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Review

Influence of stress-induced intermediates on gonadotropin gene expression in gonadotrope cells

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ABSTRACT

Despite extensive investigation, a comprehensive understanding of the mechanisms whereby stress impacts fertility remains elusive. Since the 1930s, when Hans Selye popularized studying adaptations to stress (Selye, 1937), we have learned that compensatory mechanisms involve a complex interplay of neural and hormonal processes that allow various body functions to adjust to stress, in a coordinated manner. In terms of reproduction, the adjustment to a stressor interferes with integrated functioning at multiple levels of regulation – the hypothalamus, anterior pituitary gland, gonads, and neural centers coordinating behavior. Various mediators are postulated to participate in reproductive suppression. These include catecholamines, cytokines, prostaglandins, endogenous opioid peptides, and hormones of the hypothalamic–pituitary–adrenal axis. This review focuses on one class of mediators, the glucocorticoids, and provides our views on the relevance and mode of action of this inhibitory intermediate within the anterior pituitary gonadotrope, as a potential cellular site whereby glucocorticoids contribute to stress-induced reproductive suppression.

Contents

1. Introduction to stress

A hallmark of the endocrine response to stress is an increase in glucocorticoid secretion, the final hormonal effector of the hypothalamic–pituitary–adrenal (HPA) axis. The perception of stress by higher brain centers initiates a cascade of hormone synthesis and secretion, which includes corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) from hypothalamic sites into pituitary portal vasculature, and in response, stimulates adrenocorticotrophic hormone (ACTH) release from anterior pituitary corticotrope cells. Glucocorticoids are synthesized in the adrenal

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cortex in response to activation by ACTH and initiate actions within tissues that express glucocorticoid receptors (GR). It is not surprising that, based on the diverse actions of glucocorticoids, this steroid receptor is found extensively throughout the body to compensate metabolically for the demands imposed by stressors (De Kloet et al., 1998; Sapolsky et al., 2000). Enhanced secretion of glucocorticoids plays a key role in allowing an organism to survive the challenge to homeostasis (Selye, 1937). Glucose is mobilized from storage sites and diverted to tissues necessary for survival: brain, heart, and muscles. Consequently, stress can result in pathogenic effects on metabolism, growth, tissue repair, immune defenses, and of interest to this review, reproductive physiology and behavior.

The field has clearly established the impact of stressful stimuli on the hypothalamic–pituitary–gonadal axis. Whether the nature of the stressor is physical (e.g., foot-shock and exercise), immunological (e.g., infection, administration of cytokines or endotoxins), or psychological (e.g., isolation and mental performance tasks), each has been shown to decrease circulating levels of gonadotropins (Cates et al., 2004; Dobson and Smith, 2000; Ferin, 1999; Rivier and Rivest, 1991; Saketos et al., 1993; Tilbrook et al., 2002). The observation that stress-induced impairment of reproductive function is typically associated with a concurrent rise in circulating glucocorticoids has led to the hypothesis that enhanced glucocorticoid secretion is relevant to reproductive suppression during stress. This review explores the evidence supporting this hypothesis, places our studies in context with the literature in this area, and identifies avenues for future research regarding the role of glucocorticoids and stress in the management of ovarian cycle disorders and treatment of infertility.

2. Neuroendocrine site of glucocorticoid action during stress

The possibility that elevated glucocorticoids could act at either the hypothalamic or pituitary level to inhibit gonadotropin secretion has received considerable attention over the years. A variety of animals and cell-based models have been employed to discriminate between actions at neuroendocrine sites leading to the conclusion that the relevance of glucocorticoid action likely depends on the species and stress employed.

2.1. The hypothalamus as a site of glucocorticoid action

The hypothalamus is a critical processing center for controlling reproductive function, orchestrating inputs from metabolic, circadian, gonadal systems, and potentially glucocorticoids, upon the GnRH neuron. The effects of elevated glucocorticoids are primarily mediated by GR which are highly expressed in CRH neurons and function in HPA axis regulation (De Kloet et al., 1998), but also in hypothalamic areas critical for GnRH neuron regulation (Dufourny and Skinner, 2002; Takumi et al., 2012), including expression in GnRH neurons in the rat (Ahima and Harlan, 1992). Early seminal studies implicated an action of cortisol at the hypothalamic level to inhibit pulsatile GnRH release by demonstrating in gonadectomized rhesus monkeys and pigs that chronic administration of glucocorticoids suppresses mean LH secretion in the absence of a reduction in pituitary responsiveness to a GnRH challenge (Dubey and Plant, 1985; Estienne et al., 1991). Inhibition at the hypothalamic level is further supported by evidence that glucocorticoids reduce the frequency of LH pulses in ovary-intact female sheep, ovariectomized female rats, and women during the follicular phase of the ovulatory cycle (Breen et al., 2005; Li et al., 2004; Saketos et al., 1993). As LH pulse frequency is generally modulated by the GnRH neurosecretory system, these findings suggest an action of glucocorticoids to suppress the frequency of GnRH pulses. In each of these studies, GnRH secretion was not monitored directly, rather suppression was inferred indirectly, based on LH or on the lack of reduction in pituitary responsiveness to the releasing hormone. More recent work in follicular phase sheep provides the first definitive evidence that glucocorticoids can inhibit GnRH pulses in pituitary portal blood, by modulating the frequency of pulses (Oakley et al., 2009). Whether this inhibition of GnRH by glucocorticoids is relevant to stress-induced suppression of reproduction remains a topic of later discussion (see Section 5). Indeed, evidence from the Karsch laboratory, using a layered stress paradigm in sheep, demonstrates that the effects of stress on GnRH pulsatility are not reversed by a non-selective glucocorticoid receptor (GR) antagonist (Wagenmaker et al., 2009b), suggesting that stress-induced levels of glucocorticoids may be sufficient to inhibit reproductive neuroendocrine activity, but may not be necessary for this effect. Based on this evidence, we can agree that glucocorticoids can inhibit GnRH and LH; however, we note that the mechanisms underlying suppression may differ between species, animal models, and gonadal steroid status.

Another point of discussion is the cellular mechanism whereby glucocorticoids may inhibit GnRH. In addition to the reduction of secretion noted above, glucocorticoids have been shown to decrease GnRH synthesis in male rat hypothalamus (Gore et al., 2006), illustrating a genomic effect within the GnRH neuron. A direct action within the GnRH neuron itself is supported by evidence that in rats GnRH neurons express GR, and glucocorticoids blunt GnRH synthesis and release from immortalized GnRH neurons, mouse GT1-7 cells (Attardi et al., 1997; DeFranco et al., 1994). However, increasing evidence points to the possibility that glucocorticoids may be acting via a non-GnRH cell target, such as RFamide-related peptide (RFRP) containing neurons. Stress has been shown to stimulate RFRP expression in the dorsomedial nucleus male rat hypothalamus (Kaewwongse et al., 2011), a region in which RFRP neurons are specifically known to coexpress GR (Kirby et al., 2009) and possess projections that extend to the median eminence and preoptic area making putative connections with GnRH neurons (Kriegsfeld et al., 2006). Further support for a mediatory action of the RFRP system in stress-induced suppression of reproductive neuroendocrine activity is demonstrated in a rat model of restraint stress in which adrenalectomy prevents the stress-induced increase in hypothalamic RFRP expression and subsequent suppression of LH (Kirby et al., 2009), highlighting the importance of the RFRP system in suppression of reproductive neuroendocrine activity by glucocorticoids.

2.2. The pituitary gland as a site of glucocorticoid action

Studies in several species suggest that the effects of glucocorticoids can be exerted directly on the pituitary gland to inhibit responsiveness to GnRH. For example, glucocorticoids reduce the amplitude of the LH response to a GnRH challenge in rodents, pigs, cows, and women (Li and Wagner, 1983; Melis et al., 1987; Pearce et al., 1988; Suter et al., 1988). Further, suppression of responsiveness to GnRH *in vitro* has been observed in rodent, porcine, and bovine pituitary cell cultures, indicating that glucocorticoids can act directly upon the gonadotrope cell to inhibit GnRH-induced LH secretion (Li and Wagner, 1983; Suter and Orosz, 1989; Suter et al., 1988). Consistent with a direct action upon the gonadotrope cell, GR has been identified in mouse (Breen et al., 2012) and rat gonadotrope cells (Kononen et al., 1993) and studies in mouse, rat and pig primary cells suggest that glucocorticoids can modulate signaling mechanisms downstream of the GnRH receptor, including protein kinase C and cyclic AMP (Li, 1994; Suter et al., 1988), which may lead to a reduction in gonadotropin gene expression or hormone release.