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Insulin/Hypoglycemia-Induced Adrenocorticotropin and β-Endorphin Release: Involvement of Hypothalamic Histaminergic Neurons*

ANDREAS KJÆR, ULRICH KNIGGE, ERIK LANGER MADSEN, PETER SØE-JENSEN, FLEMMING W. BACH, AND JØRGEN WARBERG

Department of Medical Physiology, Division of Endocrinology and Metabolism, The Panum Institute, University of Copenhagen, Copenhagen, Denmark

ABSTRACT

We have previously found that histamine (HA) is involved in the mediation of restraint- and ether stress-induced release of the POMC-derived peptides ACTH and β-endorphin (β-END).

In the present study we investigated the possible involvement of hypothalamic histaminergic neurons in the mediation of insulin/hypoglycemia-induced release of ACTH and β-END in conscious male rats. To do so, hypoglycemia stress was performed during 1) inhibition of HA synthesis, 2) activation of inhibitory presynaptic HA H_3-autoreceptors, or 3) blockade of postsynaptic HA H_1- or H_2-receptors.

Hypoglycemia (plasma glucose, 2.2 ± 0.3 nmol) induced by insulin (3 IU/kg, ip) caused a 3- to 5-fold increase in the plasma concentrations of ACTH and β-END. A negative exponential correlation was found between the plasma glucose concentration and the ACTH and β-END levels. Pretreatment of the animals with the HA synthesis inhibitor α-fluoromethylhistidine (1.0 μmol) intracerebroventricularly (icv) in a lateral ventricle, inhibited the ACTH and β-END responses to insulin/hypoglycemia by 60%. When administered ip (100 μmol/kg), the synthesis inhibitor decreased the β-END response 50%, but did not affect ACTH secretion significantly.

Pretreatment of the rats with the H_3-receptor agonist R(α)methylhistamine (50 μmol/kg, ip, twice) inhibited the secretory responses of ACTH and β-END to insulin/hypoglycemia by 60–80%. This inhibitory effect of R(α)methylhistamine was reversed by prior administration of the specific H_3-receptor antagonist thioperamide.

Administration of the H_1-antagonists mepyramine and cetirizine dose-dependently inhibited the ACTH and β-END responses to insulin/hypoglycemia, with the highest dose (mepyramine, 350 nmol, icv; cetirizine, 40 μmol/kg, ip) inhibiting the response by 80–100%. The H_1-antagonist SKF-93944 (226 nmol, icv) inhibited the ACTH response, but had no effect on the β-END response. Administration of the H_2-antagonists cimetidine (400 nmol, icv) and ranitidine (400 nmol, icv) inhibited the ACTH and β-END responses to insulin/hypoglycemia by 50–80%.

We conclude that histaminergic neurons are involved in the mediation of the insulin/hypoglycemia-induced release of ACTH and β-END and that the effect is mediated via activation of primarily postsynaptic H_1-receptors and, to a lesser extent, H_2-receptors. (*Endocrinology* **132:** 2213–2220, 1993)

SECRETION of the POMC-derived peptides ACTH and β-endorphin (β-END) from the anterior pituitary gland is controlled by a variety of factors, including CRH, arginine vasopressin (AVP), and catecholamines (1–3).

In addition, histamine (HA), which acts as a hypothalamic neurotransmitter (4), seems to participate in the central regulation of ACTH and β-END secretion (5) and appears to be involved in restraint- and ether stress-induced release of these hormones, since blockade of central postsynaptic HA H_1- and H_2-receptors (6) or inhibition of HA synthesis (5, 7) attenuates these responses. Furthermore, we have recently found that activation of presynaptic H_3-autoreceptors decreased the ACTH and β-END responses to restraint stress (Søe-Jensen, P., U. Knigge, M. Garbarg, A. Kjær, A. Rouleau, F. W. Bach, J. C. Schwartz, and J. Warberg, unpublished observations).

Central administration of HA or HA agonists leads to increased levels of AVP and CRH in peripheral plasma and pituitary portal blood, respectively (8, 9), and immunoneutralization of endogenous CRH or AVP or administration of AVP antagonists inhibits the ACTH and β-END responses to HA (10) (Kjær, A., U. Knigge, H. Vilhardt, F. W. Bach, and J. Warberg, unpublished observations), indicating that histaminergic neurons stimulate the release of hypothalamic CRH and AVP. This is further supported by the finding that histaminergic neurons originating in the posterior hypothalamus project to the paraventricular nucleus and the supraoptic nucleus (11, 12) where CRH and AVP neurons are located (13–15).

Insulin-induced hypoglycemia is a stressor known as a potent stimulator of ACTH and β-END secretion (16–20), and it appears that hypoglycemia rather than insulin *per se* constitutes the ACTH-releasing stimulus (21, 22). However, hypoglycemia does not stimulate ACTH release directly (23), but, rather, via activation of hypothalamic releasing factors, since lesioning of the mediobasal hypothalamus inhibits the ACTH response to hypoglycemia (19, 24, 25), and hypoglycemia stimulates the release of the ACTH-regulating factors CRH and AVP to pituitary portal blood (26–29) and periph-

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Address all correspondence and requests for reprints to: Andreas Kjær, M.D., Department of Medical Physiology, Division of Endocrinology and Metabolism, The Panum Institute (Building 12.3), University of Copenhagen, DK-2200 Copenhagen, Denmark.

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eral plasma (30, 31) and increases their turnover in the median eminence (16).

Taken together, the available evidence indicates that HA stimulation and hypoglycemia stress share the common hypothalamic mediators of ACTH and β-END secretion, CRH and AVP, and that histaminergic neurons participate in the neuroendocrine regulation of ACTH and β-END release induced by various stress stimuli. This led us to believe that HA might also play a role in insulin/hypoglycemia-induced ACTH and β-END secretion.

The aim of the present study, therefore, was to investigate the possible involvement of histaminergic neurons in insulin/hypoglycemia-induced ACTH and β-END release. To do so, we studied the effect of inhibition of HA synthesis, stimulation of inhibitory presynaptic H_3-autoreceptors, as well as blockade of postsynaptic H_1- or H_2-receptors on insulin/hypoglycemia-induced secretion of ACTH and β-END in conscious male rats.

Materials and Methods

Animals

Male rats of the Wistar strain (275–325 g) bred at the Panum Institute were housed under controlled conditions of temperature (22 ± 1 C), relative humidity (45–50%), and lighting (lights on between 0600–1800 h daily). The rats had free access to laboratory chow and tap water when not fasted.

Compounds

The compounds used were regular insulin (Actrapid, Novo-Nordisk, Copenhagen, Denmark), the HA synthesis inhibitor (S)α-fluoromethylhistidine (α-FMH; mol wt, 200; Merck, Sharpe, and Dohme, Rahway, NJ), the H_3-receptor agonist R(α)-methylhistamine (RmHA; mol wt, 198; Laboratoire Bioproject, Paris, France), the H_3-receptor antagonist thioperamide (mol wt, 292; Laboratoire Bioproject), the H_1-receptor antagonist mepyramine (MEP; mol wt, 286; DAK Laboratories, Copenhagen, Denmark), and the two nonsedating H_1-antagonists SKF-93944 (SKF; mol wt, 442; Smith, Kline, and Beecham, Welwyn Garden City, United Kingdom), and cetirizine (CET; mol wt, 461; UCB Pharma, Braine-l'Alleud, Belgium), the two H_2-receptor antagonists cimetidine (CIM; mol wt, 252; Smith, Kline, and Beecham), and ranitidine (RAN; mol wt, 314; Glaxo Research Group, Ware, United Kingdom). All compounds were dissolved in saline except thioperamide, which was dissolved in methanol.

Surgical and experimental procedures

Intact rats (for ip injections) or rats provided with a permanent metal cannula implanted in a lateral ventricle of the brain [for intracerebroventricular (icv) infusions] (32) were used. The implantation of icv cannulas was performed during pentobarbital anesthesia (60 mg/kg, ip) 5–7 days before the experiment.

All experiments were performed in conscious, freely moving rats. Before experimentation, the rats were fasted overnight, but had free access to tap water. On the day of experimentation, the icv cannulas were extended by Silastic tubings, and the rats were left undisturbed in individual cages in a quiet room for an adaptation period of at least 90 min. In all experiments the animals were quickly decapitated at 0 min (1100–1230 h). This time was chosen for the experiments to be performed during the circadian nadir of ACTH secretion and in order to avoid interruption of the dark period for pretreatment of the animals (see below). Immediately after decapitation, trunk blood was collected in polyethylene tubes containing 50 μl 0.5 M EDTA and 50 μl aprotinin (20,000 kallikrein inhibitor units/ml; Trasylol, Bayer, Leverkusen, Germany). Blood samples were immediately centrifuged at 4 C, and plasma was stored at −20 C until analyzed for glucose, ACTH, and β-END immunoreactivity (β-ENDir).

Exp 1: effect of HA synthesis inhibition on basal or insulin/hypoglycemia-induced ACTH and β-ENDir secretion

The HA synthesis inhibitor α-FMH was administered either icv (5 μl; 2 μl/min) at −60 min in a dose of 1.0 μmol or ip (1 ml) at −360 min in a dose of 100 μmol/kg. Saline served as control.

Insulin (3 IU/kg) or saline was injected ip at −45 min.

Exp 2: effect of presynaptic H_3-receptor activation on basal or insulin/hypoglycemia-induced ACTH and β-ENDir secretion

The H_3-receptor agonists RmHA was administered ip at −180 and −60 min, each time in a dose of 50 μmol/kg. The dose used has previously been shown to inhibit restraint stress-induced ACTH and βEND release (Søe-Jensen, P., U. Knigge, M. Garbarg, A. Kjær, A. Rouleau, F. W. Bach, J. C. Schwartz, and J. Warberg, unpublished observations). Saline served as control. In these experiments, methanol was administered at −180 min as a control solution for thioperamide (see the next paragraph).

In some animals the H_3-receptor antagonist thioperamide was administered ip at −180 min in a dose of 17 μmol/kg in addition to administration of RmHA, which was injected in the doses and at the times described above.

Insulin (3 IU/kg) or saline was injected ip at −45 min.

Exp 3: effect of postsynaptic H_1- or H_2-receptor blockade on basal or insulin/hypoglycemia-induced ACTH and β-ENDir secretion

The H_1-receptor antagonists MEP (87, 175, or 350 nmol, icv), SKF (113 or 226 nmol, icv), and CET (10, 20, or 40 μmol/kg, ip) were administered at −60 min. The high dose of MEP has previously been shown to inhibit HA-induced ACTH and β-END release (34). Saline served as control.

The H_2-receptor antagonists CIM (200 or 400 nmol, icv) and RAN (200 or 400 nmol, icv) were administered at −60 min. The high doses of CIM and RAN have previously been shown to inhibit HA-induced ACTH and β-END release (32). Saline served as the control.

Insulin (3 IU/kg) or saline was injected ip at −45 min.

Analysis of glucose, ACTH, and β-ENDir

Plasma glucose was determined by an enzymatic fluorometric method (33).

ACTH and β-ENDir were measured by RIAs, as previously described (32). The ACTH determinations were performed in unextracted plasma samples, whereas the β-ENDir determinations were performed in plasma samples prepared by solid phase extraction using C18 Sep-Pak cartridges (Waters, Milford, MA). The ACTH antiserum used had less than 0.4% cross-reactivity with α-MSH and β-MSH. The β-END antiserum cross-reacted 100% with β-lipotropin, but did not cross-react with ACTH-(1–24), α-END, γ-END, γ-MSH, dynorphin-(1–13), Met-enkephalin, or Leu-enkephalin. Synthetic human ACTH-(1–39), generously provided by the National Pituitary Agency, NIH, and synthetic human β-END (Peninsula Laboratories, Inc., Belmont, CA) served as reference preparations. The least detectable quantities were 1 and 4 pmol/liter plasma of ACTH and β-ENDir, respectively. Intra- and interassay coefficients of variation were 4% and 5% for the ACTH assay, respectively, and 8% and 15% for the β-END assay.

Statistical analysis

Results are presented as the mean ± SEM and represent groups of six to nine animals. Data were evaluated by one-way analysis of variance, followed by Duncan's test for multiple comparisons when appropriate. Correlations between blood glucose and hormone levels were tested using the equation: $y = \exp(a + bx)$, where y and x represent ACTH/β-

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ENDir levels and plasma glucose, respectively. The limit of significance was $P < 0.05$.

Results

Exp 1: effect of HA synthesis inhibition on basal or insulin/hypoglycemia-induced ACTH and β-ENDir secretion

Insulin (3 IU/kg) reduced the average plasma glucose concentration from 6.8 ± 0.5 to 2.2 ± 0.3 mmol/liter ($P < 0.01$; Fig. 1) and increased the plasma concentrations of ACTH and β-ENDir 5- and 3-fold, respectively ($P < 0.01$). In insulin-treated animals, a strong negative exponential correlation was found between plasma glucose levels and the plasma concentration of ACTH (r = −0.90; n = 19; $P < 0.01$; Fig. 1) or β-ENDir (r = −0.91; n = 19; $P < 0.01$; Fig. 1).

Pretreatment with the HA synthesis inhibitor α-FMH administered icv reduced the ACTH and β-ENDir responses to insulin/hypoglycemia by 60% ($P < 0.01$; Figs. 2 and 3).

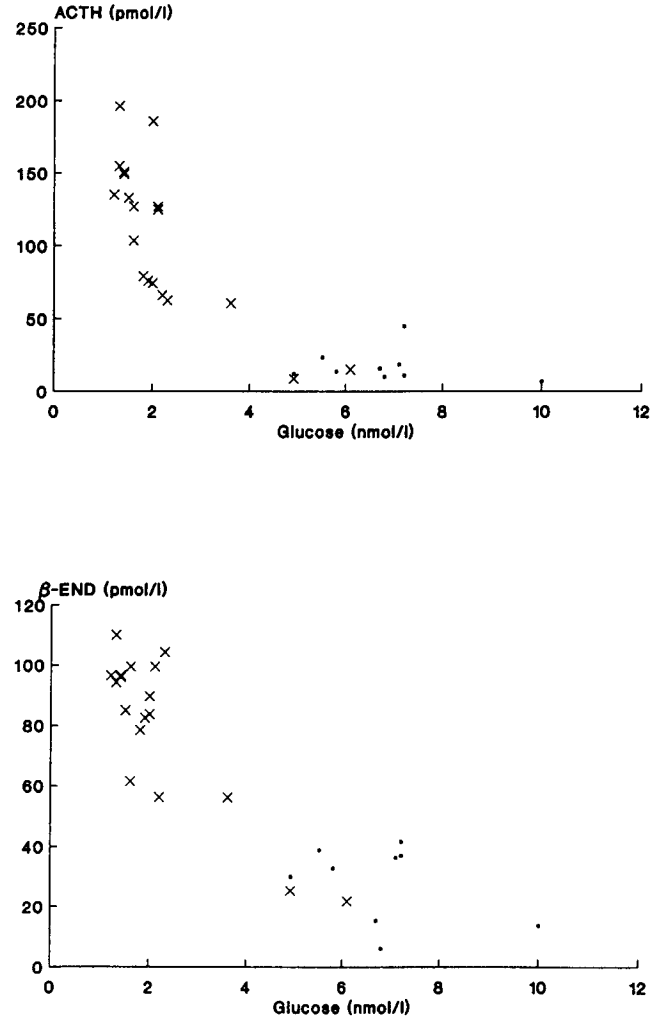

FIG. 1. Individual corresponding values of the plasma glucose concentrations and the plasma concentrations of ACTH (*upper panel*) and β-ENDir (*lower panel*) in male rats. At −45 min, the rats were injected ip with either insulin (X; 3 IU/kg) to generate hypoglycemia or saline (■). The animals were decapitated at 0 min. Each *point* represents one animal.

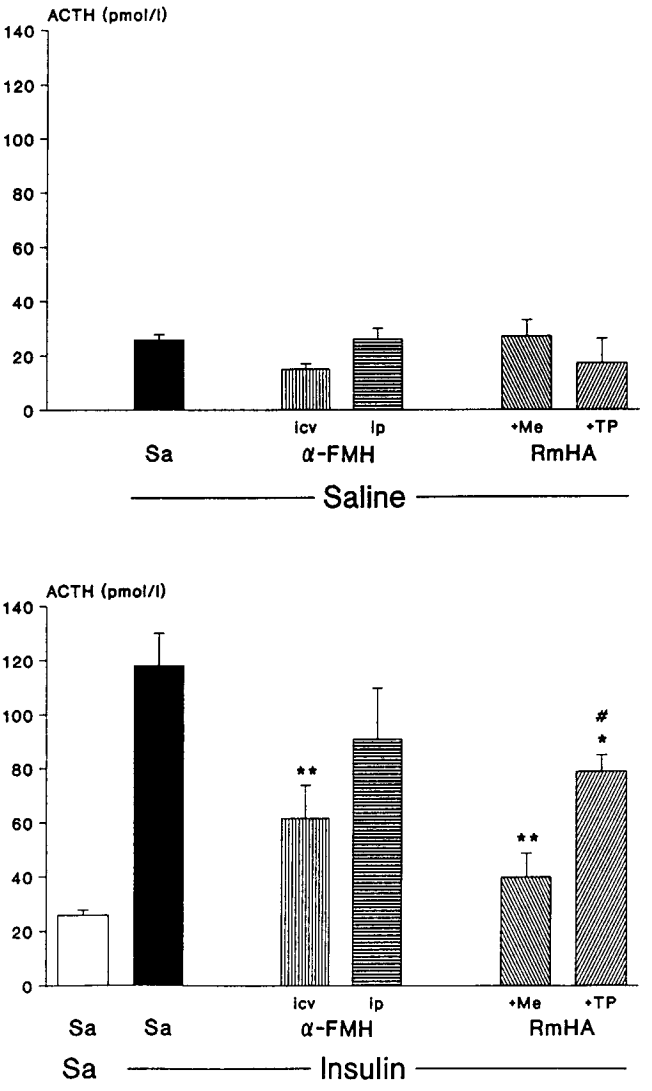

FIG. 2. Effects of the HA synthesis inhibitor α-FMH and the H_3-receptor agonist RmHA on basal [saline-injected (Sa); *upper panel*] or insulin-induced (*lower panel*) secretion of ACTH. α-FMH (or Sa; ■) was administered icv at −60 min in a dose of 1 μmol (▥) or ip at −360 min in a dose of 100 μmol/kg (▤). RmHA (or Sa) was injected ip at −180 and −60 min in a dose of 50 μmol/kg. At −180 min, the H_3-receptor antagonist thioperamide (TP; ▨) or its diluent methanol (Me; ▧) was injected ip together with RmHA. Hypoglycemia was induced by insulin administered ip at −45 min in a dose of 3 IU/kg. The animals were fasted overnight and decapitated at 0 min. The results represent the mean ± SEM of six to nine animals. *, $P < 0.05$; **, $P < 0.01$ (*vs.* insulin plus saline). #, $P < 0.05$ (*vs.* insulin plus RmHA).

When administered ip α-FMH inhibited the β-ENDir secretion by approximately 50% ($P < 0.05$; Fig. 3), but had no significant effect on ACTH secretion (Fig. 2).

Administration of α-FMH icv or ip had no effect on the basal secretion of ACTH or β-ENDir.

Exp 2: effect of presynaptic H_3-receptor activation on basal or insulin/hypoglycemia-induced ACTH and β-ENDir secretion (Figs. 2 and 3)

Inhibition of neuronal HA release and synthesis by pretreatment with the H_3-receptor agonist RmHA lowered insulin/hypoglycemia-induced ACTH release by 80% ($P <$

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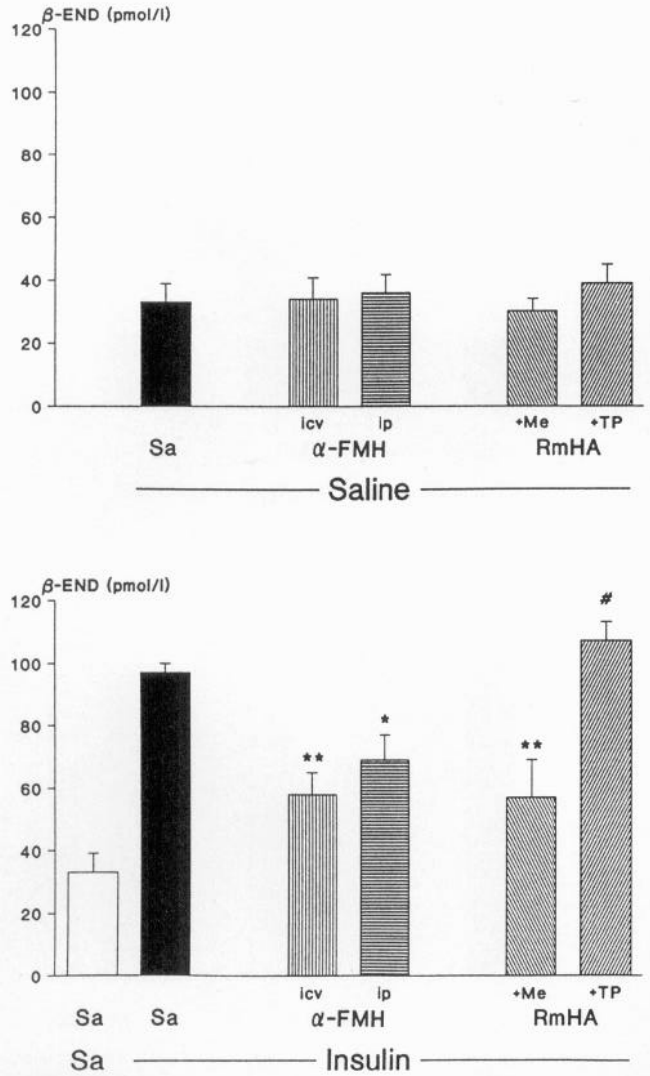

FIG. 3. Effects of the HA synthesis inhibitor α-FMH and the H_3-receptor agonist RmHA on basal [saline-injected (Sa); *upper panel*] or insulin-induced (*lower panel*) secretion of β-ENDir. For further information, see Fig. 2.

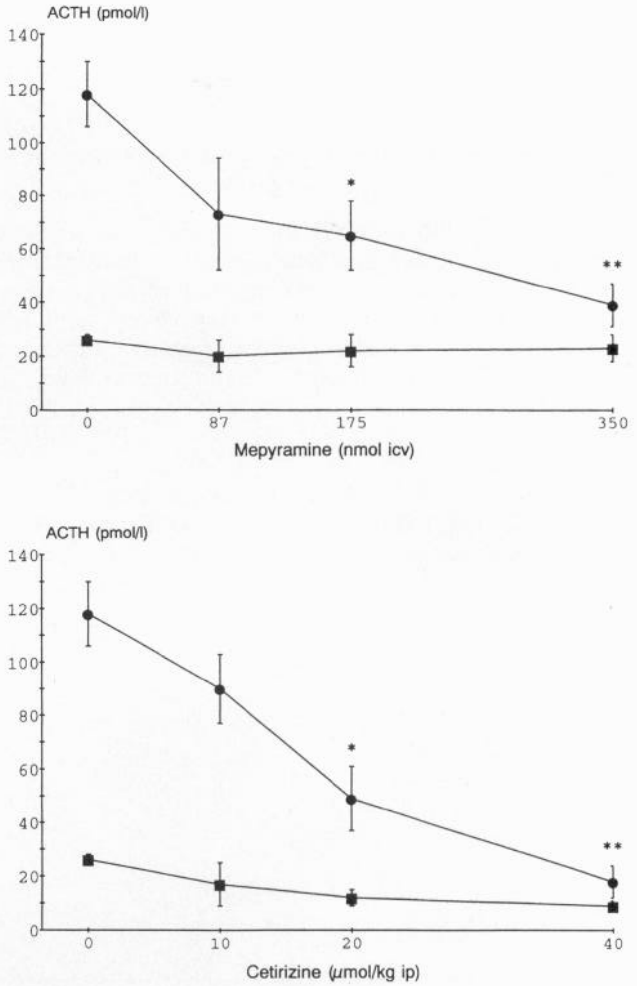

FIG. 4. Effects of the H_1-receptor antagonists mepyramine (87, 175, or 350 nmol, icv, at −60 min; *upper panel*) and cetirizine (10, 20, or 40 μmol/kg, ip, at −60 min; *lower panel*) on basal (■) or insulin-induced (●) secretion of ACTH. Saline served as the control. The animals were fasted overnight and decapitated at 0 min. Insulin (3 IU/kg) was injected ip at −45 min. The results represent the mean ± SEM of six to nine animals. *, $P < 0.05$; **, $P < 0.01$ (*vs.* insulin plus saline).

0.01; Fig. 2) and β-ENDir release by 60% ($P < 0.01$; Fig. 3). When the specific H_3-antagonist thioperamide was administered simultaneously, the inhibitory effect of RmHA on insulin/hypoglycemia-induced hormone release was attenuated by more than 50% (ACTH; $P < 0.05$; Fig. 2) or eliminated (β-ENDir; $P < 0.01$; Fig. 3).

Administration of RmHA or RmHA plus thioperamide had no effect on basal ACTH or β-ENDir secretion.

Exp 3: effect of postsynaptic H_1- or H_2-receptor blockade on basal or insulin/hypoglycemia-induced ACTH and β-ENDir secretion (Figs. 4–7 and Table 1)

H_1-Receptors. Pretreatment with the H_1-receptor antagonists MEP and CET inhibited insulin/hypoglycemia-induced ACTH and β-ENDir secretion dose-dependently ($P < 0.05$–0.01; Figs. 4 and 5). MEP inhibited ACTH and β-ENDir secretion by 60–70% at the intermediate dose ($P < 0.05$; Figs. 4 and 5), and by 80–100% at the high dose ($P < 0.01$; Figs. 4 and 5). CET at the intermediate or high dose inhibited the insulin/hypoglycemia-induced ACTH response by 70% ($P < 0.05$; Fig. 4) or 100% ($P < 0.01$; Fig. 4), respectively. The β-ENDir response was inhibited 80% by the high dose of CET ($P < 0.01$; Fig. 5). Administration of the H_1-receptor antagonist SKF, which does not readily cross the blood-brain barrier, had no effect at the low dose, while the high dose decreased the ACTH response to insulin/hypoglycemia by 50% ($P < 0.05$; Table 1). SKF did not affect the β-ENDir response significantly ($0.05 < P < 0.1$; Table 1).

The H_1-receptor antagonists had no effect on basal ACTH or β-ENDir secretion.

H_2-Receptors. The H_2-receptor antagonists CIM (high dose) and RAN (low and high doses) inhibited insulin/hypoglycemia-induced ACTH secretion by 60–80% ($P < 0.05$–0.01; Fig. 6). At the low dose, CIM had no inhibitory effect on ACTH secretion. Both H_2-receptor antagonists inhibited β-

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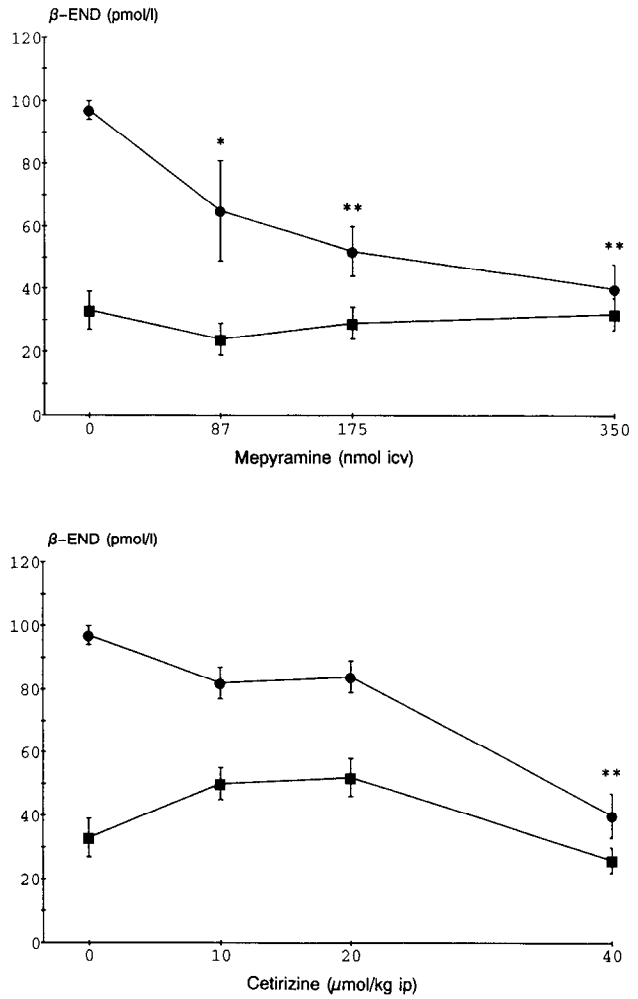

FIG. 5. Effects of the H_1-receptor antagonists mepyramine (87, 175, or 350 nmol, icv, at −60 min; *upper panel*) and cetirizine (10, 20, or 40 μmol/kg, ip, at −60 min; *lower panel*) on basal (■) or insulin-induced (●) secretion of β-ENDir. For further explanation, see Fig. 4.

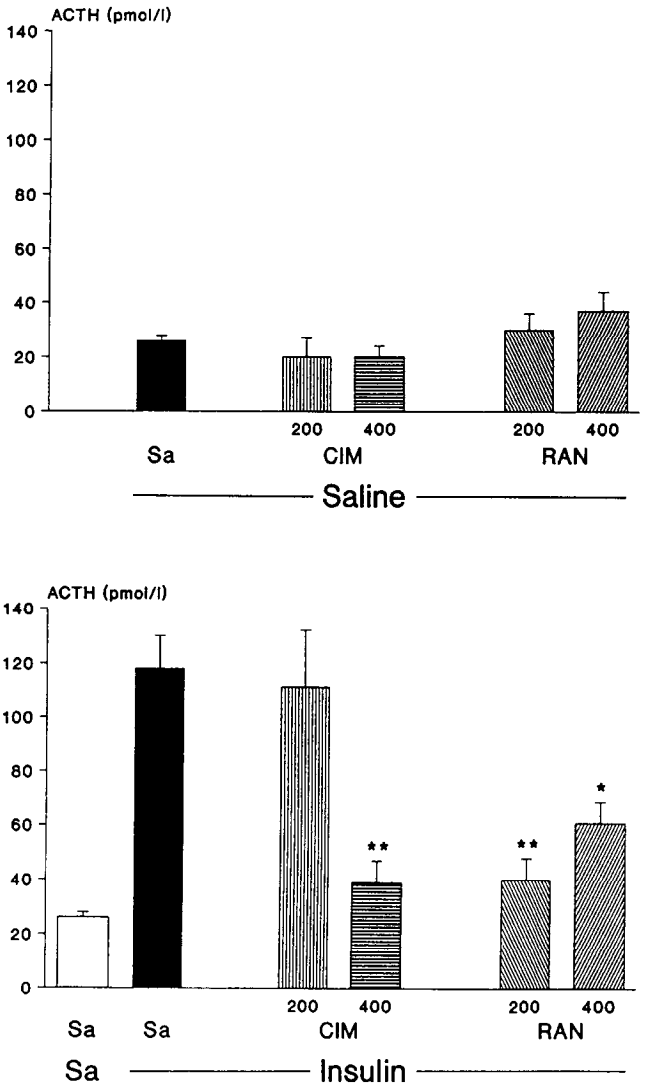

FIG. 6. Effects of the H_2-receptor antagonists CIM [200 (▥) or 400 nmol (▤)] and RAN [200 (▧) or 400 nmol (▨)], infused icv at −60 min, on basal (*upper panel*) or insulin-induced (*lower panel*) secretion of ACTH. Saline (Sa; ■) served as the control. The animals were fasted overnight and decapitated at 0 min. Insulin (3 IU/kg) was injected ip at −45 min. The results represent the mean ± SEM of six to nine animals. *, $P < 0.05$; **, $P < 0.01$ (*vs.* insulin plus saline).

ENDir secretion by 40% at the high doses ($P < 0.05$; Fig. 7).

The H_2-receptor antagonists had no effect on basal ACTH or β-ENDir secretion (Figs. 6 and 7), except for the high dose of RAN, which stimulated β-END slightly ($P = 0.05$; Fig. 7).

Discussion

In accordance with previous studies (16–20), we found that insulin-induced hypoglycemia stimulated ACTH and β-END secretion. The time schedule of the experiment was chosen so that blood samples were taken at the time after insulin injection when the ACTH response to hypoglycemia was predicted to peak (19). In accordance with other reports (21, 27), we found a very strong negative exponential correlation between plasma glucose concentrations and plasma levels of ACTH and β-END. This indicates that hypoglycemia is the stimulator of ACTH and β-END secretion rather than insulin *per se*. This would also explain the observed time lag between insulin administration and the ACTH response, which does not occur until low glucose levels in the cerebrospinal fluid are obtained (21). Furthermore, glucose clamping of the brain (infusion of glucose in the carotid arteries) during insulin infusion eliminates the hormonal response (22).

Inhibition of HA synthesis by α-FMH administered according to a time schedule which ensured that only the neuronal HA pool was affected within the experimental period (34, 35) attenuated the ACTH and β-END responses to insulin-induced hypoglycemia. The effect of α-FMH was stronger when the compound was administered icv than when it was given ip. This is probably due to higher concentrations of α-FMH in the hypothalamus after the administration of α-FMH into cerebrospinal fluid. We have previously found a similar effect of α-FMH on ether- and restraint stress-induced ACTH and β-END secretion (7), indicating that HA as a neurotransmitter is involved in the mediation of pituitary hormone responses to these kinds of stress. The

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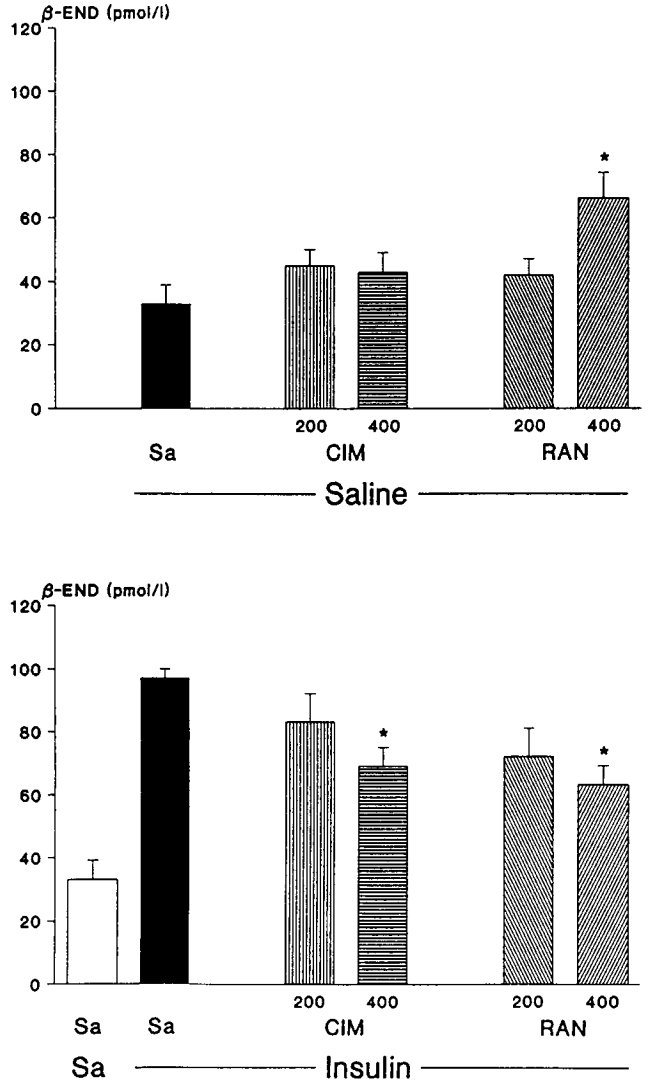

FIG. 7. Effects of the H_2-receptor antagonists CIM (200 or 400 nmol) or RAN (200 or 400 nmol), infused icv at −60 min, on basal (*upper panel*) or insulin-induced (*lower panel*) secretion of β-ENDir. *, $P < 0.05$; **, $P < 0.01$ (*vs.* insulin/saline plus saline. For further explanation, see Fig. 6.

TABLE 1. The effect of the nonsedating H_1-receptor antagonist SKF-93944, administered icv at −60 min, on basal or insulin-induced (3 IU/kg, ip, at −45 min) secretion of ACTH or β-ENDir

	ACTH (pmol/liter)		βEND (pmol/liter)	
	Control	Insulin	Control	Insulin
Saline	26 ± 2	118 ± 12	33 ± 6	97 ± 3
SKF-93944 (113 nmol)	18 ± 6	93 ± 16	43 ± 5	98 ± 8
SKF-93944 (226 nmol)	17 ± 5	68 ± 13[a]	43 ± 7	77 ± 12

Saline served as the control. The animals were decapitated at 0 min. The results represent the mean ± SEM of six to nine animals.
[a] $P < 0.05$ *vs.* insulin plus saline.

present findings indicate that histaminergic neurons may also be involved in ACTH and β-END release in response to hypoglycemia stress.

Activation of presynaptic H_3-autoreceptors (36, 37) by the specific H_3-receptor agonist RmHA, which inhibits HA release as well as HA synthesis (38, 39), also diminished the responses of ACTH and β-END to insulin-induced hypoglycemia. The inhibitory effect of RmHA was reduced or prevented by administration of the H_3-receptor antagonist thioperamide, which supports the view that the action of RmHA is specifically mediated via H_3-receptors. These findings further indicate that HA plays a role in the mediation of insulin/hypoglycemia-induced ACTH and β-END secretion. However, we cannot totally exclude the possibility that the effect obtained with RmHA is caused by activation of the recently demonstrated H_3-heteroreceptors that are located on nonhistaminergic neurons, *e.g.* serotonergic or adrenergic neurons (40, 41).

Blockade of postsynaptic H_1-receptors by MEP or CET strongly and dose-dependently inhibited the ACTH and β-END responses to insulin/hypoglycemia, whereas the H_1-receptor antagonist SKF had a much weaker effect. This may be explained by a more hydrophilic character of SKF (42), making its diffusion into hypothalamic tissue slower than that of MEP and CET (43, 44). It may be argued that the effect observed with MEP could be due to its nonspecific anticholinergic action, but this is unlikely, since CET, which is devoid of anticholinergic and antiserotonergic properties (45), had a similar inhibitory effect on the hormonal response to hypoglycemia. The inhibitory effect of MEP on insulin/hypoglycemia-induced ACTH and β-END secretion was more pronounced than that previously observed on the responses of ACTH and β-END to HA stimulation, ether stress, or restraint stress (6, 32). This suggests that H_1-receptors play a relatively more important role in insulin/hypoglycemia-induced release of ACTH and β-END than in other types of stress-induced ACTH and β-END release.

Blockade of postsynaptic H_2-receptors by CIM or RAN also inhibited the ACTH and β-END responses to insulin/hypoglycemia significantly. However, the inhibitory effect of CIM and RAN was generally weaker than that previously observed on HA-, ether stress-, or restraint stress-induced ACTH and β-END secretion (6, 32) and was weaker than the effect of equimolar doses of the H_1-receptor antagonists MEP. We found that RAN was more potent than CIM in inhibiting insulin/hypoglycemia-induced hormone release. This is in accordance with the reported higher antagonist potency of RAN compared to that of CIM (43). Taken together, the relative importance of H_2-receptors *vs.* H_1-receptors seems to be smaller in insulin/hypoglycemia-induced ACTH and β-END release than in other types of stress. We have no obvious explanation for this difference, but the involvement of other transmitter systems or histaminergic interneurons may play a role.

The present results and our recent findings that insulin-induced hypoglycemia increases the turnover of neuronal HA in the hypothalamus (Søe-Jensen, P., U. Knigge, M. Garbarg, A. Kjær, A. Rouleau, F. W. Bach, J. C. Schwartz, and J. Warberg, unpublished observations) indicate that activation of histaminergic neurons is important for the induction of ACTH and β-END responses to insulin/hypoglycemia and that this is mediated primarily via activation of postsynaptic H_1-receptors, with H_2-receptors playing a less promi-

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nent role. In accordance with the present findings, it has recently been shown that hypoglycemia increased the release of HA from hypothalamic tissue *in vitro* (46).

Since HA has no direct effect on the release of ACTH and β-END from pituitary tissue *in vitro* (47, 48), it is likely that the mediating role of HA in the hormone response to insulin/hypoglycemia is exerted by an action at the level of the hypothalamus. It has previously been reported that insulin/hypoglycemia (26–31) as well as HA (8, 9) stimulate the secretion of the hypothalamic corticotropic factors AVP and CRH. Since HA stimulation and hypoglycemia stress seem to share these common ACTH and β-END secretagogues, we suggest that the increased histaminergic activity, triggered by the insulin/hypoglycemia stress, is responsible at least in part for the increased release of CRH and AVP in this condition.

In summary, we conclude 1) that the insulin/hypoglycemia-induced release of ACTH and β-END involves hypothalamic histaminergic neurons, since inhibition of HA synthesis, stimulation of presynaptic inhibitory H_3-autoreceptors, or blockade of postsynaptic HA receptors attenuated the hormonal response; and 2) that the effect of neuronal HA released by hypoglycemia is caused by activation of primarily postsynaptic H_1- and, to a lesser extent, H_2-receptors.

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