General and Comparative Endocrinology 171 (2011) 253–257

Contents lists available at ScienceDirect

General and Comparative Endocrinology

journal homepage: www.elsevier.com/locate/ygcen

Review

Stress and reproduction: Controversies and challenges

Dhan Chand, David A. Lovejoy *

Department of Cell and Systems Biology, University of Toronto, Toronto, Ontario, Canada M5S 3G5

ARTICLE INFO

Article history:
Received 25 January 2011
Revised 2 February 2011
Accepted 20 February 2011
Available online 22 March 2011

Keywords:
Corticotropin-releasing factor
Gonadotropin-releasing hormone
Urocortin
Urotensin-I
HPA
HPG

ABSTRACT

Inhibition of reproductive function by the activation of the stress–response has been observed since times of antiquity, however delineating a molecular mechanism by which this occurs in vertebrates continues to present a major challenge. Because recent genome sequencing programs have identified the presence of numerous paralogous peptides and receptors, our understanding of the complexity of the interaction between the reproductive and stress axes has expanded. At the neuroendocrine level, numerous studies have focused on the interaction between the corticotropin-releasing factor (CRF) and gonadotropin-releasing hormone (GnRH) systems in vertebrates. Moreover, most of these studies have been performed using rodent models and may not be completely relevant for non-mammalian vertebrates. A further problem lies in the variation of the functional expression of paralogous genes in the different taxa. In particular, the urocortin 2 and GnRH-II systems have been lost in some lineages, where its function has been taken over by urocortin 3 and GnRH-I, respectively. Establishing an integrated model that incorporates all paralogous systems for both the stress and reproductive system remains to be achieved.

1. Introduction and history

Since times of antiquity, observations of the stress-induced inhibition of reproductive ability have been recorded. However, it was not until the first part of the 20th century when Hans Selye provided the first working definition of biological stress [29,30] has it been possible to provide a mechanistic understanding of this interaction. Although the term 'stress' and its usage has been controversial, and its definition modified a number of times [31], the concept provides a succinct term to describe all factors and events, whether real or perceived, that challenge homeostasis. A stressful event, therefore, has to be of sufficient magnitude and duration to disrupt a homeostatic mechanism. However, our understanding of the physiology of stress has continued to evolve with the description of new molecular components associated with the stress response, particularly with respect to the neurological level. Likewise, our understanding of the regulation of reproduction has similarly increased. But despite the knowledge obtained from a modern systems approach obtained from genomics, proteomic and metabolomics studies, for example, and the role that epigenetics plays with the inheritance of physiological systems, numerous questions remain.

Establishing a modern paradigm for our understanding of the actions of stress on reproduction, Selye [29] proposed that an activated hypothalamo–pituitary–adrenal (HPA) axis was capable of inhibiting the hypothalamo–pituitary–gonadal (HPG) axis. Consequently, gross homeostatic modulation via hypothalamic suppression of gonadotropin secretion during stress-induced activation of the sympathetic nervous system involved a resource-driven trade-off with parasympathetic function. Although corticorticoid up-regulation during stress links the HPA and HPG axes through its inhibitory regulation of GnRH production and subsequently reduces the release of the gonadotropins at the level of the pituitary, numerous studies indicated a direct action of CRF on GnRH regulation.

Although many comparative studies established both the conservation of the HPA and HPG systems, and the existence of associated paralogous genes in vertebrates, the majority of mechanistic studies of the interaction of these systems have been performed on mammals, notably rodents. As a result, our generalized model of the interaction of stress on reproduction has a strong mammalian bias.

Nevertheless, a number of key studies utilizing mammalian models began to finger CRF as a peptide that could have a direct effect on reproduction. Thus, for example, although glucocorticoid feedback was well established to inhibit aspects of reproduction, adrenalectomized rats also exhibited decreased luteinizing hormone (LH) levels during stress situations [28]. Further, GnRH release from rat hypothalamic slices could be inhibited after superfusion with rat CRF [22] and the α-helical CRF antagonist abolished foot-shock induced suppression of LH release. Moreover, infusion of CRF into the medial preoptic area (mPOA) inhibited GnRH release into the median eminence [27]. Furthermore, peripherally administered CRF failed to disrupt LH and GnRH release, whereas intracerebroventricular [24] or median eminence (ME) [5]

* Corresponding author. Fax: +1 416 978 8532.
E-mail address: david.lovejoy@utoronto.ca (D.A. Lovejoy).

0016-6480/$ - see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.ygcen.2011.02.022

injection inhibited pituitary LH secretion. Although CRF does not pass through the blood–brain barrier in rats, injection into the periphery or ME would be expected to elicit ACTH activation and resulting glucocorticoid release into the blood stream. Given then, that these steroids do pass the blood–brain barrier, it would be expected that if there was an inhibitory action of glucocorticoids on GnRH or the gonadotropins, suppression of the HPG axis via central regulation would be expected to occur. A number of studies have also noted significant suppression of LH activity as CRF is increased and have demonstrated a reinstatement of the LH pulse after the subsequent administration of CRF antagonists [see [32] for review].

2. Direct actions of CRF paralogs on GnRH regulation

The mechanism by which CRF regulates GnRH activity likely involves a combination of direct and indirect mechanisms. CRF can potentially modulate aspects of the HPG axis by activation of the sympathetic nervous system, glucocorticoid release by HPA axis activation and by limbic activation. However, these mechanisms rely on a number of indirect processes and may also involve norepinephrine, GABA, opioids and kisspeptin regulation [12]. A more parsimonious type of HPG modulation could involve the direct regulation of CRF and its paralogs, urocortin/urotensin-I, urocortin 2 and urocortin 3. Among these paralogs, CRF has been studied the most. But a conclusive demonstration of a direct effect of CRF on GnRH neurons has been difficult to achieve. However, recent studies provide new evidence of a direct inhibitory effect of CRF on the HPG axis. Tellam and colleagues [33] demonstrated that, using the Gn11 cell line stably transfected with mouse or chicken GnRH promoter luciferase constructs, CRF, urotensin-1 and sauvagine could significantly reduce luciferase activity, suggesting that CRF could exert a direct suppressive effect on GnRH-expressing neurons either at signal transduction or transcriptional regulation levels. Similar findings were reported by Kinsey-Jones and associates [9] using the GT1-7 cell line.

Chronic and profound stress can affect the time of puberty and may be related to the effect of CRF on GnRH pulse frequency. Administration of CRF to rats delays puberty whereas CRF antagonist administration advances the onset of puberty. CRF type 1 receptor (R1) mRNA, after CRF administration, is altered in the mPOA but not the arcuate nucleus, suggesting that CRF may, in part, regulate GnRH neurons directly [12]. The type of stress perceived, however, may involve different CRF-associated mechanisms. For example, lipopolysaccharide (LPS), insulin-induced hypoglycemia and restraint stress all inhibit LH pulsitivity in rats. However, these effects are mediated by different complements of CRF receptors, where restraint stress appears to involve both CRF R1 and type 2 (R2) receptors, whereas LPS and hypoglycemic stress, the R2 receptor may be predominantly involved [11].

These investigations indicated that CRF may act directly upon GnRH neurons instead of interaction through the induction of the glucocorticoid cascade and its subsequent inhibition of GnRH-mediated processes. Even if this is the case, the origin of this CRF remains unclear. CRF is synthesized in a number of central nervous system (CNS) sites that also express GnRH including the preoptic area and olfactory bulbs [17]. Also, both CRF and urocortin immunoreactivity are found in the septal nuclei of the forebrain. In fishes, in contrast to mammals, one of the major regions of CRF expression is found in the preoptic region [26,37] and are, therefore, anatomically situated to provide direct input into GnRH neurons. Also distinct from the mammalian brain, CRF is not highly expressed in the teleost versions of the amygdala and hippocampus [18]. Thus, it is plausible that teleosts may utilize a more direct action of CRF on GnRH systems during the regulation of stress on reproduction, whereas mammalian species utilize more indirect routes. This hypothesis remains to be tested however. Urotensin-I is the fish ortholog of urocortin and possesses many of its pharmacological and physiological characteristics. Although in fish, a detailed study of the comparative expression of CRF and urotensin-I, with respect to GnRH expression in the brain, appears not to have been carried out. It remains to be determined whether urocortin plays a physiological role in the regulation of reproduction although its detection in the external plexiform layer of the olfactory bulb and in the lateral septal nucleus of the rat by immunohistochemistry places it anatomically near GnRH-expressing regions.

If mammals utilize different systems to transmit stress-associated sensory information to the reproductive system, then when addressing the physio–psychological problems associated with stress, adjustments of control for variables that confound the in vivo milieu, are not complete until the consequences of higher order cognitive function are considered. For example, Herman and Cullinan [7] distinguished between system stressors that constitute an immediate physiological threat and are relayed directly to the PVN, and processive stressors which require limbic interpretations. Consequently, structures within the prefrontal cortex, hippocampus and amygdala may be of particular importance when considering processive inhibition of the reproductive system. Although each of these structures have been well established to provide input into the CRF regulation of the PVN [14,32] and hence modification of the HPA axis, this provides only a partial understanding of the regulation of stress-associated pathways on reproduction.

Our understanding of the actions of CRF on GnRH is further confounded by studies that indicate that GnRH may exert a reciprocal inhibitory mechanism on the CRF system. For example, the GnRH agonist, leuprolide, can dose-dependently increase social interaction time and decrease immobility in a forced swim model in rats indicating anti-anxiety and anti-depressant effects, respectively. Interesting, this effect endures even in castrated rats indicating that the effects are independent of testosterone feedback. Typically, CRF administration decreases social interaction and increases immobility times in rats and mice. This effect is exacerbated when animals are treated with CRF and GnRH antagonists together [34]. However, there may be a pronounced sex difference in such findings. For example, estradiol can enhance the CRF and stress-induced suppression of pulsatile LH secretion. In the GnRH-secreting cell line, GT1-7, CRF can induce a dose-dependent inhibition of GnRH mRNA, where this effect is synergized by the addition of estradiol to the CRF regimen [9]. This mechanism may involve norepinephrine regulation by locus coeruleus (LC) neurons following CRF activation of the LC neurons. LC activation can inhibit LH pulse frequency and estradiol can increase the CRF-induced activation of LC neurons to synergistically reduce pulse frequency [19].

3. CRF paralog interaction with reproductive function

There are few studies on the role of the other CRF paralogs on the regulation of the HPA axis. Within the vertebrates, CRF is the most conserved of CRF-family paralogs [16]. Thus, given the relatively higher rates of base-pair and amino acid substitution among the urocortin/urotensin-I, urocortin 2 and urocortin 3 lineages, establishing a consistent function across taxa may be problematic. For example, in fishes, the majority of urotensin-I is found in the urophysis [2] and may play a primary role in the stress-associated osmoregulatory acclimatizations of moving between waters of differing salinities, experienced by many fish species [13,14]. In tetrapods however, where the urophysis is not present, the majority of urocortin is found in the Edinger–Westphal (EW) nucleus of the midbrain and may serve as, in part, a redundant back-up system to the CRF system.