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REVIEW ARTICLE

Nicotinic Cholinergic System in the Hypothalamus Modulates the Activity of the Hypothalamic Neuropeptides during the Stress Response

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Abstract: ***Background*:** The hypothalamus harbors high levels of cholinergic neurons and axon terminals. Nicotinic acetylcholine receptors, which play an important role in cholinergic neurotransmission, are expressed abundantly in the hypothalamus. Accumulating evidence reveals a regulatory role for nicotine in the regulation of the stress responses. The present review will discuss the hypothalamic neuropeptides and their interaction with the nicotinic cholinergic system. The anatomical distribution of the cholinergic neurons, axon terminals and nicotinic receptors in discrete hypothalamic nuclei will be described. The effect of nicotinic cholinergic neurotransmission and nicotine exposure on hypothalamic-pituitaryadrenal (HPA) axis regulation at the hypothalamic level will be analyzed in view of the different neuropeptides involved.

***Methods*:** Published research related to nicotinic cholinergic regulation of the HPA axis activity at the hypothalamic level is reviewed.

***Results*:** The nicotinic cholinergic system is one of the major modulators of the HPA axis activity. There is substantial evidence supporting the regulation of hypothalamic neuropeptides by nicotinic acetylcholine receptors. However, most of the studies showing the nicotinic regulation of hypothalamic neuropeptides have employed systemic administration of nicotine. Additionally, we know little about the nicotinic receptor distribution on neuropeptide-synthesizing neurons in the hypothalamus and the physiological responses they trigger in these neurons.

***Conclusion*:** Disturbed functioning of the HPA axis and hypothalamic neuropeptides results in pathologies such as depression, anxiety disorders and obesity, which are common and significant health problems. A better understanding of the nicotinic regulation of hypothalamic neuropeptides will aid in drug development and provide means to cope with these diseases. Considering that nicotine is also an abused substance, a better understanding of the role of the nicotinic cholinergic system on the HPA axis will aid in developing improved therapeutic strategies for smoking cessation.

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1. INTRODUCTION

Stress, reward and eating behavior all have evolutionary significance, display similar neurobiological regulation in shared brain regions, and interact. Several reviews published during the past decade emphasize the role of the hypothalamus and the hypothalamic neuropeptides in addiction, including nicotine/tobacco addiction, and the stress response [1-9]. The hypothalamus lies at the intersection of homeostatic and reward pathways, and harbors high levels of cholinergic neurons and axon terminals [10, 11]. Nicotinic acetylcholine receptors, which play an important role in cholinergic neurotransmission, are expressed abundantly in the hypothalamus [12-14]. Accumulating evidence reveals a regulatory role for nicotine in diverse functions mediated by the hypothalamus, including the regulation of stress (Reviewed in [1, 15]).

Neuropeptides were discovered nearly five decades ago [16]. Although neuropeptides are produced by neurons, they reach farther and affect not only synaptic but also extrasynaptic receptors; this provides them with the opportunity to regulate different behaviors harmoniously. Neuropeptides released by hypothalamic neurons regulate stress, reward and feeding as well as autonomic nervous system activity. Most of these neuropeptides [melanin-concentrating hormone (MCH), hypocretins/orexins, α-melanocyte stimulating hormone (α-MSH), agouti-gene related protein (AgRP), neuropeptide Y, oxytocin, ghrelin, cocaine and amphetamine-

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regulated transcript (CART), neuropeptide W and the galanin-like peptides] have been initially noted for their impact on feeding behavior [17]. Eating is a complex behavior and is closely related to addiction and stress. Subsequently, following the discovery and localization of most of the hypothalamic peptides involved in feeding behavior, other functions and modulatory mechanisms were evaluated. This review will describe the anatomical distribution of the cholinergic neurons, axon terminals and nicotinic receptors in discrete hypothalamic nuclei, and will examine the possible regulatory role of the nicotinic cholinergic system and exogenous nicotine on the stress response. It is worth noting that, although this review will cover only stress, nicotine and the nicotinic cholinergic system are implicated as important actors in the modulation of almost all of the physiological functions of the hypothalamic neuroactive peptides that are included in this review. The hypothalamic neuropeptides that will be evaluated in the current review are:

- Corticotropin-Releasing Hormone **(**CRH)
- Orexin
- Melanin Concentrating Hormone (MCH)
- Pro-OpioMelanoCortin (POMC) and Alpha- Melanocyte Stimulating Hormone (α-MSH
- Cocaine and Amphetamine Regulated Transcript (CART)
- Neuropeptide Y (NPY) and Agouti-Related Peptide (AgRP)
- Opioid Peptides

2. HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

The hypothalamic-pituitary-adrenal (HPA) axis initiates the main endocrine response to a homeostatic challenge [18]. When the organism is confronted with a stressful condition, neural mechanisms activate the HPA and this activation is required for both basal and stress-induced glucocorticoid hormone release from the adrenal cortex. Neuroendocrine cells located in the medial parvocellular subdivision of the paraventricular nucleus (PVN) of the hypothalamus release CRH, into the hypothalamo-hypophysial portal system, which in turn induces adrenocorticotropic hormone (ACTH) secretion from the anterior pituitary cells. Neuroendocrine CRH cells co-express arginine-vasopressin (AVP) as well as other neuropeptides. The AVP synthesis in the parvocellular PVN is remarkably upregulated with chronic stress (reviewed in [19]). Thus, chronic stress increases the number of CRH+AVP co-expressing cells in the PVN and axons in the median eminence [20, 21]. AVP is co-released with CRH from the axon terminals in the external layer of median eminence and potentiates CRH-induced ACTH release from anterior pituitary. Adrenal cortex is a major target for ACTH in the systemic circulation. In the final step of the HPA axis, ACTH stimulates glucocorticoid hormone release from the adrenocortical fasciculata cells [22].

Sex hormones are among the important regulators of the HPA axis activity and the stress response [23]. Although today we know that there are sex hormone receptors throughout the entire brain that affect brain and behavior, these receptors were initially discovered in the hypothalamus [24]. Sex hormone receptors are expressed in various hypothalamic nuclei including the PVN, as well as in other brain regions, which project directly, or indirectly to the PVN [23, 25]. Sex differences in reactivity to stress are reported in rodent studies, and women are more vulnerable to stress related pathologies, *e.g*. post traumatic stress disorder, than men [26]. Sex differences depicted in the hypothalamus and hypothalamic functions point to the importance of including sex as a variable in experimental studies and in designing therapeutic interventions in pathologies involving the hypothalamus.

3. CORTICOTROPIN-RELEASING HORMONE:

The key role of the hypothalamus in the stress response is secreting corticotropin-releasing hormone (CRH), which triggers ACTH release. However, CRH is not only a releasing factor, but is also involved in different functions in the central and peripheral nervous system. CRH -expressing neurons are distributed widely in the neocortex, limbic system and brainstem. CRH neurons are located mainly in the prefrontal, cingulate and insular cerebral cortices, central nucleus of the amygdala, bed nucleus of the stria terminalis, hypothalamus, central gray matter, parabrachial nucleus, locus coeruleus and the nucleus of the solitary tract [22]. CRH neurons integrate neuronal and hormonal inputs and serve as a final common pathway to regulate the HPA axis. CRH not only activates the HPA-axis and mediates the stress response, but also plays an important role in addiction; transition from use to dependence, maintenance of dependence [27] and relapse [28] are closely related to stress and CRH.

In the hypothalamus, choline acetyltransferase (ChAT) immunoreactive (IR) cells are found in the periventricular and arcuate (ARC) nuclei, posterior and lateral hypothalamic areas and in the perifornical region [29]. However, PVN does not exhibit ChAT-IR cells. Instead, ChAT-IR cells are demonstrated in the matrix surrounding the PVN [29]. Additionally, although the PVN contains few or no nerve terminals immunoreactive for ChAT at the light microscopic level, they are demonstrated in the hypothalamic areas that immediately surround the PVN, such as zona incerta, perifornical nucleus, and dorsal hypothalamic nuclei [30]. Cholinergic afferents may innervate the neurons in the peri-PVN region which, in turn, project to the PVN CRH cells [31].

Nicotinic acetylcholine receptors (nAChRs) are present in the PVN. Radioligand binding [12, 14, 32], in situ hybridization [32, 33] and immunohistochemistry [13, 34] studies show that there are significant numbers of nAChRs (especially α7, α4, β2 subtypes) in the parvocellular PVN and in the neuropil surrounding PVN. The activity of the CRH neurons, hence the activity of the HPA axis, may be regulated through these nicotinic receptors in the PVN or in the vicinity of the PVN. *In vitro* studies in the rat hypothalamus show that nicotine increases hypothalamic CRH content and CRH release [35, 36]. Acetylcholine (ACh) induces hypothalamic CRH release *in vitro* and nicotinic receptor antagonists, hexamethonium or mecamylamine inhibits this release [35-37]. In parallel, in rats, when mecamy-

lamine is injected into the third ventricle, which lies adjacent to the PVN, basal plasma corticosterone (CORT) levels decrease [38]. Also, nicotine injections into the third ventricle elevates plasma ACTH levels in a dose-dependent manner [39]. In rats, intracerebroventricular (ICV) ACh induces CRH release into the hypothalamo-hypophyseal portal system, which is attenuated by the administration of ICV nicotinic receptor antagonists [40]. However, ICV hexamethonium did not abolish the increase in plasma ACTH levels induced by ACh microinjection into the dorsolateral border of the PVN [41]. The mechanisms by which nicotinic receptors regulate the CRH neuron activity in the PVN need further clarification.

CRH synthesized in the parvocellular PVN is released into the hypothalamo-hypophysial portal system in the median eminence. Intense localization of cholinergic axon terminals have been identified in the external layer of the median eminence [42]. Demonstration of vesicular acetylcholine transporter mRNA [43] and ChAT immunoreactivity [29] in many hypothalamic nuclei such as the ARC nucleus and lateral hypothalamic area (LHA) have led to the idea that there may be a short cholinergic projection system extending from the hypothalamic nuclei [*e.g*. ARC nucleus] to the median eminence [42]. Together with the evidence that the nicotinic receptors are present on CRH-IR axon terminals in the median eminence [44], these observations imply that nicotinic receptors may regulate CRH release in the median eminence.

Nicotine, when administered systemically, readily crosses the blood brain barrier and acts upon nicotinic receptors located in the brain [45, 46]. In rats, acute systemic nicotine administration activates PVN CRH neurons [47] and increases plasma ACTH and CORT [48, 49]. However, this increase in ACTH and CORT levels following a single dose of nicotine displays sex differences: the effect on female rats is more pronounced than in males [50-52]. These sex differences observed in rodents may also have implications in clinical settings. Higher salivary cortisol levels are reported in boys below the age of eight than girls of the same age, but this difference is reversed in adulthood [53]. Sex differences in nicotine/tobacco addiction are also clearly demonstrated in rodents and human smokers [54]. Smokers aiming to quit attended two stress sessions, one before and one after quitting smoking. About 60% of the subjects relapsed during the 4-week follow-up; lower cortisol in men and higher cortisol levels in women predicted relapse [55]. Additionally, when smoking precedes a stressful situation, cardiovascular responses (*e.g*. increased blood pressure) observed in men are more pronounced than those in women [56]. These findings point to the importance of sex differences in hormonal responses to stress and may have implications in developing protocols with higher success rates for smokers wishing to quit.

Pretreatment with systemic dihydro-β-erythroidine, a nicotinic chlolinergic antagonist, prevents the CORT elevation induced by a single subcutaneous nicotine injection; this observation supports the role of α4β2 nicotinic receptors in the effects of systemic nicotine [57]. On the other hand, chronic systemic nicotine administrations lead to the desensitization of the HPA axis activity in both male and female rats [50]. Chronic nicotine self-administration reduces CRH mRNA expression in the parvocellular PVN [58]. The rise in plasma ACTH and CORT levels following the first dose of nicotine is transient, gradually decreases and completely disappeares on the third day of nicotine exposure [59]. Interestingly, a large number of studies report that desensitization response is not observed in humans receiving chronic systemic nicotine [9]. Nicotine increases the activity of the HPA axis in habitual smokers [60-62]. Systemic nicotine may regulate the HPA axis activity *via* a direct action on nicotinic receptors in the hypothalamic nuclei surrounding the third cerebral ventricle, such as the PVN. Bugajski *et al*. [63] showed that ICV mecamylamine abolished the ACTH and CORT elevations induced by systemic nicotine. On the other hand, Fu *et al*. [64] had shown that microinjection of mecamylamine into the PVN did not block the ACTH elevation in response to intravenous nicotine. Consequently, the authors proposed that the nicotinic receptors localized in the PVN are not involved in the stimulation of the HPA axis by systemic nicotine. Instead, nicotinic receptors present in the noradrenergic brainstem nuclei are suggested to play an important role during this regulatory action [46].

Nicotinic receptors in the hypothalamus may play important roles in the mediation of stress-induced HPA axis activity. ICV mecamylamine abolished the plasma CORT response to auditory stress in rats [38]. In parallel, ICV administration of anti-nicotinic acetylcholine receptor antibodies inhibited the CORT response to acute ether stress [65]. Subcutaneous injection of a blood brain barrier crossing antagonist, mecamylamine, blunted predator stress-induced rise in plasma CORT levels [66]. Similarly, chronic daily systemic administration of mecamylamine in rats also reduced chronic restraint stress-induced increase of CORT levels in blood [67]. Additionally, there are numerous studies which show that there is an interaction between the regulatory effects of stress and systemic nicotine on HPA axis activity in rodents [38, 58, 59, 63, 68-72] and in humans [9].

Nicotine is suggested to regulate the axonal release of neurotransmitters such as noradrenaline, glutamate and gamma-aminobutyric acid (GABA), which are well known for their regulatory effects on PVN CRH neurons. PVN receives dense catecholaminergic innervation from brainstem nuclei [46]. Nicotinic receptors are located presynaptically on catecholaminergic axon terminals in the hypothalamus [73]. *In vitro* studies show that nicotine induces noradrenaline release from rat hypothalamic slices [74-76]. Acute, systemic nicotine administration also increases paraventricular noradrenaline release [77]. However, mecamylamine administration into the PVN does not prevent the noradrenaline release induced by acute systemic nicotine exposure [64]. Thus, the same group [46] proposed that nicotinic receptors located in the brainstem nuclei rather than in the PVN mediate the paraventricular noradrenaline release induced by systemic nicotine. When nicotine is self-administered chronically, increased noradrenaline release is sustained throughout the acquisition, early and late maintenance phases [78].

Parvocellular PVN CRH neurons receive both glutamatergic and GABAergic afferents [79, 80] and express ionotropic $GABA_A$ and glutamate receptors [81, 82]. Within the hypothalamus, inhibitory GABAergic axons arise from

peri-PVN region, medial preoptic area, dorsomedial (DMH) and LHA [10]. Similarly, DMH, LHA and posterior hypothalamic nuclei are suggested as the potential sources of hypothalamic glutamatergic inputs to the PVN [18]. Interestingly, nicotinic receptors are present in all of these hypothalamic nuclei, which regulate CRH neuron activity [12, 34, 83]. Furthermore, glutamate and GABA release in PVN is regulated by nicotine, an effect that may occur *via* presynaptic nicotinic receptors on axon terminals in the PVN. In a study by Yu *et al*. [84], chronic nicotine self-administration did not affect basal levels of glutamate and GABA in the PVN. However, footshock-induced PVN glutamate release was augmented and GABA release was further decreased by chronic nicotine self-administration when compared to rats self-administering saline. On the other hand, an electrophysiological study in hypothalamic slices showed that nicotine caused membrane depolarization and increased spike firing rate in the CRH mRNA-expressing neurons of the parvocellular PVN in a concentration-dependent manner, which is abolished by the addition of ionotropic glutamate receptor antagonist [85]. The authors suggested that nicotine excited PVN CRH mRNA-expressing neurons indirectly, through the enhancement of the presynaptic glutamate release.

Overall, nicotine and nicotinic receptor stimulation mediate stress induced HPA-axis activity and modulate the release of neurotransmitters that regulate PVN CRH neurons. ACTH and CORT levels are increased; this effect shows sex differences and is more pronounced in females than males.

4. OREXIN

The orexin (hypocretin) neuropeptides are important in motivated behaviors and reward, including feeding [86]. Orexin is also implicated in various physiological processes such as sleep and wakefulness and the stress response [87]. Accumulating evidence supports the role of orexins in drug reward and stress [88]. Orexin/hypocretin neurons are located mainly in the lateral, posterior and perifornical areas of the hypothalamus and project widely throughout the brain [89], including reward [90] and cardiovascular control centers [91]. Nicotine is one of the major abused drugs whose reinforcing properties are regulated by the orexin neuropeptide system [92]. Drugs targeting orexin signalling in the hypothalamus may present a possibility for treating addictions and related pathologies [93].

Studies suggest that the orexin system may play an important role in the endocrine and autonomic stress response. Orexin neurons are activated by psychological and physical stressors such as immobilization, restraint, cold exposure and swim stress [94-98]. Orexin peptides have been shown to increase the autonomic nervous system responses (*e.g*. elevation of blood pressure, heart rate and body temperature) to stress [95, 99-102].

Orexin neurons residing in the LHA directly innervate the PVN [103]. Orexin receptor 1 (OX-R1) immunoreactivity was demonstrated on parvocellular CRH neurons in the PVN [104]. High levels of OX-R2 mRNA is also expressed in in the PVN [105]. Electrophysiological studies demonstrate that orexin peptides depolarize parvocellular PVN neurons in hypothalamic slices [106-108]. Furthermore, ICV injection of orexin peptides activate the HPA axis resulting in increased CRH synthesis [109] and a consequent release of ACTH and CORT [109-111]. Moreover, a reciprocal interaction between CRH and orexin is suggested. Winsky-Sommerer *et al*. [98] showed that CRH axons terminated on LHA orexin neurons expressing high levels of CRH-R1/2 receptors. Furthermore, CRH depolarized membrane potential and increased firing rate in some orexin neurons. Based on these results, the authors proposed that CRH induces orexin neuron activity, which in turn, triggers arousal during the stress response.

Regulation of the CRH neurons through nicotinic receptors located on LHA orexin neurons is possible. Nicotinic receptors (α4 subunit) are expressed on LHA orexin neurons [86]. In parallel, a number of studies demonstrated that orexin neurons are regulated *via* nAChRs. Acute systemic nicotine increased the number of Fos co-expressing orexin neurons [112]. This effect was reduced following treatment with nicotinic receptor antagonists mecamylamine and dihydro-beta- erythroidine, indicating the role of α4β2 subunits. Nicotinic receptor blokade with systemic mecamylamine injections also reduced chronic nicotine-induced Fos immunoreactivity in orexin neurons [113]. Furthermore, chronic systemic nicotine injections increased prepro-orexin mRNA levels in rat hypothalamus, orexin A and B peptide levels in the rat PVN and dorsomedial nucleus [114] and orexin immunoreactivity in piglet hypothalamus [115]. Chronic exposure to cigarette smoke also upregulated prepro-orexin mRNA and orexin A peptide levels in rat hypothalamus [116]. Zhou *et al*. [117] showed that orexin neuron activity is modulated by postsynaptic nAChRs on orexin neurons and presynaptic nAChRs on glutamatergic terminals. ACh enhanced the firing rate in a subset of orexin neurons through postsynaptic nAChRs. The authors concluded that α4β2* and, to a lesser extent, α7 subunits contribute to this response. In another study by Pasumarthi and Fadel [118], a single dose of nicotine administration into the LHA increased ACh and glutamate release from axon terminals, which in turn may regulate orexin neuron activity. Furthermore, pretreatment with systemic OX-R1 antagonists blocked nicotine-induced anxiogenic effects and the activation of CRH neurons, which expressed OX-R1 [119].

In conclusion, there appears to be a reciprocal relationship between nicotinic and orexinergic systems. Nicotinic receptors located on the orexin neurons in the LHA may regulate CRH neuron activity. On the other hand, the rewarding properties of nicotine are modulated by orexins, which are released under stress and increase HPA axis activity and the autonomic responses.

5. MELANIN CONCENTRATING HORMONE

Melanin concentrating hormone (MCH) is involved in the regulation of energy homeostasis (*i.e*. feeding and metabolism), sleep/wakefulness, anxiety and the HPA axis [120-122]. Similar to orexin neurons, MCH-synthesizing neurons are found principally in the LHA with widespread projections throughout the central nervous system [123]. In the LHA, orexin and MCH neurons constitute distinct neuronal populations [124].

MCH-IR fibers are demonstrated in the PVN [125]. Furthermore, MCH receptor 1 expression is found on parvocellular PVN CRH neurons [126]. MCH increases CRH release from hypothalamic explants [127]. ICV [127-129] and intra-PVN [127] MCH injections increase plasma ACTH and CORT. On the contrary, there are studies which show that ICV MCH inhibited ACTH release induced by stress such as mild handling [130] or ether stress [131]. Additionally, stress regulates MCH expression, indicating a possible role during the stress response. MCH responses under stress may vary according to the type of stressor encountered. Chronic restraint stress increased MCH immunoreactivity in the LHA [132], whereas chronic footshock stress decreased MCH mRNA levels in the hypothalamus [133].

In vitro studies showed that the cholinergic agonist carbachol increased MCH mRNA in hypothalamic slices, an effect that was abolished by hexamethonium [134]. In parallel, Chang *et al*. [135] showed that prenatal nicotine exposure increased MCH mRNA levels and MCH-IR cells in the perifornical lateral hypothalamus. Anatomical studies also support the nicotinic regulation of MCH. ChAT-positive [134] and vesicular ACh transporter containing nerve fibers are located in close proximity with MCH neurons [136]. Bayer *et al*. [134] reported that most of the ChAT-positive axons in the LHA originated in the laterodorsal and pedunculopontine tegmental nuclei of the brainstem. Moreover, high levels of nicotinic receptors (α2, α4, α7, β2) are expressed in the LHA [32, 137]. Jo *et al*. [136] suggested that endogenous ACh and nicotine enhances GABAergic transmission and inhibits LHA MCH neurons *via* activation of presynaptic α7 nicotinic receptors. All of these data imply that nAChRs in the LHA may exert control over CRH neurons (hence the HPA axis) *via* modulation of LHA MCH neuron activity.

6. PRO-OPIOMELANOCORTIN AND α-MELANOCYTE STIMULATING HORMONE

Pro-opiomelanocortin (POMC) is a polypeptide that is cleaved by converting enzymes to produce peptide products, including melanocortins. Melanocortins are involved in feeding, sexual behavior and stress [138]. POMC is synthesized in two principle sites in rodent brain: ARC nucleus in the hypothalamus and nucleus tractus solitarius in the brainstem (reviewed in [139]). Hypothalamic ARC nucleus harbors two main groups of neuropeptide co-expressing neurons: POMC/cocaine-and amphetamine-regulated transcript (CART) [140] and neuropeptide Y (NPY)/agouti-related peptide (AgRP) [141]. In the hypothalamus, as mentioned above, POMC is cleaved to yield several biologically active peptides such as melanocortins [*e.g*. α-melanocyte stimulating hormone (α-MSH)] and the opioid peptide, β-endorphin [142]. Alpha-MSH binds to the melanocortin 3 (MC3R) and melanocortin 4 (MC4R) receptors, which are the main melanocortin receptor subtypes expressed in the brain [143]. α-MSH plays important roles in the regulation of appetite, energy balance, reward and HPA axis activity [139, 144]

Hypothalamic CRH neurons in the PVN receive extensive innervation from POMC neurons located in the ARC [145]. In parallel, melanocortin 4 receptors (MC4R) are expressed on PVN CRH neurons [146]. There are conflicting results regarding the regulatory action of α-MSH on HPA axis activity. Administration of α-MSH to the rat hypothalamic explants increased CRH release when compared to the basal release [147]. Acute ICV injection of melanocortin receptor agonists activated the HPA axis, induced PVN CRH gene transcription [146] and increased plasma CORT both in control rats and stressed rats [146, 148]. Furthermore, intra-PVN injection of an α-MSH analogue increased plasma ACTH and CORT [147]. On the other hand, there are also studies which suggest that α-MSH supresses the HPA axis activity [149-153]. Additionally, stress has been shown to regulate POMC expression. Acute restraint stress increases [154, 155], whereas acute and chronic immobilization stress decreases POMC [156, 157] in the ARC nucleus.

Chronic nicotine exposure also yielded apparently conflicting results. Both up-regulation [158-160] and down-regulation [7, 161, 162] of the POMC mRNA in the ARC has been reported in response to chronic systemic nicotine administration. Additionally, maternal nicotine exposure during lactation increased α-MSH-containing fibers in the PVN [163]. Immunocytochemistry studies show that cholinergic axons innervate ARC POMC neurons [164]. This indicates that endogenous ACh may signal through nicotinic receptors in the ARC nucleus to regulate POMC expression. Indeed, electrophysiological studies demonstrated that nicotine excites hypothalamic POMC neurons in mice through activation of α4β2 and α7 nAChRs present on these neurons [164]. In this patch clamp study, nicotine depolarized the membrane and increased spike frequency of POMC neurons in hypothalamic slices. Mineur *et al*. [165] also reported that POMC neurons in the ARC nucleus express β4 nAChRs and signaling through α3β4 nAChRs activates POMC neurons, which leads to the activation of MC4Rs in the PVN. Taken together, these data suggest that regulation of the HPA axis through nicotinic receptors located on POMC neurons is possible.

7. COCAINE- AND AMPHETAMINE-REGULATED TRANSCRIPT

Cocaine- and amphetamine-regulated transcript (CART) peptide is involved in the regulation of reward and reinforcement [166], feeding [167], endocrine and autonomic regulation [168, 169], anxiety [170], and stress [171]. In 1995, Douglass *et al*. [172] described CART mRNA as a transcript that increases after acute administration of cocaine and amphetamine, in the striatum of rat brain. CART was a novel cDNA with no significant homology to any known cDNA. Later, CART peptide fragments were identified in the brain [173] and accepted as mediators of the interaction between stress, addiction and feeding [171]. Anatomical studies show that CART neurons are widely distributed throughout the brain [174]. In the hypothalamus, CART mRNA and peptides are highly expressed in the medial parvocellular PVN, ARC and LHA [174, 175].

Functional studies demonstrate that CART regulates HPA axis activity [171]. ICV CART injections induce c-Fos expression in the CRH-synthesizing PVN neurons [176]. Addition of CART peptides increases CRH release from hypothalamic explants [177]. In parallel, ICV and intra-PVN CART injections increase blood ACTH and CORT levels

[177]. Interestingly, there is a bidirectional relation between glucocorticoids and CART. Studies show that CORT regulates CART mRNA expression and CART immunoreactivity in the hypothalamus [178, 179]. Additionally, various psychological and physical stress procedures affect CART expression in the hypothalamus [180-187].

Systemic nicotine injections regulate hypothalamic CART expression and reduce body weight. Acute (two days) systemic nicotine treatment increased CART-IR cells and fibers in the PVN, CART-IR fibers in the ARC [188] and CART mRNA in the PVN [189]. Chronic systemic nicotine treatment also enhanced CART mRNA in the hypothalamus while reducing body weight [159]. However, maternal nicotine exposure during lactation decreased CART-IR cells in the PVN [163]. In the ARC, 90% of the CART neurons co-express POMC [140]. Furthermore, axon varicosities which co-contain CART and α-MSH are demonstrated in close apposition to PVN CRH nerons [190]. Additionally, CART neurons in the LHA and perifornical area also innervate the PVN [191] and 70% of the CART neurons in this area co-express MCH [192]. High level of CART co-expression with these two neuropeptides implies that nicotinic regulation of CART in the ARC nucleus and LHA is also possible. Consequently, HPA axis activity may be altered through nicotinic regulation of CART in the ARC or LHA.

8. NEUROPEPTIDE Y AND AGOUTI-RELATED PEPTIDE

Neuropeptide Y (NPY) has important roles in food intake, energy homeostasis, sleep, anxiety and the stress response [193-195]. NPY neurons are distributed widely in rodent brain [196]. The highest NPY mRNA levels are found in the ARC nucleus [197]. On the contrary, agouti-related peptide (AgRP)-synthesizing neurons are restricted to the hypothalamic ARC nucleus [198]. 95% of ARC NPY neurons co-express AgRP [199]. Initially, AgRP proteins were described by their important role in controlling body weight and leptin signaling [200]. Later, in addition to its role in the regulation of feeding behavior, AgRP is indicated in reward and HPA axis activity [144, 201]. NPY mainly binds to Y1, Y2 and Y5 receptors in the brain (reviewed in [195]). On the other hand, AgRP binds to MC3R and MC4R with high affinity and acts as a competitive antagonist of α-MSH at these receptors [200].

NPY/AgRP neurons highly innervate parvocellular CRH neurons in the PVN [145, 202] and 80% of PVN CRH neurons express NPY Y1 receptors [203]. Studies demonstrate contradictory results regarding the regulatory effect of NPY on HPA activity. *In vitro* studies show that NPY increased CRH release from rat hypothalamus [204]. In parallel, ICV NPY administration increased CRH gene expression, plasma ACTH and CORT levels [203, 205]. Furthermore, microinjection of NPY into the PVN also increased plasma ACTH and CORT levels [206]. On the other hand, an inhibitory action on HPA axis activity is indicated by several studies [207, 208]. AgRP may bind to the MC4Rs expressed on PVN CRH neurons and may regulate HPA axis activity. Indeed, AgRP administration to the hypothalamic explants elevated CRH and AVP release and injection of AgRP into the PVN increased plasma ACTH levels in rats [147]. ICV AgRP treatment increased basal ACTH and cortisol release also in primates [209]. Furthermore, in this study, ICV AgRP enhanced interleukin-1 beta-induced ACTH levels.

Various stress procedures regulate NPY and AgRP expression in the ARC. Acute restraint [210], immobilization [211] and inescapable footshock stress [148] upregulated NPY mRNA in the ARC nucleus. Data regarding the effects of chronic stress is contradictory. One study showed an increase in the ARC NPY mRNA levels [211], whereas another showed a decrease in the ARC NPY immunoreactivity [212] following chronic immobilization stress. On the other hand, AgRP mRNA levels and the number of AgRP-IR cells decreased in the ARC nucleus with acute inescapable footshock stress [148] and acute restraint stress [213], respectively. Chronic footshock stress upregulated AgRP mRNA [214], whereas chronic restraint stress downregulated the number of AgRP-IR cells in the ARC [213]. Interestingly, some of the AgRP neurons are innervated by PVN CRH neurons and express CRH-R1 type receptors [215]. This may be one factor contributing to the stress-induced AgRP response.

Regulation of the HPA axis through nicotinic receptors located on ARC NPY/AgRP neurons is possible. Nicotine regulates NPY neurons in hypothalamus. Acute systemic nicotine exposure decreased hypothalamic NPY mRNA and ARC NPY immunoreactivity [216]. Similarly, acute ICV administration of nicotine reduced ARC NPY immunoreactivity [217]. By contrast, Rangani *et al*. [218] reported that acute systemic nicotine treatment enhanced and restored colchicine-induced reduction in ARC NPY-IR cells to basal levels. Studies report conflicting results regarding the effects of chronic nicotine treatment on ARC NPY. Some studies showed that chronic systemic nicotine administration in rats increased hypothalamic NPY mRNA levels [216, 219]. However, Martínez de Morentin *et al*. [162] reported a decrease in ARC NPY mRNA expression. Chronic maternal nicotine exposure reduced ARC NPY mRNA also in newborn monkeys [220]. On the other hand, chronic systemic nicotine decreased ARC NPY immonureactivity in some studies [216, 217] and increased in another [219]. In the literature, several studies also investigated the effect of nicotine on hypothalamic AgRP expression. Some of these studies [158, 159] reported that chronic systemic nicotine treatment increased AgRP mRNA expression in rodent hypothalamus, whereas Martínez de Morentin *et al*. [162] reported a reduction in ARC AgRP mRNA expression. In the study by Younes-Rapozo *et al*. [163], maternal nicotine exposure during lactation did not change the number of AgRP-IR cells in the ARC nucleus of adult progeny. Some anatomical and electrophysiological findings also support the nicotinic regulation of NPY/AgRP neurons in the ARC nucleus. Cholinergic axons terminate on NPY neurons [164] and nicotinic receptors (α4, α7, β2) are expressed in the ARC nucleus [13, 137, 221]. Furthermore, nicotine depolarized NPY neurons, and increased the frequency of action potentials through α4β2 and α7 nicotinic receptors in hypothalamic ARC slices [164]. Based on the observation that NPY neurons highly coexpress AgRP in the ARC nucleus, it is possible that these nicotinic receptors may also regulate AgRP activity. In parallel, Huang and Winzer-Serhan [158] showed that chronic systemic nicotine administration in-

creased both NPY and AgRP mRNAs, an effect that was blocked by α4β2 nAChR antagonists.

Different groups, using different types of stressors and different nicotine exposure regimens, have investigated the regulation of NPY and AgRP neuron activity by nicotine during the stress response. However the results are somewhat contradictory and preclude reaching definite conclusions. Further research in this field is warranted.

9. OPIOID PEPTIDES

Opioid peptides play essential roles in diverse physiological processes such as pain, feeding behavior, learning and memory, reward and stress [222-226]. Endogenous opioid peptides, β-endorphin, enkephalins and dynorphins are derived from three precursor peptides in the brain: POMC, proenkephalin (PENK) and prodynorphin (PDYN), respectively. As mentioned above, the one principle site for POMC-expressing neurons in the brain is the ARC nucleus in the hypothalamus. β-endorphin is released from the axon terminals of ARC POMC neurons [227]. On the other hand, the expression sites for PENK and PDYN mRNAs are more widespread in the rodent brain. PENK mRNA is highly expressed in the hypothalamus, especially in the anterior nucleus, parvocellular PVN, ventromedial nucleus, LHA and perifornical area [228]. Hypothalamus also displays intense PDYN mRNA labeling. Among the regions expressing the highest levels of PDYN mRNA are the magnocellular PVN, supraoptic nucleus, ventromedial and dorsomedial hypothalamic nuclei, LHA and perifornical area [229]. Interestingly, enkephalin is co-expressed in 20% of PVN CRH neurons and CRH is co-expressed in 40% of PVN enkephalin neurons [230]. Paraventricular CRH neurons also co-express dynorphin immunoreactivity [231]. Endogenous opioid peptides exert their effects via, μ- (MOR), δ- (DOR), and κ- (KOR) opioid receptors. MORs and DORs are the main receptors for β-endorphin and enkephalins. β-endorphin binds with a higher affinity to MOR, whereas enkephalins have a higher affinity for DOR [232]. Dynorphins are the main endogenous ligands for KOR [233].

β-endorphin, enkephalin and dynorphin-containing neurons innervate the PVN [234, 235]. In parallel, MOR, DOR and KOR mRNAs are expressed in the PVN [236, 237]. Additionally, MOR-IR and KOR-IR fibers are also present in the PVN [238, 239]. Opioid peptides are generally considered as inhibitors of the HPA axis by many studies. ICV [240] or intra-PVN [241] administration of β-endorphin or dynorphin decreased CRH secretion. Furthermore, ICV β-endorphin blocked the hypotension induced elevation of CRH [240]. Addition of β-endorphin and other MOR agonists, enkephalin analogs, or KOR agonists suppressed *in vitro* release of CRH from the hypothalamus [242, 243]. However, there are other studies, which show the excitatory effects of opioid peptides on the HPA axis. These studies showed that β-endorphin and other MOR agonists, enkephalin analogs or KOR agonists increased CRH release from hypothalamus *in vitro* [244-246]. ICV administration of β-endorphin in rats increased PVN CRH mRNA [247], plasma ACTH [248] and CORT [249]. Furthermore, ICV anti-β-endorphin gamma globulin injection attenuated restraint stress-induced ACTH increase [248]. Acute ICV administration of MOR-and DOR agonists increased plasma ACTH and CORT in rats, whereas chronic treatments led to tolerance [250, 251]. ICV enkephalin administration also potentiated mild stress-induced plasma ACTH and CORT elevations [252].

Studies show that opioid peptides and their mRNAs are regulated by stress. Psychological stress such as tail-pinch and fox odour [253] or forced walking stress [254] significantly increased β-endorphin in the ARC nucleus. However, conditioned fear-induced stress decreased β-endorphin levels in the hypothalamus [255]. Cold stress, a type of physical stress, enhanced β-endorphin immunoreactivity and reduced dynorphin immunoreactivity in the hypothalamus [256]. Acute footshock stress increased dynorphin immunoreactivity in the hypothalamus [257]. Environment-induced conditioned suppression of motility and forced swimming-induced immobility increased dynorphin and decreased met- and leu-enkephalin levels in the hypothalamus [258]. In parallel, prolonged single housing down-regulated met-enkephalin-Arg(6) Phe(7) levels in the hypothalamus [259]. However, chronic mild stress increased enkephalin gene expression in the PVN of hypothalamus [260]. Chronic variable stress [261] and social deprivation [262] also increased enkephalin mRNA and immunoreactivity in the hypothalamus. Additionally, maternal separation increased Met-enkephalin-Arg6Phe7 levels in the hypothalamus. These findings indicate that the response of the opioidergic systems to stress varies according to the type of stress encountered.

Approximately 90% and 30% of the orexin neurons in the LHA contain dynorphin and enkephalin, respectively [263, 264]. Additionally, 30% of POMC neurons in the ARC co-express dynorphin [265]. A substantial amount of evidence indicating the presence of nicotinic receptors on the ARC POMC neurons and LHA orexin neurons implies that nicotinic regulation of β-endorphin and enkephalin synthesis in the ARC nucleus and LHA is possible. Consequently, nicotine may also regulate the opioid peptide release from the axon terminals of these neurons in the PVN and modulate HPA axis activity. Indeed, numerous studies demonstrate that systemic nicotine administration changes the opioid peptide and mRNA levels in the hypothalamus. Acute nicotine injections increased β-endorphin release from hypothalamic cultures, whereas the response desensitized with the chronic treatment [266]. *In vivo* studies showed that acute and chronic systemic nicotine treatments decreased β-endorphin content in the hypothalamus [161, 267]. Höllt and Horn [268] reported that acute systemic nicotine injection and chronic systemic nicotine infusion *via* osmotic minipump for 4 days increased PDYN mRNA levels in the whole hypothalamus [268], whereas in other studies an opposite finding was obtained. Isola *et al*. [269] showed that chronic systemic nicotine injections for 14 days decreased dynorphin immunoreactivity in the hypothalamus. We [270] also observed decreased PDYN mRNA expression in the LHA following chronic systemic nicotine injections for 6 days. Acute and chronic systemic nicotine administration did not change PENK mRNA [268] or [met5]-enkephalin [267] in the hypothalamus. Also, six nicotine injections repeated every 30 minutes did not alter met-enkephalin levels in the hypothalamus [271]. However, these studies used whole

hypothalamus and did not analyze subregional effects. On the other hand, enkephalinergic cells localized in the hypothalamic PVN may be yet other targets for nicotine. Nicotine administration by gavage for 5 days increased enkephalin mRNA in the PVN [272]. In parallel, Loughlin *et al*. [273] also showed that an acute single dose of nicotine induced c-fos expression in the enkephalin cells of PVN. Although the evidence mentioned above supports the possibility that opioidergic signaling in the hypothalamus may participate in the nicotine-induced activation of the HPA axis activity, there are some studies that argue the opposite. These studies reported that systemic injection of opioid receptor antagonists, naloxone or naltrexone, did not suppress nicotine or epibatidine (an agonist of nAChR)-induced blood CORT levels [57, 274]. However, when selective KOR antagonists are injected, nicotine-induced CORT elevations were blocked in rats [275].

Human studies also show that chronic nicotine exposure regulates the HPA axis activity through altered opioid signaling. Stress responses are reduced in smokers and stress increases the vulnerability to relapse in those who quitted [276]. Opioid receptor antagonists increase serum ACTH levels both in smokers and nonsmokers with smokers exhibiting less ACTH elevation than nonsmokers [277].

While various stressors affect the hypothalamic opioidergic systems differently, the effect of nicotine on opioid signaling is also inconsistent. Different opioidergic peptides, acting on different receptors located in the hypothalamus and different routes and durations of nicotine administration employed in reported findings preclude making direct comparisons. Future research may elucidate the effect of nicotine and the nicotinic cholinergic system on opioidergic activity in the hypothalamus during the stress response.

CONCLUSION

Hypothalamus and hypothalamic neuroactive peptides are key players in the stress response, which is the major survival tool an organism possesses. These peptides not only integrate the stess response, but also mediate in other physiological functions, including, but not limited to feeding and energy balance, reward, autonomic responses, sleep/wakefulness, and sexual behavior. The localization and connections of the neuropeptide neurons, their receptors and mRNAs within the hypothalamic nuclei provide clues to their functions and interactions. The nicotinic cholinergic system is apparently one of the major modulators of the HPA axis and there is substantial evidence supporting its regulatory role in the hypothalamus on the neuractive peptides discussed in this review. However, most of the studies showing the nicotinic regulation of hypothalamic neuropeptides have employed systemic administration of nicotine. Currently, we know little about the nicotinic receptor distribution on neuropeptide-synthesizing neurons in the hypothalamus and the physiological responses they trigger in these neurons. In addition, the effects of selective nicotinic agonists/antagonists on the HPA axis activity should be investigated with administration of the drugs directly into the discrete hypothalamic nuclei during basal and stress-induced conditions. Although sex, region and stressor type related differences are observed, based on our current understanding, overall nicotine and the nicotinic cholinergic system evidently supports the HPA axis driven stress response and modulates the activity of the neuropeptides involved. However, considering the controversial reports in some cases, one should be cautious and avoid making generalizations. Especially studies that aim at elucidating the mechanisms underlying the nicotinic regulation of the hypothalamic neuropeptides directly through the hypothalamic nicotinic receptors are warranted for a clearer picture. Disturbed functioning of the HPA axis and hypothalamic neuropeptides results in pathologies such as depression, anxiety disorders and obesity, which are common and significant health problems. A better understanding of the hypothalamic peptides, their interrelations and their nicotinic regulation will also aid in drug development and provide means to cope with these diseases. Considering that nicotine, specifically in the form of tobacco products, is also an abused substance and the major cause of preventable deaths, a better understanding of the role of the nicotinic cholinergic system on the HPA axis will aid in developing improved therapeutic strategies for smoking cessation.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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