

Studies on the involvement of histamine in the hypothalamic-pituitary-adrenal axis activation induced by nerve growth factor

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Abstract

Nerve growth factor (NGF) has been shown to stimulate the hypothalamic-pituitary-adrenocortical (HPA) axis. Since NGF induces the release of histamine from mast cells and in consideration of the fact that histamine is an HPA axis activator, we investigated whether NGF adrenocortical stimulation is mediated by histamine. To accomplish with it, the H₁ histamine antagonist promethazine and the H₂ antagonists metiamide and zolantidine were used in freely-moving cannulated rats. The increase in plasma corticosterone concentration induced by histamine administration was prevented completely by promethazine pretreatment but was unaffected by the H₂ antagonists. Neither H₁ nor H₂ antagonists affected the adrenocortical stimulation induced by NGF administration. Moreover, since mast cells are reportedly present in the rat adrenal gland and the locally released histamine mediates the release of adrenaline which, in turn, stimulates glucocorticoid synthesis and secretion, we studied the effect of NGF on basal and ACTH-stimulated corticosterone release from *in vitro* isolated quartered adrenal glands and collagenase-dispersed adrenal cells. The results from these *in vitro* experiments have indicated that NGF modified neither spontaneous nor stimulated corticosterone release. Altogether these observations suggest that endogenous histamine is unlikely to be involved in HPA axis stimulation by NGF and reinforce the previously proposed concept of an active participation of NGF in the control of adrenocortical activity. © 2000 Elsevier Science Inc. All rights reserved.

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Introduction

Nerve growth factor (NGF) is generally regarded as a protein capable of promoting the development and differentiation of sympathetic and embryonic sensory nerve cells. In addition to

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this trophic action, NGF seems to be involved in phenomena related to hypothalamic-pituitary adrenocortical (HPA) axis activity. In fact, besides the documented adrenocortical stimulatory effect following NGF administration [1–3], which is mediated by the release of hypothalamic vasopressin [4], there are indications that aggressive behavior, a form of social stress, increases serum and hypothalamic NGF levels [5–8]. In agreement with a relationship between stress and NGF is the evidence that pretreatment of rat with anti-NGF immunoglobulin G reduces adrenocortical stress activation [9]. Moreover, recent data indicate that serum levels of NGF increase in humans in response to stressful situation [10].

NGF also seems implicated in the control of mast cells activity and, consequently, a role in the inflammatory response has been suggested [11]. This hypothesis is supported by evidence that peritoneal, cutaneous and brain mast cells release histamine in response to NGF [12–14]. As described by Pearce and Thompson [15], the NGF-induced histamine release differs markedly (e.g.: calcium dependency) from that induced by polycationic inducers and anaphylactic reaction.

Histamine acts as a neurotransmitter in the hypothalamus [16], and is involved in the neuroendocrine regulation of pituitary hormone secretion [17–19]. With regard to the HPA axis, histamine induces the release of ACTH through the activation of hypothalamic neurons containing vasopressin and corticotropin-releasing hormone (CRH) [18–20]. Several studies have been made to determine the relative contribution of histamine H_1 , H_2 and H_3 receptor types in the stimulation of the adrenocortical axis. The results indicate that HPA axis stimulation induced directly or indirectly by histamine (e.g.: compound 48/80, bacterial lipopolysaccharide, etc.) is governed mainly by H_1 receptors, although in some instances H_2 and H_3 receptors play a cooperative role [21–29].

Glucocorticoid hormone release could also be stimulated by histamine through an ACTH-independent mechanism. Mast cells are in fact present in the rat adrenal gland [30]; histamine, through the activation of H_1 receptor, induces the local release of adrenaline [31], which, in turn, stimulates corticosterone release from adrenocortical cells [32].

On this basis we performed a series of *in vivo* and *in vitro* experiments aimed at determining the relevance of endogenous histamine to the accomplishment of the stimulatory effect of NGF on adrenocortical activity.

Materials and methods

Animals

Adult (2.5–3 months) male Wistar rats (Harlan, Italy) weighing 300–325 g were housed two per cage in a temperature-controlled room ($24 \pm 2^\circ\text{C}$), with a 12-h light, 12-h dark period (lights on: 07.00–19.00 h) for at least 2 weeks before the experiments. Food (Standard Diet 4RF21, Charles River) and tap water were provided *ad libitum*. No female rats were present in the animal room. The week before the experiment, the rats were daily handled gently by the same operator between 09.30 and 10.30 to minimize stress response to manipulation. All experiments were started at 10.00 h. In some experiments, rats were surgically implanted, under Pentobarbital (60 mg/kg i.p.) anesthesia, with a permanent cannula in the right atrium through the jugular vein. The rats were allowed to recover for 3 days after the opera-

tion. All experiments were conducted in agreement with the Italian national rules laid down by the Ministry of Health.

In vivo studies

Mouse (m)- β NGF (Harlan Bioproduct for Science, Inc. USA) was dissolved in PBS immediately before use and was injected through the jugular cannula at concentrations ranging from 0.1 to 1.0 nmol/kg. NGF has long been known to be a “sticky” protein that can non-specifically bind laboratory plasticware. To prevent such adsorption, all the material was washed the day before the experiment with a solution of cytochrome C (Sigma Chemicals, USA, 2 mg/ml) and thoroughly rinsed with deionized water. Cytochrome C was used because it has similar physicochemical properties to NGF. Control rats received cytochrome C (2 μ g/kg). Histamine (histamine dihydrochloride, Fluka Chemie AG), promethazine (promethazine hydrochloride, an H_1 antagonist, Sigma Chemicals) and zolantidine (zolantidine dimaleate, an H_2 antagonist, Tocris Cookson) were dissolved in 0.9% NaCl. Metiamide (an H_2 antagonist, SmithKline Beecham) was dissolved in 1.0 N HCl, adjusted to pH 4–6 with 0.1 N NaOH, and then diluted with saline [21]. Experiments aimed at testing the antagonistic property of promethazine and metiamide on histamine-induced corticosterone release were accomplished following a protocol (time and doses) in agreement with Reilly and Sigg [21]. Zolantidine (5 mg/kg i.p.) was injected 30 min prior to histamine. Trunk blood was collected into plastic tubes containing 200 μ l of 0.13 M EDTA. After centrifugation at $1,900 \times g$ at 4 °C for 15 min, plasma was separated and kept frozen at –20 °C for later corticosterone determination. Plasma corticosterone concentrations were determined by RIA (ICN Biomedicals, USA). The cross reactivity of the polyclonal corticosterone-antisera with respective related substances was negligible. The inter- and intraassay coefficients of variation were 8% and 3%, respectively, with a detection limit of 0.01 μ g/100 ml.

In vitro studies

The rats were killed by decapitation. The adrenal glands were removed by the ventral approach, separated from the adherent adipose tissue, quartered into 4 equal pieces and pre-incubated for 2 h in 1 ml of Krebs-bicarbonate medium containing D-glucose (11 mM) and bovine serum albumin (0.25%) at 37 °C under 95% O₂ - 5% CO₂ atmosphere changing the medium every 30 min, and then exposed for 1 h to 1 ml fresh medium containing the test substances. The corticosterone released into the medium was measured by RIA (see above). Collagenase-dispersed adrenal cells were prepared according to Sayers et al. [33]. The cells (250,000/ml) were incubated for 2 h with medium containing the test substance. Cell death, assessed at the end of the experiment by the Trypan blue exclusion method, was less than 2%. Corticosterone released into the medium was measured as described above.

Statistical analysis

Data were analyzed using one-way analysis of variance followed by Duncan's new multiple range test, Dunnett's post hoc test or Tukey's post hoc test. The results were considered to differ significantly if $p < 0.05$.

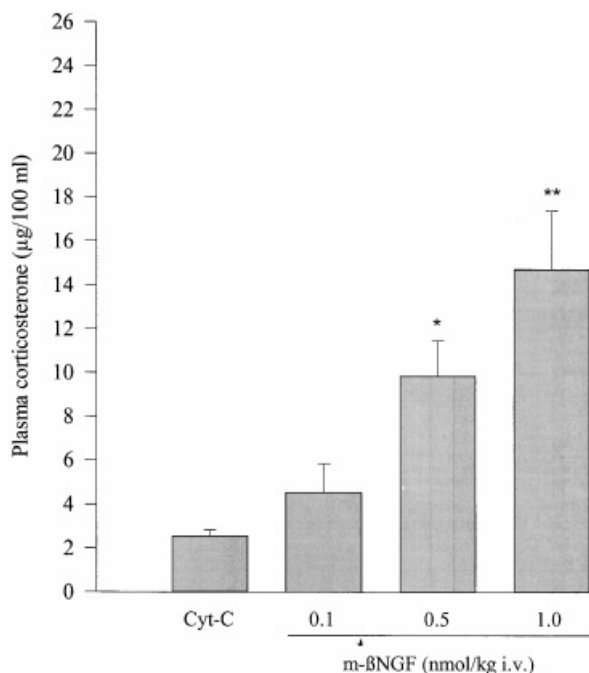


Fig. 1. Plasma corticosterone levels in male Wistar rats 30 minutes after the injection of m-βNGF (0.1–1.0 nmol/kg) or cytochrome C (Cyt-C). Animals were freely moving and injected via a permanent cannula in the jugular vein. Mean values \pm SEM; $n=6$. * $p<0.05$; ** $p<0.01$, vs. vehicle (Dunnett's post hoc test).

Results

Effect of m-βNGF on adrenocortical activity

Treatment with a commercially available preparation of the trophic factor was followed by adrenocortical activation (Fig. 1), in agreement with our previous experiments [4] carried out using a purified preparation of m-βNGF. Intravenous injection of m-βNGF in freely moving cannulated rats, 30 min after administration, produced a dose dependent increase in plasma corticosterone concentrations. This time point was chosen since we had previously demonstrated that the maximum effect on plasma corticosterone is achieved 20 min after i.v. NGF treatment and remained unchanged for up to 2 h [4].

Effect of promethazine, zolantidine and metiamide on corticosterone release induced by histamine

The effect of antihistamines on histamine-induced corticosterone release is showed in figure 2. As shown, intraperitoneal histamine injection (3.5 mg/kg) significantly increased plasma corticosterone concentrations measured 30 min after the treatment. The H_1 histamine antagonist promethazine (0.5 mg/kg i.p.), injected 60 min before histamine, completely prevented the stimulatory response. On the contrary, none of the H_2 antagonist affected the corti-

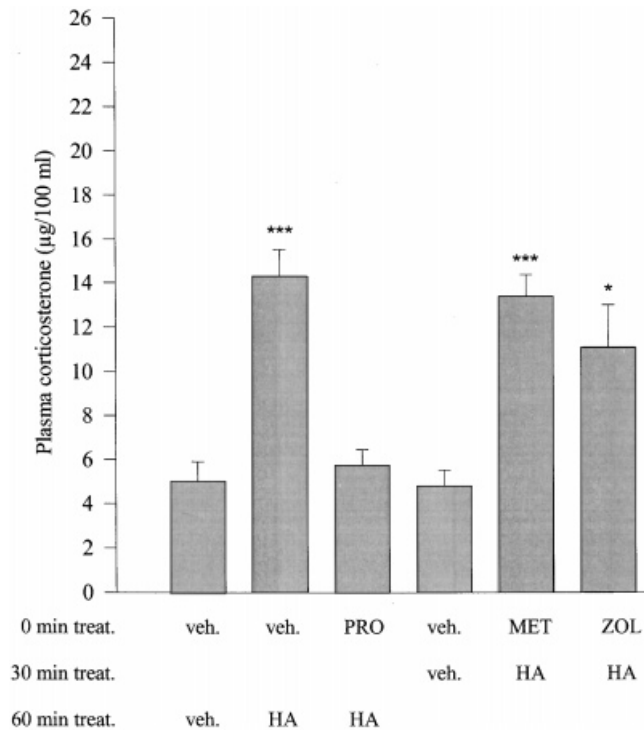


Fig. 2. Effect of histamine (HA, 3.5 mg/kg i.p.) on plasma corticosterone concentrations in vehicle (veh.), promethazine (PRO, 0.5 mg/kg i.p.), metiamide (MET, 80 mg/kg i.p.) and zolantidine (ZOL, 5 mg/kg i.p.)-pretreated male Wistar rats. Blood for hormone determination was collected 30 min after the last treatment. Mean values \pm SEM; $n=6$. * $p < 0.05$; *** $p < 0.001$ vs. respective veh./veh. group (Tukey's post hoc test).

costerone stimulation elicited by histamine. Indeed, neither metiamide (80 mg/kg i.p.) nor zolantidine (5 mg/kg i.p.) inhibited adrenocortical activation.

Effect of promethazine, zolantidine and metiamide on corticosterone release induced by m-βNGF

In this experiment, freely moving cannulated rats were treated with antihistamines and, after 60 min, in the case of promethazine or 30 min, in the case of zolantidine and metiamide, they received m-βNGF (1.0 nmol/kg i.v.). Trunk blood was collected 30 min after NGF injection. As shown in figure 3, the antihistamines did not influence corticosterone response to NGF.

Effect of m-βNGF on corticosterone release from adrenal tissue

The presence of m-βNGF (20 nM) in the incubation medium of *in vitro* isolated adrenal quarters did not affected basal and ACTH-stimulated corticosterone release (Table 1). Results of the same profile were obtained using a different preparation of adrenal tissue. As shown in Table 2, basal and ACTH-stimulated corticosterone release from collagenase-dispersed adre-

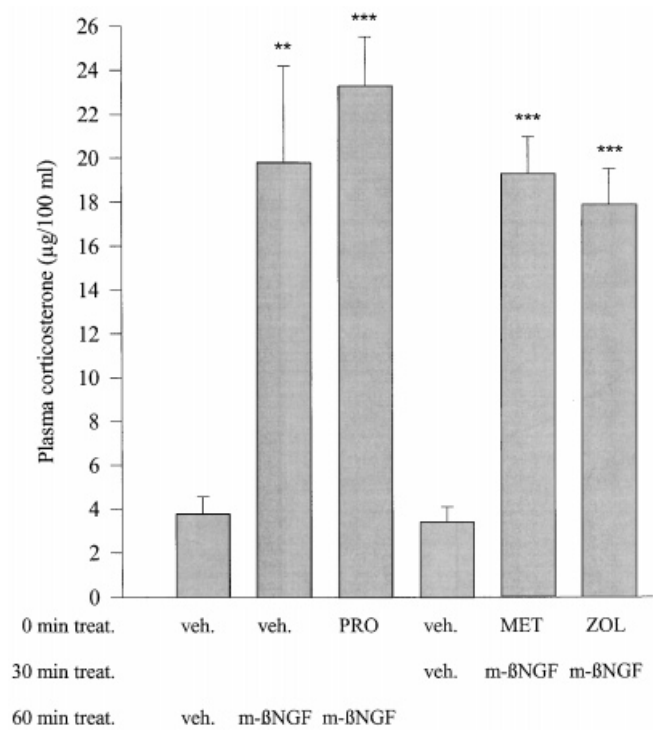


Fig. 3. Effect of m-βNGF (1.0 nmol/kg i.v.) on plasma corticosterone concentrations in vehicle (veh.), promethazine (PRO, 0.5 mg/kg i.p.), metiamide (MET, 80 mg/kg i.p.) and zolantidine (ZOL, 5 mg/kg i.p.)-pretreated male Wistar rats. Animals were freely moving and m-βNGF was injected via a permanent cannula in the jugular vein. Blood for hormone determination was collected 30 min after the last treatment. Mean values ± SEM; n=6-8. ** p<0.01; *** p< 0.001, vs. respective veh./veh. group (Tukey's post hoc test).

nal cells was unaffected by m-βNGF. In these experiments, the NGF dose chosen was such as to produce in the incubation medium a concentration comparable to that produced in the rat blood after an intravenous injection of 1 nmol/kg of NGF, assuming the rat plasma volume to be 27.4 ml/kg [34].

Table 1
Effect of m-βNGF on basal and ACTH-stimulated corticosterone release from *in vitro* isolated adrenal quarters

Treatment	Corticosterone ng/ml/mg wet tissue/h
Vehicle	6.25 ± 0.87
ACTH (1 nM)	10.06 ± 0.71**
m-βNGF (20 nM)	7.07 ± 0.70
ACTH (1 nM) + m-βNGF (20 nM)	10.15 ± 1.23*

The results are the mean values ± SEM of 6 determinations per group; ** p<0.01; * p<0.05 vs. vehicle (Duncan's new multiple range test).

Table 2

Effect of m- β NGF on basal and ACTH-stimulated corticosterone release from collagenase-dispersed adrenal cells

Treatment	Corticosterone ng/ 2.5×10^5 cells/ml/h
Vehicle	9.34 ± 1.17
ACTH (30 pM)	$329.91 \pm 6.22^{***}$
m- β NGF (20 nM)	12.64 ± 0.97
ACTH (30 pM) + m- β NGF (20 nM)	$341.18 \pm 7.63^{***}$

The results are the mean values \pm SEM of 6 determinations per group; *** $p < 0.001$ vs. vehicle (Duncan's new multiple range test).

Discussion

The first demonstration that NGF dose-dependently activates the hypothalamic-pituitary-adrenal axis was provided by Otten and colleagues in 1979 [1]. More recent studies by our group indicated that the trophic factor could be a modulator of HPA axis activation during stress [9] and that adrenocortical activation was triggered by the release of hypothalamic vasopressin [4]. Several indications prompted us to undertake a study aimed at investigating whether endogenous histamine plays a role in the HPA axis activation induced by NGF. NGF is able to liberate histamine from mast cells [12–14] through a mechanism of action that is different from that induced by other histamine liberators [15]. Among the actions exerted by histamine, its ability to cause the release of ACTH through the release of the main corticotropin secretagogues (i.e. CRH and vasopressin) [18,20,35] is relevant to the aim of this study.

Histamine exerts its actions through three distinct classes of receptors, designated as H_1 [36], H_2 [37], and H_3 [38]. The predominant importance of H_1 receptors in histamine induced HPA axis activation was originally suggested by observations that this effect was completely prevented by several H_1 antihistamines and only partially inhibited by H_2 antagonists [25]. More recent studies corroborated this finding, indicating that H_1 activation is the more critical stimulus [22–24,26–29]. In our research, we used the H_1 antihistamine promethazine, applying an experimental protocol that, as demonstrated by Reilly and Sigg [21] and verified by us in the present study, allows the complete prevention of the adrenocortical activation induced by histamine. When the same experimental conditions were used to test the involvement of histamine H_1 -receptor on NGF-induced HPA axis stimulation, the results led to the conclusion that the blockade of this class of receptors does not affect the NGF stimulation of the corticotrope axis.

Most H_2 -receptor antagonists are polar compounds and have difficulty in passing the blood-brain barrier. Although this property is of great use in selective action limited on peripheral tissues, it does limit the use of the compounds for the *in vivo* evaluation of H_2 -receptor function within the CNS. However, zolantidine, which is a potent and selective brain-penetrating histamine H_2 -receptor antagonist [39,40], recently became commercially available. At present, there are no reports on the effect of zolantidine on the histamine-induced adrenocortical activation. However, existing data [41,42] indicate that this compound, at a dose of 5 mg/kg, reduces some responses elicited by stress (e.g.: gastric ulcer formation, stress-induced analgesia). In our experiment we used this dose also in consideration of the fact that doses greater than

5 mg/kg may inhibit histamine methyltransferase (the catabolic enzyme for histamine), causing an increase in levels of histamine which could oppose its antagonism at H₂-receptor [39].

Unlike the paucity of available data on zolantidine and HPA axis-related phenomena, metiamide has been used in several experiments aimed at testing the relative contribution of H₂ receptors in histamine-induced adrenocortical activation [21,24,28]. For this reason, we included also this antagonist in our experiments. As for H₁ antagonist, blockade of the H₂ receptor did not influence corticosterone response to NGF.

A different experimental approach to study the eventual implication of endogenous histamine on the NGF-induced adrenocortical activation could have been the measurement of circulating histamine levels after NGF injection. This latter approach was not adopted because the results would have not taken in consideration the CNS. In fact, effects circumscribed only at CNS level would have been ignored. The use of antihistamines that act at both the CNS and the peripheral level is, in our opinion, a better tool to investigate the putative role of histamine in the NGF modulation on HPA axis.

In the present report we have also studied, by means of an *in vitro* approach, whether the plasma corticosterone release following NGF administration is achieved through an ACTH-independent mechanism. The rationale behind this hypothesis was that i) mast cells have been identified in the rat adrenal gland, located close to the adrenal arterioles as they penetrate the connective tissue capsule of the gland [30]; ii) histamine H₁ receptor activation in the adrenal gland leads to the release of adrenaline [31]; and iii) adrenaline has been reported as being able, by means of an autocrine and/or paracrine regulatory mechanism, to stimulate glucocorticoid synthesis and secretion from the adrenal gland [32,43,44]. In planning the relative experiments, we chose to use two preparations of adrenal tissue: adrenal segments and dispersed cells. This was done considering that a degree of cellular architecture is preserved by using adrenal quarters, while the collagenase preparation, which does not affect mast cells activity [45], is more sensitive to corticosteroidogenic stimuli. In our experiments, we found that the presence of NGF in the incubation medium of *in vitro* isolated adrenal quarters or collagenase-dispersed adrenal cells did not modify basal and ACTH-stimulated corticosterone release.

In conclusion, the present findings indicate that endogenous histamine is not involved in the HPA axis activation induced by NGF.

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