ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

https://ijpp.com

Indian Journal of Physiology and Pharmacology

Original Article

The role of histamine in anterior pituitary secretion

Afrah Nasserallah Faris[1], Khalid G. Al-Fartosi[1], Ali Esmail Al-Snafi[2]

Departments of [1]Biology and [2]Pharmacology, College of Medicine, University of Thi-Qar University, Nasiriyah, Iraq.

***Corresponding author:**
Ali Esmail Al-Snafi,
Department of Pharmacology,
College of Medicine, University
of Thi-Qar, Nasiriyah, Iraq.

aboahmad61@yahoo.com

Received : 14 May 2020
Accepted : 11 October 2021
Published : 25 February 2022

DOI
10.25259/IJPP_73_2020

Quick Response Code:

ABSTRACT

Objectives: The aim of the present study was to determine the effects of histamine on the anterior pituitary secretion in rats.

Materials and Methods: In the first experiments rats were injected with histamine 5 mg/kg i.p., and blood samples were collected to determine the effect of histamine on serum level of adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), prolactin, FSH, and luteinizing hormone (LH) after 10, 20, and 30 min of histamine injection. In the second experiments, rats were treated with (H 1 blocker), chlorphenramine 10 mg/kg, i.p. or (H 2 blocker), cimetidine 80 mg/kg, i.p. respectively, and after 30 min they were injected with histamine and blood samples were taken 30 min after the injection of histamine to determine the same hormones.

Results: Histamine significantly elevated serum ACTH and LH level, and these stimulatory effects were inhibited by both H1 and H2 receptor blockers. However, histamine significantly inhibited the serum level of thyroid-stimulating hormone and this inhibitory effect was blocked by H2 receptor blocker, while it showed no effect on the secretion of both prolactin and FSH, although H2 blocker significantly decreased prolactin level and H1 blocker significantly elevated FSH level.

Conclusion: The results clearly indicated that histaminergic pathways were involved in the anterior pituitary secretion.

Keywords: Histamine, Pituitary, Adrenocorticotropic hormone, Follicle-stimulating hormone, Prolactin, Luteinizing hormone

INTRODUCTION

Histamine is an effective biogenic monoammine synthesized from the primary amino acid histidine. It is stored in special granules inside the basophiles or mast cells and is secreted in cases of inflammation or allergies when a reaction occurs between the antibody and the IgE.[1] Histamine is found in the brain in abundant quantities and in smaller quantities in other tissues such as skin, lung, small intestine, white blood cells, liver, kidney, placenta, and neurons in the posterior part of the hypothalamus.[2]

The level of histamine in the brain tissue is lower than the rest of the biological amines, but its metabolic rate is much faster (within minutes), depending on the functional condition, as the half-life of histamine is 30 min,[1,3] histamine reaches the highest level in the anterior segment or anterior lobes of the hypothalamus during the waking period, and its lowest levels during the sleep period. The synthesis and release of histamine are controlled by the H_3 auto-receptors located in the presynaptic membrane, in addition to other receptors such as M1 and $\alpha 2$ receptors.[4,5]

It was found that the content of histamine in the brain regions, approximately 50 nanogram histamine per gram.[2] The number of neurons that make up histamine in rats is approximately 2000 neurons located in the tuberomammillary nucleus.[6] There is a similar structure in humans located in the posterior part of the hypothalamus, where the number of histamine-forming neurons is about 64,000 neurons, and from this region a network of nerve fibers branches from these cells to the cerebral cortex.[7]

There are two ascending pathways of the histamine cells that can be distinguished in the brain of rats, one of these paths is comes from the middle bundle of the anterior brain, from which the fibers of the nerve cells are spread in the posterior brain, and the second pathway is in the region around the third ventricle, peri-ventricular, and the nerve connections to these two ascending pathways end in some regions. From the brain, including olfactory bulb, hippocampus, caudate putamen, globus pallidus, and amygdaloid complex, and besides, there are descending pathways of cells that spread from the hypothalamus to the brain areas.[8-10]

Brain histamine is considered as neuro-endocrine transmitter. Histamine possessed stimulatory effect on growth hormone secretion in man mediated by both H1 and H2 receptors.[11,12] It also increased both basal and stimulated plasma level of adrenacorticotrophic hormone and corticosteroids through H1 and H2 receptors, while it possessed inhibitory effects through H3 receptors. However, histamine possessed inhibitory effect on the secretion of prolactin through H2 receptors,[13,14] while histamine stimulated both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion.[15]

The present study aims to determine the effects of histamine on the anterior pituitary secretion in rats. In addition, it aims to investigate the type of receptor responsible for the stimulatory or inhibitory effect of histamine, to know if the H1 and H2 receptor blocker (extensively used) could interfere with the endocrine control especially when used in critical hormonal conditions such as ovulation (such as in patients with peptic ulcers who used H2 blocker, or patients with allergic conditions who used H1 blocker for long period).

MATERIALS AND METHODS

Animals

Sixty male rats (*Rattus norvegicus*) were used in this study; they were obtained from the animal house of the Department of Biology - College of Education, Thi-Qar University, aged 10–14 weeks and weighted 250–300 g. They were placed in plastic cages, 25 ± 3°C and 14 h light/10 h darkness and were given water and food *ad libitum*. The study was approved by the ethical committee of the postgraduate studies of Thi-Qar University- Iraq.

Drugs used

Histamine HCl, chlorpheniramine, and cimetidine were purchased from Sigma.

Acute effect of histamine on the secretion of hormones of anterior pituitary

In this experiment, 24 rats were used, and the animals were divided into four subgroups, as follows: First (control group): rats were injected with distilled water and blood samples were taken 10 min after injection. In the second, third, and fourth groups rats were injected with histamine and then blood samples were taken 10, 20, and 30 min after injection of histamine, respectively. Histamine was used in a dose of 5 mg/kg i.p.[16]

Determining the type of receptors mediating the histamine action

This experiment was conducted to determine the type of receptor by which histamine stimulating or inhibiting the anterior pituitary hormones. Eighteen rats were used in the experiment, and the animals were divided into three subgroups, as follows: First (control group): Was injected with distilled water and after 30 min rats were injected with histamine and blood samples were taken 30 min after the injection of histamine. The second and third groups: Were treated with (H 1 blocker), chlorpheniramine 10 mg/kg, i.p. or (H 2 blocker), cimetidine 80 mg/kg, i.p.,[17] respectively, and after 30 min they were injected with histamine. Rats were anaesthetized with chloroform and venous blood samples were collected by cardiac puncture, sera were stored in a deep freezer.[18] LH, FSH, prolactin, thyroid-stimulating hormone (TSH), and adrenocorticotropic hormone (ACTH) were determined using radioimmunoassay as described by Al-Tahan *et al*.[19] The significance among groups was determine using student-*t*-test.[20]

RESULTS

The results of histamine administration to male rats revealed that histamine significantly ($P < 0.05$) declined the level of TSH (0.29 ± 0.13 vs. 0.82 ± 0.28 IU/l) and significantly ($P < 0.05$) increased the level of prolactin (1.8 ± 0.38 vs. 0.9 ± 0.23 ng/ml) after 10 min of injection. When serum hormones were estimated after 20 min of histamine injection, the ACTH level was significantly ($P < 0.01$) increased (90.75 ± 10.53 vs. 48.00 ± 4.78 pg/ml), while prolactin level which significantly increased after 10 min of histamine injection, was significantly ($P < 0.05$) declined below the normal limit (0.49 ± 2.05 vs. 0.9 ± 0.23 ng/ml) after 20 min of injection. However, after 20 min of injection, histamine also significantly *($P < 0.05$) elevated the serum

level of LH (2.58 ± 0.86 vs. 1.41 ± 0.55 IU/l). On the other hand, after 30 min of injection, histamine elevated both ACTH (62.00 ± 5.82 vs. 48.00 ± 4.78 pg/ml) ($P < 0.05$) and LH level (4.03 ± 1.15 vs. 1.41 ± 0.55 IU/l) ($P < 0.01$). Histamine did not affect the level of FSH after 10, 20, and 30 min of administration [Table 1], [Figure 1].

As shown in [Table 2], both chlorpheniramine (H 1 blocker) and cimetidine (H 2 blocker) inhibited the stimulatory effect of histamine on ACTH secretion, but it appeared that chlorpheniramine was more potent ($P < 0.01$) than cimetidine ($P < 0.05$) in blocking the histamine effect on ACTH. Histamine induced significant decline in the serum level of TSH ($P < 0.05$), chlorpheniramine did not affected the inhibitory effect of histamine, while, cimetidine blocked this effect, and restored the TSH level to the normal limit. Prolactin level was not affected by histamine after 30 min of injection, and also after injection of chlorpheniramine, but it significantly declined after cimetidine injection ($P < 0.05$). Neither histamine nor cimetidine affected the FSH level, but chlorpheniramine significantly elevated serum FSH level ($P < 0.01$). Histamine significantly ($P < 0.05$) elevated serum LH level and this elevation was inhibited by both chlorpheniramine and cimetidine.

DISCUSSION

The aim of the present study was to determine the effects of histamine on the anterior pituitary secretion, and to investigate the role of H1 and H2 receptors in the histaminergic effects on the endocrine hormones. The H1 and H2 blockers were used extensively in patients with allergic conditions and peptic ulcer disease, respectively. Their prolong use could interfered with normal physiological role of histamine and may resulted in public health problems.

The study revealed that histamine significantly elevated serum ACTH level, and this stimulatory effect was inhibited by both H1 and H2 receptor blockers. Previously, it was recorded that intracerebroventricular injection of histamine in dogs increased ACTH secretion. Histamine stimulated both the primary and stimulating ACTH secretion through H1 and H2 receptors,[21,22] while it exerted a depressing effect and can neutralize the induced stimulation of ACTH hormone through H3 receptors.[14]

Our study showed that histamine induced insignificant elevation of prolactin serum level. However, H2 blocker caused significant decline in the serum prolactin level. In rats and dogs, histamine released prolactin hormone when given intracerebroventricularly.[23-26]

The effect of histamine on TSH secretion in the resent study, which antagonized by H2 receptor blocker, could be attributed to its effect at hypothalamic level, so histamine inhibited TRH which stimulated pituitary secretion of TSH. The inhibitory effect of histamine on the secretion of TSH in male rats was mediated through H2 receptors located in median eminence. H2 agonist drugs possessed strong inhibitory effect on TSH

Table 1: The effect of histamine (5 mg/kg) on the levels of pituitary hormones in male rats.

Groups	Hormonal levels (mean±SD)				
	ACTH pg/ml	TSH m IU/l	PRL ng/ml	FSH IU/l	LH IU/l
Control group	48.00±4.78	0.82±0.28	0.9±0.23	6.42±0.61	1.41±0.55
First group after 10 minutes of histamine injection	50.75±2.05	0.29±0.13*	1.8±0.38*	6.32±1.02	2.05 0.43
Second group after 20 minutes of histamine injection	90.75±10.53**	0.42±0.20	0.49±2.05*	6.18±1.30	2.58±0.86*
Third group after 30 minutes of histamine injection	62.00±5.82*	0.46±0.10*	1.32±0.17	6.14±1.20	4.03±1.15**

*($P<0.05$), **($P<0.01$), ACTH: Adrenocorticotropic hormone, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, TSH: Thyroid-stimulating hormone

Table 2: Effect of histamine injection on rat's pituitary hormones after treatment with chlorpheniramine (H1 blocker) and cimetidine (H2 blocker).

Groups	Hormonal levels (mean±SD)				
	ACTH pg/ml	TSH m IU/l	PRL ng/ml	FSH IU/l	LH IU/l
First group (control): Treatment with distilled water	48.00±4.78	0.82±0.28	0.9±0.23	6.42±0.61	1.41±0.55
Second group treatment with distilled water+histamine	64.00±5.90*	0.45±0.07*	1.20±0.19	6.43±1.97	3.38±0.30*
Third group treated with chlorpheniramine+histamine	24.16±4.34**	0.47±0.07*	1.32±0.42	18.36±4.83**	1.70±0.25*
Fourth group treated with cimetidine+histamine	49.00±1.50*	0.81±0.11 *	0.32±0.16*	6.75±1.75	1.80±0.47*

The second group was compared with the first group, while the third and fourth groups were compared with the second group: *($P<0.05$), **($P<0.01$), ACTH: Adrenocorticotropic hormone, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, TSH: Thyroid-stimulating hormone

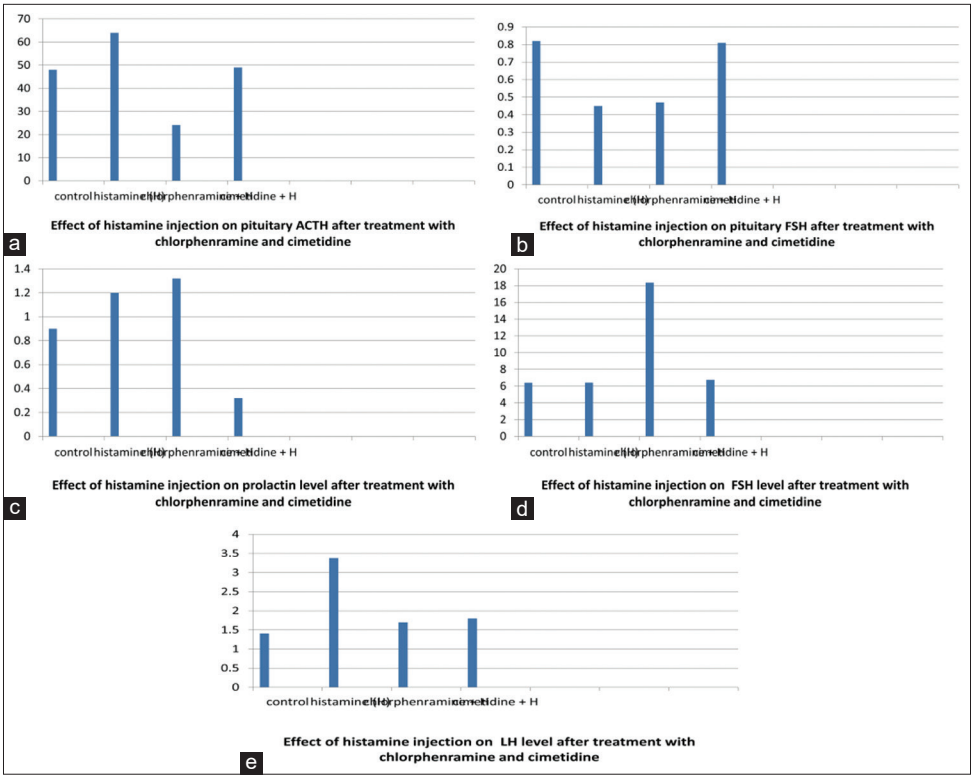

Figure 1: (a-e) Effect of histamine on rat's pituitary hormones after treatment with chlorpheniramine (H1 blocker) and cimetidine (H2 blocker).

secretion.[27] Our study also showed that histamine induced insignificant elevation of serum prolactin level. However, H2 blocker caused significant decline in the serum prolactin level. In rats, histamine released prolactin hormone when given intracerebroventricularly.[23,25,26]

The results of the current study also revealed that histamine significantly elevated serum LH level, and this stimulatory effect was inhibited by both H1 and H2 receptor blockers. The same results were recorded by Horno and Alvarez,[28] who mentioned that the stimulatory action of histamine in secretion of LH in female rats occurred, indirectly by stimulating the GnRH release, and both H2 and H1 receptors participated in this stimulatory action. Incubation of the pituitary gland of female rats with histamine resulted in stimulation of the secretion of GnRH and LH.[29] Many histaminergic neurons contain estrogen receptors, project to luteinizing hormone (LH)–releasing hormone neurons in preoptic and infundibular regions, and may constitute, an important relay in the estradiol-induced preovulatory LH surge.[30,31]

However, histamine significantly elevated serum LH level, but it did not affected FSH secretion. On the other hand, FSH secretion was significantly enhanced by H 1 blockers. This could be attributed to the different sensitivity of LH and FSH receptors for the fluctuation in the GnRH, so LH receptors were more sensitive, and responded more early than FSH receptors.[32]

The elevation of FSH level with the using of H1 blocker could be attributed to anticholinergic effects of H 1 blocker, which enhance the secretion of FSH.[33]

These results clearly indicated that histaminergic innervation of hypothalamic and pituitary glands was involved in the anterior pituitary secretion.

CONCLUSION

It appeared that histamine significantly elevated serum ACTH and LH level, and these stimulatory effects were inhibited by both H1 and H2 receptor blockers. However, histamine significantly inhibited serum level of TSH and this inhibitory effect was blocked by H2 receptor blocker, while it showed no effect on the secretion of both prolactin and FSH, although H2 blocker significantly decreased prolactin level and H1 blocker significantly elevated FSH level. According to these results, histamine represented one of the neuroendocrine factors which affected the endocrine secretion. These results indicated that histaminergic pathways were involved in the anterior pituitary secretion.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Theoharides TC. Neuroendocrinology of mast cells: Challenges and controversies. Exp Dermatol 2017;26:751-9.
2. Haas HL, Panula PP. Histamine receptors. Neuropharmacology 2016;106:1-2.
3. Cataldi M, Borriello F, Granata F, Annunziato L, Marone G. Histamine receptors and antihistamines: From discovery to clinical applications. Chem Immunol Allergy 2014;100:214-26.
4. Sadek B, Stark H. Cherry-picked ligands at histamine receptor subtypes. Neuropharmacology 2016;106:56-73.
5. Panula P, Chazot PL, Cowart M, Gutzmer R, Leurs R, Liu WL, *et al*. International union of basic and clinical pharmacology. XCVIII. Histamine receptors. Pharmacol Rev 2015;67:601-55.
6. Parmentier R, Kolbaev S, Klyuch BP, Vandael D, Lin JS, Selbach O, *et al*. Hormone excitation of histaminergic tuberomamillary neurons by thyrotropin-releasing. J Neurosci 2009;29:4471-83.
7. Hass HL, Sergeeva A, Selbach O. Histamine in the nervous system. Physiol Rev 2008;88:1183-241.
8. Wouterlood FG, Steinbusch HW. Afferent and efferent fiber connections of histaminergic neurons in the rat brain: Comparison with dopaminergic, noradrenergic and serotonergic systems. In: Histaminergic Neurons: Morpbology and Function. Vol. 12. Boca Raton: CRC Press: 1991. p. 145-62.
9. Ericson H. GABA-like immunoreactivity in the tuberomammillary nucleus in the rat brain: Delineation of subgroups with antibody against L-histidine decarboxilase as a marker. J Comp Neurol 1991;305:462-9.
10. Scaccianoce S, Lembarco K, Nicolai R, Affrica D, Angelucci I. Studies in the involvement of histamine in hypothalamic- pituitary- adrenal axis activation. Life Sci 2000;67:3143-52.
11. Yoshikawa T, Nakamura T, Yanai K. Histamine N-methyltransferase in the brain. Int J Mol Sci 2019;20:737.
12. Arvat E, Maccagno B, Ramunni J, Gianotti L, Di Vito L, Deghenghi R, *et al*. Effects of histaminergic antagonists on the GH-releasing activity of GHRH or hexarelin, a synthetic hexapeptide, in man. J Endocrinol Invest 1997;20:122-7.
13. Al-Snafi AE, Al-Baldawi AT, Al-Rubaei AK. The efficacy of bromocriptine with and without ovarian stimulation in the treatment of hyperprolactinemic infertile women. Middle East Fertil Soc J 2003;8:1-4.
14. Knigge U, Søe-Jensen P, Jorgensen H, Kjaer A, Møller M, Warberg J. Stress-induced release of anterior pituitary hormones: Effect of H3 receptor-mediated inhibition of histaminergic activity or posterior hypothalamic lesion. Neuroendocrinology 1999;1:44-53.
15. Al-Snafi AE. The role of histamine in prolactin, LH, FSH and ACTH secretion. J Fac Med (Baghdad) 2002;44:664-9.
16. Malmberg-Aiello P, Lamberti C, Ghelardini C, Giotti A, Bartolini A. Role of histamine in rodent antinociception. Br J Pharmacol 1994;111:1269-79.
17. Frisch C, Hasenohri RV, Huston JP. The histamine H1 antagonist chlorpheniramine facilitates learning in aged rats. Neuroscience 1997;229:89-92.
18. Parasuraman S, Raveendran R, Kesavan R. Blood sample collection in small laboratory animals. J Pharmacol Pharmacother 2010;1:87-93.
19. Al-Tahan FJ, Al-Janabi AS, Al-Snafi AE. Effect of chronic diazepam treatment on fertility and sexual ability of male rats. Dirasat 1993;20:151-8.
20. Duncan RC, Knapp RG, Clinton-Miller M. Experimental design and analysis of variance. In: Introductory Bio for the Health Sciences. 2nd ed. New York: John Wiey and Sons; 1983.
21. Netti C, Guidopono F, Olgiati VR, Sibilia V, Pecile A, Dannies PS. Comparison of the effects of histamine H2-receptor antagonists on prolactin secretion in the rat. Endocrinology 1983;113:412-4.
22. Jorgensen EA, Knigge U, Warberg J, Kjaer A. Histamine and the regulation of body weight. Neuroendocrinology 2007;86:210-4.
23. Moguilevsky JA, Szwarcfarb B, Faigón MR, Paolini J, Scacchi P. Effects of H1 and H2 histamine receptor antagonists on positive feed-back effect of estrogen on LH in prepubertal female rats. Horm Metab Res 1989;21:658-60.
24. Rudolph C, Richards GE, Kaplan S, Ganong WF. Effect of intra-ventricular histamine on hormone secretion in dogs. Neuroendocrinology 1976;29:169-77.
25. Donoso AO. Induction of prolactin and luteinizing hormone release by histamine in male and female rats and the influence of brain transmitter antagonists. J Endocrinol 1978;76:193-202.
26. Donoso AO, Banzan AM, Borzino MI. Prolactin and luteinizing hormone release after intraventricular injection of histamine in rats. J Endocrinol 1976;68:171-2.
27. Di Renzo GF, Basile V, Amoroso S, Taglialatela M, Maurano F, Annunziato L. Possible inhibitory role of histamine H2 receptors in the control of basal secretion in male rats: Studies with dimaprit, a selective H2 receptor agonist. J Neural Transm 1987;69:313-8.
28. Horno NM, Alvarez EO. The probable role of histamine in the rostral hypothalamus on the prolactin and luteinizing hormone release induced by estrogen in conscious spayed rats. J Neural Transm 1989;78:249-64.
29. Miyake A, Ohtsuka S, Nishizaki T, Tasaka K, Aono T, Tanizawa O, *et al*. Involvement of H1 histamine receptor in basal and esterogen stimulated luteinizing hormone-releasing hormone secretion in rats *in vitro*. Neuroendocrinology 1987;45:191-6.
30. Fekete CS, Strutton PH, Cagampang FR, Hrabovszky E, Kalló I, Shughrue PJ, *et al*. Estrogen receptor immunoreactivity is present in the majority of central histaminergic neurons: Evidence for a new neuroendocrine pathway associated with luteinizing hormone-releasing hormonesynthesizing neurons in rats and humans. Endocrinology 1999;140:4335-41.
31. Noris G, Hol D, Clapp C, Escalera GM. Histamine directly stimulates gonadotropin-releasing hormone secretion from GT1-1 cells via H1 receptors coupled to phosphoinositide hydrolysis. Endocrinology 1995;136:2967-74.

32. Al-Snafi AE. The Effect of Multiple Administration of Diazepam on the Reproductive Characteristic of Male Rats. MSc Thesis. College of Veterinary Medicine, University of Baghdad; 1990.
33. Krsmanovic LZ, Mores N, Navarro CE, Saeed SA, Arora KK, Catt KJ. Muscarinic regulation of intracellular signaling and neurosecretion in gonadotropin-releasing hormone neurons. Endocrinology 1998;139:4037-43.

How to cite this article: Faris AN, Al-Fartosi KG, Al-Snafi AE. The role of histamine in anterior pituitary secretion. Indian J Physiol Pharmacol 2021;65:211-6.