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Hypothalamic α_{2A}-adrenoceptors stimulate growth hormone release in the rat

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Abstract

Oxymetazoline, the relatively selective α_{2A}-adrenoceptor agonist (with more than 60-fold selectivity over the α_{2B}-adrenoceptor subtype), was administered into the lateral ventricle (i.c.v.) of rats and plasma growth hormone (GH) levels were measured. Oxymetazoline was more potent to release GH after i.c.v. administration than was clonidine; 0.01 μg i.c.v. oxymetazoline already caused a significant release of GH, while at least 0.1 μg clonidine had to be administered to cause a similar response. The dose-response curve was of an inverted U shape since with 10 μg of oxymetazoline the plasma GH did not rise. When oxymetazoline was injected i.c.v. to rats with somatostatin fibres to the median eminence transected by an anterolateral cut in the hypothalamus there was a significant rise in plasma GH, suggesting that oxymetazoline stimulated GHRH rather than inhibited somatostatin release. Pretreatment with CH-38083 (7,8-(methylenedioxy)-14-α-hydroxy-alloberban HCl, selective for α_2-adrenoceptors but not differentiating between α_{2A} and α_{2B} subtypes), prevented the plasma GH rise normally elicited by 1 μg i.c.v. oxymetazoline. The α_{2A}- and α_1-selective adrenoceptor antagonist, WB-4101 (2-(2,6-dimethoxyphenoxyethyl)-aminomethyl-1,4-benzodioxane hydrochloride), prevented the GH rise normally induced by oxymetazoline while prazosin, the α_{2B}- and α_1-selective adrenoceptor antagonist, prolonged the elevation occurring in the control rats between 30 and 60 min after oxymetazoline injection. Since both prazosin and WB-4101 are α_1-adrenoceptor antagonists but differ in their action on α_{2A} and α_{2B} subtypes as well as in their action on oxymetazoline-induced GH secretion, the antagonist studies suggest that oxymetazoline stimulates GH release through activation of α_{2A}-adrenoceptors stimulatory to GHRH release, and not by an action through α_{2B}- or α_{2C}- or α_1-adrenoceptors. Since WB-4101 also antagonized clonidine action on GH release we also suggest that the major component may be the stimulation of the α_{2A}-adrenoceptors in the clonidine action on GH release.

Keywords: Hypothalamus; Pituitary; α_2-Adrenoceptor; Growth hormone; Clonidine; Oxymetazoline; α_2-Adrenoceptor antagonist; α_{2A}-Adrenoceptor subtype; α_{2B}-Adrenoceptor subtype

1. Introduction

The regulation of growth hormone (GH) secretion involves a number of complex interactions involving the hypothalamus (for references see Müller, 1987). Neurotransmitters acting in the *anterior* hypothalamus may alter the secretion of somatostatin, the powerful inhibitor of GH secretion in anterior pituitary GH cells. In the *medial basal* hypothalamus, neurotransmitters acting on the GH releasing hormone (GHRH)-secreting neurons alter the release of GHRH into the portal circulation and thus modify the stimulatory neurohormonal control of GH release. The two hypothalamic neurohormonal systems have opposite actions on the GH cell and reciprocally innervate each other in the hypothalamus (Liposits et al., 1988; Horváth et al., 1989). The hypothalamic regulation can act in a push-pull manner which may facilitate rapid and large amplitude alterations in the plasma hormone levels.

The major role of noradrenaline in controlling GH release (see Al-Damluji, 1993) is widely accepted. Both the somatostatin and GHRH containing regions of the hypothalamus receive a massive noradrenergic innervation (Palkovits, 1981). Depletion of hypothalamic noradrenaline blocks episodic GH release (Terry and Martin, 1981), injection of noradrenaline or the α_2-adrenoceptor agonist, clonidine, strongly stimulates GH secretion, with the noradrenaline effect seen even after a hypothalamic cut blocking somatostatin release (Kakucska and Makara, 1983).

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In recent years pharmacological and molecular biological techniques have clearly shown that there are at least four different subtypes of α_2-noradrenergic receptors (α_{2A}, α_{2B}, α_{2C}, and α_{2D}) (Bylund, 1988). The previously widely studied adrenoceptor agonist, clonidine, and the adrenoceptor antagonist, yohimbine, are not selective for any subtype. Rat brain contains at least two populations of α_2-adrenoceptor sites (Bylund, 1985, 1988), designated as α_{2A} and α_{2B}. Oxymetazoline was found to be a relatively selective α_{2A}-adrenoceptor agonist with more than 60-fold selectivity over the α_{2B}-adrenoceptor subtype (Bylund, 1985; Uhlen and Wikberg, 1991).

The $_{2B}$-adrenoceptor-selective antagonists (such as prazosin) used to define the subtypes are generally only 10- to 50-fold selective (Bylund, 1988); their α_1-adrenoceptor antagonist properties have to be taken into account since, through α_1-adrenoceptor antagonism, they are expected to act on the somatostatin cells and raise GH levels. The potential α_2-adrenoceptor agonist drugs such as clonidine and oxymetazoline are rather weak α_1-adrenoceptor agonists.

Neuropeptide (vasopressin (AVP), corticotrophin releasing hormone (CRH), somatostatin, thyrotropin releasing hormone (TRH))-containing innervation of the median eminence may be surgically cut in rats, using anterolateral deafferentation of the medial basal hypothalamus; after this surgery endogenous somatostatin action in the median eminence is abolished and the neural control of plasma GH occurs predominantly via GHRH. Such deafferented rats respond to noradrenaline infused into the third ventricle with an elevation of plasma GH (Kakucska and Makara, 1983). We used this surgical approach to try to localize the site of action of oxymetazoline on GH secretion.

2. Materials and methods

Male Wistar rats, weighing 250–300 g, were housed 3–5 per cage at 23–25°C and 50–60% humidity with a 12/12 h light-dark (light on 06.00 h, off 18.00 h) cycle. They were given pelleted rat food and tap water ad libitum. Handling was once a day for at least 3 consecutive days preceding the experiments. One day before the experiment the rats were given an i.c.v. injection of 5 μl saline.

When anterolateral hypothalamic deafferentation was used the stereotaxic surgery was performed under pentobarbital anaesthesia (40 mg/kg i.p.) 7–8 days before i.c.v. and i.v. cannula placement, as described earlier (Kakucska and Makara, 1983).

Two days before blood sampling the rats were anaesthetized with pentobarbital (40 mg/kg i.p.) and a polythene cannula was introduced into the right lateral cerebral ventricle and secured to the skull with the aid of small screws and dental cement. A Silastic cannula was placed into the right atrium via the jugular vein and exteriorized at the back, filled with heparinized saline and sealed.

The rats were housed singly in experimental cages and an extension cannula was attached to the venous cannula for blood sampling at least 1 h before the sampling procedure began. All sampling was performed between 9.00 and 11.00 h. Samples were collected in heparinized plastic tubes on ice 5 min before and 7, 15, 30 and 60 min after an i.c.v. drug injection. Pretreatment with various drugs was given 30 min before i.c.v. injections. All animals were maintained according to the NIH Guidelines for the care and use of laboratory animals.

The blood was centrifuged at 4°C at 2000 rpm and the plasma was frozen at −20°C until radioimmunoassay (RIA). The plasma GH was measured by RIA, using materials kindly supplied by the NIDDK Rat Pituitary Hormone Distribution Program. Assay characteristics were: sensitivity 1.6 ng/ml, intraassay variation 4–7%, interassay variation 10%.

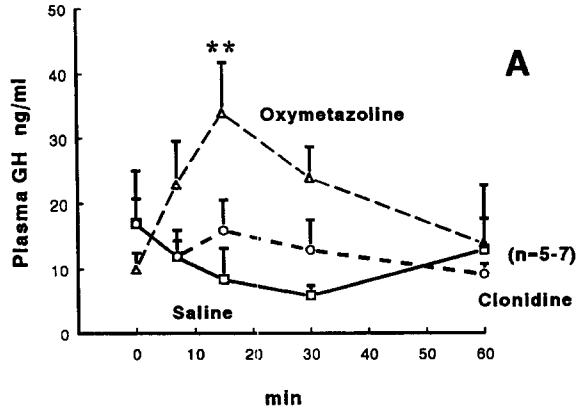
All i.c.v. injections were given in a volume of 5 μl of saline which was also injected into the controls. Control i.p. injections of 1 ml/kg physiological saline were given 30 min before i.c.v. injections. Oxymetazoline was purchased from Sigma (St. Louis, MO, USA). Clonidine was from Boehringer (Ingelheim, Germany). CH-38083, 7,8-(methylenedioxy)-14-α-hydroxy-alloberban HCl, a novel selective, potent antagonist of α_2-adrenoceptors (Chinoin, Hungary) (Vizi et al., 1986) was dissolved in saline and used at a dose of 1 mg/kg i.p. WB-4101 (2-(2,6-dimethoxyphenoxyethyl)-aminomethyl-1,4-benzodioxane hydrochloride) was purchased from RBI (Natick, MA, USA) and was used at a dose of 0.5 mg/kg in 1 ml/kg saline i.p. given 30 min before i.c.v. injection of oxymetazoline. Prazosin was first dissolved with the help of a few drops of 0.01 N HCl, then diluted with physiological saline. It was given in a dose of 0.5 mg/kg/ml i.p. 30 min before i.c.v. injection of oxymetazoline.

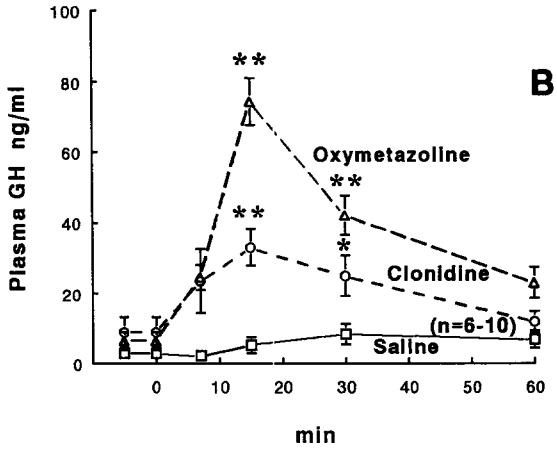
Statistical analysis was done by two-way analysis of variance (ANOVA) for repeated measures followed by Dunnett's test for multiple comparisons (Crunch Software, San Diego, CA, USA). Since the means were roughly proportional to the standard deviation we used logarithmic transformation of data for the statistical analysis.

3. Results

3.1. The α_2-adrenoceptor agonist action on GH release

Oxymetazoline was more potent to release GH after i.c.v. administration than was clonidine. Oxymetazoline





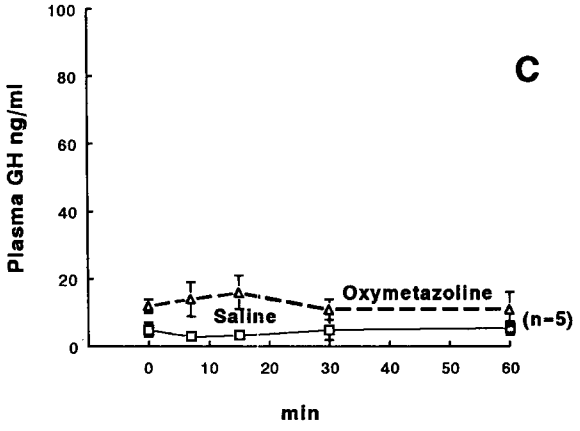


Fig. 1. The effect of oxymetazoline or clonidine on plasma GH secretion. A: Effect of 0.01 μg/rat adrenoceptor agonist into the lateral ventricle (i.c.v.). B: Effect of 0.1 μg/rat agonist i.c.v. C: Effect of 10 μg/rat oxymetazoline i.c.v. * $P < 0.05$, ** $P < 0.01$ compared to the value at time zero. 5 μl saline i.c.v.: open circles; oxymetazoline i.c.v.: open squares; clonidine i.c.v.: open triangles.

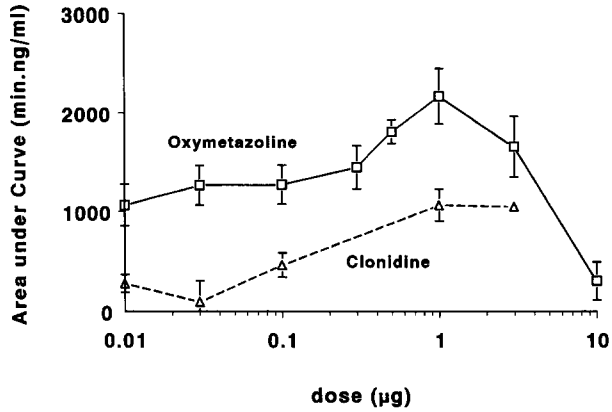


Fig. 2. The effect of oxymetazoline (open squares) and clonidine (open triangles) on GH secretion as measured by the area under the curve (AUC).

already caused a significant release of GH at a dose of 0.01 μg (Fig. 1A) while even 0.03 μg clonidine was ineffective and 0.1 μg had to be administered to cause a similar response (Fig. 1B). During a gradual increase of the dose to 3 μg the response to clonidine was always smaller than was that to oxymetazoline. With a further increase of the dose of oxymetazoline to 10 μg the plasma GH rise disappeared (Fig. 1C), giving an inverted U shaped dose-response curve with the area under the GH curve as the response measure (Fig. 2).

3.2. Oxymetazoline effect after anterolateral hypothalamic cut

Whether oxymetazoline influenced the secretion of hypothalamic somatostatin or that of the GHRH was studied using rats in which somatostatin fibres were surgically transected, and that were equipped with i.c.v. and intravenous cannulas. Such rats have no somato-

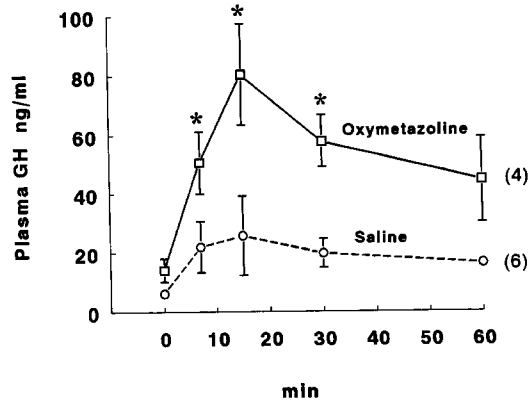


Fig. 3. The effect of oxymetazoline on the plasma GH in rats with an anterolateral cut around the medial basal hypothalamus. Saline i.c.v.: open circles; oxymetazoline: open squares. * $P < 0.05$ compared to the value at time zero.

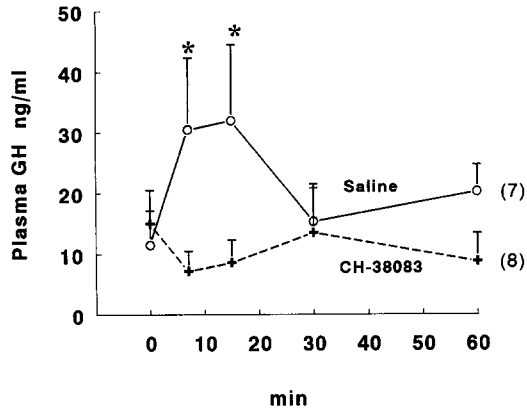


Fig. 4. CH-38083 (1 mg/kg i.p.) prevented the oxymetazoline (1 μg/rat i.c.v.)-induced rise in plasma GH. Saline + oxymetazoline: open circles; CH-38083 + oxymetazoline: +. $^{*}P < 0.05$ compared to the CH-38083-treated group.

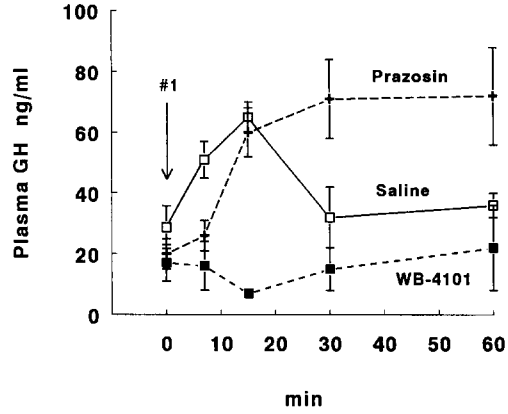


Fig. 6. The effects of WB-4101 and prazosin on oxymetazoline-induced plasma GH rise. Injection of saline, 0.5 mg/kg WB-4101 or prazosin i.p., 30 min before injection of oxymetazoline (1 μg/rat i.c.v. at #1) at 0 min. Saline i.p.: open squares; WB-4101 i.p.: filled squares; prazosin i.p.: +.

statin, AVP, CRH or TRH in the stalk-median eminence region; their plasma corticosterone and thyroid hormone levels are low; without supplementation with the appropriate peripheral hormones their GH responses are smaller than the responses of the controls (Kakucska and Makara, unpublished data). When oxymetazoline was injected i.c.v. to rats with a hypothalamic cut, there was a small, significant ($P < 0.05$) rise in plasma GH (Fig. 3), suggesting that oxymetazoline stimulated GHRH release.

3.3. CH-38083, WB-4101 and prazosin interaction with oxymetazoline-induced GH rise

Pretreatment with 1 mg/kg CH-38083 (selective for α_2-adrenoceptors but not differentiating between α_{2A} and α_{2B} subtypes) prevented the plasma GH rise normally elicited by 1 μg i.c.v. oxymetazoline (Fig. 4).

Pretreatment with 0.5 mg/kg WB-4101, a well known α_1- and α_{2A}-adrenoceptor antagonist, prevented the plasma GH rise normally produced by *clonidine* (Fig. 5). Next, WB-4101 or prazosin (an α_1-adrenoceptor antagonist which antagonizes α_{2B}-adrenoceptor-mediated actions) were given before *oxymetazoline* (Fig. 6); WB-4101 prevented the GH rise normally induced by oxymetazoline while prazosin potentiated its action by preventing the return to baseline occurring in the control between 30 and 60 min after oxymetazoline injection.

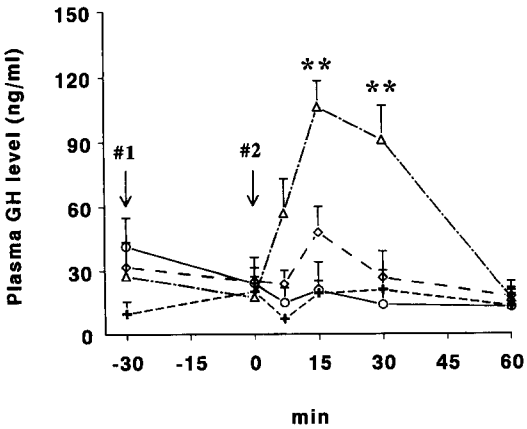


Fig. 5. The effect of WB-4101 on clonidine-induced plasma GH rise. At #1 injection of saline or 0.5 mg/kg WB-4101 i.p., at #2 injection of saline or clonidine (1 μg/rat i.c.v.). Saline i.p. + i.c.v.: open circles; saline i.p. + clonidine i.c.v.: triangles; WB-4101 i.p. + saline i.c.v.: +; WB-4101 + clonidine i.c.v.: diamonds. $^{**}P < 0.01$ compared to time zero.

4. Discussion

The present findings are consistent with the proposal that the α_2-adrenoceptors belonging to the α_{2A} subtype mediate the noradrenergic stimulation of GHRH and of GH. This is supported by the potent GH releasing action of i.c.v. oxymetazoline, the antagonism of oxymetazoline by the selective α_2-adrenoceptor antagonist CH-38083, and the antagonism of the oxymetazoline-induced GH release by WB-4101 but not prazosin.

The use of the relatively specific agonists and antagonists as well as antisera to GHRH also contributed to the evidence implicating endogenous noradrenaline acting on α_2-adrenoceptors on or near the GHRH cells to stimulate GH release, and α_1-adrenoceptors in the anterior hypothalamus on, or near the somatostatin cells which may inhibit the release of GH from the anterior pituitary gland (Durand et al., 1978; Krulich et al., 1982; Miki et al., 1984; Eden et al., 1981; Willoughby et al., 1993).

Oxymetazoline was found to be selective for the human platelet α_{2A}-adrenoceptor compared to the α_{2B}-adrenoceptor subtype on neonatal rat lung membranes (Uhlen and Wikberg, 1991), and shows a selectivity of over 60-fold for α_{2A} over α_{2B}. Recent radioligand binding data with computer modelling revealed oxymetazoline to be highly α_{2A}-selective (Uhlen and Wikberg, 1991).

In rat cerebral cortex α_{2A} and α_{2B} subtypes are found in about equal proportion (Bylund, 1985); there are no data available on the relative proportion of the various subtypes in the hypothalamus (Wamsley et al., 1992). On HT29 cells exhibiting α_{2A}-adrenoceptors, oxymetazoline was found to act as a partial agonist inhibiting cyclic AMP production by up to 80% (Langin et al., 1989). When studied on acetylcholine release from the guinea pig Auerbach's plexus, oxymetazoline was equipotent with xylazine as an α_{2A}-adrenoceptor agonist inhibiting acetylcholine release (Blandizzi et al., 1991).

Oxymetazoline is known not to penetrate the blood-brain barrier and Jurcovicova et al. (1989) showed that it did not release GH on systemic injection. In the present study oxymetazoline via i.c.v. injection was about 10 times more potent than clonidine as a releaser of GH. The high GH releasing potency of a selective α_{2A}-adrenoceptor agonist suggests that α_{2A}-adrenoceptors participate in the stimulatory control of GH secretion.

In large doses, oxymetazoline was ineffective to release GH, possibly because at the large dose it has α_1-adrenoceptor agonist activity and stimulates somatostatin release to a significant degree and somatostatin inhibition of GH secretion counteracts the effect mediated by the GHRH neurons (Willoughby et al., 1993). Another possibility is that, at high doses, oxymetazoline may be stressful and stimulate somatostatin secretion by a nonspecific central nervous system (CNS) mechanism.

Recently it has been shown that oxymetazoline also interacts with a number of receptor subtypes of the 5-HT_1 receptor family. Important for the release of GH may be its 5-HT_{1C} receptor stimulatory actions (Aulakh et al., 1992), where oxymetazoline may be a partial agonist/antagonist (Schoeffter and Hoyer, 1991). Since the GH release induced by oxymetazoline was prevented by the α_2-adrenoceptor antagonist, CH-38083, and α_{2A}-adrenoceptor antagonist, WB-4101, we think it unlikely that the oxymetazoline action on GH release is due to its putative actions on 5-HT receptors.

Selectivity of the general α_1- and α_2-adrenoceptor drugs may reach 1000-fold whereas selectivity of the α_2 subtype specific drugs is much lower; prazosin is about 222-fold selective for the α_{2B}-adrenoceptor over α_{2A}. CH-38083 is highly selective for the α_2-adrenoceptors, it is about 1000-fold less active on the α_1-adrenoceptors (Vizi, 1986; Vizi et al., 1986,1987); however, it does not have α_2 subtype selectivity, having almost equal K_D values on human platelet and rat lung membranes (Fejér et al., 1990). In isolated organ tests it failed to antagonize 5-HT receptors (Vizi et al., 1986). Thus the antagonism of the oxymetazoline effect on GH by CH-38083 offers a good argument in favour of oxymetazoline acting via α_2-adrenoceptor activation rather than via direct 5-HT_{1C} receptor action. Further studies with various selective 5-HT receptor antagonists are needed for deciding whether the serotonergic receptor system has a role in mediating the effect of oxymetazoline on GH secretion, as might be extrapolated from the results of Conway et al. (1990) and Aulakh et al. (1992).

The effects of WB-4101 and prazosin were helpful for dissecting the α_2-adrenoceptor subtypes activated by oxymetazoline. Both WB-4101 and prazosin are known to antagonize α_1-adrenoceptors but they have contrasting actions on the α_2-adrenoceptors, with WB-4101 being a selective antagonist for the α_{2A}-adrenoceptor as opposed to α_{2B} or α_{2C}, and prazosin being selective for the α_{2B}- and α_{2C}-adrenoceptors (Bylund et al., 1988). Since these two drugs have different actions on oxymetazoline-induced GH release, we may conclude that antagonist studies also support the proposition that oxymetazoline stimulates GH release through activation of α_{2A}-adrenoceptors stimulatory to GHRH release, and not by an action through α_{2B}- or α_{2C}-adrenoceptors. Since WB-4101 also antagonized clonidine action on GH release we can also suggest that the major component in the clonidine action on GH release may be stimulation of the α_{2A}-adrenoceptors.

The anatomical site of action of i.c.v. oxymetazoline may be anywhere within the CNS. The results of the experiment with an anterolateral cut around the medial basal hypothalamus argue against a dominant action on the somatostatinergic neurons located in the anterior hypothalamus since those are prevented by the anterolateral hypothalamic cut from affecting GH release. The noradrenergic innervation of the region of the GHRH neurons is also removed by the anterolateral cut (Palkovits et al., 1977) and the results of this experiment argue that the site of action of oxymetazoline-induced stimulation of GH release may be in the medial hypothalamus, on or near the GHRH neurons.

Results of two recent pharmacological studies suggest that the clonidine-induced GH release is mediated by the 5-HT receptor system (Aulakh et al., 1992; Conway et al., 1990). Taken together, these results suggest that there are α_2 heteroreceptors on 5-HT fibers serving as stimulatory input to the GHRH neurons, and the α_2 heteroreceptors may stimulate GH release by the mediation of 5-HT release from the terminals acting on 5-HT_{1C} receptors on the GHRH

neurons. The present study was not designed to test the hypothesis of serotonergic mediation of α_2-adrenoceptor-stimulated GH release, and most of the results may be reconciled with either an α_{2A} action linked with serotonergic mediation or a direct action of α_{2A}-adrenoceptors on the GHRH neuron or on its non-serotonergic interneurons.

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