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# Sex Differences and the Role of Sex Steroids in Sympatho-Adrenal Medullary System and Hypothalamo-Pituitary Adrenal Axis Responses to Stress

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## 1. Introduction

We have undertaken a critical analysis of the role of sex and sex steroids in influencing stress responsiveness. We have reviewed the current literature regarding the manner in which the stress-induced activation of the sympatho-adrenal medullary system and the hypothalamo-pituitary adrenal axis are influenced by the sex of individuals and the sex steroids that are present and how these vary with different types of stress and in different physiological conditions. The chapter focuses predominantly on sheep and human research, although research in rodents is introduced where pertinent. Where appropriate, we draw on our extensive research published over the last two decades using sheep as an experimental model and consider how these data inform and compliment the current findings in human studies. It is clear from the literature reviewed here that there is a major need for research to understand stress responsiveness. The gaps in knowledge requiring this research are highlighted.

## 2. What is stress and what are the physiological responses to stress?

For a term used frequently in everyday language, stress has proven surprisingly difficult to define. Stress is a term that can appear diffuse, lacking in rigor and certainty of meaning. Nevertheless, most published definitions of stress are concerned with challenges to, or disruptions of, homeostasis. Indeed, our own working definition of stress is “a complex physiological state that embodies a range of integrative physiological and behavioral processes that occur when there is a real or perceived threat to homeostasis” [1, 2]. Certainly, the importance of the maintenance of homeostasis has long been recognized. For example, the ancient Greek philosopher Empedocles (500-430 BC) acknowledged the

concept of a steady or harmonious state [3] and, in the 19<sup>th</sup> century, the work of French physiologist Claude Bernard (1813-1878) laid the groundwork for appreciating the importance of adaptive internal mechanisms to challenges [3]. Bernard developed the concept that organisms maintain a stable internal environment (*milieu intérieur*). This concept and understanding was substantially extended by the groundbreaking research of American physiologist Walter Cannon (1871-1945) [3]. It was Cannon who devised the term “homeostasis” and who noted that animals and humans in dangerous situations showed adaptive responses in which they may choose to fight or to escape, termed the “fight or flight” syndrome [4]. Clearly, this requires rapid responses of the body and the physiological system primarily responsible for these adaptive responses is the sympatho-adrenal medullary system. The work of Cannon inspired another researcher, Hans Selye (1907 Vienna-1982, Montreal), whose seminal work during the 1930’s at McGill University in Montreal, Canada, led to the development of a theory to describe the concept of stress. He developed the “General Adaptation Syndrome”, defined as “the sum of all non-specific, systemic reactions of the body which ensue upon long continued exposure to stress” [5]. He depicted three stages in this response: 1) the alarm reaction, which involved activation of the hypothalamo-pituitary adrenal axis, 2) the period of resistance, where the organism “coped” with the challenge and 3) the stage of exhaustion, where the organism’s ability to resist or adapt to the challenge declined [5]. A premise of this theory is that organisms have a generalized and non-specific response to all noxious stimuli [5]. While it is now recognized that there may be different types of physiological responses to different stressful environments [1], Selye unquestionably founded the field of stress physiology and provided the framework to define and understand stress. His work continues to stimulate debate and research. Importantly, his work demonstrated the paramount role of the hypothalamo-pituitary adrenal axis in adaption to stressful situations [5].

It follows from the work of Cannon and Selye that the two most common physiological responses to stress are activation of the sympatho-adrenal medullary system and the hypothalamo-pituitary adrenal axis (Figure 1). The former is activated immediately upon threat or detection of a noxious stimulus and the response is transient, whereas the latter is activated less rapidly and the response is more prolonged. It is common practice to define threats and noxious stimuli that cause stress responses as stressors [1, 2]. While the sympatho-adrenal medullary system and hypothalamo-pituitary adrenal axis are considered the primary means of dealing with stressors, there are other responses, mostly of a neural and neuroendocrine nature, such as the opioidergic system [2], which contribute to an integrated stress response.

The sympatho-adrenal medullary system consists of the sympathetic nervous system and the adrenal medulla (Figure 1). The catecholamines epinephrine and norepinephrine induce the actions of the sympatho-adrenal medullary system which are primarily to stimulate rapid and vigorous neural, behavioral and muscular activity, to stimulate the cardiovascular system to increase cardiac output and redistribute blood flow to the pulmonary blood system and appropriate organs to deal with the stressor [6]. The catecholamines bind to adrenergic receptors, of which there are different subtypes, termed  $\alpha$  and  $\beta$ , and this allows for divergent effects in target tissues [6]. The sympathetic component, or “arm”, of the sympatho-adrenal medullary system, comprises pre-ganglionic neurons that project from the spinal cord to the various ganglia in the body where they synapse with post-ganglionic neurons that project to, and innervate, target tissues. Acetylcholine from the pre-ganglionic neurons stimulates the post-ganglionic neurons which release norepinephrine into the target tissue. In the adrenal arm of the sympatho-adrenal medullary system, pre-ganglionic

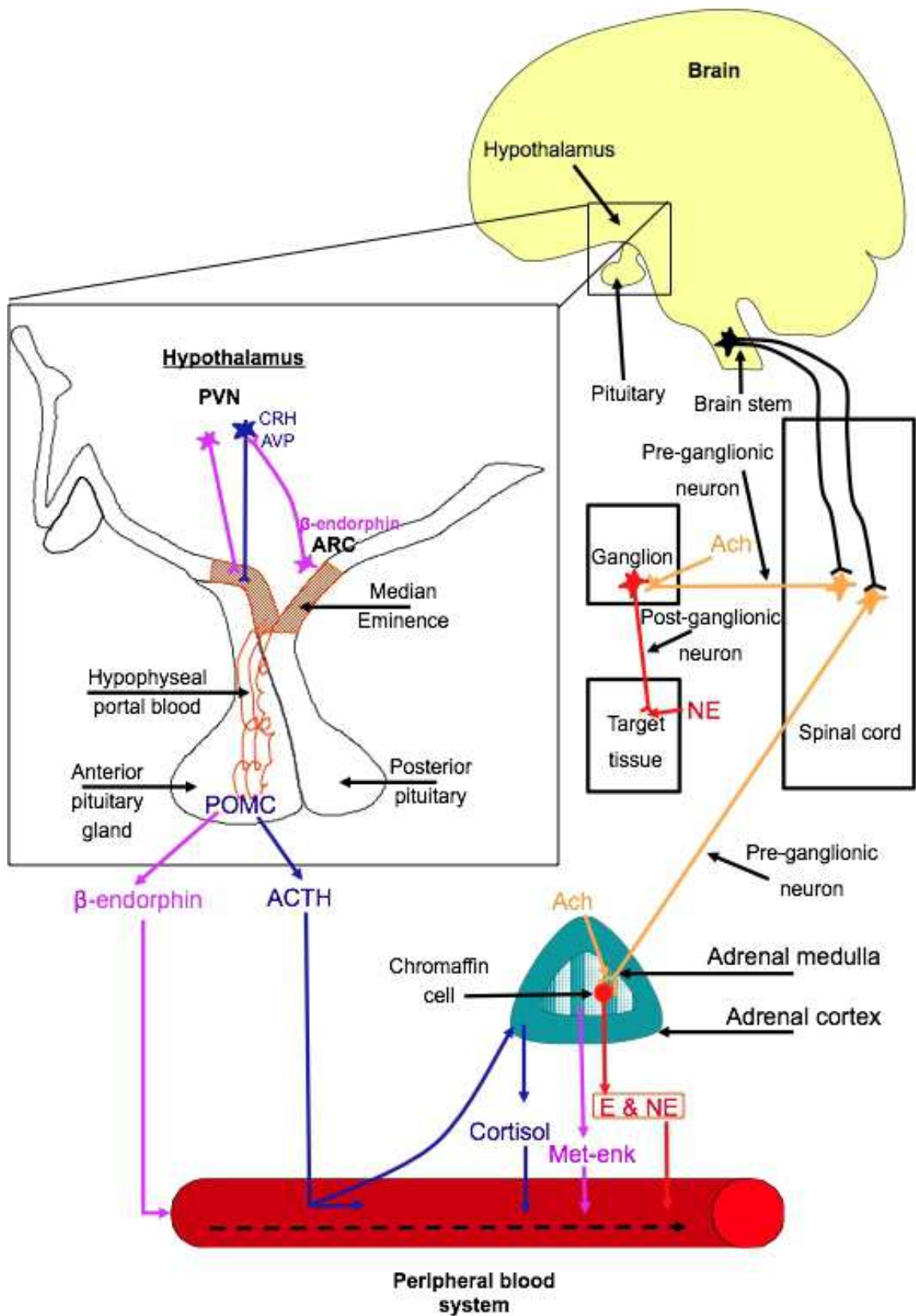


Fig. 1. Schematic diagram of the sympatho-adrenal medullary system, hypothalamo-pituitary adrenal axis and some opiodergic pathways. The sympatho-adrenal medullary system consists of the sympathetic nervous system and adrenal medulla. Pre-ganglionic neurons

extend from the spinal cord to ganglia and to the adrenal medulla. When activated the pre-ganglionic neurons release the neurotransmitter acetylcholine (ACh) that stimulates post-ganglionic neurons to release norepinephrine (NE) directly into target tissue and endocrine cells called chromaffin cells in the adrenal medulla to release epinephrine (E) and NE into the peripheral blood system. The hypothalamo-pituitary adrenal axis is regulated by corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) in the paraventricular nucleus (PVN) of the hypothalamus which are released into the hypophyseal portal blood system and transported to the anterior pituitary. They stimulate the synthesis of pro-opiomelanocortin (POMC) resulting in various products including adrenocorticotrophic hormone (ACTH) and the opioid  $\beta$ -endorphin, which are secreted into the peripheral blood system. ACTH acts at the adrenal cortex to stimulate synthesis of the glucocorticoids which are cortisol in humans and non-rodent species (shown here) and corticosterone in rodents and avian species.  $\beta$ -endorphin is also synthesized in the arcuate nucleus (ARC) and the opioid met-enkephalin (Met-enk) in the adrenal medulla in response to stress.

neurons innervate endocrine cells, called chromaffin cells, in the adrenal medulla, stimulating them to synthesize epinephrine and norepinephrine, and to secrete both catecholamines into the systemic circulation. These catecholamines then act as classic hormones, affecting target tissues throughout the body. It is generally considered that more epinephrine than norepinephrine is released from the adrenal medulla into the systemic circulation [7] because norepinephrine is converted to epinephrine [6]. While this may be the case in various species, possibly including humans, in sheep the adrenal medulla secretes substantially more norepinephrine than epinephrine [8].

The hypothalamo-pituitary adrenal axis is often referred to as the “Stress System” and one might imagine that this is a result of the work of Selye that effectively identified the importance of the adrenal glands in coping with stress. This is a classic neuroendocrine axis where the hypothalamus of the brain controls the activity of the adrenal glands via the anterior pituitary gland (Figure 1). The adrenals are located in the visceral cavity superior to the kidneys. Neurons in each paraventricular nucleus of the hypothalamus synthesize the neuropeptides that are released when stressors activate the hypothalamo-pituitary adrenal axis. These are referred to as hypophysiotropic hormones [9] and in the case of the hypothalamo-pituitary adrenal axis are corticotrophic releasing hormone (CRH) [10] and, in all species studied except the pig, arginine vasopressin (AVP) [11]. In the pig, lysine substitutes for arginine to form lysine vasopressin [2]. CRH and AVP are secreted from the terminals of neurons directly into the primary capillary bed of a specialized portal blood system that communicates between the hypothalamus and anterior pituitary gland. This is the hypophyseal portal blood system [9]. CRH and AVP are transported by portal vessels to the secondary capillary bed where they exit and act upon corticotropes, the endocrine cells that produce peptides derived from pro-opiomelanocortin (POMC). These include adrenocorticotrophic hormone (ACTH), the opioid  $\beta$ -endorphin and  $\alpha$ -melanocyte stimulating hormone [12-16]. Of these, ACTH is of major importance when it comes to regulation of the hypothalamo-pituitary adrenal axis. ACTH acts on the cortex of the adrenal glands to stimulate the synthesis of steroids, including the glucocorticoids, which are essential in responding to stress. In many species, including humans, the predominant glucocorticoid released from the adrenal glands is cortisol. In rodents and avian species it is corticosterone [1]. As the name suggests, glucocorticoids have glucoregulatory actions,



evident as widespread effects to mobilize energy stores throughout the body [17-24]. Furthermore, these hormones have far reaching effects on most tissues, organs and systems with the objective of re-establishing homeostasis [17-24].

The hypothalamo-pituitary adrenal axis is regulated by various neural inputs and negative feedback by the glucocorticoids. There are extensive neuronal pathways within the central nervous system that are activated during stress and there are multiple interactions between these systems (for review see [1]). For example, there are reciprocal connections between noradrenergic neurons located in the brain stem ( $A_1$ ,  $A_2$  and  $A_6$  noradrenergic cell groups) and CRH and AVP neurons in the paraventricular nuclei of the hypothalamus that are important in mounting a stress response [1]. There are also reciprocal interactions between CRH and AVP neurons and cells in the arcuate nucleus, particularly those expressing peptides derived from POMC, including  $\beta$ -endorphin [1]. It has been shown in rats that serotonergic neurons project from the raphe nucleus of the midbrain to the hypothalamus, and there are interactions between serotonergic cells, the hypothalamo-pituitary adrenal axis and the sympathetic nervous system [1]. There are also neurons that produce the opioid peptide enkephalin in the paraventricular nucleus but the significance of these with respect to stress responses are unknown [1].

The negative feedback effects of glucocorticoids on the brain are mediated via high affinity mineralocorticoid receptors (MR) and low affinity glucocorticoid receptors (GR). MR are present in the hippocampus and other regions of the limbic system, including the amygdala and lateral septum, and in the hypothalamus [1, 2]. Glucocorticoids act via MR to maintain the basal activity of the hypothalamo-pituitary adrenal axis [25, 26]. The distribution of GR within the brain is much more widespread than for MR and they are found extensively within the hypothalamus and also the anterior pituitary gland [27]. GR are involved in the negative feedback actions of both basal and stress-induced levels of glucocorticoids, particularly the latter and facilitate homeostasis when stress levels of glucocorticoids prevail [25, 26, 28]. The hypothalamo-pituitary adrenal undergoes a circadian rhythm of regulation and this is evident in the negative feedback actions of the glucocorticoids [17-24].

While the sympatho-adrenal medullary system and the hypothalamo-pituitary adrenal axis are acknowledged as the front-line physiological systems to deal with stress, the opioids (Figure 1) also have a diverse range of stress-related actions [2]. There are three classes of opioids:  $\beta$ -endorphin, the enkephalins (met-enkephalin and leu-enkephalin) and dynorphin. The opioids act via different receptor subtypes (termed  $\mu$ ,  $\delta$  and  $\kappa$ ) and  $\beta$ -endorphin is the opioid most studied in terms of responses to stress (for review see [2]). As indicated above,  $\beta$ -endorphin is involved in the regulation of the hypothalamo-pituitary adrenal axis and the opioids are generally considered to attenuate and terminate stress responses [2]. Furthermore, these neuropeptides regulate sympathetic, cardiovascular and neural control systems and are involved in the regulation of pain, reinforcement and reward, the release of neurotransmitters and other autonomic and neuroendocrine functions [2].

Although the opioids clearly play various roles in responses to stress, and in regulating hypothalamo-pituitary adrenal axis responses to stress, it remains the case that most research on stress, particularly with respect to responses to, and impact of, different stressors has been on the sympatho-adrenal medullary system and the hypothalamo-pituitary adrenal axis. Consequently, we focus on these systems here, while acknowledging the need for a greater understanding of the roles of the opioidergic and other central systems in stress responses, and in the impact of stress on physiology and behaviour.

### 3. Stress and health

Irrespective of the precise definition of stress that one chooses, it is clear that stress embodies a range of physiological and behavioral processes that occur when there is a real or perceived threat to homeostasis. These adaptive responses are designed to re-establish homeostasis and allow coping. For the most part, this is what they do but if the various stress systems are repeatedly or continuously activated over long periods the effects can be deleterious for health [18, 20-24, 29-33]. This is not surprising when one considers the actions of catecholamines and glucocorticoids, as well as other stress hormones and neuropeptides like the opioids. For example, stimulation of the cardiovascular system and mobilization of energy have clear benefits in the short term in dealing with stress but the longer term effects will likely have harmful outcomes, increasing the chance of cardiovascular disease and energy deficits. This premise holds for most body systems as all tissues are affected by stress hormones. Initial benefits can become serious drawbacks, with the stress response becoming pathological.

Severe stress is associated with the increased prevalence of devastating conditions such as major depression, dementia and impaired cognition; cardiovascular disease; impaired immune function with increased vulnerability to disease; impaired growth and reproductive function; osteoporosis; diabetes, the metabolic syndrome and reduced life expectancy [18, 20-24, 29-47]. Some of the conditions associated with severe stress, such as major depression and cardiovascular disease, are amongst the most serious and costly to treat [17][48]. As with most areas of stress research, it is the hypothalamo-pituitary adrenal axis that has received most attention in terms of the impact on health. Nevertheless, as indicated, repeated and chronic activation of the sympatho-adrenal medullary system can lead to disorders and the increased prevalence of ill-health. In addition to stress, there are clinical conditions where the concentrations of glucocorticoids are pathologically high, and this is associated with physiological and behavioral dysfunction similar to that seen during chronic stress. These conditions include Cushing's Syndrome [35, 36], Cushing's Disease [35, 36] obesity [37], metabolic syndrome [37], functional hypothalamic amenorrhea [38, 39], hyperthyroidism [24], Diabetes Mellitus type II [37], hypertension [37] and major depression [37].

It follows that understanding stress responses is important if preventions and treatments of the deleterious effects of stress are to be established. This understanding will need to encompass the mechanisms of responses under a range of conditions, and in response to various stressors, as well as the effects of these responses on the body. The latter is not the focus of the current discussion but the former is. Individuals react to stressors in different ways and various physiological conditions including the sex of an individual will influence stress responses [1, 49]. Given that physiological responses to stress are important determinants for health, we will consider different types of stressors, sex differences in response to stress and the importance of physiological state, particularly reproductive state, in influencing responses to stress.

### 4. Different types of stressors

There are many different stressors that we encounter in our daily lives. It is commonly considered that stressors can be categorized as physical stressors or psychological stressors [1]. Physical stressors are those that pose a real threat to homeostasis and which result in "reactive" glucocorticoid responses to stress, whereas psychological stressors are those that

are perceived to pose a threat to homeostasis and which result in “anticipatory” glucocorticoid responses to stress. Herman and colleagues [50] asserted that “reactive” glucocorticoid responses to stress are those induced by a genuine challenge to physiological homeostasis that is recognized by sensory pathways. Such challenges may include a change in cardiovascular tone, respiratory distress, pain or circulating cytokines. In such cases, there is a direct neuronal pathway to CRH neurons in the paraventricular nucleus via the brain stem to activate the hypothalamo-pituitary adrenal axis. In contrast, “anticipatory” glucocorticoid responses to stress are not mounted in response to an actual disruption to physiological homeostasis but to the anticipation of such a disruption. These responses require some higher cortical processing involving limbic pathways [50].

Physiological responses to physical stressors may be considered appropriate since the body is being prepared for a real threat and the elevated heart rate and blood pressure and energy stores mobilised by catecholamines and glucocorticoids (see Section 2) are required to deal with the stressor. For example, a direct physical threat may require vigorous skeletal muscle activity in order to avert detrimental consequences imposed by the stressor. Conversely, physiological responses to psychological stressors are potentially more harmful since the body does not usually need to respond with a physical use of energy, certainly not for a prolonged period. This would be evident where there may be a stressful environment induced without the need for physical exercise, such as being caught in traffic on the way to an important appointment. Heart rate and blood pressure may be elevated, and energy stores mobilized, but with no obvious benefit to dealing with the stressor. An exception would be the possible beneficial effects of increased mental acuity. Nevertheless, it follows that psychological stress may be detrimental to health, particularly if it is prolonged or repeated frequently, because it unnecessarily elevates heart rate and blood pressure and mobilizes energy stores placing unnecessary strain on essential physiological systems. It is important to appreciate that excessive activation of the stress systems can have a negative impact on normal physiological functioning [19, 20, 32].

Since different types of stressors activate the physiological stress systems via different mechanisms, it is important to consider different types of stressors when considering the roles of sex and the sex steroids in influencing the responsiveness of the sympatho-adrenal medullary system and the hypothalamo-pituitary adrenal axis.

## 5. Sex differences in responses to stress

Men and women differ in the prevalence of chronic diseases. For example, men have a higher risk of infectious disease [51] and incidence of cardiovascular disease than women [52, 53] whereas women have a higher incidence of major depression and anxiety [54-56] and autoimmune disorders, including rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis [57] than men. Since there are also sex differences in the response to stress, the response to stress poses a potential candidate in the etiology of the chronic disease progression. As indicated above, we will focus on the sympatho-adrenal medullary system and hypothalamo-pituitary adrenal axis when considering sex differences in response to stress.

There has been relatively little research on sex differences in the response of the sympatho-adrenal medullary system to stress compared to the hypothalamo-pituitary adrenal axis, where most of the effort has been concentrated. We conducted one study comparing plasma catecholamine concentrations in gonadectomized sheep subjected to isolation and restraint



stress [58]. Plasma concentrations of epinephrine were significantly elevated above pretreatment concentrations for longer in rams (2-180 minutes after the commencement of stress) than in ewes (2-25 minutes after the commencement of stress). Nevertheless, there were no consistent significant differences between rams and ewes in plasma concentrations of epinephrine [58]. Interestingly, plasma concentrations of norepinephrine were not influenced by the isolation/restraint stress in either sex [58]. The reasons for this are not apparent given that the source of both catecholamines in plasma would have been the adrenal medulla.

In humans, the issue of sex differences in responses of the sympatho-adrenal medullary system to stress has been extensively reviewed [49] and sex differences are evident, although they do not always appear consistent. One reason for this is that physiological state influence these responses [49] and only a small number of studies have standardized the stage of the menstrual cycle thereby standardizing the sex steroid milieu of females. For example, one study reported that women in both the luteal and follicular phases of the menstrual cycle had a higher increase in heart rate in response to a psychological stress (mental arithmetic) compared to men but this sex difference was not present for a physical stress (cold pressor test) [59]. Women also tended to have a higher increase in diastolic blood pressure following the mental arithmetic stress compared to men ( $p < 0.07$ ) but, again, this was not the case for the physical stress and there were no differences between the sexes for systolic blood pressure [59]. In a different study, it was found that heart rate response to a psychosocial stress (Trier Social Stress Test) was significantly higher in luteal phase women compared to men [60]. Collectively, these findings indicate that sex differences in response of the sympatho-adrenal medullary system to stress will vary with different stressors, and this has also been apparent in various other studies [49]. This is not surprising and is also the case with respect to the hypothalamo-pituitary adrenal axis (see below). Furthermore, sex differences in the response of the sympatho-adrenal medullary system to stress in humans are influenced by age and reproductive hormonal status of the women [49].

We have demonstrated sex differences in the responsiveness of the hypothalamo-pituitary adrenal axis to stress in sheep. This was quantified on the basis of plasma concentrations of cortisol and it is evident that sex differences in responses to stress vary with the stressor. For instance, female sheep had a greater cortisol response to isolation/restraint stress (Figure 2)[61], an audiovisual stress (Figure 3)[62] and a wetting stress (Figure 4)[63] compared with male sheep, whereas male sheep had a greater cortisol response to insulin induced hypoglycaemia compared with female sheep (Figure 5) [61]. It is tempting to speculate that the direction of differences between females and males in cortisol responses to stress may be explained on the basis of psychosocial compared to metabolic stressors but further research is required to ascertain this. Besides, not all stressors elicit sex differences in cortisol responses, there being no differences between the sexes in the cortisol response to exercise stress (Figure 6) [63] or to endotoxin (Figure 7) [63]. Nevertheless, when sex differences do occur in sheep, it appears that the mechanisms for this are in place early in life, at least for some stressors. In lambs, we found that females had a significantly higher cortisol response to tail docking compared to males and that this sex difference developed between one and eight weeks of age [64]. We have also investigated the mechanisms for sex differences in hypothalamo-pituitary adrenal axis responses to stress and have found various differences between males and females at each level of the axis, some of which depend on gonadal factors [65, 66], which are discussed in the next section. These include differences in neuropeptide distribution in the paraventricular nucleus of the hypothalamus [66] as well as adrenal size and adrenal responsiveness to ACTH [65].

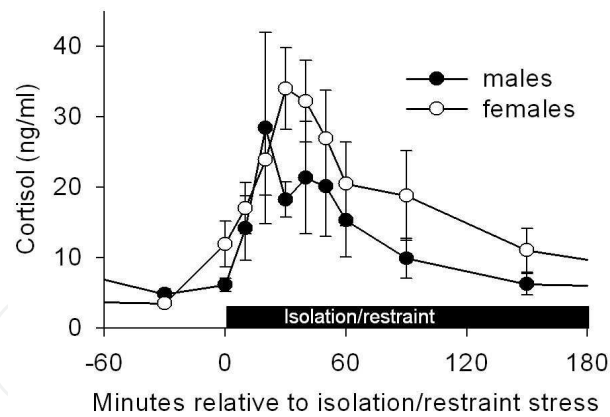


Fig. 2. Mean ( $\pm$ SEM) plasma concentrations of cortisol in gonadectomized male and female sheep before and during exposure to 180 min of isolation/restraint stress (indicated by the black bar). From [61].

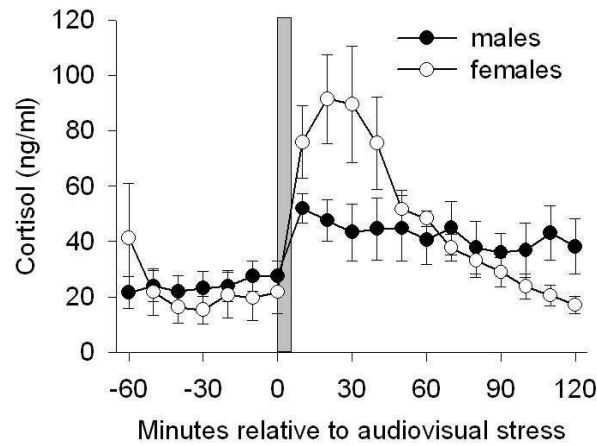


Fig. 3. Mean ( $\pm$ SEM) plasma concentrations of cortisol in gonadectomized male and female sheep before, during and after exposure to 5 min of audiovisual stress (barking dog; indicated by the grey bar). From [62]. Copyright S. Karger AG, Basel

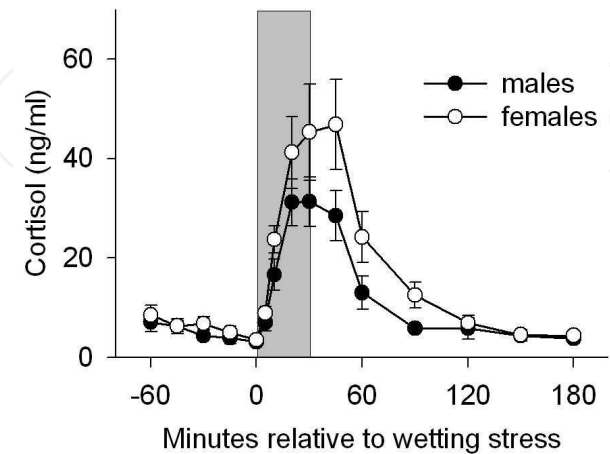


Fig. 4. Mean ( $\pm$ SEM) plasma concentrations of cortisol in gonadectomized male and female sheep before, during and after exposure to 30 min of wetting stress (indicated by the grey bar). From [63]. Copyright 2010, The Endocrine Society.

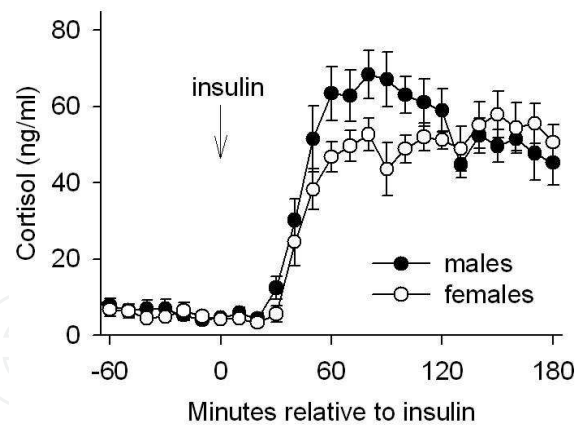


Fig. 5. Mean ( $\pm$ SEM) plasma concentrations of cortisol in gonadectomized male and female sheep before and after injection of insulin (indicated by the arrow). From [61].

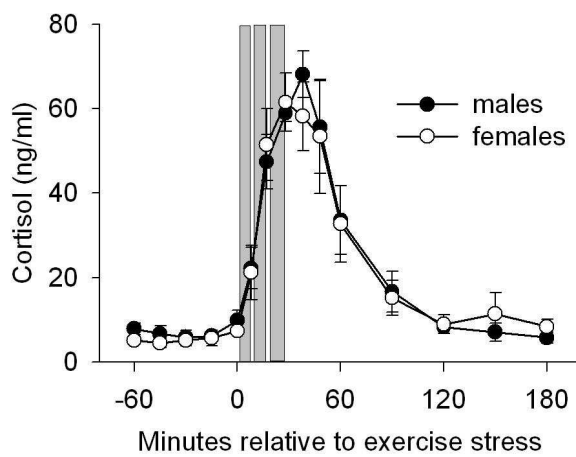


Fig. 6. Mean ( $\pm$ SEM) plasma concentrations of cortisol in gonadectomized male and female sheep before, during and after exercise stress, which consisted of running 3 x 0.6 km (indicated by the grey bars). From [63]. Copyright 2010, The Endocrine Society.

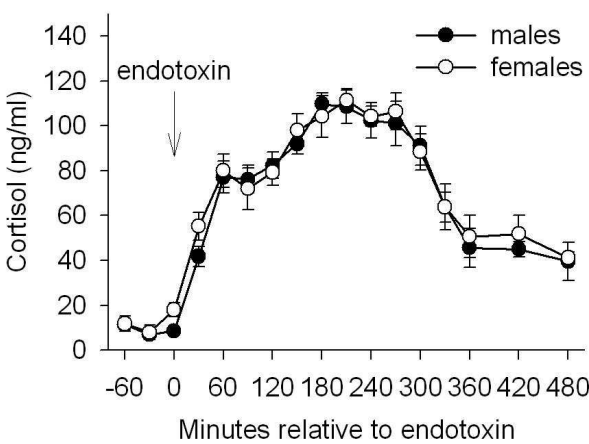


Fig. 7. Mean ( $\pm$ SEM) plasma concentrations of cortisol in gonadectomized male and female sheep before, during and after injection of endotoxin (indicated by the arrow). From [63]. Copyright 2010, The Endocrine Society.

In humans, there is also evidence that hypothalamo-pituitary adrenal axis responses to stress differ between adult men and women (see [49] for an extensive review of the literature). The initial research effort in humans was hampered by a lack of treatments that adequately activated the hypothalamo-pituitary adrenal axis [49]. More recent research has shown that there are only subtle sex differences in the basal activity of the hypothalamo-pituitary adrenal axis but these become more pronounced with the imposition of a psychological stressor. In general, it seems that between puberty and menopause, cortisol responses to psychosocial stress are lower in women compared with aged matched men [49, 67]. Nevertheless, as in our sheep studies, there is also some evidence from human studies that sex differences in cortisol responses to stress may depend on the stressor encountered since men had significantly greater cortisol responses to achievement challenges than women and women had significantly greater cortisol responses to social rejection challenges than men [49]. In contrast to studies in post-pubertal humans, few studies have found sex differences in stress responsiveness during infancy and childhood [49]. Unlike sheep where a window of development of sex differences has been identified [64], the precise stage of development of sex differences is unknown in humans. Nonetheless, there is a prolonged activation of the hypothalamo-pituitary adrenal axis to stress during adolescence (for review see [68, 69]).

While there has been various research across a range of species to try and understand the mechanisms for sex differences in responses to stress, with a large emphasis on the role of gonadal factors such as the sex steroids (see Section 6), there has been little attention paid to understanding the physiological importance of these sex differences. This needs to be considered from both an adaptive perspective, and from consideration of the impact of stress on health. With regard to the former, if one considers that stress responses are designed to re-establish homeostasis, to ward off the detrimental effects of noxious stimuli (Section 2), then one could argue that the sex with the greater catecholamine and cortisol responses to a particular stressor is the better equipped to deal with the stress. On the other hand, if one considers that prolonged or repeated activation of stress systems can be damaging to health (Section 3), then the sex with the greater response may be in the greater danger of the deleterious effects of the response. Unfortunately, these hypotheses have hitherto not been tested and this highlights an important issue requiring research. There is a need to determine the salience of stressors when undertaking sex comparisons, and there is a need to undertake sex comparisons over extended periods, and under conditions of repeated stress, to ascertain the relative impact of stress on each sex.

## **6. The role of sex steroids and reproductive state on stress responsiveness**

It is apparent that there are interactions between the stress systems and sex steroid producing systems. This is most marked with the interactions between the hypothalamo-pituitary adrenal axis and reproductive axis, which are bidirectional. Activation of the stress systems can impact the reproductive axis [16, 70-75] and sex steroids can affect activation of the stress systems. When it comes to trying to appreciate the role of sex steroids in influencing the stress systems one is compelled to consider research in rodents because this is where the majority of investigation has been. Furthermore, most research concerning the effects of steroids on stress systems has concentrated on the hypothalamo-pituitary adrenal axis, with relatively little attention paid to the sympatho-adrenal medullary system. Nevertheless, there are actions of sex steroids on catecholaminergic neurons in various brain

regions [76-80]. For example, it has been demonstrated that estradiol benzoate treatment of ovariectomized rats increased extracellular levels of norepinephrine and dopamine in the pre-optic area of the hypothalamus during the dark phase [81], although this is not considered the predominant locus in regulating the sympatho-adrenal medullary system. Furthermore, sexually dimorphic responses in activation of the locus coeruleus-norepinephrine system have been shown in rats [82] although it is possible that this is more important to regulation of the hypothalamo-pituitary adrenal axis than the sympatho-adrenal medullary system. An *in vitro* study showed that estradiol-17 $\beta$  stimulated catecholamine synthesis from adrenal medullary cells, which is direct evidence that this steroid is capable of influencing the sympatho-adrenal medullary system [83]. In human females, one study found that sympathetic nervous activity in response to mental stress was similar between the early follicular phase and mid-luteal phase but the recovery was prolonged during the mid-luteal phase [84]. A number of other investigations in women have reported that estrogen attenuates sympathetic activity in response to stress although this has not been found in all studies (for review see [49]). An attenuating effect on sympathetic activity in response to mental arithmetic was also demonstrated in young men treated with estradiol [85]. Nonetheless, these were not extended to the complete sympatho-adrenal medullary system and little is known about the effects of progesterone and testosterone on this stress system.

The body of work in rodents and humans has generally suggested that females have higher basal glucocorticoid levels than males [86, 87]. In rodents, females also have higher stress-induced ACTH and glucocorticoid responses [88-90] than males and this is due, at least in part, to a stimulatory effect of estradiol on the hypothalamo-pituitary adrenal axis [91-93]. One possible mechanism for this may involve enhanced CRH expression because there are estrogen-responsive elements on the 5' regulatory region of the CRH gene [93]. Estradiol has also been shown to act directly on neurons within the paraventricular nucleus via estrogen receptor  $\alpha$  [94]. Given this effect of estradiol it follows that reproductive state will affect the hypothalamo-pituitary adrenal axis and variations in activity occur across the estrous cycle of the rat [95, 96] and menstrual cycle of the monkey [97]. In contrast to estrogens, in rodents androgens are considered to inhibit the activity of the hypothalamo-pituitary adrenal axis [88, 92, 94, 98], possibly via a mechanism that involves direct actions of testosterone on neurons within the paraventricular nucleus via estrogen receptor  $\beta$  (for extensive review see [94]). It has been proposed that testosterone is converted to an androgenic metabolite, 5 $\alpha$ -androstane-3 $\beta$ ,17 $\beta$ -diol, that binds estrogen receptor  $\beta$  to regulate oxytocinergic neurons in the paraventricular nucleus [94]. Despite these opposing actions of estrogens and androgens on the activity of the hypothalamo-pituitary adrenal axis in rodents, the roles of sex steroids in influencing stress responses are less clear-cut in other species, and it is unknown if similar mechanism of action exist in non-rodent species.

We have not directly addressed the effects of steroids on the sympatho-adrenal medullary system in sheep but have considered sex differences and the importance of the gonads when it comes to the hypothalamo-pituitary adrenal axis. In adult sheep we identified a range of differences between males and females in the hypothalamo-pituitary adrenal axis and some, but not all, of these differences depended on gonadal factors [99]. Of significance in this study was an enhanced adrenocortical response to ACTH in females compared to males, and this occurred irrespective of the presence or absence of gonads. Males had higher AVP in the median eminence than females and gonadectomy increased this in both sexes [99].



Gonadectomy also elevated median eminence content of CRH but there was no difference between sexes. There was no effect of *in vitro* ACTH secretion in response to treatment with AVP, CRH and the two in combination [99]. Our research in prepubertal sheep has also shown that some sex differences in the activity of the hypothalamo-pituitary adrenal axis endure in the absence of the sex steroids [64]. Consistent with these findings, we also showed that sex and gonadal status affect the distribution of CRH, AVP and enkephalin in the paraventricular nucleus of sheep, providing a neuroanatomical basis for sex differences in the central regulation of the hypothalamo-pituitary adrenal axis [66]. Others have shown that steroids and reproductive state can affect the activity of the hypothalamo-pituitary adrenal axis in female sheep [100], but there were no comparisons with males. In a series of studies in ewes it was shown that progesterone inhibits ACTH stimulation of cortisol [101, 102, 103] and stress, induced secretion of cortisol estrogens and androgens influence hypothalamic concentrations of CRH and AVP [104], and that ovariectomy affects hypothalamo-pituitary adrenal axis responses to stress [105, 106]. While it is clear that gonadal factors, such as the sex steroids, and reproductive state, influence the activity of the hypothalamo-pituitary adrenal axis in sheep, there is a need for more extensive research to establish the precise roles of steroids and reproductive state, including with regard to different stressors.

In women the stage of the reproductive cycle has been shown to affect the hypothalamo-pituitary adrenal axis responses to stress (for an extensive review see [49]). It has been consistently reported that cortisol responses to psychosocial stress were lower in women in the follicular phase of the menstrual cycle compared with women in the luteal phase of the menstrual cycle [49]. This suggests that there is attenuation of the hypothalamo-pituitary adrenal axis in response to psychosocial stress in an estrogenic environment (i.e. the follicular phase), and this is supported by studies showing that women taking a synthetic estrogen as an oral contraceptive had similar cortisol responses to psychosocial stress compared to women in the follicular phase of the menstrual cycle and lower than those in the luteal phase [49]. An attenuating action of estradiol on stress-induced hypothalamo-pituitary adrenal axis activity in women is similar to the effects of estrogen on the autonomic nervous system but contrasts with the situation in rodents, where estradiol generally has facilitatory actions (see above). There has been considerably less research on the role of the other principal ovarian steroid, progesterone, in influencing the hypothalamo-pituitary adrenal axis. In rodents, progesterone has been reported to suppress the hypothalamo-pituitary adrenal axis response to stress [107-109] and there is now direct evidence to suggest that this is also the case in men, although there may be divergent effects on the sympatho-adrenal medullary system [110]. Administration of progesterone to men attenuated cortisol responses to the Trier Social Stress Test and reduced negative mood and alertness after stress but increased plasma norepinephrine and systolic blood pressure [110]. A similar approach has not been undertaken in women although in a study that utilised positive emotion-arousing there was a positive correlation between salivary progesterone and cortisol in men and in women taking hormonal contraceptives but not in women undergoing natural menstrual cycles, prompting the authors to suggest that progesterone may play a role in down-regulating the stress response [111]. Testosterone may also have a down regulating effect on the stress systems in humans because administration of testosterone to women resulted in decreased stress responsiveness [112-114], which is similar to the case in rodents (see above). While a role for testosterone in regulating the activity of the hypothalamo-pituitary adrenal axis was suggested [112], the collective work

of these authors (e.g. [112-114]) also implicates a regulatory role for testosterone on the autonomic nervous system and, possibly, the sympatho-adrenal medullary system. Further research is necessary to confirm this and the research needs to be extended to males.

Lactation is a physiological state that can have profound effects on both the basal and stress-induced activity of the hypothalamo-pituitary adrenal axis. In many species, including humans, ungulates and rodents, it has been consistently found that lactating females show attenuated neuroendocrine responses to stress (for reviews see [115-117]) and anxiety-related behaviours (for reviews see [116, 118, 119]). The alterations in the hypothalamo-pituitary adrenal axis that result in reduced responses to stress begin to emerge in late pregnancy and occur in a continuum throughout lactation (for reviews see [116, 118, 120, 121]). Although the mechanisms for attenuated hypothalamo-pituitary adrenal axis responses to stress during lactation are not fully known, it appears that they include reduced synthesis and secretion of CRH and AVP due to enhanced negative feedback by glucocorticoids and/or reduced noradrenergic stimulatory input from the brain stem, reduced pituitary responsiveness to CRH and AVP and, possibly, inhibition by oxytocin and prolactin [1]. We have shown in sheep that the greatest attenuation of the hypothalamo-pituitary adrenal axis is achieved when the lactating mother is suckled [122] and this is likely to also be the case for humans when breastfeeding [1]. Despite the many published reports of attenuated stress responses in lactating females this has not always been the case and the nature of the stressor seems to be important. It has been shown in both sheep [123] and humans [87] that there is activation of the hypothalamo-pituitary adrenal axis in response to a stressor that may threaten the welfare of the infant by virtue of harming the mother. This makes perfect sense given that the mother would require a stress response in order to dispose of the threat posed to herself and her offspring. This underscores the importance of being able to mount stress responses so that homeostasis can be restored (Section 1).

## 7. Conclusions

Although there are various ways to define stress there is generally acceptance that stress responses occur in response to noxious stimuli, whether perceived or real, commonly called stressors. A range of physiological systems are activated with the two of the most prominent being the sympatho-adrenal medullary system and the hypothalamo-pituitary adrenal axis. The catecholamines and glucocorticoids, released by each system respectively, have far-reaching effects within the body to re-establish the homeostasis that was disrupted by stressors. Such stress responses are vital for a healthy life. Nevertheless, when the stress systems are frequently or continually activated, the on-going action of the catecholamines and glucocorticoids can be destructive and lead to pathological conditions. An inability to mount an appropriate stress response may also result in illness. Therefore, it follows that understanding stress responses, and the factors that affect stress responses, is paramount to develop strategies and treatments to avoid or cure stress-induced disorders and pathologies. These factors include sex, sex steroids and physiological state, particularly reproductive state. There are differences between males and females in various illnesses and pathological states and many of these are those induced or exacerbated by frequent or chronic stress. Males and females respond differently to some stressors and not others. The implications for health and survival of these different stress responses are unknown and research is required to determine this. At least some of the mechanisms for sex differences in stress responses are

due to gonadal factors, such as the sex steroids, but others are not. There also appear to be differences between species in the impact of sex steroids on the stress systems. For example, whereas estrogens appear to facilitate and androgens abrogate stress responses in rodents, the actions of estrogens on stress responses in humans may be the opposite, at least in some cases, and the effects of androgens have received insufficient research in non-rodent species to draw definitive conclusions. Nevertheless, since there are effects of sex steroids on stress responsiveness, there are differences in stress responsiveness at different stages of the female reproductive cycle. Furthermore, during lactation, stress responses are generally attenuated, unless the stressor threatens the well-being of the mother and, in turn, the offspring. This review has highlighted substantial gaps in knowledge that are required to fully appreciate the field of stress physiology. These include understanding mechanisms of stress responses to different types of stressors, between sexes and in different physiological states. They also include the mechanisms by which different stressors impact the body of males and females in different physiological states.

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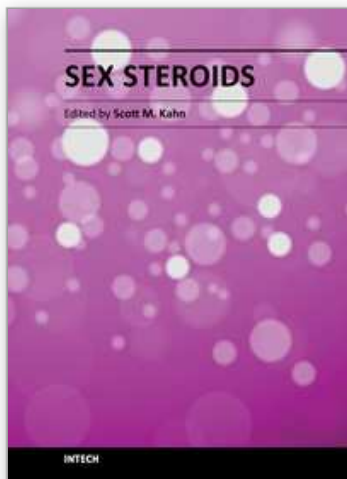
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## **Sex Steroids**

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This book, entitled "Sex Steroids", features a valuable collection of reviews and research articles written by experts in signal transduction, cellular biology, diseases and disorders. "Sex Steroids" is comprised of four sections, "The Biology of Sex Steroids", "Sex Steroids, Memory, and the Brain", "Sex Steroids and the Immune Response", and "Therapy"; individual chapters address a broad range of recognized and predicted functions and applications of sex steroids. "Sex Steroids" is intended to provide seasoned veterans as well as newcomers to this area of research with informative, resourceful, and provocative insights. Readers of "Sex Steroids" should emerge with an appreciation and understanding of the multitude and complexity of biologic processes attributed to these important hormones, and possible future directions of research in this fascinating and ever evolving field.

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