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Review

Neuroendocrine mechanisms of innate states of attenuated responsiveness of the hypothalamo-pituitary adrenal axis to stress

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Abstract

Neuroendocrine responses to stress vary between sexes and reproductive states and are influenced by the type of stressor. Stress responses are attenuated in some physiological states, such as lactation and conditions of low visceral adipose tissue. Moreover, some individuals within a species characteristically display reduced stress responses. The neuroendocrine mechanisms for stress hyporesponsiveness are likely to include reduced synthesis and secretion of corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) from the hypothalamus as a result of enhanced glucocorticoid negative feedback and/or reduced noradrenergic stimulatory input from the brain stem. A major limitation of research to date is the lack of direct measures of CRH and AVP secretion. Attenuated stress responsiveness is also commonly associated with reduced pituitary responsiveness to CRH and AVP. The possible roles of inhibitory central inputs to CRH and AVP neurons and of oxytocin and prolactin in attenuating the HPA axis responses to stress are unknown.

Keywords: Stress; Stress hyporesponsiveness; Hypothalamo-pituitary adrenal axis; Stress responsiveness; Lactation; Visceral adiposity; CRH; AVP; Glucocorticoids; Norepineprhine

1. Introduction

Stress is a complicated physiological mechanism that embodies a range of integrative physiological and behavioral processes that occur when there is a real or perceived threat to homeostasis. While it is generally accepted that these processes are adaptive, designed to re-establish homeostasis and allow coping, it is also apparent that inadequate or excessive and/or prolonged activation of stress systems can disturb normal physiological and behavioral function. This can result in a range of adverse consequences such as depression, impaired cognition, cardiovascular disease, impaired immune function with increased vulnerability to disease, impaired growth and reproductive function, osteoporosis, diabetes, dementia and reduced life expectancy [22,24,220,221,236,238]. Despite a vast literature on stress responses in a range of species, there is still much to be learned about the mechanisms of stress responses so that strategies can be developed to prevent and overcome stress-induced disorders.

Under some physiological conditions, responses to stress are naturally attenuated while still being adequate to allow adaptation to adverse threats to homeostasis. There are various physiological states where this occurs but one of the best known examples is seen in the female during late pregnancy and lactation. It is also apparent that stress responses vary between humans and animals with differing amounts of visceral adipose tissue. Lean individuals generally display reduced responses to stress. Furthermore, neuroendocrine and behavioral responses to stress often vary substantially between individuals, within the same species, such that some individuals inherently display reduced responsiveness of the stress systems, including the hypothalamo-pituitary adrenal (HPA) axis. An understanding of the neuroendocrine mechanisms that underlie natural physiological states of reduced stress responsiveness, defined here as stress hyporesponsiveness, will provide knowledge that could be utilized to generate

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physiological treatments for people at risk of illness due to chronic stress and/or disorders of the stress systems. This is conceptually attractive because the most effective mechanisms to suppress stress responses will undoubtedly be those that the body itself uses. In this review we explore some of the mechanisms of stress hyporesponsiveness in lactating females, lean individuals and individuals that display naturally attenuated neuroendocrine responses to stress. Our focus is upon the regulation of the HPA axis.

2. Physiological responses to stress

The intrinsic or extrinsic stimuli, whether real or perceived, that challenge homeostasis, are commonly termed stressors. Stressors are many and varied (e.g. psychological, physical, surgical trauma, strenuous exercise, undernutrition) and activate a range of physiological systems, the most commonly studied being the HPA axis (Fig. 1) and the sympathoadrenal system. Activation of the HPA axis results in stimulation of parvocellular neurons of the paraventricular nucleus (PVN) of the hypothalamus and the release of the neuropeptides corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) into the hypophyseal portal blood system. The combined action of CRH and AVP on the corticotropes of the anterior pituitary gland stimulates the secretion of peptides derived from pro-opiomelanocortin which include adrenocorticotropin (ACTH), the opioid peptide β-endorphin and α-melanocyte-stimulating hormone [38,49,74,123,179]. Although the physiological importance of the secretion of β-endorphin and α-melanocyte-stimulating hormone in response to stress is not well understood, ACTH acts on the cortex of the adrenal glands to stimulate the synthesis of glucocorticoids. Glucocorticoids regulate the secretion

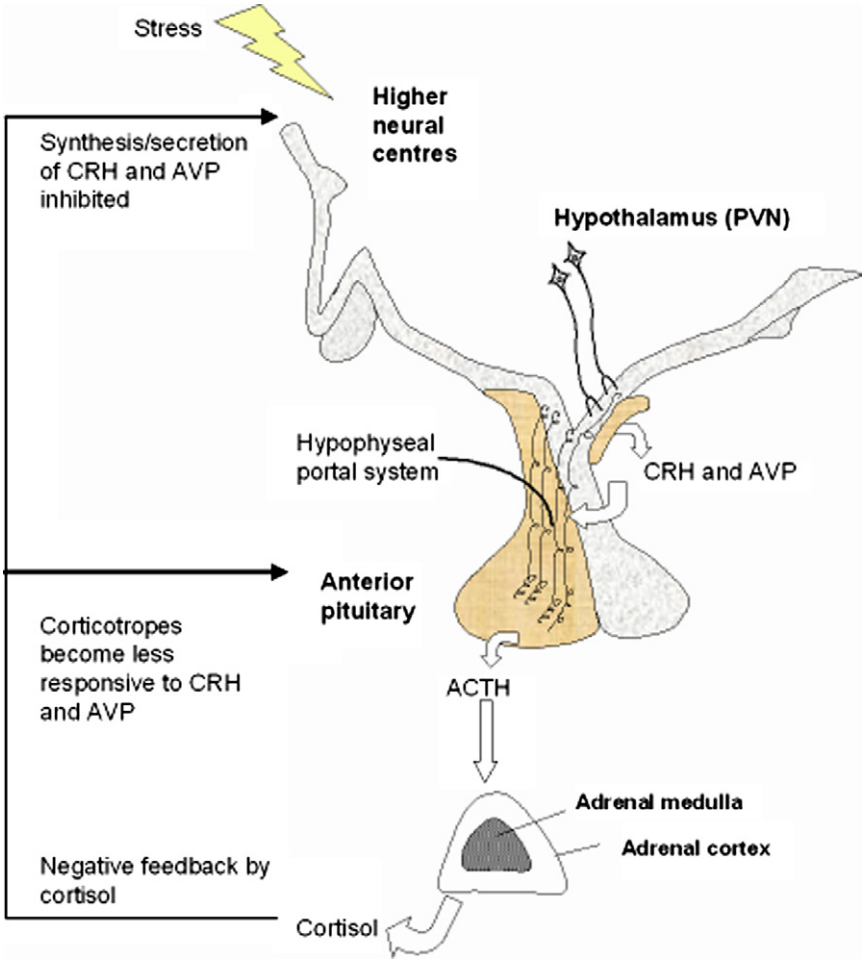

Fig. 1. Schematic representation of the hypothalamo-pituitary adrenal (HPA) axis. Stress causes activation of parvocellular neurons of the paraventricular nucleus (PVN) of the hypothalamus and the consequent release of the neuropeptides corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) into the hypophyseal portal system. The combined action of CRH and AVP on corticotrope cells of the anterior pituitary gland stimulates the secretion of peptides derived from pro-opiomelanocortin which include adrenocorticotropin (ACTH), the opioid peptide β-endorphin and α-melanocyte-stimulating hormone (not shown). ACTH acts on the cortex of the adrenal glands to stimulate the synthesis of glucocorticoids. Glucocorticoids regulate the secretion of CRH, AVP and ACTH through negative feedback actions in the brain, to ultimately inhibit the synthesis and secretion of CRH and AVP, and anterior pituitary gland, where corticotropes become less responsive to CRH and AVP. In humans and many mammalian species, the predominant glucocorticoid is cortisol (illustrated here), whereas in rodents and avian species the key glucocorticoid is corticosterone.

of CRH, AVP and ACTH through negative feedback actions (*vide supra*) in the brain and anterior pituitary gland [18]. In humans and many mammalian species, the predominant glucocorticoid is cortisol, whereas in rodents and avian species the key glucocorticoid is corticosterone. The sympathoadrenal system consists of the sympathetic nervous system and the adrenal medulla. Activation by stress causes the release of the catecholamine, norepinephrine from postganglionic nerve terminals, while preganglionic innervation of the adrenal medulla results in increased secretion of catecholamines, principally epinephrine, into the peripheral circulation [60]. Both glucocorticoids and catecholamines act widely to mediate the stress response.

Extensive research conducted with rodents has identified that many neuronal pathways within the central nervous system are activated during stress and there are multiple interactions between these systems (for reviews see [22,24,50,70,71,169,234,261]. Reciprocal connections between CRH and AVP neurons in the paraventricular nucleus and noradrenergic neurons located in the brain stem (A_1, A_2 and A_6 noradrenergic cell groups) are considered of major importance in the mounting of a stress response. Reciprocal connections also exist between CRH and AVP neurons and the cells of the hypothalamic arcuate nucleus. In particular, the cells of the arcuate nucleus that produce POMC products, including β-endorphin, project to the CRH and AVP neurons [52,92,94,111,130,223]. In rats, serotoninergic neurons of the raphe nuclei of the midbrain also project to the hypothalamus and there are neural connections between the serotoninergic system, HPA axis and the cells of the sympathetic nervous system [21,70]. The catecholaminergic, opioidergic [134,169] and serotoninergic systems are extensively activated in rodents during stress (for reviews see [21,66,83,171]). Cells producing enkephalin are found within the paraventricular nucleus [125,126,188] although the significance of this in relation to stress responsiveness is not understood. Identification of the central pathways that are activated during stress in non-rodent species has received far less attention.

3. Physiological states can influence stress responsiveness

Neuroendocrine responses to stress vary between sexes and in different physiological states. It is well established for various species that there are sex differences in responses of the HPA axis to stress and it has been proposed that these are due principally to the influence of the sex steroids [64]. Most research has been conducted with rodents where it has generally been found that females have higher basal circulating levels of cortisol [30,97] and respond to stress with greater excursions in ACTH and cortisol [64,88,133] than males. A longer duration and higher magnitude of the stress response has also been reported in female rodents than in males [87,96,174]. This suggests that the negative feedback mechanisms of glucocorticoid feedback that regulate the HPA axis may be less sensitive in females [174]. The increased stress responses in female rats are considered to be due, at least in part, to a stimulatory effect of estrogen on the HPA axis [12,163,241]. This mechanism may involve enhanced CRH expression since there are estrogen-responsive elements in the 5′ regulatory region of the CRH gene [241]. Thus, activation of the HPA axis varies with different reproductive states. For example, variations in HPA activity have been demonstrated across the estrous cycle in rats [16,244] and at different stages of the menstrual cycle in monkeys [206]. By way of contrast to the effects of estrogens, androgens are thought to inhibit the activity of the HPA axis [11,64,163]. Although the influence of sex steroids in causing sex differences in the activity of the HPA axis has received little attention in other species, we have found differences between male and female sheep at the adrenal, pituitary [19] and hypothalamic [177,194] levels of the HPA axis and some of these differences are clearly influenced by the presence and absence of the gonads.

Despite the general finding that female rodents exhibit greater response of the HPA axis to stress, we have found in sheep that the direction of the sex difference is influenced by the type of stressor. For example, the cortisol response to isolation and restraint stress is greater in female sheep than in males (Fig. 2), whereas the response to insulin-induced hypoglycemia (Fig. 3) was higher in males [236]. Similarly, in one study in rats it was found that females released more ACTH in response to foot-shock stress whereas males released more ACTH in response to alcohol injections [178]. These findings suggest that different pathways and systems are involved in the relay of critical neural information in relation to different stressors. Certainly it is well accepted that different stressors activate different areas of the rodent brain (reviewed by [2,242]). This has also been demonstrated in pre-pubertal pigs [157] and castrated rams [1,243] subjected to different stressors. Furthermore, as indicated in studies of rodents, it is apparent that distinct

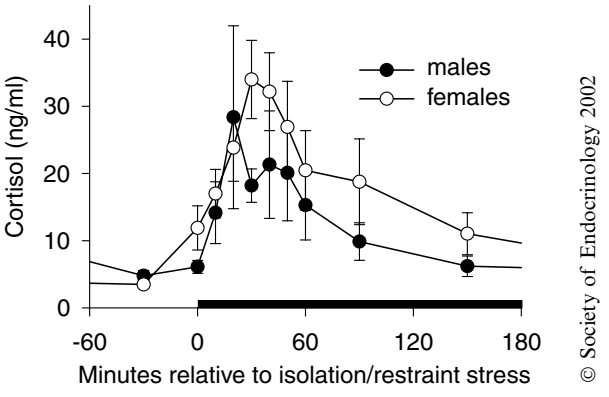

Fig. 2. Mean (±SEM) plasma concentrations of cortisol (ng/ml) in male and female sheep for 60 min before and 180 min of isolation and restraint stress. The period of isolation and restraint stress is illustrated by the black bar. The plasma concentrations of cortisol were significantly ($P < 0.05$) higher in female than in male sheep. Adapted from Ref. [236]. Reproduced by permission.

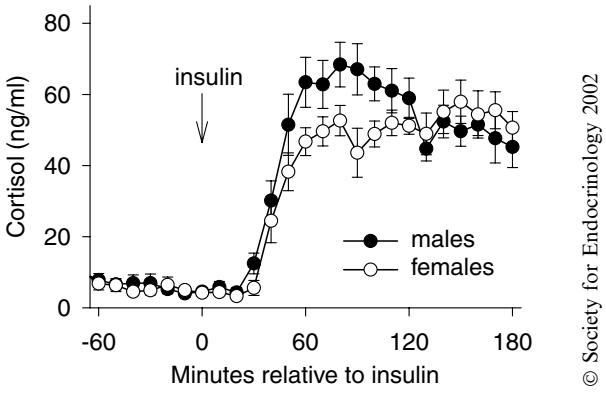

Fig. 3. Mean (±SEM) plasma concentrations of cortisol (ng/ml) in male and female sheep for 60 min before and 180 min following an i.v. injection of insulin (2 IU/kg live-weight). The plasma concentrations of cortisol were significantly ($P < 0.05$) higher in male than in female sheep. Adapted from [236]. Reproduced by permission.

afferent pathways mediate stressor-specific stress responses [70,71]. 'Reactive' stress responses are those that represent an immediate threat to physiological homeostasis and invoke somatic, visceral or circumventricular sensory pathways whereas 'anticipatory' responses require a degree of higher cortical processing and activate limbic-sensitive pathways [70,71]. In this regard, the relevance of the particular stressor has been emphasized in rodent studies [235,250]. Thus, stress responsiveness will be influenced by the type of stressor in addition to the sex and reproductive state of individuals.

4. Physiological states in which stress responses are attenuated

4.1. Lactating females

It has been consistently found in many species that lactating females show attenuated neuroendocrine responses to stress [115,235,254] and alleviated anxiety-related behaviors [143,235,240]. Extensive studies in rats have revealed that there is alteration of both the basal and stress-induced activity of the HPA axis during lactation. Thus, in non-stressed lactating rats, concentrations of ACTH and corticosterone are elevated [53,113,212,251,266] due predominantly to a flattening of the diurnal rhythm of secretion with a rise in the nadir levels of corticosterone and a decrease in the peak evening levels [6]. Both increased nadir concentrations of ACTH [251] and reduced concentrations of ACTH in the face of elevated corticosterone [53] have been reported. The reasons for these contrasting findings are not apparent. Such extensive studies have not been carried out in humans to present clear evidence of altered basal secretion of cortisol during lactation although breastfeeding does reduce plasma concentrations of cortisol in non-stressed lactating women [4,90]. Increase in the basal secretion of glucocorticoids and ACTH and a loss of the normal diurnal rhythmic activity of the HPA axis during lactation was found in one study in sheep [28] although we failed to find differences between lactating and non-lactating ewes in the plasma concentrations of ACTH or cortisol during times of no stress ([222], Fig. 4), indicating that more research is required in this species to understand the basal activity of the HPA axis during lactation.

Reduced responsiveness of the HPA axis to stress in lactating rats has been demonstrated for a diverse range of stressors including foot shock [218], conditioned foot shock [200], electrical shocks or handling [207], ether stress [213,218,251], noise [266], cold stress [271], forced swimming [231,232,255], restraint [7,34], a combination of elevated plus maze and forced swimming [145,147], mild air-puff [144], resident/intruder paradigm [148], odor of fox urine [41] and intraperitoneal injection of sodium chloride [117] and lipopolysaccharide [113,203]. In mice, blunted HPA axis responses were found in pregnant but not lactating females in response to novelty stress, while blunted ACTH responses to swim stress occurred in both pregnant and lactating females [45]. Lactating rats also display

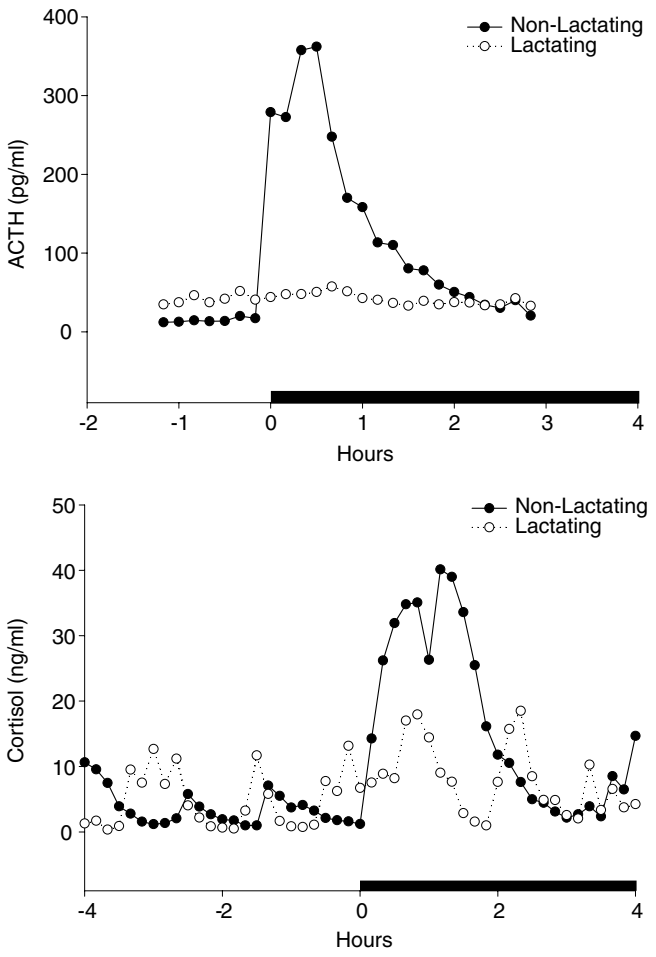

Fig. 4. Plasma concentrations of ACTH (ng/ml) and cortisol (ng/ml) before and during isolation and restraint stress in a lactating and non-lactating female sheep. The period of isolation and restraint stress is illustrated by the black bar (A.J. Tilbrook, M.D. Ibbott, A.I. Turner, I.J. Clarke, unpublished).

reduced responsiveness of physiological 'stress' systems with reduced circulating concentrations of catecholamines [73], oxytocin [20,72,141] and prolactin [7,73] and reduced heart rate [131] compared to non-lactating rats. The alterations in the HPA axis begin to emerge in late pregnancy and occur in a continuum throughout lactation (for reviews see [46,143,185,235]). This is generally considered to be an adaptive change that occurs in order for appropriate maternal behavior to be established to allow optimal development of the infant [235].

In humans, HPA axis responses to cold temperature appeared to be blunted during the final trimester of pregnancy [86] and there is evidence that the activity of the HPA axis is altered during the postpartum period [122] with attenuated stress responses and altered behavioral parameters occurring in lactating women in response to some stressors. Nevertheless, many of these studies have focused on the importance of breastfeeding, without comparisons between lactating and non-lactating females (for details see [235]). In one study, lactating women had lower basal plasma concentrations of norepinephrine and reduced ACTH, cortisol and glucose responses to treadmill exercise than non-lactating women [42]. In contrast, there was no difference between lactating and non-lactating women in response to social stress [3] or in response to CO_2 inhalation [90], which illustrates that stress responses during lactation depend upon the nature of the stressor. Indeed, it was considered that the lack of attenuated HPA axis response of lactating women exposed to CO_2 inhalation may be due to this stressor being perceived as threatening to the mother's survival and, in turn, the welfare of the infant [90]. In lactating sheep, the plasma cortisol response to introduction of an audiovisual stress (barking dog) was lower in lactating ewes than in non-lactating ewes [28] and we have found reduced plasma concentrations of both ACTH and cortisol during isolation and restraint stress in lactating ewes ([222], Fig. 4).

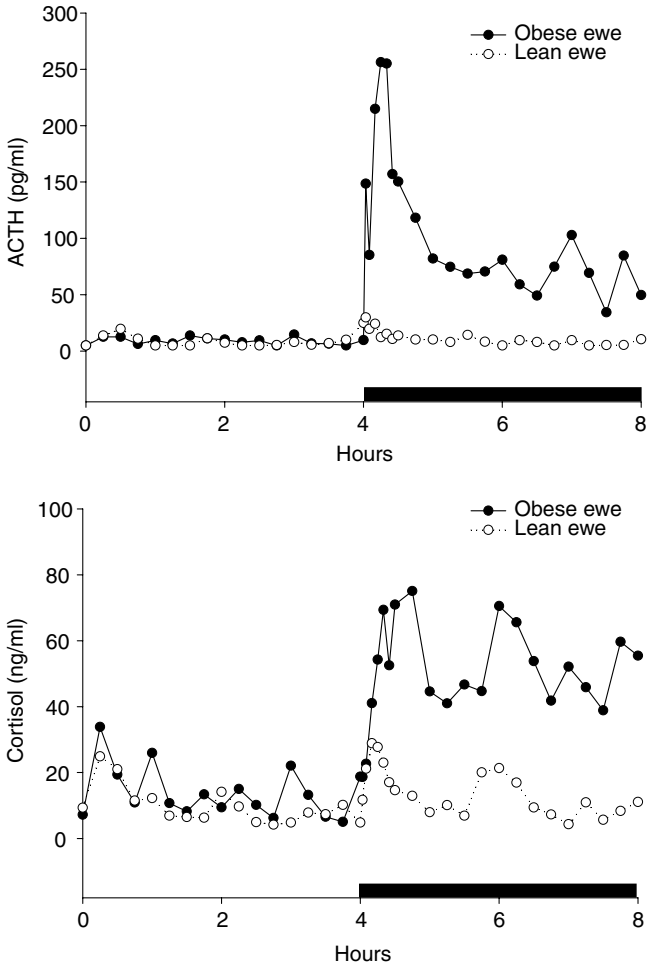

Fig. 5. Plasma concentrations of ACTH (ng/ml) and cortisol (ng/ml) before and during isolation and restraint stress in an obese (Obese ewe) and lean (Lean ewe) female ovariectomized sheep. The period of isolation and restraint stress is illustrated by the black bar (A.J. Tilbrook, A.I. Turner, I.J. Clarke, unpublished).

4.2. Level of visceral adipose tissue

It is common for the stress-induced activity of the HPA axis to be substantially reduced in humans and rats that have low levels of visceral adipose tissue compared to those with abdominal obesity. We found that ewes with low levels of abdominal fat (lean) had substantially reduced stress responses compared to obese ewes. Ewes with characteristics of obesity, including increased abdominal fat depots and insulin resistance, consistently showed increased plasma concentrations of ACTH and cortisol during isolation and restraint, whereas the reverse was true for lean ewes (Fig. 5). Women with abdominal obesity have been shown to have increased activity of the HPA axis compared to lean women in response to insulin-induced hypoglycemia [257], mental challenges [124,137], physical stress (cold pressor) [124] and various dietary factors [158]. Similarly, obese men had increased cortisol secretion in response to stress [181,182] and treatment with ACTH [65]. Despite differences in the stress-induced activity of the HPA axis, no differences were found between obese and lean women in basal peripheral plasma levels of AVP, β-lipoprotein [257], ACTH and cortisol [189,257] and between obese and normal men in basal ACTH and cortisol [189]. No formal sex comparisons were conducted in any of these studies.

Not only is the amount of adipose tissue important in relation to activity of the HPA axis but it is also apparent that the particular distribution of fat is important in humans. Many studies have compared individuals in relation to altered visceral and subcutaneous distribution of adipose tissue, although direct comparisons to lean individuals have not always been made. In general, hyperresponsiveness to stress in individuals is seen with central rather than peripheral adiposity. For instance, abdominal obesity has been associated with higher levels of anxiety, anger and depression [269] and psychiatric and psychosomatic complaints [110] compared to peripheral obesity. Positive correlations between waist to hip ratio and parameters of

cardiac output have been reported in young white men [77], in older black men and women [249] and in black and white adolescents with a positive family history of hypertension [9]. No differences were found in ACTH or cortisol levels in women with visceral or subcutaneous obesity in relation to several mental stress tasks, although there was an increase in pulse rate (but not mean arterial pressure) in women with visceral obesity [159], which is suggestive of an increased responsiveness to this stressor by the sympathoadrenal system. There was no comparison to normal females in this study, so it is not possible to establish if there would have been attenuated responses of the HPA axis and/or sympathoadrenal system to stress in these individuals. The effect of altered adipose tissue distributions on various responses to stress is illustrated by varying cardiovascular responses to hemodynamic stress in women with both central and peripheral adiposity [35]. Women with central adiposity exhibited a greater stress-related increase in diastolic blood pressure and total peripheral resistance, whereas women with peripheral adiposity exhibited greater stress-related increases in cardiac output [35] but, once again, there were no comparisons to normal women and there were no measures of the activity of the HPA axis.

Many studies have shown that lean rats have reduced activity of the HPA axis while genetically obese (Zucker) rats exhibit increased activity of the HPA axis. Obese rats generally have elevated basal secretion of corticosterone [62,66,118,119,154,170,175,224,226,252]. Moreover, obese male rats had increased adrenal weight, intra-adrenal phenylethanolamine-*N*-methyl transferase activity and decreased thymus weight compared to lean rats which is indicative of overall elevation in HPA axis activity in obese animals [252]. Increased stress-induced activity of the HPA axis has also been found in obese rats compared to lean animals. Male and female obese rats had greater elevations of plasma ACTH levels in response to immobilization, ether, and cold stresses than did lean animals in one study [62] although no difference between obese and lean male rats was found in another, where ACTH levels were measured during ether stress [252]. Nevertheless, greater ACTH responses to immobilization, ether, and cold stresses were seen in obese rats than lean rats [62]. Similar disparity was seen in corticosterone responses to immobilization [62,154], restraint [127], ether [62,252] and cold stress [62]. Increased urinary excretion of corticosterone and hyperplastic adrenal glands are generally seen in obese rats [66,118,119,170]. Whereas many studies have compared male obese and lean rats [127,154,252], there are few sex comparisons. It has been observed, however, that corticosterone responses to immobilization, ether and cold stress were more marked in male than in female obese rats [62]. The authors of this study did not suggest a reason why obese males rather than obese females had greater corticosterone responses and there is a need to understand sex differences in response to stress in animals with different levels and distribution of adipose tissue.

4.3. Individuals with attenuated stress reactivity

In any normal population of humans or animals, large individual variation exists in relation to stress responses, typified by the response of the HPA axis to a variety of stressors [36,37]. Whereas isolation and restraint leads to increased plasma concentrations of cortisol in sheep [219,237], we consistently observe a proportion of animals that do not respond to this stressor (Fig. 6). It is possible that such animals are genetically predisposed to stress hyporesponsiveness, since genetic factors are known to be involved [235,267,268,273]. Nevertheless, environmental effects may also be important [136] and it has been recognized that individual differences in stress responsiveness in humans may be the result of a combination of factors such as genetic disposition, personality traits, social interactions, life experience and socioeconomic and demographic influences [235]. There is also evidence that the endogenous pulsatility of the HPA axis may contribute to the inter-individual variation in stress responses [267,268,273]. Studies of laboratory species illustrate that postnatal environmental events can alter the development of the HPA axis (e.g. [202,203]). The role of genetic factors on stress responsiveness is evident from studies where different strains of mice have been used in stress studies. Differences in corticosterone [55,197,199] and behavioral [195–197] responses to uncontrollable footshock are found in different strains of mice and strain differences in the ability to mount immune responses have also been noted in mice [201]. There are also various laboratory animal models of differences in reactivity to stress. Exposure of outbred rats to a novel environment revealed that some animals, termed 'high locomotor response' rats, showed lower levels of anxiety in standard tests [85] but had higher levels of circulating corticosterone than low locomotor response rats

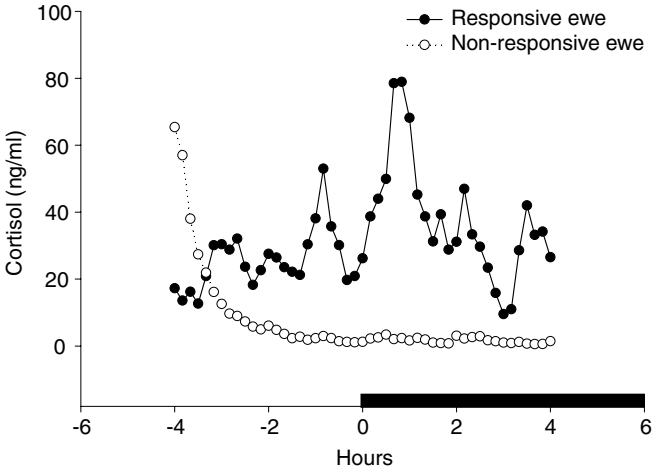

Fig. 6. Plasma concentrations of cortisol before and during isolation and restraint stress in a stress responsive female (Responsive Ewe) and stress non-responsive female (Non-responsive ewe) ovariectomized sheep. The period of isolation and restraint stress is illustrated by the black bar (A.J. Tilbrook, I.J Clarke, unpublished).

[39,85]. Genetically selected mouse and rat lines also display differences in activity of stress systems [13,104–106] with some lines showing attenuated ACTH and corticosterone responses to stress with others exhibiting enhanced stress reactivity. For example, "Short Attack Latency" mice have an innate coping style in environmental challenges and show high sympathetic activity and low HPA axis activity in response to stress whereas "Long Attack Latency" mice demonstrate a passive coping style and higher HPA axis response to stress [13]. The Lewis and Fischer rat strains have different levels of HPA activity, with Lewis rats of both sexes showing reduced ACTH and corticosterone responses to various stressors [42,204, 214–216]. Two other rat lines that were developed on the basis of their behavioral responsiveness to the dopamine agonist apomorphine [21] demonstrate differences in the activity of the HPA axis in response to exposure to a novel environment [183]. Apomorphine-susceptible rats had a higher and prolonged release of ACTH and free corticosterone compared to apomorphine-unsusceptible rats which essentially had a hyporesponsive HPA axis response to stress [183]. In addition to stress responses, there are individual differences in habituation to repeated stress, which is exhibited by reduced responsiveness of the HPA axis to stress, in humans [57,95,193,273] and differences between rat strains [43]. Sex comparisons have generally not been made in the study of these genetic lines and there has been little consideration in regard to the type of stressor used.

5. Mechanisms for attenuated responsiveness of the HPA axis

The mechanisms for stress hyporesponsiveness in different physiological states are not well understood but there is good evidence for modification at each level of the HPA axis. Mechanistic studies have been carried out on lactating women and animals, but little has been done to determine the mechanisms of hyporesponsiveness in humans or animals with different levels of visceral adiposity or with naturally different responses to stress. It is evident that altered activity of the HPA axis may be due to a number of mechanisms, including reduced synthesis of CRH and AVP, altered efficacy of negative feedback by glucocorticoids, changes in stimulatory noradrenergic inputs to the paraventricular nucleus and reduced responsiveness of the pituitary to the actions of CRH and/or AVP. It is also possible that there are changes in regulatory neuronal input to the paraventricular nucleus in different states of stress responsiveness and oxytocin and prolactin and appetite regulating peptides may contribute to reduced activity of the HPA axis.

5.1. Synthesis and Secretion of CRH and AVP

The hypothalamic regulators of the HPA axis are the neuropeptides CRH and AVP and alterations in the secretion of these neuropeptides into the hypophyseal portal system is a likely mechanism for influencing the responsiveness of the HPA axis both under basal and stressful conditions.

5.1.1. Lactating females

Most research on the synthesis and secretion of CRH and AVP during basal and stress conditions in lactating females has focused on the rat. In this species, it is clear that lactation affects the synthesis of CRH in both resting and stressful situations. The basal level of expression of CRH mRNA is reduced in the paraventricular nucleus of lactating rats compared to non-lactating rats [53,117,253,254,263,266]. The effect of lactation on mRNA level of AVP is less clear. A microdialysis study failed to show any elevation in AVP release in either the supraoptic nucleus or paraventricular nucleus during lactation [142] and the number of neurons expressing vasopressin hnRNA transcripts is reported not to be increased during lactation [203]. Since hypophysiotropic secretion of CRH and AVP occurs at the level of the median eminence, measurement of secretion at this level, or measurement of secretion into hypophyseal portal blood is more relevant to the operation of the HPA axis than measurement of secretion within the nucleus of the perikarya of the hypophysiotropic neurons. Other studies showed an increase in the level of expression of AVP mRNA in the parvocellular region of the paraventricular nucleus [53,116,253,254,266] and peptide levels are also increased [253] in lactating rats compared to non-lactating rats. Moreover, a greater number of AVP immunoreactive fibres were found in the external zone of the median eminence in lactating rats than in virgin rats [254] and a high degree of co-localization of CRH and AVP has been found in neurons in the paraventricular nucleus and the secretory terminals of the median eminence in lactating compared to non-lactating rats [253]. Increased synthesis of AVP may compensate for the reduced synthesis of CRH thereby providing the necessary stimulus for increased plasma concentration of ACTH and corticosterone seen in non-stressed lactating rats (see above). Indeed, it has been found that there is an increased pituitary responsiveness to the stimulatory effect of vasopressin during lactation, [230,254]. Despite these studies, the extent to which there may be altered secretion of CRH and AVP in lactating females is unknown because there have been no direct measures of CRH and AVP in the hypophyseal portal blood during lactation.

The reduced activation of the HPA axis in response to stress during lactation may be due, in part at least, to reduced secretion of CRH into the hypophyseal portal system. In lactating rats, it has been shown that there is a decrease in stress-induced levels of mRNA for CRH [33,114,117,253] and *c-fos* [34,41,203,270] in neurons of the paraventricular nucleus, compared to non-lactating rats, but whether this translates into secretion from the median eminence is not known. It is apparent that the paraventricular nucleus is not the only area of the brain

where there is altered neuronal activation during lactation because the appearance of *c-fos* mRNA is reduced in response to stress in several areas including the medial nucleus of the amygdala, ventral lateral septum and cingulated cortex [34]. Following immune stress in rats, induced by injection of lipopolysaccharide, there was a greater increase in primary mRNA transcripts for AVP in virgin females than in lactating females [203], leading to the suggestion that secretion of AVP may also be reduced in response to stress during lactation but, as for CRH, there have not been direct measurements of AVP in the hypophyseal portal blood. The plasma concentrations of ACTH were not increased during isolation and restraint stress in lactating ewes ([222], Fig. 4) which may reflect a reduction in the secretion of CRH and/or AVP and/or a reduction in the sensitivity of the pituitary to CRH and/or AVP (see below). A complete understanding of the extent to which altered activity of the HPA axis during lactation, whether basal or in response to stress, awaits direct measures of CRH and AVP in lactating females during stress but this has not been done in any species.

5.1.2. Level of visceral adipose tissue

The extent to which hyporesponsiveness to stress in humans with low levels of visceral adipose tissue is due to reduced secretion of CRH and/or AVP is unknown, since such studies are not possible for obvious reasons. Nonetheless, it has been hypothesized that increased CRH drive is a likely mechanism for the increased activity of the HPA axis in obese humans [245]. These authors also considered that further evidence for increased CRH activity in obese individuals was provided from a study in which there was a strong association between daytime salivary cortisol levels and some subjectively perceived stress indices, abdominal fat distribution, and several parameters of the metabolic syndrome in chronically stressed middle-aged men [180,181]. Nonetheless, this interpretation is circumstantial at best and there is a need to fully understand the central drive of the HPA axis in obese and lean humans. There is indirect evidence in rats to suggest hyporesponsiveness to stress in lean animals may be due to altered secretion of CRH and/or AVP but direct measures of the secretion of these neuropeptides in conscious animals during basal and stress conditions are lacking. Increased secretion of ACTH in obese but not lean rats following cold stress led to the conclusion that the increased activity of the HPA axis in obese animals is of central origin [62], but neither CRH nor AVP were measured. Hypothalamic CRH content was higher in the hypothalamus of obese male rats compared to lean rats [10] and the level of expression of CRH hnRNA in the paraventricular nucleus during treadmill running was lower in lean rats than in obese rats [175], suggesting increased synthesis of CRH in obese rats. Removal of food stimulates stress pathways in obese rats but not in lean females and this stressor has been used to provide evidence that there is increased synthesis of CRH in response to stress in obese animals and reduced synthesis in lean animals. For instance, food deprivation activated the majority of CRH neurons and increased the level of CRH mRNA in the paraventricular nucleus [225,226] of obese rats whereas no similar effects were seen in lean animals. In contrast, there is a report that secretion of CRH and AVP into the hypophyseal portal circulation is lower in obese than in lean rats [170]. It should be noted that these measurements were made in anaesthetized animals and no studies have measured the secretion of CRH and AVP in conscious lean and obese animals of any species during stress and related this to CRH and AVP gene expression. We have provided indirect evidence to suggest that the lower HPA axis response to stress in lean sheep compared to obese females may be due, in part at least, to reductions in the secretion of CRH and/or AVP because of reduced secretion of ACTH in response to stress in lean ewes compared to obese ewes (Fig. 5). This could, however, also represent reduced pituitary responsiveness to CRH and/or AVP. Again, definitive measures of CRH and AVP secretion are required to discriminate between these possibilities.

5.1.3. Individuals with attenuated stress reactivity

As to whether the secretion of CRH and AVP differs in low and high responders to stress is unknown. Hypothalamic discriminators are confined to measurement of gene expression and neuropeptide levels within the brains of rats that exhibit different behavioral and neuroendocrine responses to stress. In rats classed as having high locomotor responses to a novel environment and displaying less anxiety and increased circulating levels of corticosterone, there was decreased CRH mRNA expression in the central nucleus of the amygdala in comparison to low locomotor response rats [85]. This is consistent with these high locomotor animals displaying less anxiety in tests because CRH in the central nucleus of the amygdala is known to induce anxiolytic effects [84] but CRH expression was not measured in the paraventricular nucleus. Under basal conditions, CRH mRNA levels were higher in the paraventricular nucleus of apomorphine-susceptible rats, which show enhanced HPA axis activity [183], but no data were presented for CRH mRNA levels in stressed animals. Nevertheless, female Lewis rats showed reduced HPA axis responses to immune/inflammatory challenge compared to other strains and this was associated with decreased CRH mRNA and CRH content [215] illustrating reduced synthesis and secretion of CRH in this animal model of stress hyporesponsiveness. Furthermore, rats that showed high anxiety and a hyperactive HPA axis had a higher number of Fos positive cells in the paraventricular nucleus [187] indicating increased cellular activity at this level. There has been little consideration of the role of AVP in individuals that display different responsiveness to stress. Healthy men that showed high ACTH and cortisol responses to exercise stress also showed increased levels of circulating AVP compared to men who had low HPA axis responses to exercise stress [167]. Although this led

to the conclusion that enhanced AVP, and possibly CRH, drive in the high responders resulted in increased HPA axis activity [140], an index of secretion of the neuropeptides cannot be inferred. Peripheral measurements of AVP are almost certainly a reflection of a magnocellular source of AVP rather than being indicative of the AVP available to stimulate corticotropes of the anterior pituitary. Higher levels of AVP mRNA have also been reported in the paraventricular nucleus of rats that show high levels of anxiety related behavior compared to rats that show low levels of anxiety-related behavior [139,260].

5.2. Glucocorticoid negative feedback

Glucocorticoids exert feedback actions on the brain via high affinity mineralocorticoid receptors (MR) and low affinity glucocorticoid receptors (GR). MR localise to the hippocampus and other regions of the limbic brain such as the lateral septum and amygdala as well as hypothalamic sites. The glucocorticoids act via MR to control gene networks that underlie stabilization of neuronal activity thereby maintaining basal activity [132,173]. GR have a more extensive distribution within the brain, being most abundant in the hypothalamus and in pituitary corticotropes [37] and are involved in feedback actions of both basal and stress-induced levels of glucocorticoids [93,132,173]. GR facilitate the re-establishment of homeostasis when stress levels of cortisol prevail [36,37]. Glucocorticoids may also act by non-gemonic mechanisms on cell signalling processes [135,152], but the relevance of this to the negative feedback action of glucocorticoids has not been established. Alterations in the effectiveness of negative feedback by glucocorticoids have profound effects on the activity of the HPA axis and regulation of stress responses, such that aberrant action can increase the vulnerability of the individual to stress-induced disorders or diseases [37]. There is also evidence that changes in the effectiveness of negative feedback by glucocorticoids contribute to attenuated HPA responses to stress in some physiological states, thereby resulting in stress hyporesponsiveness.

5.2.1. Lactating females

It has been proposed that changes occur during lactation in the effectiveness of negative feedback by glucocorticoids and that this could contribute to the attenuated HPA responses to stress [115] such as reduced synthesis and secretion of CRH and possibly AVP. It is feasible that both the diurnal and rapid components of the negative feedback effects of glucocorticoids are modified during lactation [115]. Indeed, there is evidence to suggest that humans are less sensitive to diurnal negative feedback of cortisol during pregnancy and lactation because the ability of dexamethasone to suppress the circulating concentrations of cortisol was reduced during pregnancy [149,151], and lactation [153]. This effect developed during the course of pregnancy [149,151], extending into lactation. Despite these findings in humans, there are reports that negative feedback operates in lactating rats [117,212,251] and may even be increased [192], although these conclusions have been questioned on the basis of experimental approach [115]. During late pregnancy, rats were less sensitive to rapid glucocorticoid feedback but similarly sensitive to delayed glucocorticoid feedback compared to non-pregnant rats [81]. Moreover, there was a marked increase in 11β-hydroxysteroid dehydrogenase Type 1 activity in the paraventricular nucleus during late pregnancy, which would stimulate the conversion of inactive metabolites to active corticosterone thereby raising local glucocorticoid levels which may augment their negative feedback effects to reduce CRH [81] and possibly AVP synthesis. It was suggested that these raised local concentrations of glucocorticoids may inhibit the electrical excitability of neurons in the paraventricular nucleus [115] although direct evidence for this is not forthcoming. It is not known if these findings in pregnant rats extend into lactation. It has been suggested that altered negative feedback by glucocorticoids during lactation may be a result of changes in the expression of GR in the brain [115]. Hippocampal binding of [^{3}H] corticosterone was reduced during lactation [128] and reduced MR mRNA expression was observed in the CA1 region of hippocampus of lactating rats [115]. In contrast, no changes in GR mRNA occurred in the hippocampus and paraventricular nucleus [115]. Nonetheless, it is difficult to formulate definitive conclusions about the extent to which altered activity of the HPA axis during lactation is due to increased negative feedback by glucocorticoids because it was observed that stress-induced increases in ACTH were attenuated in both adrenal-intact and adrenalectomized lactating rats [255].

There is clearly a need for systematic research to fully understand the negative feedback actions of cortisol during lactation, particularly in terms of synthesis and secretion of CRH and AVP. If differential secretion of CRH and AVP does indeed occur during lactation, this may indicate that glucocorticoids have different effects on the synthesis and secretion of these neuropeptides, as hypothesized [254]. Indeed, we have preliminary data suggesting that rapid cortisol negative feedback suppresses CRH but not AVP secretion in non-lactating ewes (A.J. Tilbrook, A.I. Turner, P. Ligam, B.J. Canny, E.A. Young, I.J. Clarke, unpublished). This has not been investigated in lactating ewes although the effectiveness of low concentrations of cortisol to inhibit ACTH responses to hypotension was increased during pregnancy [91]. Direct measures of CRH and AVP in the hypophyseal portal blood are necessary to accurately define the negative feedback actions of glucocorticoids on the secretion of these neuropeptides during lactation.

5.2.2. Level of visceral adipose tissue

It is highly likely that the negative feedback effects of cortisol are increased in lean humans whereas there appears to be a resistance to the negative feedback effects of cortisol in obese humans. Based on the finding that

the increased metabolic clearance rate of cortisol in obese women led to reduced plasma cortisol levels rather than an increase in cortisol production, it was suggested that there is a defect in the feedback regulation of ACTH secretion by cortisol in obese women [217]. Furthermore, in men with an elevated waist to hip ratio, the reduction in cortisol levels during treatment with dexamethasone was less than in controls [120], suggesting that resistance to glucocorticoid feedback contributes to hyperactivity of the HPA axis in obese humans. When obese and lean men were infused with hydrocortisone during insulin-induced hypoglycemia, the obese men showed resistance to the steroid-induced inhibition of ACTH response to this stressor [79]. There are reports of normal dexamethasone tests in obese women [124] and men [65,120] and lower urinary free cortisol excretion in women with abdominal obesity compared to those with peripheral fat distribution or lean women [245] but none of these studies systematically investigated negative feedback by cortisol.

It is also likely that obese rats are more resistant to the negative feedback effects of glucocorticoids than are lean rats although there are some inconsistencies in the literature in this regard. For example, the dissociation constant for GR and binding capacity in the brain of obese rats have been found to be unchanged or increased [108,109,259] and the plasma concentrations of corticosterone in obese rats following treatment with the steroid receptor antagonist RU486 were variably found to be either increased [107] decreased [70] or unchanged [165,166]. It should be noted, however, that RU486 is a non-specific GR antagonist, blocking the progesterone receptor also. Treatment with dexamethasone suppressed corticosterone secretion in both lean and obese male rats, but during the recovery from the treatment, the levels of corticosterone rose to higher values in obese than in lean rats [62] which may suggest a difference in the glucocorticoid negative feedback although this treatment would only block the GR and not the MR. Using a combination of *in situ* hybridization and Western blotting, it was shown that obese male Zucker rats had reduced MR mRNA levels but normal GR mRNA and protein levels in all areas of the hippocampus and frontal cortex [127]. Whilst these authors suggested that the divergence in the findings for mRNA and protein for MR may have been due to the technique used, they also acknowledged that changes in expression may not have reflected changes in protein levels. This highlights the need for functional studies and for measurements of the synthesis of the relevant factors, in addition to gene expression. Obese rats also had reduced 11β-hydroxysteroid dehydrogenase type 1 mRNA in a subpopulation of hippocampal cells, which would result in impaired local production of corticosterone. Following restraint stress, obese rats had higher plasma concentrations of corticosterone than lean rats and treatment with a MR antagonist (spironolactone) before restraint stress resulted in a smaller rise in corticosterone in response to the stressors in obese rats than in lean rats so that there was no difference between the groups. It was concluded that the lower levels of MR in obese rats, exacerbated by reduced 11β-hydroxysteroid dehydrogenase type 1, contribute to increased HPA axis activity in obese rats. There was no difference in the basal concentrations between lean and obese animals and spironolocatone did not influence the basal levels, indicating that the effect of the reduced MR activity was on feedback during (associated with) response to stress. In one study, corticosterone treatment following adrenalectomy was similarly effective in lowering ACTH secretion in both obese Zucker and lean rats suggesting that the sensitivity of ACTH to negative feedback by corticosterone was not altered by degree of adiposity [252]. In another recent study, adrenalectomy failed to prevent the stress response of obese rats to food deprivation [47] which may indicate that these rats are relatively resistant to glucocorticoid negative feedback. More systematic studies are required on the negative feedback effects of glucocorticoids in individuals with different levels of visceral adiposity to determine if this is a mechanism for stress hyporesponsiveness in lean individuals. There is also a need for comprehensive sex comparisons in lean and obese humans and animals and consideration of stress responses to different categories of stressors.

5.2.3. Individuals with attenuated stress reactivity

There is evidence that humans who display enhanced responsiveness to stress are resistant to negative feedback by glucocorticoids implying that the converse is true for subjects who are hyporesponsive to stress. For instance, when normal healthy men who showed different responses of the HPA axis to exercise stress were treated with dexamethasone, 30% of subjects exhibited increased ACTH responses to the stress despite the prior treatment with dexamethasone [168]. A similar finding was made in a subsequent study with subjects who were highly responsive to exercise stress and had increased ACTH and cortisol responses during placebo and dexamethasone treatment and higher AVP levels during placebo and enhanced AVP after dexamethasone and hydrocortisone treatment [167]. It has also been suggested that individuals who show a reduced or delayed habituation of cortisol responses to repeated psychosocial stress may have decreased sensitivity to glucocorticoid feedback [271]. Although the mechanisms for differences in glucocorticoid negative feedback are unknown, there is evidence that variants of the GR gene may contribute to the variability in the activity of the HPA axis between normal individuals [40] since polymorphisms have been reported (see [272]). In a recent study of healthy males with polymorphisms in the GR, it was found that there were differences between genotypes in ACTH and cortisol responses to psychosocial stress and in morning ACTH levels [272], which suggests that variation between individuals in the feedback actions of cortisol contribute to individual differences in the activity of the HPA axis. Comparison of five inbred strains of rats showed differences in release of ACTH and corticosterone to stressors and glucocorticoid negative feedback, based on the

dexamethasone suppression test. There were also differences in the effects of pharmacological adrenalectomy. The strains with the greatest inhibition by glucocorticoid negative feedback were also those that showed maximal hyporesponsiveness of the HPA axis to stress [58]. This demonstrates a functional index of genetic predisposition to stress hyporesponsiveness. In apomorphine susceptible rats, stress resulted in elevated ACTH and free corticosterone levels, increased hippocampal MR (but not GR) receptor capacity and increased MR retention of [^{3}H] corticosterone in hippocampal cells after adrenalectomy, suggesting that these rats exhibit resistance to glucocorticoid feedback [184]. The hippocampal expression of GR was higher in rats with high locomotor responses to a novel environment, less anxiety and increased circulating levels of corticosterone compared to rats with the opposite behavioral and neuroendocrine characteristics [84]. In one wild mouse strain, males that showed prolonged corticosterone responses to 5 min of swim stress had higher expression of hypothalamic MR and CRH (but not GR) at 24 h after forced swimming compared to a strain that showed low HPA axis responses to swim stress [243]. There were also structural differences in the hippocampus of these strains of mice (see [36] for review). Thus, it is clearly apparent that there are innate (genetic) variants in stress responsiveness, especially hyporesponsiveness.

5.3. Noradrenergic inputs to the paraventricular nucleus

The paraventricular nucleus is the principal integration center of the brain for the HPA axis [191] and receives extensive excitatory [71,75] and inhibitory [71,78] input from various regions of the brain that process information resulting from different stressors. These include direct input from the limbic system and brain stem with indirect input from the cerebral cortex. Major excitatory input arises from noradrenergic afferents of the brain stem [44,54,70,71,169,190,191,210]. Activation of these pathways during stress stimulates the HPA axis, through increased synthesis and secretion of CRH and AVP (for recent review see [44]). Modifications in excitatory inputs will alter the activity of the HPA axis and reduction in the noradrenergic stimulatory input to the paraventricular nucleus may be a mechanism by which the stress-induced activity of the HPA axis is attenuated in various physiological conditions. It is also feasible that inhibitory input to the paraventricular nucleus is increased in states of stress hyporesponsiveness.

5.3.1. Lactating females

Research in rats indicates a reduction in the noradrenergic stimulatory input to CRH neurons in the paraventricular nucleus during lactation (for reviews see [44,115,235,250]). Indeed, a recent and extensive review of the literature on the role of central noradrenergic mechanisms in regulation of HPA axis responsiveness, concluded that reduced central noradrenergic drive to the paraventricular nucleus is a key factor in altered HPA axis function during physiological states of stress hyporesponsiveness [44]. This may be manifest as reduced noradrenergic release in the paraventricular nucleus and/or altered adrenergic receptor expression and/or function in the paraventricular nucleus during lactation. Altered synaptic input to the relevant cells may also be a mechanism.

Lesioning of the noradrenergic input to the paraventricular nucleus can be achieved with 6-hydroxydopamine infusion over the paraventricular nucleus and this reduces ACTH and corticosterone responses to swim stress in virgin rats [232]. Sham-lesioned lactating rats showed blunted ACTH and corticosterone responses to swim stress compared to virgin rats but the 6-hydroxydopamine lesion did not reduce ACTH responses further [232], suggesting that at least part of the mechanism of hyporesponsiveness during lactation is via the brain stem noradrenergic system. In accordance with this, basal concentrations of norepinephrine and epinephrine levels in microdialysate collections from the paraventricular nucleus of lactating rats were lower when pups were present than when pups were removed [231]. In an earlier study, the *in vitro* turnover rates of norepinephrine were found to be unchanged or increased in oxytocin rich regions of the paraventricular nucleus in lactating rats with offspring present compared to lactating females with offspring absent [31] suggesting intra-nuclear regionalization of noradrenergic influence during lactation. Despite evidence for a loss of noradrenergic function and input to the paraventricular nucleus during lactation, altered stress-induced activity of the HPA axis may not necessarily be entirely due to reduced input from the brain stem. For example, one study showed that norepinephrine content of A_6 cells bodies was unaltered in lactation and stress did not change content in either non-lactating or lactating rats [138]. Also, stress-induced *c-fos* mRNA expression in cells of A_6 and other brain stem regions was similar in non-lactating and lactating rats [34].

Beyond changes in the level of noradrenergic activity, reduced noradrenergic stimulation of the paraventricular nucleus may involve alterations in the function of both α_1 and α_2-receptors. Following i.c.v. injection of the α_1 agonist methoxamine, significant elevation of plasma concentrations of corticosterone and levels of CRH mRNA in the paraventricular nucleus occurred in virgin but not in lactating rats [266], without an effect on AVP mRNA expression. Moreover, *in vitro* electrophysiological recordings revealed that both the proportion of paraventricular nucleus neurons responding to a threshold dose of methoxamine and the magnitude of the methoxamine-induced excitation were lower during lactation [266]. ACTH response to swim stress was decreased in virgin females but not in lactating females following i.c.v. injection of the α_1 receptor antagonist corynanthine [231]. The density of α_2 adrenoreceptors in the paraventricular nucleus and the affinity of hypothalamic α_2 adrenoreceptors for norepinephrine was reduced during lactation and, following i.c.v. injection of the α_2 receptor antagonist idazoxan, an

associated increase in ACTH response to swim stress was observed in virgin females with the opposite response in lactating females [231]. Interestingly, binding of the α_1 receptor was greater in the paraventricular nucleus of lactating compared to non-lactating rats, whereas expression of the α_{1D} receptor mRNA in the paraventricular nucleus was decreased during lactation which may highlight a possible dissociation between protein and mRNA expression in this system [21].

Despite the body of evidence suggesting that the ability of neurons in the paraventricular nucleus to respond to norepinephrine is reduced, and/or that there is reduced secretion of norepinephrine in the paraventricular nucleus during lactation, there have been no comprehensive studies to establish the extent to which the central noradrenergic system influences the CRH and AVP neurons during stress in the lactating female. Functional physiological studies are required to establish the extent to which attenuated responsiveness of the HPA axis to stress during lactation is due to reduced noradrenergic function. Furthermore, it seems appropriate to extend investigations on the role of the central noradrenergic system in stress hyporesponsiveness during lactation to other species including humans.

5.3.2. Level of visceral adipose tissue

It is not known if stress hyporesponsiveness in lean individuals is due to decreased central noradrenergic inputs to CRH and/or AVP neurons as it appears to be in lactating females, but such a mechanism has been hypothesized to explain hyperresponsiveness of the HPA axis in humans with abdominal obesity [162]. In support of this, obese women were seen to have enhanced ACTH response to a CRH/AVP challenge with increased noradrenergic tone compared to controls who had a reduced response [162]. In addition to this, women with visceral adiposity had elevated pulse rates compared to women with a subcutaneous body fat distribution suggesting increased sympathetic response [159] although this study lacked a control because there was no comparison to lean females.

There have been no studies in rats to directly assess whether noradrenergic inputs to the paraventricular nucleus differ between lean, normal or obese rats. Nevertheless, there appears to be altered regulation of the paraventricular nucleus in obese rats and this may be somewhat different to the situation in lactating females. Lower tissue levels of norepinephrine and higher densities of α_2-adrenergic binding sites in the paraventricular nucleus were found in obese rats compared to lean controls [80,112]. Immobilization-induced elevation in norepinephrine levels in the paraventricular nucleus, as measured by microdialysis, was lower in obese than in lean male rats, whereas stress-induced corticosterone levels were higher in obese rats, leading to the conclusion that obese rats have diminished central noradrenergic and sympathetic nervous system responses to immobilization alone with a chronically hyperactive HPA axis [154]. Nonetheless, the obese rats in this study had significantly greater corticosterone responses to immobilization than did lean rats and the authors suggested that there was likely to be some sustained nonadrenergic stimulatory input [154].

5.3.3. Individuals with attenuated stress reactivity

The extent to which inherent hyporesponsiveness of the HPA axis to stress is due to reduced noradrenergic input to the paraventricular nucleus has not been systematically investigated and is unknown. Differences in norepinephrine activity in the hypothalamus [197,198], prefronatal cortex mesocortex [197,198], hippocampus and locus coeruleus [197,198,205] are seen in different strains of mice following inescapable footshock. In three strains that differ in the activity of the HPA axis to stress, levels of tyrosine hydroxylase mRNA in the locus coeruleus was similar between strains but the strain with the minimal HPA axis responses to stress showed greater initial norepinephrine release into the lateral bed nucleus of the stria terminalis [156]. Nonetheless, norepinephrine levels were not measured in the paraventricular nucleus and the release of norepinephrine in the lateral bed nucleus of the stria terminalis may be more likely to influence behavioral reactivity than the activity of the CRH/AVP system in the paraventricular nucleus. It is feasible that these rats have reduced noradrenergic input to other brain regions that facilitate the activity of the HPA axis, a possibility that was acknowledged by the authors.

5.4. Influence of other central factors on function of the paraventricular nucleus

There is complex integration of a hierarchical circuitry that regulates the HPA axis (for review see [71]) and any alterations in this integrated system may influence responsiveness to stress. While attenuated responses of the HPA axis to stress may be due partly to reduction of the stimulatory noradrenergic input to the paraventricular nucleus, it is also possible that inhibitory tone increases. This could involve the GABA system which appears to be upregulated in lactating rats [172]. Increased GABAa receptor affinity is also apparent during lactation [51,258]. It has also been hypothesized that increased neurosteroid production in the brain of lactating females contributes to enhanced GABAergic neurotransmission [235] thus resulting in attenuated HPA axis activity, although this hypothesis has not been tested. Interactions between the serotoninergic and opioidergic systems may lead to altered HPA axis responses in humans with differing adipose distribution. Hyperactivity of the HPA axis in obese women was demonstrated following treatment with naloxone and this was reversed by increasing serotonegic receptor activation [14]. Other neurotransmitter systems that are reset with alteration in body composition and body weight may also have profound influence on the HPA axis and the sympathetic outflow from the brain (*vide supra*). Differences between strains of mice were found in brain content of dopamine and serotonin [198,205] following inescapable

footshock [205] and mesocorticolimbic dopamine levels differed between strains following inescapable footshock [197]. These studies indicate at least some of the non-noradrenergic central systems that may be involved in stress hyporesponsiveness.

5.5. Pituitary responsiveness to CRH and AVP

5.5.1. Lactating females

Evidence from studies with rats suggests that altered responsiveness of the HPA axis during lactation may be partly due to altered responsiveness of the pituitary to CRH and AVP. For instance, the increase in ACTH secretion following treatment with CRH was greater in virgin rats than in lactating rats [230]. In contrast, lactating rats showed a robust increase in ACTH secretion following treatment with high dose of AVP or following a combination of AVP and CRH whereas the response of virgin females was much smaller [230] and increased pituitary responses to AVP during lactation were reported in another study [254] suggesting that the actions of CRH and AVP to stimulate ACTH secretion are altered differently during lactation. Reduced responsiveness of the pituitary to CRH has also been found in late pregnant [81,145] and parturient [144] rats. The cellular mechanisms that underlie changes in sensitivity of pituitary corticotropes to the actions of hypothalamic secretagogues have not been deciphered.

5.5.2. Level of visceral adipose tissue

There is evidence that the pituitary responsiveness to CRH and/or AVP is influenced by the amount of visceral adiposity with lean individuals generally exhibiting a reduced responsiveness. Women with abdominal obesity have been shown to have increased activity of the HPA axis compared to lean women treated with CRH alone [160] or CRH in combination with AVP [160,162,245]. Similarly, obese men had increased ACTH secretion in response to CRH [161,208] compared to lean men. Contrasting findings have also been reported with levels of cortisol following injection of CRH being less in obese than in normal women [98] or being similar in obese and normal women [14]. There have been no formal sex comparisons of pituitary responsiveness to CRH and/or AVP in lean and obese individuals and no studies have ascertained the relative effectiveness of CRH and AVP in stimulating ACTH secretion from the pituitary in different states of visceral adiposity.

In addition to the likely different neuroendocrine mechanisms of regulation of the HPA axis in lean and obese individuals, there is evidence that the level of visceral adiposity may affect the responsiveness of the adrenal glands to the actions of ACTH. Some studies show that adrenal responsiveness to ACTH is higher in women [124,159] and men [65] with central adiposity whereas others [121] showed no effect in terms of cortisol, aldosterone and dehydroepiandrosterone responses to ACTH in obese and lean women.

5.5.3. Individuals with attenuated stress reactivity

To our knowledge there have not been systematic studies in any species to establish whether alterations in pituitary responsiveness to ACTH occur between individuals with naturally differing tendencies to display stress responses. Nonetheless, this is a common locus for alterations in the operation of the HPA axis in different physiological states of stress hyporesponsiveness.

5.6. Oxytocin and prolactin as mediators of stress hyporesponsiveness

The neuropeptides/hormones oxytocin and prolactin are potentially involved in attenuation of the HPA axis response to stress, since both are secreted in response to stress. Nevertheless, oxytocin levels are not increased in response to all types of stress (for review see [58]), which again illustrates the importance of the category of stressor being considered. Of the three innate states of stress hyporesponsiveness considered in this review, most research has been conducted with pregnant and lactating females and there has not been direct consideration of the roles of oxytocin and prolactin in mediating stress hyporesponsiveness in humans and animals with low levels of visceral adiposity or naturally attenuated responses to stress and this is an area requiring investigation.

Oxytocin is known to act centrally to attenuate the activity of the HPA axis and i.c.v. infusion of ovariectomized estradiol-treated rats with oxytocin reduces the response to noise [265] and restraint [264] stress. This treatment also attenuated the elevation in CRH mRNA levels in the paraventricular nucleus that is normally associated with restraint [264]. Further, administration of an oxytocin receptor antagonist by either i.c.v. infusion or by retrodialysis into the paraventricular nucleus increased both basal and stress-induced activity of the HPA axis [146,147]. Female mice that had undergone oxytocin gene deletion displayed increased anxiety-related behavior and corticosterone secretion in response to stress compared to wild type mice [5]. In humans, suckling and breast stimulation increased plasma oxytocin levels and decreased plasma ACTH levels, prompting the conclusion that there is an inhibitory influence of oxytocin on ACTH/cortisol secretion under physiological conditions [5,23]. Infusion of oxytocin into the paraventricular nucleus also suppressed the cortisol response to an audiovisual stressor in non-lactating ewes and, to a lesser extent, in lactating ewes [25] and we have identified oxytocin neurons in the paraventricular nucleus of sheep in close proximity to CRH and AVP neurons (Fig. 7). Oxytocin is not considered to readily cross the blood barrier [58] so it is important to delineate between central and peripheral effects. Within the central nervous system, oxytocin fibers and nerve endings are widely distributed, and oxytocin receptors are present in many forebrain areas, including regions of hippocampus and amygdala, bed nuclei of the stria terminalis, ventrolateral septum, and several hypothalamic nuclei [8,25,56,233].

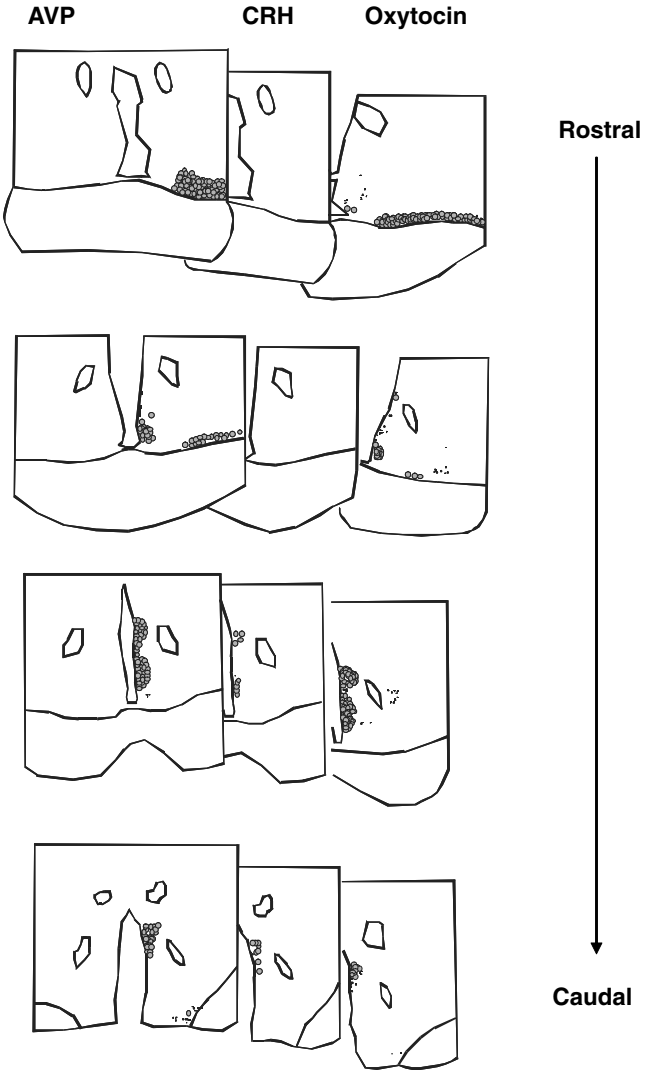

Fig. 7. Distribution of immunoactive AVP, CRH and oxytocin from the rostral to the caudal extent of the paraventricular nucleus of a female sheep. (E.T.A. Rivalland, J. Iqbal, I.J. Clarke, A.I. Turner, A.J. Tilbrook, unpublished).

Central oxytocinergic pathways are stimulated during lactation [176] and it has been suggested that this may mediate, at least in part, some of the attenuated responses of the HPA axis that are observed in lactating females [115]. The possibility also remains that peripheral oxytocin may directly influence anterior pituitary responsiveness to CRH and or AVP. For instance, infusion of oxytocin into normal humans inhibited the plasma ACTH responses to CRH [155].

The role of prolactin in attenuation of anxiety and stress responses has been extensively reviewed [227]. Prolactin has been implicated as a possible mediator of HPA axis hyporesponsiveness, particularly in lactating females [20,192,255]. Suckling increases the secretion of prolactin [61] which can gain access from the peripheral circulation to the brain through receptor-mediated active transport via the choroid plexus [256]. There are also central neuronal prolactin pathways and immunoactivity for prolactin [164] and prolactin mRNA expression [48] have been found in regions relevant to regulation of the HPA axis including the hypothalamus. The distribution of prolactin receptors [32] and prolactin receptor mRNA have also been mapped throughout the brain, including the medial preoptic nucleus, the supraoptic and the paraventricular nuclei, the arcuate nucleus, the preoptic area and the choroid plexus [227]. An action of prolactin on CRH neurons has also been suggested [89], possibly mediated by adrenergic neurons [17]. Prolactin was found to exert an anxiolytic effect and inhibit HPA axis responses to stress in both male and female rats [229]. There is evidence of an inhibitory role for prolactin on HPA axis during lactation since i.c.v. infusion of antisense nucleotides against the long form of the brain prolactin receptor into lactating rats resulted in an increase in stress-induced ACTH [228].

5.7. Influence of appetite regulating peptides on stress hyporesponsiveness

Various appetite-regulating peptides have been shown to interact with the HPA axis and may influence the responsiveness of the axis to stress. For example, leptin, which is synthesized in adipocytes, inhibits appetite and plays a role in regulating energy expenditure [17,186], can also influence the activity of the HPA axis although there are conflicting findings (for review see [78]). Whereas the i.c.v. injection of leptin increased CRH content in the hypothalamus of rats [239], peripheral administration of leptin down-regulated CRH expression in the paraventricular nucleus and prevented the increase in CRH expression following adrenalectomy [129]. Moreover, treatment of rats with leptin blocked the increase in ACTH and corticosterone in response to restraint stress [69] or exposure to a novel environment [150]. In young adult female rhesus monkeys, subcutaneous infusion with leptin for 28 days attenuated plasma ACTH and cortisol in an unpredictable situation, enhanced glucocorticoid negative feedback and blunted CRH-induced ACTH secretion suggesting that leptin can attenuate activation of the HPA axis by enhancing glucocorticoid negative feedback [262] and possibly by reducing pituitary responsiveness to CRH. Obese individuals have higher levels of circulating leptin than lean individuals [27] but the implications in terms of regulation of stress-induced HPA activity have not been fully elucidated.

In addition to leptin, there is evidence that the activity of the HPA axis may be influenced by other appetite regulating peptides including orexin, neuropeptide Y (NPY), agouti-related protein, cocaine-and-ampetamine-regulated transcript (CART) and ghrelin. The hypothalamic peptides orexin-A and orexin-B have been studied extensively with respect to their roles in control of feeding and sleep but it is also evident that these peptides can modulate the activity of the HPA axis both centrally and peripherally and these mechanisms have recently been comprehensively reviewed [209]. Orexin receptors are widely distributed and are found in the paraventricular nucleus, median eminence,

pituitary corticotropes and the adrenal cortex and medulla and there is evidence that these peptides can stimulate the release of CRH and AVP as well as have direct stimulatory effects on the adrenal cortex [209]. The central stimulatory effects of orexins may be mediated by NPY [76]. Despite this, the physiological importance of orexins in regulating the basal and stress induced activity of the HPA axis are not known. Furthermore, the role of orexins in regulating stress responsiveness has not been investigated in a substantial way, although i.c.v. injection of orexin-A increased ACTH and corticosterone secretion and CRH mRNA expression in virgin rats but these HPA responses were reduced in late pregnant rats [15]. It is also clear that NPY can influence the activity of the activity of the HPA axis (for reviews see [67,103]) but, as with leptin, there are conflicting findings. One paradox is that, on one hand, NPY has been found to act centrally to antagonize CRH release [68], whereas on the other, it was shown to stimulate HPA axis activity by increasing the release of CRH [103]. NPY mRNA has also been shown to increase in the arcuate nucleus and hilus of the dentate gyrus following restraint stress in rats [26], although the functional significance of this in terms of stress response requires elucidation. Agouti-related protein is an appetite stimulant that is co-expressed in the arcuate nucleus with NPY [63] and there is differential regulation of this neuropeptide in relation to stress. Foot shocks resulted in a decrease in agouti-related protein and an increase in NPY mRNA [89]. CART mRNA and protein are located in various hypothalamic structures including the paraventricular and arcuate nuclei [29,99–101,246] and glucocorticoids can influence expression via a GR-dependent mechanism [248]. Injection of CART peptides i.c.v. [247] and directly into the paraventricular nucleus [211] were found to activate the HPA axis in rats. Finally, levels of ghrelin, which is produced by the A-like cells of the stomach, have been shown to increase after water avoidance stress [102], central administration of a ghrelin agonist increased hypothalamic CRH mRNA in rats fed *ad libitum* [82] and ghrelin has been found to cause release ACTH and cortisol in humans [59]. Despite the possibility that various appetite regulating peptides may affect the activity of the HPA axis there have not been systematic studies to establish the extent to which these peptides influence the responsiveness of the HPA axis to stress in individuals with different levels and distributions of visceral adipose tissue.

6. Conclusions and future directions

For an organism to survive and be healthy, the ability to elicit appropriate physiological and behavioral responses to stressful situations is paramount. If such responses are inadequate or excessive, physiological dysfunction occurs at various levels. An understanding of the mechanisms by which stress systems are regulated is essential in the development of strategies to overcome and prevent stress-induced disorders. Research in this area is complicated, however, by the fact that activation of stress systems, such as the HPA axis is variable, differing between different physiological states and between individuals within a species. It is apparent that the HPA axis is regulated differently in males and females and, consequently, there are sex differences in response to stress. The sex steroids are relevant to the issue of sex differences in stress responses and, accordingly, there are differences in stress responses with different reproductive states. Furthermore, stress responses vary with the category of stressor. An appreciation of the mechanisms of regulation of the HPA axis can be gained by studying innate states of stress hyporesponsiveness. Such states include lactating females, humans and animals with low levels of visceral adiposity and individuals within the same species that naturally showed reduced stress responsiveness.

The mechanisms by which certain physiological states are characterized by attenuated stress responses are not fully understood and there is considerable need for further research in this area. It is likely that there is reduced synthesis and secretion of CRH and/or AVP into the hypophyseal portal system, possibly as a result of increased glucocorticoid negative feedback and reduced noradrenergic stimulatory inputs, and reduced pituitary responsiveness to CRH and/or AVP (Fig. 8) although systematic approaches are needed to establish the extent to which each of these mechanisms is important. The extent to which inhibitory central inputs to the paraventricular nucleus, such as those provided by oxytocin and prolactin and appetite regulating peptides, contribute to stress hyporesponsiveness are unknown. A major limitation of research to date is that CRH and AVP secretion have not been monitored directly. Inferences have been made on the basis of changes in mRNA expression, protein content and plasma concentrations of ACTH. Changes in expression may not always be translated into changes in protein which, in turn, may not necessarily reflect secretion. Critically, it is the secretion of these neuropeptides into the hypophyseal portal system that is necessary to drive the pituitary production of ACTH and, thereby, the HPA axis. Furthermore, interpretations based solely on the changes in the secretion of ACTH are inadequate as they do not appraise the relative contributions of CRH and AVP as ACTH secretagogues under different physiological conditions. Measurements of multiple indicators are clearly required to provide more thorough information about the status of both peripheral and central mechanisms that control the HPA axis in different physiological states. Finally, there is a need for formal sex comparisons in responses to stress in different physiological conditions and for an appreciation for the category of stressor being studied.

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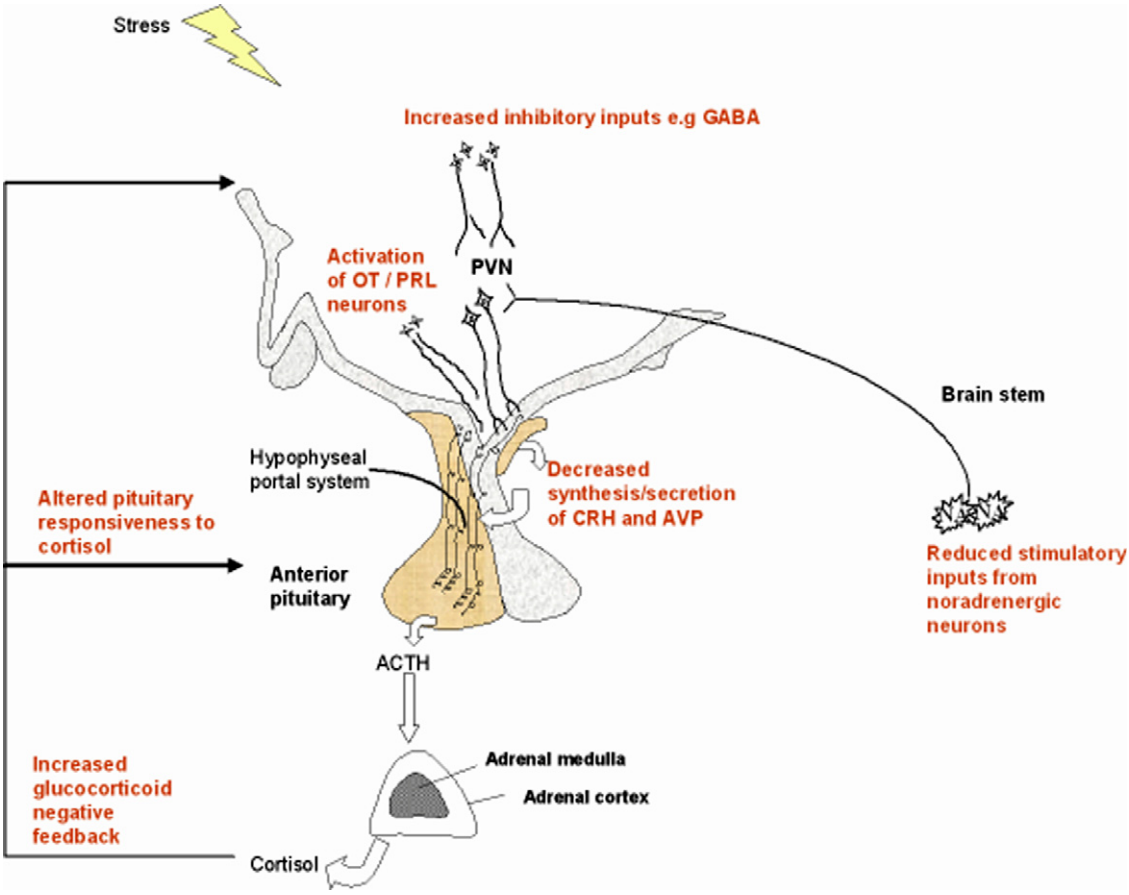

Fig. 8. Schematic representation of possible mechanisms of attenuated responsiveness of the hypothalamo-pituitary-adrenal axis to stress. It is likely that there is reduced synthesis and secretion of CRH and/or AVP into the hypophyseal portal system, possibly as a result of increased glucocorticoid negative feedback and reduced noradrenergic stimulatory inputs. There is also likely to be reduced pituitary responsiveness to CRH and/or AVP. Systematic approaches are needed to establish the extent to which each of these mechanisms is important. The contribution of inhibitory central inputs (e.g. GABA) to the paraventricular nucleus (PVN) and of oxytocin (OT) and prolactin (PRL) to stress hyporesponsiveness are unknown.

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