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HPA axis responsiveness to stress: Implications for healthy aging

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Abstract

The major neuroendocrine response mediating stress adaptation is activation of the hypothalamic pituitary adrenal axis, with stimulation of corticotropin releasing hormone (CRH) and vasopressin (VP) from parvocellular neurons of the hypothalamic paraventricular nucleus, leading to stimulation of pituitary ACTH secretion and increases in glucocorticoid secretion from the adrenal cortex. Basal production and transient increases during stress of glucocorticoids and its hypothalamic regulators are essential for neuronal plasticity and normal brain function. While activation of the HPA axis is essential for survival during stress, chronic exposure to stress hormones can predispose to psychological, metabolic and immune alterations. Thus, prompt termination of the stress response is essential to prevent negative effects of inappropriate levels of CRH and glucocorticoids. This review addresses the regulation of HPA axis activity with emphasis on the mechanisms of termination of CRH transcription, which is a critical step in this process. In addition, the actions by which glucocorticoids, CRH and VP can affect the aging process will be discussed.

Keywords

Stress; Hypothalamic pituitary adrenal axis (HPA); Corticotropin releasing hormone (CRH); Vasopressin (VP); Glucocorticoids

1. Introduction

Survival and wellbeing requires continuous adaptation to external challenges and fluctuations of the internal environment (McEwen, 2007). This is achieved through sensory signals integrated in the brain leading to the coordinated activation of behavioral, autonomic and endocrine responses directed to maintain homeostasis. The major neuroendocrine response to stress is via activation of the hypothalamic pituitary adrenal (HPA) axis, consisting of stimulation of parvocellular neurons of the hypothalamic paraventricular nucleus (PVN) and consequent release of the neuropeptides, corticotrophin releasing hormone (CRH) and vasopressin (VP), which stimulate pituitary adrenocorticotropic hormone (ACTH) release. This leads to stimulation of glucocorticoid secretion by the adrenal cortex, which is essential for stress adaptation (Antoni, 1986; Aguilera, 1994). Glucocorticoids (cortisol in humans, and corticosterone in rats and mice) act upon specific receptors present in most peripheral tissues and in the brain, initiating metabolic and

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neuromodulatory changes necessary for coping with the challenge (Munck and Naray-Fejes-Toth, 1994; McEwen, 2007).

In addition to activating the HPA axis by increasing ACTH and glucocorticoids, the hypothalamic peptides VP and CRH are released within the brain where they are largely responsible for behavioral and autonomic responses to stress (Vale et al., 1983). It is clear that acute activation of the HPA axis during stress is necessary for stress adaptation (Munck and Naray-Fejes-Toth, 1994; McEwen, 2007). On the other hand excessive exposure to sustained elevated levels of stress hormones, including CRH and corticosterone, can be harmful and predispose to psychiatric, reproductive, immune, metabolic and cardiovascular disorders (McEwen, 1998). Thus, appropriate termination of the stress response is essential to reduce the damaging effects of chronic elevations of CRH and glucocorticoids.

A number of studies in humans and experimental animals provide evidence that hyperactivity of the HPA axis contributes to neuronal and peripheral deterioration associated with aging (Sapolsky, 1999; Swaab et al., 2005; Ferrari and Magri, 2008). Thus, the inability to limit the stress response, especially during chronic stress, is likely to enhance the effects of aging due to the damaging effects of prolonged exposure to stress hormones. This review will focus on the mechanisms of how the stress response is terminated and will also discuss some of the mechanisms by which different components of the HPA axis, namely CRH, VP and glucocorticoids, could affect the aging process.

2. Regulation of the HPA axis activity

Activation of the HPA axis, initiated by the release of CRH and VP to the pituitary portal circulation, is essential for maintaining homeostasis and ultimately for survival during severe stress. Its regulation depends on adrenal steroids and afferent neural inputs to CRH neurons in the hypothalamic paraventricular nucleus (PVN). CRH is the main regulator but VP, co-expressed in about 50% of CRH neurons, potentiates the stimulatory effect of CRH on ACTH release (Aguilera, 1998). CRH and VP stimulate ACTH secretion through activation of type 1 CRH receptors (CRHR1) and type V1b VP receptors in the pituitary corticotroph (see Sections 4.2 and 4.3). In resting conditions, HPA axis activity displays circadian and ultradian variations, with pulsatile secretion of glucocorticoids (one per hour), of higher amplitude during the awake phase resulting in higher mean levels during the day in humans and during night in rats (Lightman et al., 2000; Russell et al., 2010). These basal levels of glucocorticoids are essential for neuronal plasticity and normal brain function. Stress induces transient activation of HPA axis activity paralleled by also transient increases in CRH transcription (Aguilera, 1998). During chronic stress there is a preferential increase in the expression of VP in CRH neurons and pituitary V1b receptors versus CRHR1 (Aguilera, 1994). Although, it is clear that VP and its receptors in pituitary corticotrophs are essential for the full ACTH response to acute stress, studies using genetic and pharmacological models of VP deficiency have shown adequate HPA axis responses to stress in the absence of VP (Lolait et al., 2007; Chen et al., 2008a). Conversely, CRH is essential for HPA axis responses to stress (Jacobson et al., 2000; Bale and Vale, 2004). Normally, activation of the HPA axis is associated with rapid and transient increases in CRH transcription, which are necessary to replenish CRH mRNA and peptide levels following its release (Aguilera, 1998). Failure to limit CRH transcription leads to excessive production of the peptide and consequent overstimulation of the HPA axis and CRH-dependent brain function. Therefore, elucidating the mechanisms controlling CRH transcription is essential to better understand the pathophysiology and therapeutic approaches of stress-related disorders.

3. Regulation of CRH transcription

The CRH neuron is under the direct stimulatory influence of noradrenergic ascending pathways from the brain stem and glutamatergic interneurons located in the periventricular area (Herman et al., 1996). Also, indirect pathways from sensory systems in the forebrain through the amygdala and bed nucleus of the stria terminalis can stimulate the CRH neuron by activating stimulatory (glutamatergic) or repressing inhibitory (GABAergic) interneurons (Herman et al., 1996).

3.1. Activating mechanisms

Activation of CRH transcription depends on cAMP/protein kinase A (PKA) dependent pathways, leading to recruitment of phosphorylated cAMP response element binding protein (pCREB) by the cAMP response element (CRE) of the CRH promoter (Guardiola-Diaz et al., 1994; Nicholson et al., 2004). While it is well established that CREB phosphorylation and the CRE in the CRH promoter are essential for activation of CRH transcription, it has become evident that CREB is not sufficient (Liu et al., 2008). Recent studies have shown that cyclic AMP-dependent activation of the CREB co-activator, transducer of regulated CREB activity (TORC) is essential for activation of CRH transcription (Liu et al., 2010). In basal conditions, TORC is maintained inactive in the cytoplasm of the CRH neuron, phosphorylated and bound to the scaffolding protein 14–3–3. Studies in progress (Y Liu, V Poon and G Aguilera, unpublished) suggest that the kinase responsible for TORC phosphorylation is the Ser/Thr kinase, salt inducible kinase (Takemori and Okamoto, 2008).

3.2. Repressing mechanisms

While activation of CRH transcription is important for HPA axis activation, behavioral and autonomic responses to stress, turning off the activation is essential to prevent deleterious effects of excessive CRH production. The mechanisms that contribute to limiting the stress responses involve changes in stimulatory and inhibitory neurocircuitry, glucocorticoid feedback, as well as intracellular feedback on the CRH neuron.

Negative feedback by glucocorticoids, the end product of stimulation of the HPA axis, plays a major role in curbing CRH responses to stress. While it is evident that direct inhibition of pituitary ACTH secretion and POMC transcription by glucocorticoids is the main driver of negative feedback on HPA axis activity (Dallman et al., 1987; Autelitano et al., 1989), the mechanisms of central feedback inhibition of CRH expression are less clear. Surgical or pharmacological removal of glucocorticoids stimulates CRH transcription and sensitizes HPA axis responses to stress (Makino et al., 1995; Ma and Aguilera, 1999), whereas glucocorticoid administration has the opposite effect (Lightman and Young, III, 1989; Dallman et al., 1994; Ma and Aguilera, 1999). The presence of glucocorticoid receptors (GR) in CRH neurons, as well as the inhibitory effect of intra-PVN glucocorticoid injection on CRH mRNA and the reduction in CRH promoter activity in reporter gene assays following incubation with glucocorticoids, all support a direct inhibitory effect of glucocorticoids on CRH transcription (Kovacs et al., 1986; Liposits et al., 1987; Sawchenko, 1987; Harbuz and Lightman SL, 1989; Fenoglio et al., 2004). On the other hand, there is clear evidence that glucocorticoids have indirect inhibitory effects on the CRH neuron, such as inhibition of stress-induced norepinephrine release from the PVN (Pacak et al., 1995), and reduction in the content of alpha adrenergic receptors in the PVN (Day et al., 1999). This supports the possibility that a major mechanism for glucocorticoids feedback on CRH transcription is the inhibition of afferent pathways to the PVN, and modulation of neurotransmitter receptor levels in the CRH neuron.

While glucocorticoid feedback is clearly important in restraining HPA axis activity, glucocorticoids are not essential for limiting CRH transcription during stress. This is evident from experiments in adrenalectomized rats treated with low levels of corticosterone, in which CRH hnRNA responses to prolonged restraint are transient in spite of the lack of glucocorticoid surge in response to stress (Shepard et al., 2005). As indicated above, transcriptional regulation of the CRH gene involves cAMP/CREB-dependent mechanisms and a functional CRE in the CRH promoter (Seasholtz et al., 1988). Although it has been shown that CREB phosphorylation coincides with elevations in CRH hnRNA in the PVN during ether exposure (Kovacs and Sawchenko, 1996; Shepard et al., 2005), a lack of correlation between the decline in phospho-CREB and reduced CRH hnRNA levels suggested that the termination of CRH transcription involves not only decreases in phospho-CREB levels but also a transcriptional repressor. Studies in rats have shown that the repressor, inducible cyclic AMP early repressor (ICER), a product of activation of the second promoter of the CREM gene (Molina et al., 1993), is indeed involved in the regulation of CRH transcription. This is evidenced by the induction of ICER mRNA in CRH neurons and the recruitment of ICER protein by the CRH promoter during the declining phase of transcription. In addition, ICER knock out using siRNA attenuates the late decline in CRH transcription (Shepard et al., 2005; Liu et al., 2006; Liu et al., 2010).

An additional mechanism probably involved in limiting CRH transcription during stress is regulation of the activity of the CREB co-activator, TORC. As indicated in Section 3.1, activation and inactivation of TORC appears to be the determining factor for activation of CRH transcription. Since TORC inactivation depends on the Ser/Thr kinase, SIK, it is likely that activation of SIK activity may act as a break mechanism by phosphorylating and inactivating TORC. This hypothesis is under current investigation.

4. Mechanisms by which stress and HPA axis activation contributes to aging

Stress is prevalent in society and the brain is exposed to frequent challenges as a consequence of stress, such as prolonged and/or excessive exposure to neurotransmitters, glucocorticoids or cytokines with the potential for neuronal damage. However, there are a number of defensive mechanisms, modulated by components of the HPA axis, which protect neurons against stressful stimuli throughout life. Alteration of these protective mechanisms during aging results in a loss of brain resilience to challenges and could be conducive to neuronal damage. Evidence from animal and human studies indicates that HPA axis activity contributes to biological aging, not only through inappropriate glucocorticoid secretion but also through alterations in the production of the regulatory peptides, CRH and VP. Therefore, HPA axis activity throughout life can influence the course of aging.

4.1. Glucocorticoids

High basal levels of glucocorticoids (cortisol in humans and corticosterone in rodents) and loss of circadian rhythm have been associated with greater cognitive decline at a given age. In most tissues, the effect of glucocorticoids depends on the circulating levels of the steroid. However, sensitivity to glucocorticoid is tissue-specific (and region-specific in the brain) depending on the levels of GR, the metabolizing enzyme, 11-beta hydroxysteroid dehydrogenase, as well as modulatory factors such as sex steroids and dehydroepiandrosterone (Gubba et al., 2004; Seckl, 2004). Alterations of these factors often observed during aging could lead to overexposure of the brain and peripheral organs to the effect of glucocorticoids.

Circulating glucocorticoid levels depend on the activity of the HPA axis but there is not always a correlation between plasma corticosterone and ACTH levels. A number of reports show that aging is associated with elevated basal morning levels of circulating glucocorticoids (Lightman et al., 2000; Lupien et al., 2001; Tizabi et al., 2003). However, it is also clear that individual and species variability exists not only for basal levels but also for corticosterone responses to acute stress in old rats, which have been reported to be reduced, exaggerated and/or more prolonged than in young rats (Lightman et al., 2000). In a proportion of aging rats and humans, there are also alterations in glucocorticoid circadian rhythm; in rats with mild increases in morning levels and failure to increase in the evening (Linkowski et al., 1993; Lightman et al., 2000). For example, old Sprague–Dawley rats display a loss of corticosterone circadian rhythm due to an increase in morning levels, and a loss of the nocturnal elevation, while in other strains, such as Lewis rats circadian rhythms are preserved throughout life (Honma et al., 1996). The altered diurnal variation probably involves the suprachiasmatic nucleus since fetal grafts containing the suprachiasmatic nuclei have been shown to restore the circadian rhythm in old Sprague–Dawley rats (Cai et al., 1997). High degrees of variability in plasma cortisol levels and loss of circadian rhythmicity have also been observed in humans during aging. While about 40% of older adults present with a significant increase of cortisol levels, a similar proportion shows only moderate increases and the remaining decreased their cortisol levels over time. These differences are likely to be genetically determined as shown by studies in twins and by differences between strains in laboratory animals (Linkowski et al., 1993; Franz et al., 2010).

In addition to regulation of glucocorticoid production by the HPA axis, tissue exposure to glucocorticoids depends on the levels of 11-beta hydroxy steroid dehydrogenases (11βHSD), enzymes responsible for either metabolizing glucocorticoids to the inactive steroid, cortisone (11βHSD-2), or restoring the active steroid by conversion of cortisone to cortisol in humans, or corticosterone in rats (11βHSD-1) (Chapman and Seckl, 2008). In contrast to 11βHSD-2 (which is located mostly in aldosterone-sensitive tissues and protects the mineralocorticoid receptor from binding glucocorticoids), 11βHSD-1 is present in the brain and peripheral tissues and increases glucocorticoid availability in tissues. Studies in mice have shown that the expression of 11βHSD-1 in tissues such as bone and the hippocampus increases during aging (Cooper, 2008; Holmes et al., 2010). Such changes would expose tissues to damaging levels of glucocorticoids and contribute to the aging process.

Glucocorticoid action in tissues depends markedly on the levels of GR in the tissue (Simons, 2008). Glucocorticoids enter the cell and regulate cell function by binding to receptors in the cytoplasm. Upon binding to the ligand, the activated receptor is rapidly translocated to the nucleus where it binds to glucocorticoid responsive elements in the promoter of glucocorticoid sensitive genes. It should be noted that glucocorticoids bind with even higher affinity to the mineralocorticoid receptor, and that both receptors bind to the same responsive element in the DNA (Funder, 1997). Therefore, differential effects and tissue-specific actions of glucocorticoids are determined by the glucocorticoid concentration, with only high levels able to activate the GR, and the presence of 11βHSD-2 which prevents glucocorticoids from accessing the mineralocorticoid receptor. Physiological and pathological alterations of the number of GR can lead to a parallel change in sensitivity of the tissue to the effect of glucocorticoids and transcriptional activity of the GR. Normally, increases in circulating glucocorticoids leads to GR downregulation, decreasing the sensitivity to the steroid of target genes, such as AMP activated kinase (Blalock et al., 2010) and calcium channels (Landfield and Eldridge, 2007) and attenuating elevations in intracellular calcium and free radical formation during stress-induced neuronal activation. Failure of receptor downregulation with age would potentiate the actions of glucocorticoids, increasing the vulnerability of neurons to oxidative stress and calcium altering electric activity which could contribute to alterations in learning and memory characteristic of aging.

Genetic variation can also affect GR activity. For example, mutations in the GR are associated with either increases or decreases in sensitivity to glucocorticoids (Wust. et al., 2000; Lupien et al., 2001; van Rossum and Lamberts, 2004; DeRijk, 2005). Interestingly, individuals with high sensitivity to glucocorticoids show higher incidence of depression and metabolic disorders, while the opposite occurs with individuals showing low glucocorticoid sensitivity (van Rossum et al., 2002). In addition, there is growing evidence from studies in rats that early life experiences can induce epigenetic changes that determine HPA axis activity and stress sensitivity during adulthood and probably aging.

4.2. Corticotropin releasing hormone

CRH is the principal member of a family of neuropeptides which includes urocortin 1, 2 and 3 (Bale and Vale, 2004). There are two major types of CRH receptors, both coupled to cyclic AMP/protein kinase A signaling pathways; type 1 (CRHR1) which are located mainly in the brain and pituitary corticotrophs but also in some peripheral tissues including reproductive organs and the immune system. CRHR1 bind CRH and urocortin 1 with equal affinity and do not recognize urocortins 2 and 3. Type 2 CRH receptors (CRHR2), bind urocortins 1, 2 and 3 and are located mostly in the periphery (Bale and Vale, 2004). As indicated above, in addition to stimulating the HPA axis, activation of CRHR1 by CRH plays a major role coordinating stress responses, including sympathetic systems, central suppression of the immune system, arousal and other stress-related behaviors (Bale and Vale, 2004). The questions of which are the effects of aging on CRH regulation as well as whether CRH influences the course of aging are far from clear. A number of studies in experimental animals and in humans have reported increased, unchanged or reduced CRH hypothalamic CRH expression during aging. While some studies show progressive decreases in CRH expression (Cizza et al., 1994; Kasckow et al., 1999), the majority of investigators describe findings consistent with increased CRH production with advancing age (Hauger et al., 1994; Ceccatelli et al., 1996; Tizabi et al., 2003; Swaab et al., 2005; Meijer et al., 2005). In agreement with in vitro studies showing higher CRH secretion by hypothalamic fragments of old rats (Scaccianoce et al., 1990), Hauger et al. show increased secretion of CRH to the pituitary portal circulation of old rats in spite of normal CRH mRNA levels in the PVN (Hauger et al., 1994). Immunohistochemical and in situ hybridization studies in post-mortem brains also suggest an overactivity of the CRH system in humans, a finding which is more marked in brains from Alzheimer's and depressed patients. Several studies show a decrease in type 1 CRH receptors in the pituitary of aging rats (Hauger et al., 1994; Ceccatelli et al., 1996; Tizabi et al., 2003). This is in keeping with excessive CRH production since CRH induces pituitary CRH receptor downregulation (Aguilera, 1994).

It is well established that CRH administered centrally causes anxiety and depression in rodents and non-human primates (Vale et al., 1983; Bale and Vale, 2004). The association between high CRH levels in the CSF and depression suggests that this is also the case in humans (Kling et al., 1993; Heuser et al., 1998). Thus, the high incidence of depression and anxiety in elderly humans could be related to the increased activity of CRH neurons described in the studies above (Holsboer, 2003). While stress and excessive CRH production is related to learning disability and atrophy of hippocampal neurons, these effects appear to be reversible upon cessation of the stressful stimulus or CRH neuron hyperactivity (Swaab et al., 2005). Thus, exposure of the brain to damaging levels of CRH is likely to depend on the effectiveness of mechanisms limiting CRH production. In this regard, studies by Meijer et al. (2005) have shown a good negative correlation between HPA axis activity and learning capacity in old rats. Interestingly, there was an elevation of only basal ACTH but not corticosterone levels in old rats, and correlations between HPA axis markers were dependent on their learning performance or age. ACTH responses to stress and CRH mRNA levels, as

well as the number of parvocellular neurons and VP mRNA levels were significantly higher in aged inferior learners. A concomitant reduction in GR mRNA levels suggested a decreased sensitivity to glucocorticoid feedback in the inferior learner group (Meijer et al., 2005).

In vitro studies have shown either neuroprotective, or pro-apoptotic effects of CRH, both effects mediated by type-1 receptors (Dermitzaki et al., 2002; Wang et al., 2003; Bayatti et al., 2003; Wang et al., 2004). The discrepancy is likely due to differential effects of CRH in glial and neuronal cells. While CRH could directly protect neurons through stabilization of cellular calcium homeostasis (Pedersen et al., 2001), and by depressing N-methyl-D-aspartate receptor-mediated currents (Sheng et al., 2008), the peptide could be pro-inflammatory by activating proinflammatory cytokine production by glial cells (Wang et al., 2004).

4.3. Vasopressin

There are two major vasopressinergic systems in the brain; first, magnocellular neurons in the PVN and supraoptic (SON) providing VP and oxytocin to the peripheral circulation and responsible for the actions of VP on water conservation and blood pressure, and second, parvocellular neurons in the PVN providing VP to the pituitary portal circulation responsible for HPA axis regulation (Antoni, 1993; Aguilera and Rabadan-Diehl, 2000). In addition, VP neurons in the medial amygdala and the bed nucleus of the stria terminalis project to the lateral septum and ventral hippocampal sites affecting memory and behavior (Caff et al., 1987; Alescio-Lautier et al., 2000). VP is also expressed in the suprachiasmatic nucleus (SCN) where it is believed to be involved in the regulation of circadian rhythms (Arima et al., 2002; Li et al., 2009; Kalsbeek et al., 2010). The actions of VP are mediated through G-protein coupled receptors located in the plasma membrane of target cells (Jard et al., 1987). There are two major VP receptor subtypes; V2 VP receptors, which are coupled to the adenylyl cyclase/protein kinase A pathway and are responsible for the effects of VP on water homeostasis in the kidney (Frank and Landgraf, 2008). On the other hand, V1 VP receptors, are coupled to phospholipase C (PLC), increasing intracellular Ca^{2+} and PKC activity (Jard et al., 1987), and mediate the effects of VP in the liver, smooth muscle and brain (Ostrowski et al., 1992; Aguilera and Rabadan-Diehl, 2000). VP also transactivates the mitogen activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) and phosphatidylinositol 3 kinase (PI3)/protein kinase B (Akt) pathways which are known to be involved in neuronal development, memory formation, synaptic plasticity and neuronal survival (de Wied et al., 1993).

Recent studies revealed that VP protects neuronal cell lines and primary cultures of hippocampal neurons against nutrient deprivation and glutamate-induced apoptotic cell death, through activation of the ERK/RSK, protein kinase C alpha and beta, and P13 kinase/Akt pathways (Chen et al., 2008b; 2009; Chen and Aguilera, 2010). In contrast to CRH, VP has been shown to inhibit interleukin 1 beta and tumor necrosis factor release from astrocytes in culture (Zhao and Brinton, 2004). Thus, VP could act as a neuroprotective agent by directly protecting neurons against apoptosis and indirectly by inhibiting proinflammatory cytokine production from glial cells.

The effects of aging on VP expression in the brain appear to be region-specific. While the expression of VP in parvocellular neurons increases with age parallel to the increases in HPA axis activity, VP expression in the SCN decreases and fails to show the characteristic circadian variations. These alterations in SCN VP could contribute to the abnormal circadian rhythms observed during aging. Supporting this view are studies in post-mortem brains showing a correlation between reduced VP expression in the SCN and sleep disturbances (Swaab et al., 2005). Basal levels of magnocellular VP expression and plasma VP levels are

mildly increased during aging but responses to osmotic stimulation and immune challenge are reduced.

5. Concluding remarks

While age can lead to changes in HPA axis activity depending on the genetic background, there is clear evidence that increases in glucocorticoid activity and central levels of CRH during aging can have damaging effects and contribute to pathology associated with advancing age such as depression, anxiety, neurodegeneration, immune and metabolic disorders. Although transient activation of the HPA axis is necessary for survival during increasing demand, prompt termination of the stress response is essential to prevent negative effects of excessive CRH and glucocorticoids. The processes contributing to curbing stress involve coordinated regulation of stimulatory and inhibitory neurocircuitry, glucocorticoid activity (including secretion and neuronal sensitivity) and intracellular feedback mechanisms.

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