A variety of stressors have been shown to suppress gonadal function (Kinsey-Jones et al., 2009). In fact, kisspeptin–GPR54 signaling that kisspeptin/kisspeptin receptor signaling plays a critical role in the restraint, hypoglycemia, and lipopolysaccharide, which suggests that kisspeptin-expressing neurons of the arcuate nucleus (Oakley et al., 2009). The expression of kisspeptin and kisspeptin receptor mRNA is downregulated by stressors including restraint, hypoglycemia, and lipopolysaccharide, which suggests that kisspeptin/kisspeptin receptor signaling plays a critical role in the transition of stress-induced suppression of reproduction (Kinsey-Jones et al., 2009). In fact, kisspeptin–GPR54 signaling in the arcuate nucleus of the mediobasal hypothalamus is a critical neural component of the hypothalamic GnRH pulse generator (Li et al., 2009).

Gonadotropin-inhibitory hormone (GnIH), an RFamide-related peptide, can also modulate the reproduction of vertebrates (Ubuka et al., 2008). GnIH neurons interact directly with GnRH neurons, and the action of GnIH is mediated by a novel G protein-coupled receptor, Gpr147 (Ubuka et al., 2008). In mice, higher concentrations of GnIH-like substances are expressed in the hypothalamus and GnIH reduces GnRH release from the mouse hypothalamus (Bentley et al., 2010). The glucocorticoids and corticotropin-releasing factor (CRF) receptors are expressed in a large population of GnIH/RFamide-related peptide-expressing cells (Kirby et al., 2009). Glucocorticoids increase the inhibitory actions of GnIH on GnRH secretion (Kirby et al., 2009), while the regulation of GnIH via the CRF receptor remains to be determined.

While stress activates the hypothalamic-pituitary-adrenal (HPA) axis, it suppresses the hypothalamic-pituitary-gonadal (HPG) axis. Corticotropin-releasing factor (CRF) is a major regulatory peptide in the HPA axis during stress. Urocortin 1 (Ucn1), a member of the CRF family of peptides, has a variety of physiological functions and both CRF and Ucn1 contribute to the stress response via G protein-coupled seven transmembrane receptors. Ucn2 and Ucn3, which belong to a separate paralogous lineage from CRF, are highly selective for the CRF type 2 receptor (CRF2 receptor). The HPA and HPG axes interact with each other, and gonadal function and reproduction are suppressed in response to various stressors. In this review, we focus on the regulation of gonadotropins by CRF and Ucn2 in pituitary gonadotropins and of gonadotropin-releasing hormone (GnRH) via CRF receptors in the hypothalamus. In corticotrophs, stress-induced increases in CRF stimulate Ucn2 production, which leads to the inhibition of gonadotropin secretion via the CRF2 receptor in the pituitary. GnRH in the hypothalamus is regulated by a variety of stress conditions. CRF is also involved in the suppression of the HPG axis, especially the GnRH pulse generator, via CRF receptors in the hypothalamus. Thus, complicated regulation of GnRH in the hypothalamus and gonadotropins in the pituitary via CRF receptors contributes to stress responses and adaptation of gonadal functions.

**Keywords:** corticotropin-releasing factor, urocortin, stress, gonadotropin

**INTRODUCTION**

A variety of stressors have been shown to suppress gonadal function (Chand and Lovejoy, 2011). Proteins that play key roles in vertebrate reproduction include the neuropeptides gonadotropin-releasing hormone (GnRH) and kisspeptin and their receptors (Kim et al., 2012): kisspeptin stimulates GnRH release from hypothalamic GnRH neurons via Gpr54, a G protein-coupled receptor (Messager et al., 2005), while the gonadal steroid estrogen mediates its inhibitory effect on GnRH secretion by acting on kisspeptin-expressing neurons of the arcuate nucleus (Oakley et al., 2009; Ohkura et al., 2009). The expression of kisspeptin and kisspeptin receptor mRNA is downregulated by stressors including restraint, hypoglycemia, and lipopolysaccharide, which suggests that kisspeptin/kisspeptin receptor signaling plays a critical role in the transition of stress-induced suppression of reproduction (Kinsey-Jones et al., 2009). In fact, kisspeptin–GPR54 signaling in the arcuate nucleus of the mediobasal hypothalamus is a critical neural component of the hypothalamic GnRH pulse generator (Li et al., 2009).

Gonadotropin-inhibitory hormone (GnIH), an RFamide-related peptide, can also modulate the reproduction of vertebrates (Ubuka et al., 2008). GnIH neurons interact directly with GnRH neurons, and the action of GnIH is mediated by a novel G protein-coupled receptor, Gpr147 (Ubuka et al., 2008). In mice, higher concentrations of GnIH-like substances are expressed in the hypothalamus and GnIH reduces GnRH release from the mouse hypothalamus (Bentley et al., 2010). The glucocorticoids and corticotropin-releasing factor (CRF) receptors are expressed in a large population of GnIH/RFamide-related peptide-expressing cells (Kirby et al., 2009). Glucocorticoids increase the inhibitory actions of GnIH on GnRH secretion (Kirby et al., 2009), while the regulation of GnIH via the CRF receptor remains to be determined.

Corticotropin-releasing factor activates and regulates the hypothalamic-pituitary-adrenal (HPA) axis during stress (Vale et al., 1981, 1997). Stress-induced CRF synthesis and secretion from the hypothalamic paraventricular nucleus (PVN) stimulates adrenocorticotrophic hormone (ACTH) release from pituitary corticotrophs (Gillies et al., 1982; Mouri et al., 1993), which, in turn, stimulates the release of glucocorticoids from the adrenal glands (Whitnall, 1993). These glucocorticoids then moderate the stress response by inhibiting hypothalamic PVN production of CRF and pituitary production of ACTH (Whitnall, 1993). Urocortin 1 (Ucn1), a 40-amino acid peptide originally cloned from the Edinger–Westphal nucleus, is a member of the CRF family of peptides (Vaughan et al., 1993). Both CRF and Ucn1 contribute to stress responses and cardiovascular and gonadal functions via G protein-coupled seven transmembrane receptors (Vale et al., 1997; Kageyama et al., 1999a; Suda et al., 2004). CRF exhibits high affinity for CRF type 1 receptor (CRF1 receptor; IC50 = 1.6 nM but not for CRF type 2b receptor (CRF2b receptor; IC50 = 42 nM), while Ucn1 exhibits similar affinity for CRF1 receptor (IC50 = 0.16 nM) and CRF2b receptor (IC50 = 0.86 nM; Jahn et al., 2004). CRF1 receptor is predominately expressed in the brain and pituitary gland (Chang et al., 1993; Chen et al., 1993; Vita et al., 1993; Potter et al., 1994). In the pituitary, the CRF1 receptor is mainly expressed by corticotrophs and is responsible for mediating the effects of

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hypothalamic CRF on ACTH secretion in response to stress (Wynn et al., 1985; Antoni, 1986). Ucn2 and Ucn3 prohormones were identified in the human genome database and in mouse genomic DNA, respectively (Hou and Hsu, 2001; Lewis et al., 2001; Reyes et al., 2001). From which the identity and existence of endogenous peptides were predicted (Fekete and Zorrilla, 2007). Ucn2 and Ucn3 are more similar to each other than to CRF with regard to receptor binding (Kishimoto et al., 1995; Lovenberg et al., 1995a; Perrin et al., 1995; Stenzel et al., 1995). Ucn2 exhibits high affinity for CRF2b receptor (IC50 = 0.25 nM) but low affinity for CRF1 receptor (IC50 > 350 nM; Jahn et al., 2004). Similarly, Ucn3 binds with moderate affinity to CRF2b receptor (IC50 = 14 nM), but its specific binding to CRF1 receptor is not detectable (IC50 > 2000 nM; Jahn et al., 2004). It is hypothesized that an ancient gene duplication event is behind why Ucn1 belongs to the CRF lineage and why Ucn2 and Ucn3 represent a separate paralogous lineage (Fekete and Zorrilla, 2007).

The CRF2 receptor is primarily involved in stress responses and depression, while the CRF1 receptor is believed to mediate “stress-coping” responses in the brain, such as anxiety (Suda et al., 2004), because mice deficient in the CRF2 receptor or treated with a CRF2 receptor antagonist display increased anxiety-like behaviors and hypersensitive stress responses (Iale et al., 2000). Furthermore, both Ucn2 and Ucn3 act as anorexigenic neuropeptides via the CRF2 receptor (Fekete et al., 2011; Chao et al., 2012) and Ucn3 regulates glucose-stimulated insulin secretion and energy homeostasis (Li et al., 2007). Ucn3 signaling through the CRF2 receptor is also a critical molecular mediator in the ventromedial nucleus of the hypothalamus in regulating feeding and peripheral energy metabolism (Chao et al., 2012).

Corticotropin-releasing factor is involved in the suppression of the hypothalamic–pituitary–gonadal (HPG) axis (Rivier et al., 1986), especially the GnRH pulse generator in the hypothalamus (Kniobio, 1992). Stress profoundly inhibits the reproductive function by suppressing the pulsatile release of GnRH and consequently lutenizing hormone (LH), at least in part via the CRF system as well as through the GABAergic system (Lin et al., 2012). Although CRF and Ucn clearly have potent effects on the HPG system, their possible roles and how they are regulated have yet to be fully determined. In this review, we focus on the regulation and the roles of Ucn2 in pituitary gonadotrophs and discuss the regulation of GnRH via CRF receptors in the hypothalamus.

REGULATION OF GONADOTROPS BY CRF AND Ucn2 IN THE PITUITARY

Changes in CRF, receptor expression and desensitization of the receptor in pituitary corticotrophs play a major role in modulating adaptive responses to stressors (Kageyama et al., 2006). CRF, vasopressin, lipopolysaccharides, cytokines, and glucocorticoids can negatively modulate the levels of pituitary CRF2 receptor mRNA (Pozzoli et al., 1996; Saki et al., 1996; Aubry et al., 1997). However, CRF2 receptor mRNA is also found in the anterior pituitary and combined immunohistochemistry and in situ hybridization have demonstrated that CRF2 receptor mRNA colocalizes mainly with gonadotrophs, not corticotrophs (Figure 1).

CRF2 receptor-selective ligand Ucn2 suppresses both expression and secretion of gonadotropins in rats, while a CRF2 receptor antagonist increases the secretion of gonadotropins (Nemoto et al., 2009). In addition, an anti-CRF antibody blocks stress-induced increases in plasma ACTH and corticosterone, and an anti-Ucn2 antibody blocks stress-induced suppression of LH secretion without affecting stress-induced ACTH and corticosterone release (Nemoto et al., 2010). Stress-induced increases in microRNA-325-3p also suppress gonadotropin secretion (Nemoto et al., 2012). Although the presence and/or secretion of mature Ucn2 has not been determined in the pituitary or other tissues, it is possible that stress-induced increases in CRF stimulate Ucn2 in corticotrophs, which inhibits gonadotropin secretion via CRF2 receptors in the pituitary.

REGULATION OF GnRH BY CRF AND Ucn VIA CRF RECEPTORS IN THE HYPOTHALAMUS

Although peripheral administration of CRF fails to affect LH secretion (D’Agata et al., 1984; Rivier and Vale, 1984), central injection of CRF inhibits secretion of gonadotropins (Rivier et al., 1986). These effects of CRF probably reflect a central mechanism that involves modulation of the activity of GnRH neurons in the hypothalamus (Petraglia et al., 1987; Li et al., 2010). Indeed, in monkeys, a CRF antagonist attenuates suppression of the GnRH pulse generator in response to hypoglycemic stress (Chen et al., 1996). Furthermore, a recent in vivo rat study indicated that CRF innervation of the dorsolateral bed nucleus of the stria terminalis plays a central role in stress-induced suppression of the GnRH pulse generator (Li et al., 2011).

Corticotropin-releasing factor also suppresses GnRH gene expression levels in murine GnRH-GT1-7 cells (Kimey-Jones et al., 2006). In fact, GT1-7 GnRH-producing cells have been used extensively in studies of the basic control mechanisms involved in GnRH neuronal function. Belsham and colleagues have managed to develop cell lines that are representative of the enormous range of cell types of the hypothalamus (Dalvi et al., 2011). N39,
developed from primary mouse fetal hypothalamic culture, is one of these homologous neuronal cell lines. To further understand the possible function of Ucn and the regulation of GnRH by CRF receptors in the hypothalamus, hypothalamic N39 cells have been studied because they express both CRF₁ and CRF₂ receptor mRNA and protein (Kageyama et al., 2012). It has been shown in these cells that a CRF₁ receptor antagonist, antalarmin, inhibits CRF-induced decreases in GnRH mRNA levels, which suggests that CRF decreases GnRH mRNA levels via the CRF₁ receptor (Figure 2).

The CRF₂ receptor may also be involved in the regulation of GnRH gene expression. It has been reported that CRF regulates...
on the morning of proestrus while a CRF2 receptor antagonist blocks the acute stress-induced increases in gonadotropin secretion. In GT1-7 cells (Kinsey-Jones et al., 2006). In N39 cells, Ucn2 increases GnRH mRNA levels, and these Ucn2-induced increases in GnRH mRNA levels are blocked by the CRF2 receptor antagonist (2012) with permission of the publisher. Copyright 2012, Elsevier. In the hypothalamus, glucocorticoids, released in response to stress, inhibit GnRH and gonadotropins through activation of CRF and CRF2 receptors (Li et al., 2006). On the other hand, weakly blocks the increase in FSH secretion (Traslavina and Franci, 2007), estrogen would regulate the HPA axis in vivo. Reproduction from Kageyama et al. (2008), suggesting that estrogen is involved in the positive regulation of CRF gene expression in the parvocellular region of the PVN in vitro. Neurons expressing both CRF and ERβ are found in the medial paraventricular division (Miller et al., 2004) and project to the median eminence, and CRF in parvocellular PVN neurons exerts effects on corticotroph ACTH secretion (Gillies et al., 1982, Mouret et al., 1993). Therefore, estrogen and ERβ would contribute to the enhancement of stress responses through stimulation of CRF neurons of the hypothalamus, and may constitute the basis of sexual dimorphism in the regulation of the CRF gene (Strain, 2007). In addition, estrogen also enhances CRF- and stress-induced suppression of pulsatile LH secretion (Cates et al., 2004), and upregulation of the CRF2 receptor may contribute to the sensitizing influence of estradiol on the CRF- and stress-induced suppression of the GnIH pulse generator (Kinsey-Jones et al., 2006).

Meanwhile, Ucn1 in the non-preganglionic Edinger–Westphal nucleus plays an important role in stress adaptation. Estrogens exert a differential transcriptional regulation of the Ucn1 gene through either ER type α (ERα) or ERβ receptors (Hauge et al., 2006). Ucn1 mRNA levels in the non-preganglionic Edinger–Westphal nucleus of male rats are much higher than those of females (Derks et al., 2010), and estrogens may
Contribute to stress adaptation through modulation of Ucn1 production.

CONCLUSION
In summary, Ucn2, mainly produced in corticotrophs in response to CRF, acts on gonadotrophs expressing the CRF2 receptor and inhibits the production of gonadotropins in the pituitary (Figure 3). CRF is involved in the suppression of the HPG axis, especially the GnRH pulse generator in the hypothalamus, and also decreases GnRH mRNA levels via the CRF1 receptor (Figure 3). The CRF2 receptor may be involved in the regulation of GnRH and gonadotropins via the CRF receptors contributes to stress responses and adaptation in gonadal functions.

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Kageyama Regulation of gonadotropin

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