Editorial: Stressing the Importance of Sex

Neuroendocrine responses to stress, particularly those mediated by the hypothalamic-pituitary-adrenocortical (HPA) axis, can differ significantly between males and females in many species. In laboratory rats and mice, for example, basal and stress-induced hormone secretions in the HPA axis are generally higher in females than in males in a variety of experimental situations (1, 2). Female rodents also exhibit alterations in basal and stress-induced HPA activity across the ovulatory cycle, with highest levels observed during the preovulatory period (3, 4). Which mechanisms govern the sex-specific secretion of stress hormones, and what is the adaptive significance of these phenomena? Although definitive answers to these questions have not yet been obtained, tantalizing clues—such as those provided by Speert et al. (5) in this issue of Endocrinology—suggest that sex hormones may play a key role in sculpting the features of stress hormone responses in ways that may optimally coordinate the activity of the reproductive and stress responsive systems.

The activity of the HPA axis is sexually differentiated despite the fact that both sexes are endowed with the same basic physiological response transduction system. In both females and males, stressful stimuli evoke neural and hormonal signals that activate CRH neurons in the paraventricular nucleus, prompting release of CRH into the hypothalamic portal vasculature. The CRH is conveyed to the anterior pituitary gland, where it can bind receptors on corticotrophs, and thereby stimulate synthesis and secretion of ACTH. In turn, ACTH binds its cognate receptors in zona fasciculata cells in the adrenal cortex and stimulates production of glucocorticoids. Feedback regulation in the axis is exerted by integrated effects of glucocorticoids on corticotrophs to suppress CRH-stimulated ACTH secretion and on hypothalamic neurons and limbic structures to suppress neurosecretion of CRH. In addition to its role in eliciting activity in the HPA axis, CRH is also released at synaptic endings within the central nervous system (CNS), where the peptide likely contributes to behavioral stress responses, axiogenesis, and central activation of autonomic responses. Both the postsynaptic and pituitary actions of CRH are mediated by one or both of the known G protein-coupled receptors for the peptide, the type 1 CRH receptor (CRH-R1) and the type 2 CRH receptor (CRH-R2). Other neuropeptides that play major roles in stress responses include the urocortins (6), which can bind CRH receptors with differing affinities compared with CRH itself and thereby modulate CRH-mediated responses and/or activate alternate response patterns at central and/or pituitary sites. Vasopressin is also known to act through its own receptors to amplify the actions of CRH in the stimulation of ACTH secretions (7).

A most interesting player in the HPA axis is the CRH-binding protein (CRH-BP), a glycoprotein identified by Vale and colleagues in 1991 (8) on the basis of its ability to bind CRH and attenuate CRH’s actions at CRH receptors. Consistent with its purported function, anatomical studies demonstrate expression of CRH-BP at locations of CRH synthesis and release sites (9), including limbic and basal forebrain structures and anterior pituitary corticotrophs (10). Genetic manipulations of CRH-BP expression have also provided evidence supporting CRH-BP’s role in tempering CRH actions at both central and adenohypophysial sites (11). The most potent inducers of CRH-BP expression appear to be those processes that mediate activation of HPA activity: stress (12), CRH (13), and glucocorticoids (12). The latter observations in particular have provided support for the idea that CRH-BP functions as a feedforward inhibitor in the HPA axis—an endocrine device that is engaged in concert with the activation of the HPA axis—and thereby limits the duration of HPA activation by prompting a quicker return of the system to basal homeostatic levels of activity.

Is it possible that differences in CRH-BP expression in males and females may account for the sexual differentiation of HPA axis activity, or at least some aspects of it? Speert et al. (5) examined this possibility in their studies, reasoning that higher basal ACTH levels and more robust ACTH and corticosterone responses to stress in females may be a consequence of lower CRH-BP expression. They further hypothesized that the heightened circadian peaks of ACTH and glucocorticoid secretion that are known to occur in proestrus females (3, 4) may result from an ability of preovulatory ovarian estrogen secretions to suppress CRH-BP production, thereby disinhibiting the actions of CRH on pituitary corticotrophs. As is often the case in well-designed and carefully executed studies, their results unequivocally disprove their hypothesis, and in so doing they raise a most interesting, and perhaps more illuminating, alternative scenario. Because the expression of CRH-BP is clearly higher in females than in males, and it is stimulated by estrogen, it may instead be the case that CRH-BP expression is up-regulated to ensure that HPA activity is rapidly returned to basal levels after having been stimulated and is kept at a lower level for several additional hours (see Ref. 3) before it begins its daily ascent throughout the hours of the following estrous morning. This begs the question: What is the adaptive significance of sharply higher stress hormone secretions in late proestrous, followed by a period of HPA quiescence?

The answer to the foregoing question may be tied to the larger issue of the functional relationship between HPA axis and neuroendocrine systems that govern reproduction. Indeed, the differentiated patterns of HPA activity in the two sexes may be less about stress and more about . . . well, sex. Specifically, the female pattern of HPA activation may have particular functional significance with respect to the cyclic manifestation of behavioral estrus. In response to preovulatory gonadal steroid secretions, female rats exhibit a period
of behavioral heat that begins during the late evening hours of proestrus and continues throughout the morning of estrus. This period of behavioral heat precedes and coincides with the process of ovulation, which occurs on the morning of estrus. It is reasonable to assume that the temporal coordination of behavioral heat, nocturnal wakefulness, and ovulation is an adaptive mechanism that has evolved in rodents to optimize the chances of fertilization and, hence, to provide the best chance of propagating the species. It is in this context that fluctuations in HPA axis activity may be most important in females and may be best understood. During the preovulatory period, the activity of the HPA axis is modulated first upward and then downward. The upward modulation—the potentiated peak of corticosterone on the afternoon of proestrus—may occur as a consequence of estrogen’s demonstrated ability to stimulate CRH gene transcription (14). The resultant increases in CRH secretion, and hence ACTH and glucocorticoid secretions, may occur on the afternoon of proestrus in anticipation of mating behavior and may serve to mobilize a greater allotment of metabolic energy to support the energetic requirements of mating behavior per se. The subsequent downward regulation of ACTH and corticosterone secretions may also be estrogen dependent and may serve an equally important role. Estrogen may stimulate CRH-BP expression to provide a mechanism that temporally curtails the actions of CRH. The latter process may preclude prolonged activation of CRH neurons and the HPA axis and may thereby prevent the development of anxiety states that are incompatible with the motivational components of sexual behavior. A compelling feature of the foregoing model is the key organizing role played by estrogen—this single endocrine signal may recruit and bring into temporal register all of the processes that may contribute to the chances for successful reproduction: energetic preparedness for sexual behavior, sexual motivation, sexual reflexes, ovulation, and perhaps also anxiolysis. Estrogen-stimulated CRH-BP may play its role in this convergence of regulatory mechanisms by rapidly returning the activity of the HPA axis to basal levels, thereby curtailing the anxiogenesis that would otherwise develop in response to prolonged glucocorticoid action in the CNS (15). Moreover, if a similar increase in CRH-BP occurs during this period at central sites of CRH release, then one would predict that an even more pronounced anxiolytic state would be manifest. The ability of estrogen to stimulate CRH-BP expression in central neurons remains to be determined. That stress-induced immediate early gene activation in the CNS is most suppressed on proestrus is consistent with this idea (16).

The complex interactions between the HPA and hypothalamic-hypophysial gonadal (HPG) axes has been studied at many levels, and it is generally held that there exists a functionally antagonistic relationship between systems that govern these two vitally important biological processes. Behavioral and physical stressors stimulate release of CRH both centrally and into the portal vasculature, and CRH actions thereby contribute to the activation of classic central and peripheral stress responses, respectively; these include CNS changes in arousal, alertness, vigilance, cognition, and attention, and peripheral changes in cardiovascular tone, blood pressure, heart rate, respiratory rate, and increased glucose-mediation and lipolysis (17). At the same time, however, CRH acts both centrally and via stimulation of the HPA axis to suppress reproductive function. The number of routes through which stress hormones can inhibit reproductive activity is considerable: CRH may inhibit GnRH release directly (18), thereby depressing HPG activity; CRH may also exert inhibitory actions on central circuits subserving reproductive behaviors (19); glucocorticoids appear to inhibit reproductive hormone secretions by actions at both CNS (20) and pituitary levels (21); glucocorticoids additionally suppress gonadal steroid secretions and their actions at target tissues (22). Clearly, nature has placed a premium on the suppression of reproductive activity in a high-stress milieu.

The reproductive axis, however, is not only a recipient of inhibitory signals from the HPA axis, but it also clearly effects changes in the opposite direction. It has been proposed that the HPG axis has evolved a capacity for inhibiting HPA activity to provide some buffer against excessive and/or maladaptive inhibition by stress hormones (9). Testosterone appears to exert a tonic inhibitory action on the HPA axis in males, likely through an androgen receptor-mediated inhibition of CRH expression and neurosecretion (23, 24). Estrogen appears to exert the opposite effect in females, at least in part through an estrogen receptor-mediated stimulation of CRH transcription (14). These opposing actions of the male and female gonadal steroids may thus provide a cellular basis for the sexual differentiation of HPA axis activity. The demonstration that estrogen stimulates CRH-BP expression and may thereby inhibit HPA activity adds a new dimension to the ability of the HPG axis to cross-talk with the HPA axis. This novel regulatory locus also underscores the likelihood that there exists a much greater complexity to the HPG-HPA relationship than was previously realized. That the principal gonadal hormones in the two sexes can exert differential and multiple effects on the flow of information through the HPA axis suggests that there is much more work to be done in understanding the true nature of the interactions between stress response and reproductive systems and how these interactions may differ in the two sexes.

The work of Speert et al. (5) also suggests that the potential role of CRH-BP in HPA-HPG interactions may ultimately be one of many interesting facets of the biology of this molecule. Surprisingly, only a minor portion of total CRH-BP expression in the pituitary occurs in corticotrophs. The bulk of CRH-BP expression (80%) occurs in lactotropes, with some additional expression evident in gonadotropes. Is the site of release of the glycoprotein irrelevant, or does this distribution of the molecule suggest additional functions within these other cell types? Are the functions of CRH-BP restricted to the sequestration of CRH, or does it bind other peptides? Does CRH-BP exert direct actions on cells in the absence of binding to CRH? These questions remain to be addressed, and the functional significance of CRH-BP’s dramatic estrogen dependency remains to be evaluated in the context of these other potential physiological roles.

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