10] Nader N, Chrousos GP, Kino T. Interactions of the circadian CLOCK system and the HPA axis. Trends in Endocrinology and Metabolism. 2010;**21**(5):277-286. DOI: 10.1016/j.tem.2009.12.011

[11] Nicolaides NC, Charmandari E, Chrousos GP, Kino T. Circadian endocrine rhythms: The hypothalamic-pituitary-adrenal axis and its actions. Annals of the New York Academy of Sciences. 2014;**1318**:71-80. DOI: 10.1111/nyas.12464

[12] Custodio RJ, Junior CE, Milani SL, Simões AL, de Castro M, Moreira AC. The emergence of the cortisol circadian rhythm in monozygotic and dizygotic twin infants: The twin-pair synchrony. Clinical Endocrinology. 2007;**66**(2):192-197. DOI: 10.1111/j.1365-2265.2006.02706.x

[13] Roa SLR, Martinez EZ, Martins CS, Antonini SR, de Castro M, Moreira AC. Postnatal ontogeny of the circadian expression of the adrenal clock genes and corticosterone rhythm in male rats. Endocrinology. 2017;**158**(5):1339-1346. DOI: 10.1210/en.2016-1782

[14] Reppert SM, Weaver DR. Molecular analysis of mammalian circadian rhythms. Annual Review of Physiology. 2001;**63**:647-676. DOI: 10.1146/annurev.physiol.63.1.647

[15] Kalsbeek A, Palm IF, La Fleur SE, Scheer FA, Perreau-Lenz S, Ruiter M, Kreier F, Cailotto C, Buijs RM. SCN outputs and the hypothalamic balance of life. Journal of Biological Rhythms. 2006;**21**(6):458-469. DOI: 10.1177/0748730406293854

[16] Ulrich-Lai YM, Arnhold MM, Engeland WC. Adrenal splanchnic innervations contributes to the diurnal rhythm of plasma corticosterone in rats by modulating adrenal sensitivity to ACTH. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 2006;**290**(4):R1128-R1135. DOI: 10.1152/ajpregu.00042.2003

[17] Green Green CB, Takahashi JS, Bass J. The meter of metabolism. Cell. 2008;**134**(5):728-742. DOI: 10.1016/j.cell.2008.08.022

[18] Segall LA, Perrin JS, Walker CD, Stewart J, Amir S. Glucocorticoid rhythms control the rhythm of expression of the clock protein, Period2, in oval nucleus of the bed nucleus of the stria terminalis and central nucleus of the amygdala in rats. Neuroscience. 2006;**140**(3):753-757. DOI: 10.1016/j.neuroscience.2006.03.037

[19] Oishi K, Amagai N, Shirai H, Kadota K, Ohkura N, Ishida N. Genome-wide expression analysis reveals 100 adrenal gland-dependent circadian genes in the mouse liver. DNA Research. 2005;**12**(3):191-202. DOI: 10.1093/dnares/dsi003

[20] Le Minh N, Damiola F, Tronche F, Schütz G, Schibler U. Glucocorticoid hormones inhibit food-induced phase-shifting of peripheral circadian oscillators. The EMBO Journal. 2001;**20**(24):7128-7136. DOI: 10.1093/emboj/20.24.7128

[21] Kino T, Chrousos GP. Circadian CLOCK-mediated regulation of target-tissue sensitivity to glucocorticoids: Implications for cardiometabolic diseases. Endocrine Development. 2011;**20**:116-126. DOI: 10.1159/000321232

[22] Balsalobre A, Brown SA, Marcacci L, Tronche F, Kellendonk C, Reichardt HM, Schütz G, Schibler U. Resetting of circadian time in peripheral tissues by glucocorticoid signaling. Science. 2000;**289**(5488):2344-2347. DOI: 10.1126/science.289.5488.2344

[23] Surjit M, Ganti KP, Mukherji A, Ye T, Hua G, Metzger D, Li M, Chambon P. Widespread negative response elements mediate direct repression by agonist-liganded glucocorticoid receptor. Cell. 2011;**145**(2):224-241. DOI: 10.1016/j.cell.2011.03.027

[24] Nader N, Chrousos GP, Kino T. Circadian rhythm transcription factor CLOCK regulates the transcriptional activity of the glucocorticoid receptor by acetylating its hinge region lysine cluster: Potential physiological implications. The FASEB Journal. 2009;**23**(5):1572-1583. DOI: 10.1096/fj.08-117697

[25] Doi M, Hirayama J, Sassone-Corsi P. Circadian regulator CLOCK is a histone acetyltransferase. Cell. 2006;**125**(3):497-508. DOI: 10.1016/j.cell.2006.03.033

[26] Krieger DT. Food and water restriction shifts corticosterone, temperature, activity and brain amine periodicity. Endocrinology. 1974;**95**(5):1195-1201. DOI: 10.1210/endo-95-5-1195

[27] Leal AM, Moreira AC. Feeding and the diurnal variation of the hypothalamic-pituitary-adrenal axis and its responses to CRH and ACTH in rats. Neuroendocrinology. 1996;**64**(1):14-19. DOI: 10.1159/000127092

[28] Girotti M, Weinberg MS, Spencer RL. Differential responses of hypothalamus-pituitary-adrenal axis immediate early genes to corticosterone and circadian drive. Endocrinology. 2007;**148**(5):2542-2552. DOI: 10.1210/en.2006-1304

[29] De Araujo LD, Roa SL, Bueno AC, Coeli-Lacchini FB, Martins CS, Uchoa ET, Antunes-Rodrigues J, Elias LL, Elias PC, Moreira AC, Castro M. Restricted feeding schedules modulate in a different manner the expression of clock genes in rat hypothalamic nuclei. Frontiers in Neuroscience. 2016;**10**:567. DOI: 10.3389/fnins.2016.00567

[30] Asher G, Schibler U. Crosstalk between components of circadian and metabolic cycles in mammals. Cell Metabolism. 2011;**13**(2):125-137. DOI: 10.1016/j.cmet.2011.01.006

[31] Bogdan A, Bouchareb B, Touitou Y. Ramadan fasting alters endocrine and neuroendocrine circadian patterns. Meal-time as a synchronizer in humans? Life Sciences. 2001; **68**(14):1607-1615. DOI: 10.1016/S0024-3205(01)00966-3

[32] Ajabnoor GM, Bahijri S, Shaik NA, Borai A, Alamoudi AA, Al-Aama JY, Chrousos GP. Ramadan fasting in Saudi Arabia is associated with altered expression of CLOCK, DUSP and IL-1alpha genes, as well as changes in cardiometabolic risk factors. PLoS One. 2017;**12**(4):e0174342. DOI: 10.1371/journal.pone.0174342

[33] Nonino-Borges CB, Borges RM, Bavaresco M, Suen VM, Moreira AC, Marchini JS. Influence of meal time on salivary circadian cortisol rhythms and weight loss in obese women. Nutrition. 2007;**23**(5):385-391. DOI: 10.1016/j.nut.2007.02.007

[34] Cipolla-Neto J, Amaral FG, Afeche SC, Tan DX, Reiter RJ. Melatonin, energy metabolism, and obesity: A review. Journal of Pineal Research. 2014;**56**(4):371-381. DOI: 10.1111/jpi.12137

[35] Schwartz MW, Woods SC, Porte JRD, Seeley RJ, Baskin DG. Central nervous system control of food intake. Nature. 2000;**404**(6778):661-671. DOI: 10.1038/35007534

[36] Havel PJ. Peripheral signals conveying metabolic information to the brain: Short-term and long-term regulation of food intake and energy homeostasis. Experimental Biology and Medicine. 2001;**226**(11):963-977. PMID: 11743131

[37] Leal AM, Moreira AC. Food and the circadian activity of the hypothalamic-pituitary-adrenal axis. Brazilian Journal of Medical and Biological Research. 1997;**30**(12):1391-1405. DOI: 10.1590/S0100-879X1997001200003

[38] Honma KI, Honma S, Hiroshige T. Critical role of food amount for prefeeding corticosterone peak in rats. The American Journal of Physiology. 1983;**245**(3):R339-R344. PMID: 6614204

[39] Tataranni PA, Larson DE, Snitker S, Young JB, Flatt JP, Ravussin E. Effects of glucocorticoids on energy metabolism and food intake in humans. The American Journal of Physiology. 1996;**271**(2 Pt 1):E317-E325. DOI: 10.1152/ajpendo.1996.271.2.E317

[40] Shibli-Rahhal A, Van Bee M, Schlechte JA. Cushing's syndrome. Clinics in Dermatology. 2006;**24**(4):260-265. DOI: 10.1016/j.clindermatol.2006.04.012

[41] Karatsoreos IN, Bhagat SM, Bowles NP, Weil ZM, Pfaff DW, McEwen BS. Endocrine and physiological changes in response to chronic corticosterone: A potential model of the metabolic syndrome in mouse. Endocrinology. 2010;**151**(5):2117-2127. DOI: 10.1210/en.2009-1436

[42] Cassano AE, White JR, Penraat KA, Wilson CD, Rasmussen S, Karatsoreos IN. Anatomic, hematologic, and biochemical features of C57BL/6NCrl mice maintained on chronic oral corticosterone. Comparative Medicine. 2012;**62**(5):348-360. PMID: 23114038

[43] Nieman LK, Chanco-Turner ML. Addison's disease. Clinics in Dermatology. 2006; **24**(4):276-280. DOI: 10.1016/j.clindermatol.2006.04.006

[44] Uchoa ET, Sabino HA, Ruginsk SG, Antunes-Rodrigues J, Elias LL. Hypophagia induced by glucocorticoid deficiency is associated with an increased activation of satiety-related responses. Journal of Applied Physiology. 2009;**106**(2):596-604. DOI: 10.1152/japplphysiol.90865.2008

[45] Uchoa ET, Silva LE, de Castro M, Antunes-Rodrigues J, Elias LL. Hypothalamic oxytocin neurons modulate hypophagic effect induced by adrenalectomy. Hormones and Behavior. 2009;**56**(5):532-538. DOI: 10.1016/j.yhbeh.2009.09.007

[46] Uchoa ET, Silva LE, de Castro M, Antunes-Rodrigues J, Elias LL. Corticotrophin-releasing factor mediates hypophagia after adrenalectomy, increasing meal-related satiety responses. Hormones and Behavior. 2010;**58**(5):714-719. DOI: 10.1016/j.yhbeh.2010.07.003

[47] Uchoa ET, Silva LE, de Castro M, Antunes-Rodrigues J, Elias LL. Glucocorticoids are required for meal-induced changes in the expression of hypothalamic neuropeptides. Neuropeptides. 2012;**46**(3):119-124. DOI: 10.1016/j.npep.2012.02.002

[48] Germano CM, Castro M, Rorato R, Laguna MT, Antunes-Rodrigues J, Elias CF, Elias LL. Time course effects of adrenalectomy and food intake on cocaine- and amphetamine-regulated transcript expression in the hypothalamus. Brain Research. 2007;**1166**:55-64. DOI: 10.1016/j.brainres.2007.05.077

[49] Bruce BK, King BM, Phelps GR, Veitia MC. Effects of adrenalectomy and corticosterone administration on hypothalamic obesity in rats. The American Journal of Physiology. 1982;**243**(2):E152-E157. DOI: 10.1152/ajpendo.1982.243.2.E152

[50] Yukimura Y, Bray GA, Wolfsen AR. Some effects of adrenalectomy in the fatty rat. Endocrinology. 1978;**103**(5):1924-1928. DOI: 10.1210/endo-103-5-1924

[51] McGinnis R, Walker J, Margules D. Genetically obese (ob/ob) mice are hypersensitive to glucocorticoid stimulation of feeding but dramatically resist glucocorticoid-induced weight loss. Life Sciences. 1987;**40**(16):1561-1570. DOI: 10.1016/0024-3205(87)90121-4

[52] Uchoa ET, Zahm DS, de Carvalho Borges B, Rorato R, Antunes-Rodrigues J, Elias LL. Oxytocin projections to the nucleus of the solitary tract contribute to the increased meal-related satiety responses in primary adrenal insufficiency. Experimental Physiology. 2013;**98**(10):1495-1504. DOI: 10.1113/expphysiol.2013.073726

[53] Uchoa ET, Rorato R, Ruginsk SG, Borges Bde C, Antunes-Rodrigues J, Elias LL. Corticotrophin-releasing factor receptor 2 mediates the enhanced activation of satiety-related responses through oxytocin neurons in the paraventricular nucleus of the hypothalamus after adrenalectomy. Neuroscience Letters. 2015;**606**:123-128. DOI: 10.1016/j.neulet.2015.08.045

[54] Ibrahim MM. Subcutaneous and visceral adipose tissue: Structural and functional differences. Obesity Reviews. 2010;**11**(1):11-18. DOI: 10.1111/j.1467-789X.2009.00623.x

[55] Peckett AJ, Wright DC, Riddell MC. The effects of glucocorticoids on adipose tissue lipid metabolism. Metabolism. 2011;**60**(11):1500-1510. DOI: 10.1016/j.metabol.2011.06.012

[56] Lee MJ, Pramyothin P, Karastergiou K, Fried SK. Deconstructing the roles of glucocorticoids in adipose tissue biology and the development of central obesity. Biochimica et Biophysica Acta. 2014;**1842**(3):473-481. DOI: 10.1016/j.bbadis.2013.05.029

[57] Galitzky J, Bouloumié A. Human visceral-fat-specific glucocorticoid tuning of adipogenesis. Cell Metabolism. 2013;**18**(1):3-5. DOI: 10.1016/j.cmet.2013.06.008

[58] Spencer SJ, Tilbrook A. The glucocorticoid contribution to obesity. Stress. 2011;**4**(3):233-246. DOI: 10.3109/10253890.2010.534831

[59] Ashby P, Robinson DS. Effects of insulin, glucocorticoids and adrenaline on the activity of rat adipose-tissue lipoprotein lipids. The Biochemical Journal. 1980;**188**(1):185-192. DOI: 10.1042/bj1880185

[60] Vienberg SG, Björnholm M. Chronic glucocorticoid treatment increases de novo lipogenesis in visceral adipose tissue. Acta Physiologica (Oxford, England). 2014;**211**(2):257-259. DOI: 10.1111/apha.12283

[61] Wajchenberg BL, Giannella-Neto D, da Silva ME, Santos RF. Depot-specific hormonal characteristics of subcutaneous and visceral adipose tissue and their relation to the metabolic syndrome. Hormone and Metabolic Research. 2002;**34**(11-12):616-621. DOI: 10.1055/s-2002-38256

[62] Rebuffé-Scrive M, Brönnegard M, Nilsson A, Eldh J, Gustafsson JA, Björntorp P. Steroid hormone receptors in human adipose tissues. The Journal of Clinical Endocrinology and Metabolism. 1990;**71**(5):1215-1219. DOI: 10.1210/jcem-71-5-1215

[63] Desbriere R, Vuaroqueaux V, Achard V, Boullu-Ciocca S, Labuhn M, Dutour A, Grino M. 11beta-hydroxysteroid dehydrogenase type 1 mRNA is increased in both visceral and subcutaneous adipose tissue of obese patients. Obesity (Silver Spring). 2006;**14**(5):794-798. DOI: 10.1038/oby.2006.92

[64] Rask E, Walker BR, Söderberg S, Livingstone DE, Eliasson M, Johnson O, Andrew R, Olsson T. Tissue-specific changes in peripheral cortisol metabolism in obese women: Increased adipose 11beta-hydroxysteroid dehydrogenase type 1 activity. The Journal of Clinical Endocrinology and Metabolism. 2002;**87**(7):3330-3336. DOI: 10.1210/jcem.87.7.8661

[65] Veilleux A, Rhéaume C, Daris M, Luu-The V, Tchernof A. Omental adipose tissue type 1 11 beta-hydroxysteroid dehydrogenase oxoreductase activity, body fat distribution, and metabolic alterations in women. The Journal of Clinical Endocrinology and Metabolism. 2009;**94**(9):3550-3557. DOI: 10.1210/jc.2008-2011

[66] Masuzaki H, Paterson J, Shinyama H, Morton NM, Mullins JJ, Seckl JR, Flier JS. A transgenic model of visceral obesity and the metabolic syndrome. Science. 2001;**294**(5549): 2166-2170. DOI: 10.1126/science.1066285

[67] Tiwari A. INCB-13739, an 11beta-hydroxysteroid dehydrogenase type 1 inhibitor for the treatment of type 2 diabetes. IDrugs: The Investigational Drugs Journal. 2010;**13**(4): 266-275 20373256

[68] Arner P. Insulin resistance in type 2 diabetes: Role of fatty acids. Diabetes/Metabolism Research and Reviews. 2002;**18**(Suppl.2):S5-9, 2002. DOI: 10.1002/dmrr.254

[69] Clarkson J, d'Anglemont de Tassigny X, Moreno AS, Colledge WH, Herbison AE. Kisspeptin-GPR54 signaling is essential for preovulatory gonadotropin-releasing hormone neuron activation and the luteinizing hormone surge. The Journal of Neuroscience. 2008;**28**(35):8691-8697. DOI: 10.1523/JNEUROSCI.1775-08.2008

[70] Smith JT, Cunningham MJ, Rissman EF, Clifton DK, Steiner RA. Regulation of Kiss1 gene expression in the brain of the female mouse. Endocrinology. 2005;**146**:3686-3692. DOI: 10.1210/en.2005-0488

[71] Smith JT, Clifton DK, Steiner RA. Regulation of the neuroendocrine reproductive axis by kisspeptin-GPR54 signaling. Reproduction. 2006;**131**(4):623-630. DOI: 10.1530/rep.1.00368

[72] Piet R, de Croft S, Liu X, Herbison AE. Electrical properties of kisspeptin neurons and their regulation of GnRH neurons. Frontiers in Neuroendocrinology. 2015;**36**:15-27. DOI: 10.1016/j.yfrne.2014.05.006

[73] Pineda R, Garcia-Galiano D, Sanchez-Garrido MA, et al. Characterization of the inhibitory roles of RFRP3, the mammalian ortholog of GnIH, in the control of gonadotropin secretion in the rat: In vivo and in vitro studies. American Journal of Physiology. Endocrinology and Metabolism. 2010;**299**(1):E39-E46. DOI: 10.1152/ajpendo.00108.2010

[74] Messager S, Chatzidaki EE, Ma D, et al. Kisspeptin directly stimulates gonadotropin releasing hormone release via G protein-coupled receptor 54. Proceedings of the National Academy of Sciences of the United States of America. 2005;**102**(5):1761-1766. DOI: 10.1073/pnas.0409330102

[75] Herbison AE, Xd d T, Doran J, Colledge WH. Distribution and postnatal development of Gpr54 gene expression in mouse brain and gonadotropin-releasing hormone neurons. Endocrinology. 2010;**151**(1):312-321. DOI: 10.1210/en.2009-0552

[76] Rizwan MZ, Poling MC, Corr M, Cornes PA, Augustine RA, Quennell JH, Kauffman AS, Anderson GM. RFamide-related peptide-3 receptor gene expression in GnRH

and kisspeptin neurons and GnRH-dependent mechanism of action. Endocrinology. 2012;**153**:3770-3779. DOI: 10.1210/en.2012-1133

[77] Poling MC, Kim J, Dhamija S, Kauffman AS. Development, sex steroid regulation, and phenotypic characterization of RFamide-related peptide (Rfrp) gene expression and RFamide receptors in the mouse hypothalamus. Endocrinology. 2012;**153**:1827-1840. DOI: 10.1210/en.2011-2049

[78] Poling MC, Quennell JH, Anderson GM, Kauffman AS. Kisspeptin neurons do not directly signal to RFRP-3 neurones but RFRP-3 may directly modulate a subset of hypothalamic kisspeptin cells in mice. Journal of Neuroendocrinology. 2013;**25**:876-886. DOI: 10.1111/jne.12084

[79] Dubois SL, Acosta-Martínez M, DeJoseph MR, Wolfe A, Radovick S, Boehm U, et al. Positive, but not negative feedback actions of estradiol in adult female mice require estrogen receptor α in kisspeptin neurons. Endocrinology. 2015;**156**:1111-1120. DOI: 10.1210/en.2014-1851

[80] Molnar CS, Kallo I, Liposits Z, Hrabovszky E. Estradiol down-regulates RFamide-related peptide (RFRP) expression in the mouse hypothalamus. Endocrinology. 2011;**152**: 1684-1690. DOI: 10.1210/en.2010-1418

[81] Van der Beek EM, Horvath TL, Wiegant VM, Van den Hurk R, Buijs RM. Evidence for a direct neuronal pathway from the suprachiasmatic nucleus to the gonadotropin-releasing hormone system: Combined tracing and light and electron microscopic immunocytochemical studies. The Journal of Comparative Neurology. 1997;**384**(4):569-579. PMID: 9259490

[82] Tsukahara S. Increased Fos immunoreactivity in suprachiasmatic nucleus before luteinizing hormone surge in estrogen-treated ovariectomized female rats. Neuroendocrinology. 2006;**83**(5-6):303-312. DOI: 10.1159/000095341

[83] Smith MJ, Jiennes L, Wise PM. Localization of the VIP2 receptor protein on GnRH neurons in the female rat. Endocrinology. 2000;**141**(11):4317-4320. DOI: 10.1210/endo.141.11.7876

[84] Vida B, Deli L, Hrabovszky E, Kalamatianos T, Caraty A, Coen CW, Liposits Z, Kalló I. Evidence for suprachiasmatic vasopressin neurones innervating kisspeptin neurones in the rostral periventricular area of the mouse brain: Regulation by oestrogen. Journal of Neuroendocrinology. 2010;**22**(9):1032-1039. DOI: 10.1111/j.1365-2826.2010.02045.x

[85] Williams WP 3rd, Jarjisian SG, Mikkelsen JD, Kriegsfeld LJ. Circadian control of kisspeptin and a gated GnRH response mediate the preovulatory luteinizing hormone surge. Endocrinology 2011; 152(2):595-606. DOI: 10.1210/en.2010-0943

[86] Russo KA, La JL, Stephens SB, Poling MC, Padgaonkar NA, Jennings KJ, Piekarski DJ, Kauffman AS, Kriegsfeld LJ. Circadian control of the female reproductive Axis

through gated responsiveness of the RFRP-3 system to VIP signaling. Endocrinology. 2015;**156**:2608-2618. DOI: 10.1210/en.2014-1762

[87] Beymer M, Henningsen J, Bahougne T, Simonneaux V. The role of kisspeptin and RFRP in the circadian control of female reproduction. Molecular and Cellular Endocrinology. 2016;**438**:89-99. DOI: 10.1016/j.mce.2016.06.026

[88] Whirledge S, Cidlowski JA. A role for glucocorti-coids in stress-impaired reproduction: Beyond the hypothalamus and pituitary. Endocrinology. 2013;**154**:4450-4468. DOI: 10.1210/en.2013-1652

[89] Breen KM, Mellon PL. Influence of stress-induced intermediates on gonadotropin gene expression in gonadotrope cells. Molecular and Cellular Endocrinology. 2014;**385**:71-77. DOI: 10.1016/j.mce.2013.08.014

[90] Geraghty AC, Kaufer D. Glucocorticoid regulation of reproduction. Advances in Experimental Medicine and Biology. 2015;**872**:253-278. DOI: 10.1007/978-1-4939-2895-8_11

[91] Kamel F, Kubajak CL. Modulation of gonadotropin secretion by corticosterone: Interaction with gonadal steroids and mechanism of action. Endocrinology. 1987;**121**:561-568. DOI: 10.1210/endo-121-2-561

[92] Attardi B, Tsujii T, Friedman R, Zeng Z, Roberts JL, Dellovade TL, Pfaff DW, Chandran UR, Sullivan MW, DB DF. Glucocorticoid repression of gonadotropin-releasing hormone gene expression and secretion in morphologically distinct subpopulations of GT1-7 cells. Molecular and Cellular Endocrinology. 1997;**131**:241-255. DOI: 10.1016/S0303-7207(97)00102-0

[93] Kononen J, Hokaneimi J, Gustafsson JA, Pelto-Huikko M. Glucocorticoid receptor colocalization with pituitary hormones in the rat pituitary gland. Molecular and Cellular Endocrinology. 1993;**93**:97-103. PMID: 8319836

[94] Breen KM, Karsch FJ. New insights regarding glucocorticoids, stress and gonadotropin suppression. Frontiers in Neuroendocrinology. 2006;**27**(2):233-245. DOI: 10.1016/j.yfrne.2006.03.335

[95] Breen KM, Thackray VG, Hsu T, Mak-McCully RA, Coss D, Mellon PL. Stress levels of glucocorticoids inhibit LHbeta-subunit gene expression in gonadotrope cells. Molecular Endocrinology. 2012;**26**:1716-1731. DOI: 10.1210/me.2011-1327

[96] Kotitschke A, Sadie-Van Gijsen H, Avenant C, Fernandes S, Hapgood JP. Genomic and nongenomic cross talk between the gonadotropin-releasing hormone receptor and glucocorticoid receptor signaling pathways. Molecular Endocrinology. 2009;**23**(11):1726-1745. DOI: 10.1210/me.2008-0462

[97] Takumi K, Iijima N, Higo S, Ozawa H. Immunohistochemical analysis of the colocalization of corticotropin-releasing hormone receptor and glucocorticoid receptor in kisspeptin neurons in the hypothalamus of female rats. Neuroscience Letters. 2012;**531**(1):40-45. DOI: 10.1016/j.neulet.2012.10.010

[98] Kirby ED, Geraghty AC, Ubuka T, Bentley GE, Kaufer D. Stress increases putative gonadotropin inhibitory hormone and decreases luteinizing hormone in male rats. Proceedings of the National Academy of Sciences of the United States of America. 2009;**106**(27):11324-11329. DOI: 10.1073/pnas.0901176106

[99] Luo E, Stephens SB, Chaing S, Munaganuru N, Kauffman AS, Breen KM. Corticosterone blocks ovarian cyclicity and the LH surge via decreased kisspeptin neuron activation in female mice. Endocrinology. 2016;**157**:1187-1199. DOI: 10.1210/en.2015-1711

[100] Calisi RM, Rizzo NO, Bentley GE. Seasonal differences in hypothalamic EGR-1 and GnIH expression following capture-handling stress in house sparrows (*Passer domesticus*). General and Comparative Endocrinology. 2008;**157**:283-287. DOI: 10.1016/j.ygcen.2008.05.010

[101] Kaewwongse M, Takayanagi Y, Onaka T. Effects of RFamide-related peptide (RFRP)-1 and RFRP-3 on oxytocin release and anxiety-related behaviour in rats. Journal of Neuroendocrinology. 2010;**23**:20-27. DOI: 10.1111/j.1365-2826.2010.02077.x

[102] Soga T, Dalpatadu SL, Wong DW, Parhar IS. Neonatal dexamethasone exposure down-regulates GnRH expression through the GnIH pathway in female mice. Neuroscience. 2012;**218**:56-64. DOI: 10.1016/j.neuroscience.2012.05.023

[103] Schultz R, Isola J, Parvinen M, Honkaniemi J, Wikström AC, Gustafsson JA, Pelto-Huikko M. Localization of the glucocorticoid receptor in testis and accessory sexual organs of male rat. Molecular and Cellular Endocrinology. 1993;**95**(1-2):115-120. DOI: 10.1016/0303-7207(93)90036-J

[104] Silva EJR, Queiróz DBC, Honda L, Avellar MCW. Glucocorticoid receptor in the rat epididymis: Expression, cellular distribution and regulation by steroid hormones. Molecular and Cellular Endocrinology. 2010;**325**(1-2):64-77. DOI: 10.1016/j.mce.2010.05.013

[105] Weber MA, Groos S, Höpfl U, Spielmann M, Aumüller G, Konrad L. Glucocorticoid receptor distribution in rat testis during postnatal development and effects of dexamethasone on immature peritubular cells in vitro. Andrologia. 2000;**32**(1):23-30. DOI: 10.1111/j.1439-0272.2000.tb02861.x

[106] Penson DF, Ng C, Rajfer J, Gonzalez-Cadavid NF. Adrenal control of erectile function and nitric oxide synthase in the rat penis. Endocrinology. 1997;**138**(9):3925-3932. DOI: 10.1210/endo.138.9.5402

[107] Cumming DC, Quigley ME, Yen SS. Acute suppression of circulating testosterone levels by cortisol in men. The Journal of Clinical Endocrinology and Metabolism. 1983; **57**(3):671-673. DOI: 10.1210/jcem-57-3-671

[108] Orr T, Mann DR. Role of glucocorticoids in the stress-induced suppression of testicular steroidogenesis in adult male rats. Hormones and Behavior. 1992;**26**(3):350-363. DOI: 10.1016/0018-506X(92)90005-G

[109] Almeida SA, Petenusci SO, Anselmo-Franci JA, Rosa-e-Silva AA, Lamano-Carvalho TL. Decreased spermatogenic and androgenic testicular functions in adult rats submitted to immobilization-induced stress from prepuberty. Brazilian Journal of Medical and Biological Research. 1998;**31**(11):1443-1448. DOI: 10.1590/S0100-879X1998001100013

[110] Yazawa H, Sasagawa I, Nakada T. Apoptosis of testicular germ cells induced by exogenous glucocorticoid in rats. Human Reproduction. 2000;**15**(9):1917-1920. DOI: 10.1093/humrep/15.9.1917

[111] Bambino TH, Hsueh AJ. Direct inhibitory effect of glucocorticoids upon testicular luteinizing hormone receptor and steroidogenesis in vivo and in vitro. Endocrinology. 1981;**108**(6):2142-2148. DOI: 10.1210/endo-108-6-2142

[112] Hales DB, Payne AH. Glucocorticoid-mediated repression of P450scc mRNA and de novo synthesis in cultured Leydig cells. Endocrinology. 1989;**124**(5):2099-2104. DOI: 10.1210/endo-124-5-2099

[113] Martin LJ, Tremblay JJ. Glucocorticoids antagonize cAMP-induced star transcription in Leydig cells through the orphan nuclear receptor NR4A1. Journal of Molecular Endocrinology. 2008;**41**(3):165-175. DOI: 10.1677/JME-07-0145

[114] Xiao YC, Huang YD, Hardy DO, Li XK, Ge RS. Glucocorticoid suppresses steroidogenesis in rat progenitor Leydig cells. Journal of Andrology. 2010;**31**(4):365-371. DOI: 10.2164/jandrol.109.009019

[115] Michael AE, Pester LA, Curtis P, Shaw RW, Edwards CR, Cooke BA. Direct inhibition of ovarian steroidogenesis by cortisol and the modulatory role of 11 beta-hydroxysteroid dehydrogenase. Clinical Endocrinology. 1993;**38**:641-644. DOI: 10.1111/j.1365-2265.1993.tb02147.x

[116] Huang TJ, Shirley Li P. Dexamethasone inhibits luteinizing hormone-induced synthesis of steroidogenic acute regulatory protein in cultured rat preovulatory follicles. Biology of Reproduction. 2001;**64**(1):163-170. DOI: 10.1095/biolreprod64.1.163

[117] Yuan HJ, Han X, He N, Wang GL, Gong S, Lin J, Gao M, Tan JH. Glucocorticoids impair oocyte developmental potential by triggering apoptosis of ovarian cells via activating the Fas system. Scientific Reports. 2016;**6**:24036. DOI: 10.1038/srep24036

[118] Liu YX, Cheng YN, Miao YL, Wei DL, Zhao LH, Luo MJ, Tan JH. Psychological stress on female mice diminishes the developmental potential of oocytes: A study using the predatory stress model. PLoS One. 2012;**7**(10):e48083. DOI: 10.1371/journal.pone.0048083