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The Role of the Amygdala in Regulating the Hypothalamic-Pituitary-Adrenal Axis

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Abstract

We investigated the regulatory role of the amygdala upon the function of the hypothalamic-pituitary-adrenal (HPA) axis as measured by median eminence corticotrophin releasing hormone (CRH) content and serum levels of adrenocorticotrophic hormone (ACTH) and corticosterone. Our findings showed that (1) lesions of the central amygdala inhibited the HPA axis responses to a variety of stressful stimuli. (2) Depletion of norepinephrine or serotonin in the amygdala and hypothalamus and local injections of norepinephrine and serotonin receptor antagonists into the central amygdala inhibited the HPA axis responses to neural stress. Norepinephrine and serotonin agonists injected into the amygdala caused an increase in HPA axis activity. The activation of the amygdala facilitated the *in vivo* release of serotonin from the paraventricular nucleus following electrical stimulation of the brainstem raphe nuclei. (3) Electrical stimulation of the amygdala impaired the glucocorticoid negative feedback action following neural stressful stimuli probably via a decrease in hippocampal corticosteroid receptors.

Keywords: amygdala, HPA axis, stressful stimuli

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1. Introduction

One of the major responses to various stressful conditions is the activation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in hypersecretion of glucocorticoids (GC) (cortisol in humans and corticosterone in rodents). These hormones affect a wide spectrum of body functions, and in particular, they have an essential role in regulating energy body requirements by acting on glucose, protein, and fat metabolic pathways. GC also has a

cardinal role in many aspects of immune system function. The effects of GC on body tissues, including the brain, are mediated by two main types of intracellular GC receptors known as type 1 and type 2 [1]. The HPA axis consists of corticotrophin-releasing hormone (CRH) containing neurons that are located in the paraventricular nucleus (PVN) of the hypothalamus, which send projections to the median eminence (ME). In response to stressful stimuli, CRH is released into the portal circulation, causing the secretion of adrenocorticotrophic hormone (ACTH) from the pituitary gland that in turn stimulates the secretion of the GC from the adrenal cortex [2]. The HPA axis can also be activated by various cytokines, including IL-1 β , IL-6, and TNF- α [3]. Intracerebroventricular (ICV) administration of each of these cytokines stimulated the secretion of CRH, ACTH, and GC into the bloodstream. By using specific neurotoxins and specific agonists/antagonists, it was found that the responses of the HPA axis to various stressful stimuli, including these inflammatory cytokines, were regulated by central neurotransmitters and, in particular, norepinephrine (NE) and serotonin (5-HT) [4].

It is now well established that the activity of the HPA axis is modulated by extrahypothalamic limbic structures and in particular the hippocampus and the amygdala (AMG) [4, 5]. While hippocampal neurons exert an inhibitory effect on the activation of the axis, the activity of the AMG exerts a significant facilitatory effect [4]. Indeed, data have shown that acute electrical stimulation of AMG in several animal species activated the HPA axis [4, 6], while bilateral AMG lesions inhibited the adrenocortical responses to somatosensory stimuli caused by sciatic nerve electrical current and olfactory stimuli caused by exposure to amyl acetate fumes and immobilization stress [4]. We have previously provided evidence that AMG may regulate the HPA axis responses to hypoglycemia and cytoglucopenia, known also to activate HPA axis. Complete hypothalamic deafferentation in rats that disrupts the neural pathways between the hypothalamus and limbic structures including the AMG, caused a marked inhibition of the adrenocortical responses to insulin-induced hypoglycemia and 2-deoxyglucose-induced cytoglucopenia [7, 8]. The AMG has two direct and one indirect efferent connection with the hypothalamus: (1) The stria terminalis directly connects the AMG with the preoptic area in the hypothalamus. (2) The ventral amygdalofugal pathway situated in the medial forebrain bundle directly connects the central and basolateral AMG with the hypothalamus [6]. (3) An indirect pathway consists of projections from the AMG central nucleus to the bed nucleus of the stria terminalis the efferents of which retroproject to CRH cells in the hypothalamic PVN [9]. These three connective pathways form the anatomical basis for the neural communication between the AMG and the PVN of the hypothalamus.

In this review, we have focused mainly on the studies done in our laboratory for almost 35 years under the direction of the late Prof. S. Feldman. The aim of these studies was to elucidate the influence of the AMG on the activity of the HPA axis, and they can be subdivided into three topics: (1) Determining the role of the AMG on the HPA axis responses to various stressful stimuli. (2) Determining the role of central NE and 5-HT in mediating the effects of the AMG upon the HPA axis. (3) Determining the role of AMG in regulating the negative feedback action of GC upon the HPA axis.

2. The role of the AMG on the HPA axis responses to various stress modalities

2.1. Neural stimuli

Male rats were exposed to either one of the following neural stimuli: photic stimulation that consisted of a 4-min exposure to flashes of light emitted by a photostimulator and an acoustic stimulation that consisted of a 4-min exposure to a ringing bell [10]. In intact rats, these two neural stimuli caused a significant increase in serum ACTH and CS associated with a marked depletion of ME CRH content due to the release of CRH into the hypothalamic-pituitary portal circulation. A similar activation of the HPA axis was obtained in rats with lesions in the basal nucleus of the AMG, indicating that this amygdaloid region does not participate in the modulation of the HPA axis responses. On the other hand, bilateral lesions of the medial and central nuclei of the AMG inhibited the rise in serum ACTH and CS following photic and acoustic stimuli. These results suggest that a tonic input from the medial and central AMG to the PVN is essential for the release of CRH from the ME and the subsequent pituitary-adrenocortical responses following these neural stimuli. Interestingly, while lesions of the central AMG inhibited the HPA axis responses following a short (4 min) photic and acoustic stimulation, lesions of the central AMG did not affect the HPA axis responses following longer (30 min) of neural stimulation [11]. This apparent discrepancy may be explained by the fact that activation of the AMG mediates the response to short stressful stimuli, while prolonged adrenocortical activation may involve both neural as well as systemic mechanisms. It is possible that the prolonged stimulus causes an increase in the peripheral secretion of catecholamines that are known to stimulate both the release of CRH from the PVN and ACTH from the pituitary gland [12].

In conclusion, these results demonstrate the differential effects of various AMG nuclei in modifying the HPA axis responses to neural stimuli, and the role of CRH in this mechanism. A facilitatory input from the medial and central AMG nuclei to the hypothalamus seems to play a role in the activation of the HPA axis response.

2.2. Surgical stress

Surgical stress is the combined result of tissue injury, anesthesia, and postoperative pain. It is characterized by elevated levels of serum ACTH, CS, and prostaglandin E₂ (PGE₂). PGE₂ and other eicosanoids are produced from arachidonic acid by the cyclooxygenase pathway and are involved in inflammatory responses, nociception as well as hormones secretion [13–15]. We were also interested in studying PGE₂ measurements in brain tissue as a part of the evaluation of mechanisms involved in the responses to stressful stimuli. During the previous experiments, we examined the role of AMG activation on HPA axis responses in rats that underwent laparotomy and perioperative pain management. In addition, we tested the effects of surgical stress on the production of PGE₂ in several brain regions including the AMG. The results show that surgery is associated with activation of the HPA axis and bilateral lesions of the central AMG nuclei that blocked this response [16]. The results also indicate, for the first time,

that surgical stress is associated with elevated production of PGE_2 in the AMG. Furthermore, pre-emptive pain management (as described in details in Ref. [16]) extended into the immediate postoperative period that attenuated the production of PGE_2 in the AMG and the adrenocortical response. We have shown that the analgesic procedure used in our study (consisting of pre-emptive intrathecal and continued by postoperative sustained release of morphine) provided an effective long-lasting pain relief.

The mechanisms involved in the activation of the HPA axis by surgical stress, and its attenuation by perioperative analgesia is not clearly understood. Previous studies have shown that the activation of the HPA axis following laparotomy is mediated by central mechanisms. This includes the secretion of CRH from the hypothalamic PVN into the pituitary gland that depends on noradrenergic neural input from brainstem nuclei. Thus injection of 6-hydroxydopamine (6-OHDA) into the PVN, which significantly depleted NE content in the PVN markedly inhibited the HPA axis response to laparotomy. Also, ICV injection of IL-1 β receptor antagonist inhibited the laparotomy-induced HPA axis response. This may indicate that the activation of the HPA axis may be mediated also by IL-1 β [13, 17, 18].

Previous studies demonstrated that AMG is one of the brain regions, which expresses neuronal cyclooxygenase 2 (COX-2) and PGE_2 -binding sites [19]. It has been shown that COX-2 maybe induced in brain endothelial cells and constitutively expressed in brain neurons in the cerebral cortex, the hippocampus, AMG, and glial cells [20]. PGE_2 , which is elevated in the brain during surgical stress, is involved in the activation of the HPA axis [21]. These reports lend support to the hypothesis that the decreased PGE_2 production in the AMG following preemptive analgesia could be involved in the attenuated surgery-induced HPA axis activation. It should be emphasized that our findings show a correlative relationship between changes in amygdalar PGE_2 , the HPA axis activity, and analgesic treatment. It may be assumed that one mechanism involved in this correlative relationship is the rise of nociceptive inflow including IL-1 β from the inflamed tissue. This cytokine is known to increase both brain PGE_2 and the activity of the HPA axis. The pre-emptive analgesia may attenuate these responses.

2.3. Adrenalectomy

Elimination of the negative feedback exerted by GC following adrenalectomy (Adx) causes hypersecretion of hypothalamic CRH and, consequently, ACTH from the pituitary gland. We were interested in examining the effect of lesions of the central AMG nucleus on serum ACTH following Adx. Our data demonstrated that this lesion inhibited, ACTH hypersecretion following Adx [22]. Thus, our results suggest that AMG activation is involved in the ACTH hypersecretion following Adx. The nature of the neurotransmitters that mediate Adx-induced ACTH hypersecretion has not been fully elucidated. However, we demonstrated that depletion of hypothalamic NE caused by 6-OHDA, inhibited the rise of ACTH following Adx [23]. This supports the notion that an intact noradrenergic system of the hypothalamus is important in mediating this mechanism. In summary, the central AMG nucleus, which has a facilitatory effect on the HPA axis, can also modulate Adx-induced ACTH hypersecretion.

2.4. Viral infection of the brain

It is now well established that there is a bidirectional communication between the nervous system and the immune system via three different pathways: direct neural circuits reaching lymphoid organs, circulating humoral factors such as GC and neuropeptides, and cytokines released by lymphoid cells and neurons. This communication is mediated by specific receptors found on both immune cells and neurons. Since the HPA axis activation plays a major role in the bidirectional communication between the nervous and immune system, we sought to examine the role of the AMG in mediating the activation of the HPA axis following an immune challenge caused by herpes simplex type 1 (HSV-1) infection of the brain [24]. This neurotropic virus is the most common cause of acute non-epidemic viral encephalitis. HSV-1 encephalitis typically manifests with fever and behavioral changes, including hyperactivity and aggression due to the predilection of the virus to limbic areas. We have previously shown that corneal or ICV inoculation of HSV-1 in rats results in the activation of the HPA axis and induces fever and typical behavioral changes. These effects of HSV-1 are probably mediated via toll-like receptors found on neurons and microglia, which activate signal transduction specific for the increased expression of IL-1 β and other proinflammatory mediator genes [25]. The increased expression of these genes was observed in the brainstem, hypothalamus, and AMG and depends on intact noradrenergic transmission connecting the brainstem with the hypothalamus. We showed that impairment of the noradrenergic transmission caused by 6-OHDA inhibited the HPA axis responses following this viral infection [25]. One study showed that lesions of the central AMG markedly reduced ACTH secretion, hypothalamic CRH, as well as the expression of c-Fos gene in oxytocin cells in response to systemic injection of IL-1 β [26]. We found that a bilateral lesion of the central amygdaloid nuclei markedly attenuated the HPA axis responses as well as fever, motor hyperactivity, and aggressive behavior that are induced by HSV-1 infection [27].

A plausible mechanism of reduced brain responses to HSV-1 in lesioned animals may be due to damaged neural pathways that regulate neuroendocrine and behavioral functions. The neurotransmitters that mediate the modulatory effect of the central AMG on the neuroendocrine and autonomic responses to HSV-1 infection are not entirely clear. The central AMG can influence the hypothalamus both via indirect and direct pathways. Indeed, this structure has rich projections to brainstem nuclei, including the noradrenergic and serotonergic nuclei [28, 29]. It has been demonstrated that these projections include neurons containing CRH that in this case function as a neurotransmitter in the AMG. These neurons activate, noradrenergic and serotonergic output from brainstem nuclei [26, 28, 30, 31]. These nuclei play an essential role in the activation of the HPA axis upon exposure to stressful stimuli, including immune challenges [32]. Another indirect pathway by which the central AMG can regulate hypothalamic functions is via its connection to the bed nucleus of the stria terminalis (BNST), which is known to regulate the HPA axis responses. In addition, the central AMG contains a small number of cells that project directly to the PVN. Regarding HSV-1 and HPA axis interactions, we have previously reported that HSV-1 infected the brainstem and induced IL-1 β gene expression in this region [24, 33]. In turn IL-1 β activates noradrenergic output to the hypothalamus via the ventral noradrenergic bundle (VNAB). We have shown that HSV-1-induced HPA

axis activation depends on endogenous IL-1 β , as its receptor antagonist completely blocked ACTH and CS responses to the virus [33].

We have also shown that a neurotoxic lesion of the VNAB with 6-OHDA completely prevented the HPA axis responses to HSV-1 [25]. Furthermore, central AMG lesions attenuated the recruitment of noradrenergic neurons of the brainstem and BNST and the HPA axis responses to IL-1 β [26]. Altogether these findings may suggest that the attenuation of the responses, including ACTH, CS, hyperactivity, and aggression, to HSV-1 infection in animals bearing lesions in the central AMG is due to a reduction in noradrenergic activity in the brainstem and BNST.

2.5. Direct adrenergic and glutamate stimulation of the hypothalamus

The involvement of the central AMG in the HPA axis responses to a variety of stimuli may be mediated by direct and indirect neural pathways, which at present are not fully characterized. We have previously demonstrated that the activation of central AMG has a facilitatory effect on the function of the dorsal raphe nucleus 5-HT neurons, which project to the PVN, suggesting a mechanism by which this structure may modulate the HPA axis responses [31]. In particular, we examined the role of the central AMG in modulating the HPA axis responses to specific hypothalamic noradrenergic and glutamate stimulation. Previous studies indicated that the excitatory neurotransmitter glutamate is also involved in neuroendocrine regulation. Thus, direct injection of glutamate into the PVN caused CRH release from the median eminence and consequent increase in serum ACTH and CS levels [34, 35].

Several *in vitro* and *in vivo* studies produced evidence for a reciprocal interaction between the action of NE and glutamate at the hypothalamic level. For example, the effect of hypothalamic NE on CRH release is mediated by intrahypothalamic glutamatergic interneurons [36]. Also, the activation of the HPA axis by electrical stimulation of the VNAB, or by direct PVN injection of, phenylephrine (an agonist with high affinity to α 1-adrenergic receptors) was markedly inhibited by PVN administration of selective ionotropic glutamate receptor antagonists [37].

We attempted to further elucidate the mechanisms by which the activity of the AMG regulates the function of the HPA axis. To this end, we examined the effect of bilateral lesions of the central and medial AMG on serum ACTH and CS in response to the activation of the adrenergic neurons. Our results showed that the ACTH and CS responses to electrical stimulation of the VNAB, or local PVN administration of the α 1-adrenergic receptor agonist phenylephrine, were markedly attenuated following central or medial AMG lesions. In addition, the pituitary-adrenal response to PVN injection of the excitatory neurotransmitter glutamate that is known to interact with NE at the hypothalamic level was also inhibited significantly following central or medial AMG lesions [38]. The exact neural mechanism involved in the modulatory role of the amygdaloid nuclei in the HPA axis responses to local adrenergic and glutamate stimulation is not clear at present. One mechanism may involve neural projections from the central or medial AMG to brainstem noradrenergic and/or serotonergic nuclei, which in turn project back on the hypothalamus, including the PVN [6]. These monoaminergic neurons are known

to play an essential facilitatory role in the HPA axis responses. The central and medial AMG are also targets of innervation from brainstem NE neurons [39]. This innervation was found to play an important role in the activation of the HPA axis to stressful stimuli. It has been demonstrated that lesions of the central AMG greatly reduced the noradrenergic activity, in response to stress, within the hypothalamus including the PVN and in the bed nucleus of the stria terminalis. Similarly, another study demonstrated that bilateral central AMG lesions resulted in a significant reduction of *c-fos*-positive noradrenergic cells in the A1 brainstem region and in the bed nucleus of the stria terminalis. All together, these findings suggest that lesion of the central AMG impairs the hypothalamic adrenergic activity that results in inhibition of the adrenocortical response to direct adrenergic stimulation.

At present, the mechanisms by which the central AMG regulates the HPA axis responses to PVN glutamate administration are not known. Previous studies suggested an interaction between NE, 5-HT, and glutamate systems that may be involved in the effects of glutamate. In a recent study, it was found that the NE-induced increase of excitatory postsynaptic potentials was blocked by ionotropic glutamate receptor antagonists. This result suggests that spike-mediated transmitter release in the hypothalamus resulted from presynaptic effect of NE on glutamate neurons [36].

These findings suggest that impaired ACTH and CS response to PVN glutamate administration may be due to reduced hypothalamic NE or 5-HT activity resulting from the central or medial AMG lesions.

3. The role of central neurotransmitters in mediating the effect of AMG on adrenocortical responses

The responses of the HPA axis to a variety of stimuli depend on stress-sensitive neural circuits. Among them, NE and 5-HT containing neurons in the brainstem play a major role. The role of these neurotransmitters in mediating the effect of the AMG activation upon the HPA axis is not entirely clear. We attempted to elucidate the role of NE and 5-HT systems in both the AMG and the hypothalamus by using specific neurotoxins, agonists, and antagonists to NE and 5-HT receptors and by measuring the local secretion of 5-HT by microdialysis. Direct injection of 6-OHDA into the AMG caused a marked depletion of NE in this region [40], but no change in hypothalamic NE content was found. Our results also showed that 6-OHDA injection in the AMG inhibited the release of CRH from the ME following photic stimulation and, consequently, the secretion of ACTH and CS. However, this effect was specific to photic stimulation as depletion of amygdalar NE did not affect the HPA responses to acoustic stimulation. A similar differential effect of NE system damaged either by 6-OHDA or electrolytic lesions in the medial forebrain bundle (MFB), which serves both as an afferent NE and an efferent amygdalofugal pathway from the AMG to the hypothalamus was observed in our previous studies [4]. Similarly, in these experiments, we observed a greater inhibitory effect of NE depletion in the MFB on adrenocortical and ACTH responses to photic stimulation than to acoustic stimulation.

The central nucleus of the AMG receives an important catecholaminergic innervation from the ventrolateral medulla and the nucleus of the solitary tract. A number of studies indicate that exposure to stressful stimuli activates NE terminals in the AMG [4]. For example, some experiments have demonstrated that immobilization increases synthesis, release, and metabolism of NE in the AMG in conscious rats [41, 42]. The mechanism by which NE in the AMG activates the HPA axis following photic stimulation is not entirely clear. However, it is of interest that stressful stimuli cause an increase in NE in both the PVN and the AMG. As the presence of NE in the PVN is essential for the release of hypothalamic CRH, it can be assumed that NE also plays a stimulatory role within the AMG in the activation of the HPA axis.

To examine the nature of adrenoceptors in the AMG which mediate the effects of NE on the HPA axis responses following neural stimulation, rats were injected with prazosine (α_1 blocker) or atenolol (β_1 blocker) [43]. We showed that administration of the α_1 but not beta-adrenergic antagonist into the central AMG blocks the responses of the HPA axis to photic stimulation. These findings indicate the importance of α_1 adrenoceptors in the AMG in the mediation of HPA axis responses following neural stimuli.

We have previously demonstrated that hypothalamic 5-HT plays a role in the facilitatory effect of AMG activity on the HPA axis. To elucidate the role of 5-HT in the AMG in mediating the effect on the HPA axis, the neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) was injected into the central nucleus of the AMG [44]. This treatment caused almost a complete depletion of 5-HT content in the AMG, but there was no effect on its concentration in the hypothalamus. The results indicated that 5-HT depletion in the AMG inhibited the effect of short photic stimulation on ME CRH content and ACTH and CS plasma levels. Also, in rats pretreated with ketanserin, a 5-HT₂ receptor antagonist, the rise in ACTH and CS following photic stimulation was significantly inhibited. These results suggest that the presence of 5-HT in the AMG is involved in the activation of the HPA axis by photic stimulus. All regions of the AMG have significant 5-HT innervation, which comes from the dorsal raphe nucleus with additional input from the medial raphe nucleus. Since these responses were also blocked by the direct injection of ketanserin into the AMG, it can be assumed that this subtype of 5-HT receptor is involved in the effect of the AMG function in regulating HPA responses.

Next we attempted to substantiate the importance of amygdalar NE and 5-HT in mediating the HPA axis responses. To this end, we examined the effect of direct AMG injections of phenylephrine (NE agonist) and 8-OH-DPAT (a specific 5-HT_{1A} serotonergic receptor agonist [45]). These agonists activated the HPA axis attested by increased secretion of ME CRH and a significant rise in serum ACTH and CS. We also showed that rats with hypothalamic depletion of NE and 5-HT failed to activate the HPA axis in response to electrical stimulation of AMG. Thus, direct stimulation of NE and 5-HT systems in the AMG activates the HPA axis and that this effect depends on the presence of these excitatory neurotransmitters also at the hypothalamic level [46].

To explore a possible mechanism by which the AMG affects the HPA axis function, we examined the specific role of the serotonergic system in mediating the effect of the AMG on the activity of the HPA axis [31]. Bilateral lesions of the AMG in rats reduced ACTH and CS responses to electrical stimulation of the dorsal raphe nucleus, where the cell bodies of serotonergic neurons are located. AMG lesions had no effect on the ACTH and CS responses

to administration of a 5-HT_{1A} receptor agonist directly into the PVN of the hypothalamus, indicating that there was no impairment in the activity of the postsynaptic 5-HT_{1A} receptors in the hypothalamus. *In vivo* microdialysis showed that AMG lesions markedly attenuated the effect of electrical stimulation of the dorsal raphe nucleus to increase extracellular secretion of 5-HT in the PVN. These results show that activation of the AMG influence the activity of the dorsal raphe 5-HT neurons that project to the PVN and suggests a mechanism by which the AMG may modulate the function of the HPA axis.

4. The role of AMG in regulating the negative feedback effect of GC on adrenocortical responses

The activity of the HPA axis is negatively regulated by the feedback system exerted by corticosteroids that act predominantly at the level of the hippocampus [47]. The effect of these hormones is mediated by two types of intracellular cytosolic corticosteroid receptors [1]. It was previously reported that repeated electrical stimulation of the AMG resulting in kindling caused a transient decrease in hippocampal GR mRNA expression, and this effect was associated with increased fearful behavior [48]. Many studies showed that downregulation of hippocampal GR activity, caused by exposure to severe stress or administration of high doses of CS, may affect the responses of the HPA axis due to impaired feedback action of GC [47].

In view of these observations, we attempted to examine the effect of repeated electrical stimulation of the AMG on the responses to stressful stimuli and on the function of the negative feedback exerted by GC [49]. We found that repeated electrical stimulations of the central AMG significantly attenuated the inhibitory action of dexamethasone on the HPA axis responses to both acoustic and photic stressful stimuli. We have also shown that electrical stimulation of the AMG attenuated the decline in serum corticosterone to its basal levels, suggesting that the negative feedback exerted by circulating corticosterone was impaired. To examine whether the impaired feedback caused by AMG stimulation may result by a decrease in hippocampal GR, we measured the binding of ³H-dexamethasone by the cytosolic fraction of hippocampal tissue. We found that electrical stimulation of the AMG caused a significant decrease in the binding capacity of dexamethasone to hippocampal cytosol. In summary, we showed that impaired GC feedback induced by repeated AMG electrical stimulations may be involved in the regulatory role of this limbic structure on the HPA axis.

5. Conclusions

The evidence indicates that activation of the AMG and, in particular, its central nucleus induces a facilitation of the HPA axis responses to a variety of stressful stimuli such as neural, surgical, adrenalectomy, and immune challenges. This facilitatory effect is mediated by adrenergic and serotonergic neurotransmission via α_1 and 5-HT₂ receptors. In addition, activation of the AMG may enhance GC secretion by impairing the negative feedback of this hormone via a reduction in hippocampal GC receptors. **Figure 1** illustrates the possible pathways by which

Figure 1. The facilitatory role of the amygdala on the HPA axis responses to various stressful stimuli. Various stressful stimuli activate the PVN to release CRH that causes the pituitary to release ACTH into the bloodstream, which in turn causes the secretion of glucocorticoids from the adrenal gland. The stimulatory effect of the amygdala upon the HPA axis is mediated by amygdalar and hypothalamic NE and 5-HT neurotransmission mediated by $\alpha 1$ and 5-HT₂ receptors, respectively. Neuroendocrine effects of NE in the hypothalamus are mediated by intrahypothalamic glutamatergic interneurons. Also, the activation of the HPA axis by electrical stimulation of the VNAB or by direct PVN injection of a $\alpha 1$ adrenergic agonist is markedly inhibited by PVN administration of selective ionotropic glutamate receptor antagonist. In addition, the amygdala facilitates the release of 5-HT from the PVN in response to electrical stimulation of brainstem raphe nucleus. The amygdala attenuates the negative feedback exerted by glucocorticoids probably by reducing hippocampal glucocorticoid receptors and thus facilitating the activation of the HPA axis.

the AMG regulated the function of the HPA axis. It is possible that the stimulatory effect of the AMG result in an increase in circulating GC may enhance the known modulatory effect of the AMG on the encoding and storage of hippocampal dependent memories.

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References

- [1] De Kloet, E.R., et al., Brain corticosteroid receptor balance in health and disease. *Endocr Rev*, 1998. **19**(3): pp. 269-301.
- [2] Antoni, F.A., Hypothalamic control of adrenocorticotropin secretion: advances since the discovery of 41-residue corticotropin-releasing factor. *Endocr Rev*, 1986. **7**(4): pp. 351-78.
- [3] Besedovsky, H.O., et al., Cytokines as modulators of the hypothalamus-pituitary-adrenal axis. *J Steroid Biochem Mol Biol*, 1991. **40**(4-6): pp. 613-8.
- [4] Feldman, S., N. Conforti, and J. Weidenfeld, Limbic pathways and hypothalamic neurotransmitters mediating adrenocortical responses to neural stimuli. *Neurosci Biobehav Rev*, 1995. **19**(2): pp. 235-40.
- [5] Jankord, R. and J.P. Herman, Limbic regulation of hypothalamo-pituitary-adrenocortical function during acute and chronic stress. *Ann N Y Acad Sci*, 2008. **1148**: pp. 64-73.
- [6] Gray, T.S., M.E. Carney, and D.J. Magnuson, Direct projections from the central amygdaloid nucleus to the hypothalamic paraventricular nucleus: possible role in stress-induced adrenocorticotropin release. *Neuroendocrinology*, 1989. **50**(4): pp. 433-46.
- [7] Weidenfeld, J., et al., ACTH and corticosterone secretion following 2-deoxyglucose administration in intact and in hypothalamic deafferented male rats. *Brain Res*, 1984. **305**(1): pp. 109-13.
- [8] Weidenfeld, J., et al., ACTH and corticosterone secretion following insulin in intact and in variously hypothalamic deafferented male rats. *Exp Brain Res*, 1982. **48**(2): pp. 306-8.
- [9] Sawchenko, P.E. and L.W. Swanson, The organization of forebrain afferents to the paraventricular and supraoptic nuclei of the rat. *J Comp Neurol*, 1983. **218**(2): pp. 121-44.
- [10] Feldman, S., et al., Differential effect of amygdaloid lesions on CRF-41, ACTH and corticosterone responses following neural stimuli. *Brain Res*, 1994. **658**(1-2): pp. 21-6.

- [11] Feldman, S. and N. Conforti, Amygdalectomy inhibits adrenocortical responses to somatosensory and olfactory stimulation. *Neuroendocrinology*, 1981. **32**(6): pp. 330-4.
- [12] Vale, W., et al., Chemical and biological characterization of corticotropin releasing factor. *Recent Prog Horm Res*, 1983. **39**: pp. 245-70.
- [13] DeKeyser, F.G., R.R. Leker, and J. Weidenfeld, Activation of the adrenocortical axis by surgical stress: involvement of central norepinephrine and interleukin-1. *Neuroimmunomodulation*, 2000. **7**(4): pp. 182-8.
- [14] Holte, K. and H. Kehlet, Epidural anaesthesia and analgesia—effects on surgical stress responses and implications for postoperative nutrition. *Clin Nutr*, 2002. **21**(3): pp. 199-206.
- [15] Kroin, J.S., et al., Upregulation of spinal cyclooxygenase-2 in rats after surgical incision. *Anesthesiology*, 2004. **100**(2): pp. 364-9.
- [16] Shavit, Y., et al., Effects of surgical stress on brain prostaglandin E2 production and on the pituitary-adrenal axis: attenuation by preemptive analgesia and by central amygdala lesion. *Brain Res*, 2005. **1047**(1): pp. 10-7.
- [17] Dunn, A.J., The role of interleukin-1 and tumor necrosis factor alpha in the neurochemical and neuroendocrine responses to endotoxin. *Brain Res Bull*, 1992. **29**(6): pp. 807-12.
- [18] Taylor, B.K., et al., Pituitary-adrenocortical responses to persistent noxious stimuli in the awake rat: endogenous corticosterone does not reduce nociception in the formalin test. *Endocrinology*, 1998. **139**(5): pp. 2407-13.
- [19] Matsumura, K., et al., Mapping of prostaglandin E2 binding sites in rat brain using quantitative autoradiography. *Brain Res*, 1992. **581**(2): pp. 292-8.
- [20] Quan, N., M. Whiteside, and M. Herkenham, Cyclooxygenase 2 mRNA expression in rat brain after peripheral injection of lipopolysaccharide. *Brain Res*, 1998. **802**(1-2): pp. 189-97.
- [21] Matsuoka, Y., et al., Impaired adrenocorticotrophic hormone response to bacterial endotoxin in mice deficient in prostaglandin E receptor EP1 and EP3 subtypes. *Proc Natl Acad Sci U S A*, 2003. **100**(7): pp. 4132-7.
- [22] Feldman, S., et al., The role of limbic structures in the modulation of ACTH responses following adrenalectomy. *Ann N Y Acad Sci*, 1995. **771**: pp. 73-81.
- [23] Weidenfeld, J. and S. Feldman, Effect of hypothalamic norepinephrine depletion on median eminence CRF-41 content and serum ACTH in control and adrenalectomized rats. *Brain Res*, 1991. **542**(2): pp. 201-4.
- [24] Ben-Hur, T., et al., Rescue of HSV-1 neurovirulence is associated with induction of brain interleukin-1 expression, prostaglandin synthesis and neuroendocrine responses. *J Neurovirol*, 1996. **2**(4): pp. 279-88.

- [25] Ben Hur, T., et al., Adrenocortical activation by herpes virus: involvement of IL-1 beta and central noradrenergic system. *Neuroreport*, 1996. **7**(4): pp. 927-31.
- [26] Xu, Y., T.A. Day, and K.M. Buller, The central amygdala modulates hypothalamic-pituitary-adrenal axis responses to systemic interleukin-1beta administration. *Neuroscience*, 1999. **94**(1): pp. 175-83.
- [27] Weidenfeld, J., et al., Role of the central amygdala in modulating the pituitary-adrenocortical and clinical responses in experimental herpes simplex virus-1 encephalitis. *Neuroendocrinology*, 2005. **81**(4): pp. 267-72.
- [28] Jedema, H.P. and A.A. Grace, Corticotropin-releasing hormone directly activates noradrenergic neurons of the locus ceruleus recorded in vitro. *J Neurosci*, 2004. **24**(43): pp. 9703-13.
- [29] Peyron, C., et al., Forebrain afferents to the rat dorsal raphe nucleus demonstrated by retrograde and anterograde tracing methods. *Neuroscience*, 1998. **82**(2): pp. 443-68.
- [30] Van Bockstaele, E.J., et al., Topographic architecture of stress-related pathways targeting the noradrenergic locus coeruleus. *Physiol Behav*, 2001. **73**(3): pp. 273-83.
- [31] Weidenfeld, J., et al., The amygdala regulates the pituitary-adrenocortical response and release of hypothalamic serotonin following electrical stimulation of the dorsal raphe nucleus in the rat. *Neuroendocrinology*, 2002. **76**(2): pp. 63-9.
- [32] Weidenfeld, J., O. Abramsky, and H. Ovadia, Evidence for the involvement of the central adrenergic system in interleukin 1-induced adrenocortical response. *Neuropharmacology*, 1989. **28**(12): pp. 1411-4.
- [33] Ben-Hur, T., et al., Acute effects of purified and UV-inactivated Herpes simplex virus type 1 on the hypothalamo-pituitary-adrenocortical axis. *Neuroendocrinology*, 2001. **74**(3): pp. 160-6.
- [34] Feldman, S. and J. Weidenfeld, Hypothalamic mechanisms mediating glutamate effects on the hypothalamo-pituitary-adrenocortical axis. *J Neural Transm (Vienna)*, 1997. **104**(6-7): pp. 633-42.
- [35] Makara, G.B. and E. Stark, Effect of intraventricular glutamate on ACTH release. *Neuroendocrinology*, 1975. **18**(2): pp. 213-6.
- [36] Daftary, S.S., et al., Noradrenergic excitation of magnocellular neurons in the rat hypothalamic paraventricular nucleus via intranuclear glutamatergic circuits. *J Neurosci*, 1998. **18**(24): pp. 10619-28.
- [37] Feldman, S. and J. Weidenfeld, Involvement of endogenous glutamate in the stimulatory effect of norepinephrine and serotonin on the hypothalamo-pituitary-adrenocortical axis. *Neuroendocrinology*, 2004. **79**(1): pp. 43-53.
- [38] Weidenfeld, J., et al., Adrenocortical axis responses to adrenergic and glutamate stimulation are regulated by the amygdala. *Neuroreport*, 2005. **16**(11): pp. 1245-9.

- [39] Roder, S. and J. Ciriello, Innervation of the amygdaloid complex by catecholaminergic cell groups of the ventrolateral medulla. *J Comp Neurol*, 1993. **332**(1): pp. 105-22.
- [40] Feldman, S. and J. Weidenfeld, Norepinephrine depletion in the amygdala inhibits CRF-41, ACTH, and corticosterone responses following photic stimulation. *Brain Res Bull*, 1996. **41**(2): pp. 83-6.
- [41] Pacak, K., et al., Effects of single or repeated immobilization on release of norepinephrine and its metabolites in the central nucleus of the amygdala in conscious rats. *Neuroendocrinology*, 1993. **57**(4): pp. 626-33.
- [42] Tanaka, T., et al., Noradrenaline release in the rat amygdala is increased by stress: studies with intracerebral microdialysis. *Brain Res*, 1991. **544**(1): pp. 174-6.
- [43] Feldman, S. and J. Weidenfeld, Involvement of amygdalar alpha adrenoceptors in hypothalamo-pituitary-adrenocortical responses. *Neuroreport*, 1996. **7**(18): pp. 3055-7.
- [44] Feldman, S., et al., Role of serotonin in the amygdala in hypothalamo-pituitary-adrenocortical responses. *Neuroreport*, 1998. **9**(9): pp. 2007-9.
- [45] Feldman, S., M.E. Newman, and J. Weidenfeld, Effects of adrenergic and serotonergic agonists in the amygdala on the hypothalamo-pituitary-adrenocortical axis. *Brain Res Bull*, 2000. **52**(6): pp. 531-6.
- [46] Feldman, S. and J. Weidenfeld, The excitatory effects of the amygdala on hypothalamo-pituitary-adrenocortical responses are mediated by hypothalamic norepinephrine, serotonin, and CRF-41. *Brain Res Bull*, 1998. **45**(4): pp. 389-93.
- [47] Feldman, S. and J. Weidenfeld, Neural mechanisms involved in the corticosteroid feedback effects on the hypothalamo-pituitary-adrenocortical axis. *Prog Neurobiol*, 1995. **45**(2): pp. 129-41.
- [48] Clark, M., et al., Modulation of hippocampal glucocorticoid and mineralocorticoid receptor mRNA expression by amygdaloid kindling. *Neuroendocrinology*, 1994. **59**(5): pp. 451-6.
- [49] Weidenfeld, J., A. Itzik, and H. Ovadia, Electrical stimulation of the amygdala modifies the negative feedback effect of glucocorticoids on the adrenocortical responses to stress. *Neuroimmunomodulation*, 2015. **22**(6): pp. 394-9.