The role of histamine in the neuroendocrine regulation of pituitary hormone secretion

Ulrich Knigge and Jørgen Warberg

Department of Medical Physiology C, The Panum Institute, University of Copenhagen, 2200 Copenhagen N, Denmark

Abstract. The neurotransmitter histamine participates in the neuroendocrine regulation of pituitary hormone secretion by an indirect action at a hypothalamic level where histaminergic neurons are abundant. The effect of histamine is caused by activation of postsynaptic H₁ or H₂-receptors. Histamine stimulates the secretion of ACTH, β-endorphin (mediated by CRH and AVP), α-MSH (mediated by dopamine and peripheral catecholamines), and PRL (mediated by dopamine, serotonin and AVP), and participates in the stress-induced release of these hormones and possibly in the suckling- and estrogen-induced PRL release. The release of GH and TSH is predominantly inhibited by histamine; however, uncertainty exists regarding its role and the hypothalamic factors involved. Histamine increases the secretion of LH in females (mediated by GnRH), and may be involved in the mediation of the estrogen-induced LH surge. AVP and oxytocin are stimulated by histamine, probably by an effect in the supraoptic and paraventricular nuclei of the hypothalamus.

Histamine acts as a neurotransmitter in the central nervous system (1-2). As other aminergic transmitters, neuronal histamine has an uneven distribution with the highest concentration in the hypothalamus; its turnover is rapid and is increased by several stimuli including stress and opiates. Earlier lesion experiments (2) and recent immunohistochemical studies in rats using antibodies directed against histamine (3) or the histamine synthesizing enzyme histidine decarboxylase (4) have shown that the histaminergic perikarya are exclusively located in the posterior hypothalamus. Varicose axons project rostrally to other hypothalamic and extrahypothalamic areas as well as caudally to the spinal cord. The network of histaminergic nerve fibres is dense in the hypothalamic regions where hypophysiotropic releasing hormones are synthesized, i.e. the preoptic, suprachiasmatic and periventricular areas, and the supraoptic, paraventricular, ventromedial and arcuate nuclei (3,4). The internal ependymal zone of the median eminence as well as the neurohypophysis contain some nerve fibres, whereas few or no fibres are seen in the external capillary zone of the median eminence (3,4), which is the region where hypothalamic releasing hormones are secreted to the pituitary portal blood. The median eminence has a high content of histamine, which is predominantly localized in mast cells. Autoradiographic studies have demonstrated a high density of postsynaptic H₁-receptors in the hypothalamus and revealed a good correlation between the density of H₁-receptor binding sites and the distribution of histaminergic nerve fibres (5). Postsynaptic H₂- and presynaptic H₂-receptor bindings sites are also present in the hypothalamus (6-8), but their density seems to be lower than that of H₁-receptors, and a detailed mapping of their hypothalamic localization has not been reported. Electrophysiological experiments have shown that microinfusion of histamine induces both excitatory (generally H₁-receptor mediated) and inhibitory (generally H₂-receptor mediated) responses in different hypothalamic areas (1,2).

As a neurotransmitter histamine may participate in hypothalamic control of various autonomic functions, including drinking and eating behaviour, thermoregulation, regulation of blood pressure,
and nociception (1). In addition, several studies have shown that histamine is involved in the neuroendocrine regulation of pituitary hormone secretion. These investigations have taken advantage of the development of several compounds which either specifically affect histamine synthesis or metabolism or specifically bind to histamine receptors as agonists or antagonists.

This review is based on recent findings which support the involvement of histaminergic neurons in the neuroendocrine regulation of pituitary hormone secretion (Table 1).

It is evident that histamine affects the secretion of the pituitary hormones in concert with several other important aminergic or peptidergic factors which may exert an indirect – as histamine – or a direct effect on the pituitary gland.

**Pro-opiomelanocortin-derived peptides**

The peptides ACTH, β-lipotropin, β-endorphin (β-END) and α-MSH are derived from the common precursor, pro-opiomelanocortin (POMC). The corticotropes in the anterior pituitary lobe contain larger forms of the POMC-derived peptides (ACTH and β-lipotropin) and some β-END, whereas the melanotropes in the intermediate lobe contain further processed peptides (α-MSH and β-END). The corticotropes are stimulated by CRH from the paraventricular hypothalamic nucleus and AVP from the paraventricular and supraoptic nuclei of the hypothalamus, whereas they are inhibited by the adrenal steroids. In contrast, the melanotropes are only to some extent stimulated by CRH, but are under predominant tonic inhibition by tuberohypophysial dopaminergic neurons originating in the hypothalamic arcuate and periventricular nuclei. The adrenal steroids have no effect on cells in the intermediate lobe. Central as well as peripheral catecholamines participate in the regulation of the release of POMC-derived peptides.

**ACTH**

Systemic as well as central infusion of histamine has been found to stimulate the release of ACTH or corticosterone in experimental animals (9-12). It seems evident that histamine increased ACTH secretion via activation of both H1- and H2-receptors, although contradicting results, probably owing to differences in the experimental protocols, have been obtained (9-12).

Histamine had no effect on the ACTH release from incubated pituitary tissue (13), suggesting that the effect of histamine was exerted at a hypothalamic level. CRH and AVP may be involved in the mediation of the response to histamine since pretreatment of rats with antiserum to these peptides prevented the histamine-induced ACTH release (Kjær et al., unpublished observations), and since histaminergic nerve fibres and H1-receptor binding sites are abundant in the paraventricular and supraoptic nuclei (3-5). However, it is possible that the action of the two hypothalamic peptides is permissive, i.e. that the presence of CRH and AVP is required for histamine to affect ACTH secretion.

It has been proposed that catecholamines via central α-receptors or peripheral β-receptors mediate at least part of the adrenocortical response to centrally infused histamine (12, Knigge et al., unpublished observations). The latter suggestion is supported by the findings that histamine infused centrally increased the plasma level of norepinephrine and epinephrine by activation of H1- and H2-receptors (14), and that peripheral catecholamines from the adrenal medulla may participate in the regulation of ACTH secretion via β-receptor activation.

Glucocorticoids may exert a negative feed-back effect on the release of brain histamine, since corticosterone increased the hypothalamic histamine content in male rats (15), and glucocorticoids decreased the turnover of histamine in brain synaptosomes (16).

**β-endorphin**

Histamine stimulated the release of β-END and β-lipotropin in male rats. Following systemic administration, the effect of histamine was mediated by H1-receptors (17), whereas the effect of centrally infused histamine was mediated by H1- and H2-receptors (9). The β-END release induced by histamine or by an H1- or an H2-receptor agonist was partly inhibited by dexamethasone or the dopamine agonist bromocriptine (Knigge et al., unpublished observations). Since dexamethasone only affects the anterior lobe, whereas bromocriptine selectively acts in the neurointermediate lobe, the results indicate that histamine by binding to H1- and H2-receptors stimulates the release of β-END from both lobes.

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Central administration of histamine stimulated the release of \(\alpha\)-MSH in male rats. The effect was abolished by central infusion of \(H_1\) or \(H_2\)-receptor antagonists (18). Histamine may affect the release of \(\alpha\)-MSH at the hypothalamic level, but the media-

### Table 1.
Effect of histamine on pituitary hormone release.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Effect of histamine</th>
<th>Involved receptor</th>
<th>Putative mediating transmitter</th>
<th>Possible site of histamine action</th>
<th>Physiological events involving histamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>↑</td>
<td>+ ++</td>
<td>CRH (↑) AVP (↑)</td>
<td>N. paravent. N. supraopt.</td>
<td>Stress</td>
</tr>
<tr>
<td>β-END</td>
<td>↑</td>
<td>+ ++</td>
<td>CRH (↑) AVP (↑) DA? (↓) Periph. CA (↑)</td>
<td>N. paravent. N. supraopt. N. arc. N. arc.</td>
<td>Stress</td>
</tr>
<tr>
<td>(\alpha)-MSH</td>
<td>↑</td>
<td>+ ++</td>
<td>DA? (↓) Periph. CA (↑)</td>
<td>N. arc.</td>
<td>Stress</td>
</tr>
<tr>
<td>PRL</td>
<td>↑</td>
<td>+ ++</td>
<td>DA? (↓) (iv) 5-HT (↑) AVP (↑)</td>
<td>N. arc. N. paravent. N. supraopt. M.E.</td>
<td>Stress, Suckling E-induced surge</td>
</tr>
<tr>
<td>GH</td>
<td>↓ (icv) ↑ (iv)</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>Stress?</td>
</tr>
<tr>
<td>TSH</td>
<td>↓</td>
<td>+</td>
<td>TRH (↑?) Perivent. and Paravent. area</td>
<td>N. supraopt. Ant. hyp. area N. arc. (*)</td>
<td>Stress?</td>
</tr>
<tr>
<td>LH</td>
<td>↑ (♀) + +</td>
<td>+</td>
<td>GnRH (↑)</td>
<td>N. preopt. Ant. hyp. area N. arc. (*)</td>
<td>E-induced surge</td>
</tr>
<tr>
<td>FSH</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxytocin</td>
<td>↑ (iv)</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>Suckling? Stress?</td>
</tr>
</tbody>
</table>

↑: stimulatory, ↓: inhibitory - : or no effects of histamine. 
+ : receptor involved; ++: predominant receptor involved. 
iv: intravenous administration of histamine. 
icv: intracerebroventricular or iv: intravenous administration of histamine. 
DA: dopamine; Periph. CA: peripheral catecholamines; E: estrogen. 5-HT: Serotonin. 
Ant. hyp. area: Anterior hypothalamic area; N.arc.: arcuate nucleus; M.E.: median eminence; N. paravent.: paraventricular nucleus; N.preopt.: preoptic nucleus; N.supsaopt.: supraoptic nucleus; Perivent. area: periventricular area; Post. pit.: posterior pituitary gland. 
*: some species.
tors involved are unknown at present. Since bromocriptine pretreatment prevented the α-MSH response to histamine, it is possible that the effect of histamine is mediated via the tuberohypophysial dopaminergic system (18). This is further supported by the presence of histaminergic fibres in the arcuate and periventricular areas (3,4).

It is likely that histaminergic neurons participate in the hypothalamic mediation of stress-induced release of the POMC-derived peptides in rats. However, discrepant results have been obtained. Pretreatment with H1- or H2-receptor antagonists inhibited the ACTH, β-END and α-MSH response to stress (18,19), whereas the antagonists had no effect on the stress-induced release of ACTH bioactivity or corticosterone (20). We have recently found that pretreatment with R(α)methyl histamine, which is a specific agonist at presynaptic H3- autoreceptors, inhibited the ACTH response to stress, whereas elevation of the neuronal histamine content by SKF-91488, which inhibits the enzymatic degradation of histamine, stimulated basal and enhanced the stress-induced ACTH and α-MSH release (18). Furthermore, depletion of the neuronal histamine content by (S)α-fluoro-methylhistidine (α-FMH), which inhibits the enzymatic histamine synthesis, decreased stress-induced release of ACTH, β-END, α-MSH and corticosterone in male rats (Fig. 1) (18,21), and affected the circadian rhythm of ACTH and corticosterone secretion in female rats (22). However, in other studies α-FMH had a minor or no effect on the stress response of the adrenocortical axis (20,22).

**Conclusion**

The majority of the studies indicate that histamine indirectly via activation of hypothalamic H1- and H2-receptors participates in the regulation of ACTH, β-END, and α-MSH secretion. The effect of histamine on the anterior lobe POMC-peptides is possibly mediated by CRH and/or AVP, whereas the effect on the intermediate lobe POMC-peptides may occur via tuberohypophysial dopaminergic neurons and peripheral catecholamines. Histaminergic neurons in the hypothalamus seem to be involved in the stress-induced release of the POMC-derived peptides.

**Prolactin**

PRL secretion is under tonic inhibitory hypothalamic control. The main PRL-inhibiting factor is dopamine, which is released to the pituitary portal blood from tuberoinfundibular dopaminergic neu-
rons originating in the arcuate nucleus. In addition, several other amines or peptides have been indicated as putative hypothalamic PRL-releasing factors.

Central as well as systemic infusion of histamine stimulated PRL secretion in many species including man (23). A supraptuitary site of action is evident, since histamine infused iv had no effect on PRL secretion in rats with transection of the pituitary stalk (24), and since histamine stimulated PRL secretion from incubated pituitary tissue only when this was co-incubated with hypothalamic tissue (24,25).

In rats both H₁- and H₂-receptors are involved in the mediation of the histamine-induced PRL release. However, the type of receptor involved depends on the route of administration of histamine. The effect of systemic infusion of histamine was mimicked by H₁-receptor agonists and inhibited by H₁-receptor antagonists, whereas the effect of central administration of histamine was mimicked by H₂-receptor agonists and inhibited by H₂-receptor antagonists (24,26-28). In humans, the response to iv infused histamine was mediated via H₁-receptors, since it was blocked by the H₁-receptor antagonist mepyramine but not by the H₂-receptor antagonist cimeditine (29). It has therefore been suggested that histamine when administered systematically stimulates PRL secretion via activation of H₁-receptors located in hypothalamic areas outside the blood-brain barrier and when administered centrally stimulates PRL secretion via activation of H₂-receptors located in other hypothalamic areas (24).

The effect on PRL secretion is not caused by the profound vascular actions of histamine (23), but by interaction with hypothalamic aminergic or peptidergic factors. In rats, central or systemic administration of histamine decreased the dopamine concentration in the pituitary portal blood by 25-30% (30,31). Pretreatment with dopamine receptor antagonists prevented the PRL response to systemically infused histamine in rats and in normal men, whereas the antagonists had no significant effect on the PRL increase induced by centrally administered histamine in rats (29,31). These results indicate that dopamine as well as other factors are involved in the mediation of the histamine-induced PRL release.

Serotonin (5-HT) is a potent stimulator of PRL secretion, and histamine increases the release of hypothalamic 5-HT. Blockade of serotonergic receptors inhibited the PRL response to centrally or systemically administered histamine and H₁- and H₂-receptor agonists (32), indicating that the histamine-induced PRL release involved the serotonergic system. The serotonergic neurons involved in the pituitary hormone secretion originate in the raphe nuclei of the brain stem. H₁-receptor binding sites have been identified in the raphe nuclei (5), indicating a possible site of action for histamine in these nuclei. However, only very few or no histaminergic fibres have been shown in the raphe nuclei (3,4). It is more likely that histaminergic neurons interact with the serotonergic system in the hypothalamus, e.g. the median forebrain bundle or the paraventricular or arcuate nuclei.

AVP may play a role in histamine-induced PRL secretion, since histamine stimulates the release of AVP (see later), which has PRL-releasing activity. Pretreatment with antiserum to AVP or with an AVP receptor antagonist inhibited the PRL response to centrally infused histamine (33). This indicates that AVP participates in the mediation of the PRL response to histamine. In contrast, pretreatment with a specific oxytocin receptor antagonist did not affect the PRL response to histamine (33).

The involvement of histamine in stress-induced PRL release is well established. Blockade of histamine synthesis (Fig. 1) or postsynaptic H₁- or H₂-receptors or activation of presynaptic H₂-autoreceptors inhibited the PRL response to restraint and ether stress in male rats (20,33,34, Søe-Jensen et al., unpublished observations), whereas blockade of central histamine degradation augmented basal and stress-induced PRL release (33). In addition, histaminergic nerve fibres as well as H₁-receptor binding sites are abundant in the paraventricular nucleus, which has been shown to participate in the mediation of the stress response (35).

In female rats, histamine may be involved in the mediation of the estrogen-induced PRL surge, since this response was blocked by injection of H₁- or H₂-receptor antagonists into the hypothalamus (36). In lactating rats, histamine seems to participate in the mediation of the suckling-induced PRL release, since this response was inhibited by an H₁-receptor antagonist (37). However, these findings need to be confirmed. It has recently been suggested that histamine may be involved in the mediation of the opiate and serotonergic regulation of PRL secretion (38).
Conclusion
Histaminergic neurons participate in the hypothalamic regulation of PRL secretion. The PRL stimulatory effect of histamine is indirect and occurs via H2-receptors in some areas of the hypothalamus and via H1-receptors in other areas of this region. The action of histamine is mediated by dopaminergic, serotonergic and vasopressinergic neurons. Histamine is involved in the stress-induced PRL release and may play a role in the mediation of the PRL response to estrogen and suckling.

Growth hormone
The secretion of GH is regulated from the hypothalamus by stimulatory and inhibitory inputs primarily exerted by GHRH from the arcuate and ventromedial nuclei and somatostatin from several hypothalamic areas. In addition, other hypothalamic peptides and amines take part in the regulation. The overall hypothalamic effect on GH secretion is stimulatory.

Histamine affects GH secretion indirectly, but different results have been obtained concerning its net influence. Central infusion of histamine to male rats inhibited the pulsatile GH secretion and the GH response to morphine (39). The inhibitory effect seems mediated via H1-receptors as it was mimicked by H1-receptor agonists and prevented by H1-receptor antagonists. The involvement of H2-receptors seems more controversial, since the GH response to morphine was inhibited by both agonists and antagonists to H2-receptors (39). Treatment of the animals with antiserum to somatostatin had no effect on the histamine-induced inhibition of GH secretion, suggesting that histamine suppresses GH releasing factors.

Systemic administration of histamine increased the basal or GHRH-stimulated GH release in intact or estrogen/progesterone-primed male rats and in dogs. Some investigators found that the stimulatory effect of histamine primarily involved H1-receptors (28,40), whereas others found that the effect occurred by activation of H2-receptors (41). An interaction between the somatotropinergic and the histaminergic system at a central level has been suggested, since GHRH increased and somatostatin decreased the histamine concentration in the hypothalamus (42).

In humans, infusion of histamine or histaminergic compounds had no effect on basal GH secretion. However, whereas TRH does not influence GH during basal conditions, a stimulatory effect of TRH was observed during infusion with histamine in men and in women during the luteal phase (43,44). This histamine-induced paradoxical GH response to TRH was prevented by concomitant blockade of H1-receptors. An involvement of the histaminergic system in the regulation of GH secretion in man is supported by the finding that administration of H1- or H2-receptor antagonists inhibited the GH response to arginine or insulin (45,46).

Conclusion
Histamine may be indirectly involved in the control of GH secretion. The effect of histamine depends on the route of administration: a stimulatory effect following systemic and an inhibitory effect following central infusion. The GH response to histamine is primarily mediated by H1-receptors, whereas H2-receptors seem to play a minor role. The histamine-induced paradoxical GH response to TRH in normal subjects may be of interest, since such a GH response is frequently observed in patients with acromegaly, diabetes mellitus or uremia but is absent in healthy people.

Thyrotropin
The secretion of TSH is regulated from the hypothalamus by TRH from periventricular areas and the arcuate nucleus, and by the inhibiting hormone somatostatin. TSH is also affected by hypothalamic neurotransmitters and by the negative feedback effect of the thyroid hormones.

Central as well as intraperitoneal administration of histamine inhibited basal, TRH- or cold-stimulated TSH secretion in conscious male rats (47-48). An involvement of H2-receptors in the mediation of the inhibitory effect of histamine has been suggested (47), but has not been confirmed (48).

The TSH-inhibiting effect of histamine is not exerted at a pituitary level, but appears to be mediated by factors located in periventricular areas (48-49). This may involve TRH, although contradictory results have been obtained. Histamine increased the hypothalamic content of immunoreactive TRH in vivo, suggesting that histamine decreased TSH secretion by inhibition of hypothalamic TRH release (47). However, histamine increased the output of TRH from rat or sheep
hypothalamic slices and synaptosomes by activation of \( H_2 \)-receptors (50,51). The inhibitory effect of histamine on TSH secretion did not involve catecholaminergic, serotoninergic, GABAergic, cholinergic, or opiate neurons.

In humans, histamine or \( H_1 \)- or \( H_2 \)-receptor antagonists had no significant effect on TSH secretion (43).

Conclusion
The major part of the available evidence indicates that histamine exerts an inhibitory effect on TSH secretion in male rats, and may be involved in the mediation of the TSH response to cold stress. The effect of histamine is exerted in the hypothalamus probably by an action on TRH neurons. However, both inhibitory and stimulatory effects of histamine on TRH release have been reported.

Gonadotropins
The secretion of the gonadotropins, LH and FSH, is mainly regulated by GnRH from the preoptic nucleus and other anterior hypothalamic areas, and, in some species (e.g. primates), the arcuate nucleus. The gonadotropin secretion is also regulated by peripheral gonadal steroids and by hypothalamic aminergic or peptidergic neurotransmitters.

Central infusion of histamine stimulated the release of LH only in ovariectomized estrogen-progesterone-primed rats and in pro-estrous rats (52), but histamine did not affect FSH secretion. In humans, histamine had no effect on basal LH or FSH secretion, but enhanced the LH response to GnRH in men and in women during different phases of the menstrual cycle (53,54). The action of histamine may occur in the hypothalamus, since histamine stimulated the LH release from incubated pituitary fragments only in the presence of hypothalamic tissue (55).

Histamine affects LH secretion via \( H_1 \) as well as \( H_2 \)-receptors. An involvement of \( H_2 \)-receptors has been proposed, since LH secretion was stimulated by central administration of an \( H_2 \)-receptor agonist (27). In contrast, it was shown that the histamine-induced LH release from pituitaries co-incubated with hypothalamic fragments was mimicked by an \( H_1 \)-receptor agonist and blocked by an \( H_1 \)-receptor antagonist, whereas \( H_2 \)-receptor compounds had no effect (5). Recently, it was reported that only combined \( H_1 \) and \( H_2 \)-receptor blockade prevented the estrogen-induced LH surge in ovariectomized rats (56). In men, the enhancing effect of histamine on the GnRH-stimulated LH release was inhibited by \( H_1 \)- and \( H_2 \)-receptor antagonists (54).

In ovariectomized rats, injection of the histamine synthesis inhibitor \( \alpha \)-FMH or combined blockade of \( H_1 \) and \( H_2 \)-receptors prevented the estrogen-induced LH surge (36), which suggests that histaminergic neurons in the brain are involved in the mediation of the surge. This is supported by the findings that histaminergic nerve fibres and \( H_1 \)-receptor binding sites are abundant in the preoptic and supraoptic nuclei (3-5), where GnRH neurons involved in ovulation are located, and by the finding that histamine stimulated the release of GnRH from incubated hypothalamic fragments from female (55), but not from male rats (56). Furthermore, gonadal steroids affect the histamine turnover in the hypothalamus (57,58).

Conclusion
Histamine seems by activation of \( H_1 \)- and \( H_2 \)-receptors to participate in the regulation of LH secretion, especially in females. The effect of histamine is mediated via a stimulation of GnRH in the hypothalamus, where histaminergic neurons may be involved in the estrogen-induced LH surge.

Neurohypophysial hormones
AVP and oxytocin are synthesized in the paraventricular and supraoptic nuclei of the hypothalamus and are released from nerve endings either in the neurohypophysis to the peripheral circulation or in the median eminence to the long pituitary portal vessels. In addition to their peripheral actions, AVP and oxytocin are involved in the regulation of ACTH and PRL secretion.

It is established that histamine is involved in the central regulation of AVP secretion. \( \alpha \)-FMH, which reduces the neuronal histamine concentration by inhibition of histamine synthesis, decreased plasma AVP and increased the neurohypophysial AVP content in rats (59). In addition, central infusion of histamine dose-dependently decreased urine outflow and increased plasma AVP (33,60,61). Central
infusion of the H₁-receptor antagonist mepyramine inhibited the effect of histamine (60), but the involvement of H₂-receptors has not been studied. The effect of the amine may occur in the supraoptic nucleus, since injection of histamine in this hypothalamic area decreased urine outflow (60), since histamine via H₁-receptors had an excitatory action on neurohypophysial neurons in the supraoptic nucleus (62), and since an abundant number of histaminergic nerve fibres and H₁-receptor binding sites have been identified in the supraoptic and paraventricular nuclei (3-5).

Injected systemically, histamine was found to increase plasma AVP via activation of H₂-receptors (59,61,63). The increase in plasma AVP was noted only when the blood pressure was markedly decreased by histamine (61), suggesting that the release of AVP is secondary to the hypertensive action of systemically infused histamine. Since histamine does not cross the blood-brain barrier, the effect on AVP following systemic administration may occur in the neurohypophysis or in hypothalamic areas outside the blood-brain barrier. In vitro, histamine stimulated the release of AVP from the median eminence, which is located outside the blood-brain barrier (64). In contrast, histamine had no effect on the AVP release from isolated posterior pituitary lobes (58), although histaminergic nerve fibres have been identified immunohistochemically in the neurohypophysis (3,4).

AVP seems to inhibit the synthesis of hypothalamic histamine, since the histamine content in various hypothalamic nuclei was higher in AVP-deficient dizygote Brattleboro rats than in normal control animals, and since administration of AVP to Brattleboro rats produced a decrease in histamine levels in these nuclei (65).

Only few data are available about the influence of histamine on the secretion of oxytocin. It has been reported that systemic administration of histamine increases plasma oxytocin in rats, but the mechanism of action has not been studied (63).

**Conclusion**

Histamine is involved in the regulation of AVP secretion to the peripheral circulation by an action occurring in the hypothalamus. In addition, histamine may have an effect directly at the neurohypophysis, although this effect may be secondary to the vascular action of the amine. Oxytocin is stimulated by histamine, but further studies are required to establish the significance of histamine in the regulation of oxytocin secretion.

**Concluding remarks**

It is established that histaminergic neurons participate in the neuroendocrine regulation of pituitary hormone secretion (Table 1). However, it is important to emphasize that histamine is only one of many regulatory neuroendocrine factors. The effects of histamine are indirectly exerted by an action on hypothalamic releasing factors or on other hypothalamic transmitters. The identification of dense networks of histaminergic nerve fibres and an abundant number of H₁-receptors in different hypophysiotropic hypothalamic areas support this. Histamine participates in the regulation of PRL, AVP, and the POMC-derived peptides (ACTH, β-END, α-MSH) and may play a role in the estrogen-induced LH surge in females. In addition, histamine may be involved in the regulation of GH, TSH and oxytocin, although contradictory or few results have been obtained.

It is at present unknown whether the action of histaminergic neurons is mediating (i.e. directly involved in the transmission of the stimulus) or modulatory (i.e. affect neuronal systems which exert a mediating role). However, the effect of histaminergic compounds on the stress-induced release of some pituitary hormones (PRL and POMC-derived peptides) indicates that histamine in concert with other hypothalamic transmitters has a mediating role. Although the effect of neuronal histamine on some hypothalamic transmitters or factors have been implicated, future investigations should focus upon the interaction of histamine with the abundant numbers of peptidergic and aminergic transmitters involved in the regulation of pituitary hormone secretion.

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Dr Ulrich Knigge,
Department of Medical Physiology C,
The Panum Institute,
University of Copenhagen,
Blegdamsvej 3C,
DK-2200 Copenhagen,
Denmark.