HARMFUL EFFECTS OF HISTAMINE IN THE BODY: A REVIEW

Saad S.R. Al- Janaby[1], Ali M.A. Al-Kufaishi [2], Zahraa Hameed Oda Al-quraishi[3], Ihsan Naji Atiyah Essia[4]

[1]Department of Community Health, College of Health and Medical Techniques, Al-Furat Al-Awsat Technical University, Kufa, Iraq. [2]"Assistant Professor, PhD in Clinical Biochemistry. Al-Furat Al-Awsat Technical University College of Health and Medical Techniques, Department of Medical Laboratory Techniques, Kufa, Iraq 31003", Email: Kuh.ali@atu.edu.iq. [3]"Lecturer, PhD in Biology. Al-Furat Al-Awsat Technical University College of Health and Medical Techniques, Department of Medical Laboratory Techniques, Kufa, Iraq 31003", Email: Kuh.zhr12@atu.edu.iq.[4]"Lecturer, PhD in Clinical Biochemistry. Al-Furat Al-Awsat Technical University / Kufa Technical Institute/Department of Nursing, 31003", Email: ihssan.naje@atu.edu.iq.

ABSTRACT

Histamine is a bioactive nitrogenous organic compound of the family of monoamines produced by the action of enzymes in human and animal dung by fecal bacteria on protein materials, particularly the essential amino acid histidine. This type of material is also secreted in abundance in the body by cells known as mast cells circulating in the connective tissues, and also by white blood cells known as basophils, basal white blood cells, during allergic reactions and serious and life-threatening anaphylactic shock called anaphylactic shock (and during various allergic diseases). Mast cells are abundantly present in lung tissue, nasal mucosa, eye mucosal tissue, subcutaneous and between various mucosal tissues. In addition to what was mentioned above about the characteristics and functional role of histamine in the body, it has many harms as a result of its high level secretion as a result of a specific functional disorder or microbial invasion, as well as as a result of immune sensitivity, and damages are noted in the respiratory, digestive, immune and nervous systems.

Keywords: Histamine, allergic diseases, monoamines, immune sensitivity.

INTRODUCTION

"Histamine" is an organic nitrogenous compound (2-(1H-Imidazol-4-yl)ethanamine) that controls physiological functions in the Gastrointestina intestinal tract, and as a neurotransmitter in the brain, spinal cord, and uterus**(Vuckovic and Pawliszyn, 2011)[figure 1].** Histamine has been classified as a native hormone (autocoid) since its discovery in 1910 since it absences the conventional "endocrine glands" that secrete it; yet, in recent years, histamine has been recognized as a central neurotransmitter**(Nieto-Alamilla** ***et al.,*** **2016)**. It has a function in the inflammatory response **(Keppel Hesselink, 2015).** "Histamine" is gnerated by mast cells and basophils in adjacent connective tissues as part of an immune response to assaulting infections, and macking the capillaries more permeable to white blood cells and certain proteins, permitting them to interact with pathogens in suffering

tissues**(Andersen** *et al.,* **2015)**. It consists of an imidazole ring connected to an ethylamine chain, with the amino group of the side-chain protonated under physiological conditions**(Di Giuseppe and Fraser, 2003).**

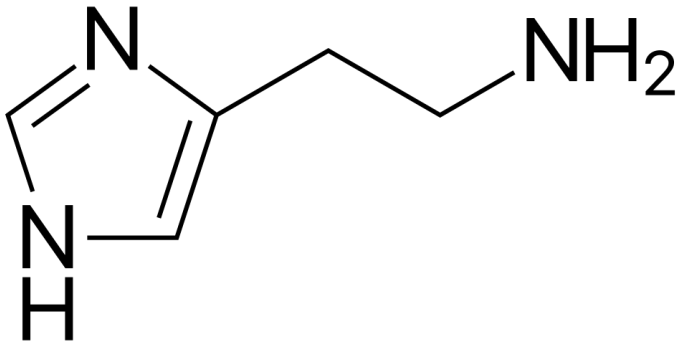

Figure 1. The chemical structure of histamine(Marieb, 2001).

HISTAMINE RECEPTORS

The receptors of Histamine are G protein–coupled receptors that bind histamine as their primary endogenous ligand, resulting in a variety of join variantions of Histamine type III in different classes Despite the fact that all of the receptors are 7-transmembrane g protein linked receptors, (H type I and H type II) have very distinct functions than (H type III, and H type VI. PIP2 hydrolysis is increased by H1, stomach acid production is stimulated by H2, and histamine feedback inhibition is mediated by H3**(Hill** *et al.,* **1997).**

There are four known HRs. (table 1).

Table 1: Histamine receptors

receptors	**mechanism**	**Functions**
H type I	G_q	• ileum contraction • modulate circadian cycle • itching • Systemic • Vasodilatation • bronchoconstriction (allergy-induced asthma)
H type II	G_s ↑ cAMP2+	• speed up sinus rhythm • Stimulation of gastric acid secretion • Smooth muscle relaxation • Inhibit antibody synthesis, T-cell proliferation and

		cytokine production
H type III	G_i	• Decrease Acetylcholine, Serotonin and Norepinephrine Neurotransmitter release in CNS • Presynaptic autoreceptors
H type VI	G_i	mediate mast cell chemotaxis**(Hofstra *et al.*, 2003)**

HISTAMINE WITH IMMUNE AND INFLAMMATION

The H1 receptor's constitutive activity, and agonists that attached to the receptor, enhance the production of NF-B, a transcription factor that governs inflammatory processes. The "Histamine receptor type I" is a trans membrane protein that belongs to the G-protein linked receptor family. When a GPCR is activated by a specific agonist, signal transformation from the extracellular to the intracellular circumstances happens. Following this, a subunit of the "G-protein" disassociates and influences intracellular messaging, concluding downstream signaling mediated by cyclic Adenosine Monophosphate , cyclic Guanosine Monophosphate, calcium, and Nuclear Factor kappa B (NF-B), a prevasise transcription factor thought to play an important task in immune-cell chemotaxis, proinflammatory cytokine production, expression of cell adhesion molecules, and other allergic and inflammatory conditions. 1,8,12,30–32 The receptor of "histamine I", for instance, stimulates NF-B both constitutively and agonist-dependently, therapeutically available H type I-antihistamines block constitutive H receptor I-mediated NF-B synthesis**(Canonica and Blaiss, 2011)**[figure 2].

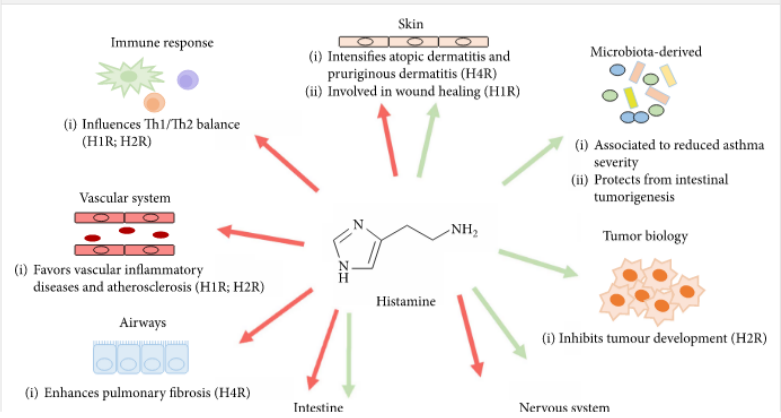

Figure 2. The function of "histamine" in inflammation and immune response**(Anna *et al.*, 2018).**

HISTAMINE AND DIGESTIVE SYSTEM

The identification of functional expression of 9histamine receptor)H4R and other GPCR is still a topic of debate that is currently lacking in momentum. The specificity of H4R-selective antibodies has been questioned since 2012**(Beermann** *et al.,* **2012)**. This problem hasn't been thoroughly investigated. As a result, antibodies against H.R. (VI) that have been thoroughly tested in accordance with some general guidelines are reticence unavailable (**Michel** *et al.,* **2009).** These issues aren't unique to the use of selective antibodies to identify H.R. (VI) proteins. Other tachniques, such as RT-(q)PCR for mRNA detection testing with [agonistic or antagonistic ligands], are similarly fraught with uncertainty. RT-PCR is a very sensitive detection technology, however it comes with the risk of contaminating genomic DNA with trace amounts of particular mRNA(**Hashemipetroudi** *et al.,* **2018)**, It's unclear what level of mRNA expression is required for effective receptor expression**(Maier** *et al.,* **2009)**. As a result, the inflammation manifests itself as scattered lesions throughout the digestive tract, penetrating deep into the intestinal wall and potentially impacting all layers. Inflammatory lesions in UC, on the other hand, begin in the "rectum", progress upward without reach the intestine, and stay superficial at the mucosa **(Maier** *et al.,* **2009)**. CD and UC also differ in terms of immunological response: whereas CD is characterized via a Th1/Th17- subjugated response, UC is characterized by a Th2-dominated reply**(Elson and Weaver, 2006).** Nonetheless, both diseases cause a slew of related signs (e.g., edema, ulcers, mucosal lesions, , diarrhea, , abdominal pain and bloody stool), wreaking havoc on patients' quality of life and eventually shortening their lifespan due to extra- and intra-intestinal problems like "colorectal cancer" (CRC)(**Eaden** *et al.,* **2001)**. The current medication schemes, which are confused on immunosuppressive drugs as glucocorticoid receptor 5-aminosalicylic acid or agonists, increase the risk of developing such complications. Although these drugs have only a 50% remission rate, long-term use can initiate and / or support immunosuppression-related disorders (**Baumgart and Carding, 2007)**[figure 3].

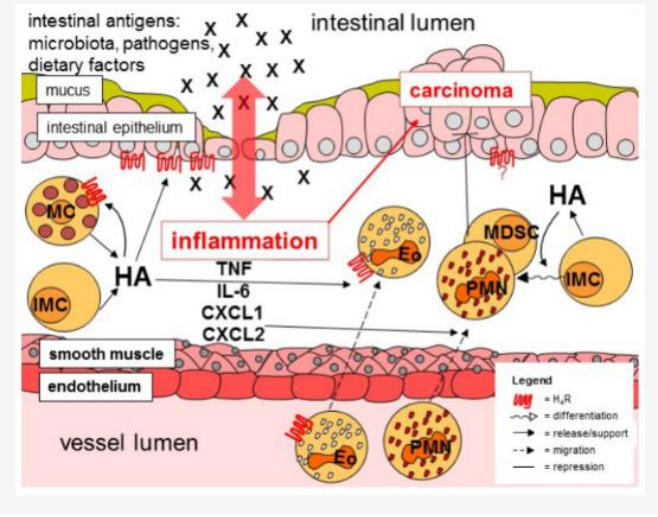

Figure 3. The role of histamine in inflammation of Gastrointestinal tract. [MC, mast cell; IMC, immature myeloid cell; HA, histamine; Eo, eosinophil; PMN, neutrophil; MDSC, myeloid-derived suppressor cells].**(Schirmer and Neumann, 2021).**

HISTAMINE AND RESPIRATORY DISEASES(BRONCHOCONSTRICTION)

The constriction of smooth muscle in bronchi intermediated via (H.R. type I) is one of the most recognized biological proceedings of histamine in the respiratory system. It was recounted long before that "histamine" induced a bronchi-construction in human, and bronchoconstriction was established firstly as one of the biological histamine's actions **(Curry, 1946)**(figure 4)**.** While histamine has the same effect on bronchial smooth muscles as muscarinic [M1] receptor agonists, it has a greater impact on pulmonary peripheral tissue samples than [M1] receptor agonists. For a long time, histamine has been thought to work a serious role in "asthma" pathophysiology, as it is a well-known chemical mediator discharged from mast cells in the immediate allergic reaction**(White, 1990).** Breath in allergens and direct associate with a broncho-scope delivery histamine into the surface of the airway, which is re-daimed in broncho-alveolar lavage fluid.

Histamine caused smooth muscles constriction in bronchi (asthmatics clinical status) in case of injection or inhalation at a low dose that had no impact in healthy people**(Hogg *et al.*, 1979).** The perception of airway hyper-responsiveness to histamine as a physical feature of asthmatics status was offered depended on these signs. so that, because asthmatics' airways were hyperresponsive to a variety of smooth-muscle-contracting agents, it was labeled nonspecific airway hyper-responsiveness, designating airway irreglularity**(Rafferty *et al.*, 1987).** Histamine is created and stored in the vesicles of basophils and mast cells , and it is released from storage vesicles into the extracellular space due to responsing to the immunological stimulation of mast cells and basophils, activating G-protein-coupled receptors HR (I), HR(II), HR(III), and HR(VI)(**Thangam** *et al.*, **2018)**. conversly, the content of histamine in the extracellular space should be managed by histamine breakdown to end the affect of histamine by (HRs) on target cells such as bronchial smooth muscle cells(**Yoshikawa and Yanai (2017).**

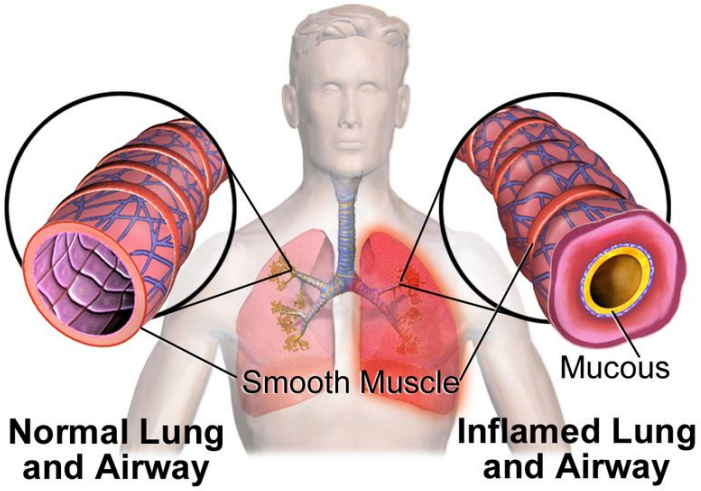

Figure 4. illustration of bronchoconstrivction(Asthma).

CONCLUSIONS

In Brief, the histamine has multifunction in which considered in immunity situation in the body and in inflammation as a pro-inflammatory materials. In other hand the profuse secretion of its due to many factors risk (diseases or functional disorders) causes organic harms in more than one systems and organs e.g. respiratory, digestive, skin, and immunity suppression.

REFERENCS

Andersen H.H., Elberling J., Arendt-Nielsen L (2015). "Human surrogate models of histaminergic and non-histaminergic itch". Acta Dermato-Venereologica. 95 (7): 771–7. doi:10.2340/00015555-2146. PMID 26015312.

Anna C. Calvielli C. B., Fábio S. Y. Y. ,1 Anna J.P., Maria N. S. (2018). Role of Histamine in Modulating the Immune Response and Inflammation. Volume |Article ID 9524075 | https://doi.org/10.1155/2018/9524075 [review article].

Baumgart D.C., Carding S.R.(2007). Inflammatory bowel disease: Cause and immunobiology. Lancet, 369, 1627–1640. [Google Scholar] [CrossRef].

Beermann S. Seifert R. Neumann D.(2012). Commercially available antibodies against human and murine histamine H4 receptor lack specificity. Naunyn Schmiedebergs Arch. Pharmacol. 385, 125–135. [Google Scholar] [CrossRef] [PubMed].

Canonica G.W., Blaiss M. (2011). "Antihistaminic, anti-inflammatory, and antiallergic properties of the nonsedating second-generation antihistamine desloratadine: a review of the evidence". The World Allergy Organization Journal. 4 (2): 47–53. doi:10.1097/WOX.0b013e3182093e19. PMC 3500039. PMID 23268457.

Curry J.J.(1946). The effect of antihistamine substances and other drugs on histamine bronchoconstriction in asthmatic subjects. J. Clin. Investig. 25:792–799. doi: 10.1172/JCI101765. [PMC free article] [PubMed] [CrossRef] [Google Scholar].

Di Giuseppe M., Fraser D. (2003). Nelson Biology 12. Toronto: Thomson Canada. p. 473. ISBN 0-17-625987-2.

Eaden J.A., Abrams, K.R., Mayberry J.F.(2001). The risk of colorectal cancer in ulcerative colitis: A meta-analysis. Gut, 48, 526–535. [Google Scholar] [CrossRef] [PubMed].

Elson C.O., Weaver C.T.(2006). Experimental mouse models of inflammatory bowel disease: New insights into pathogenic mechanisms. In Inflammatory Bowel Disease: From Bench to Bedside; Springer: Berlin/Heidelberg, Germany, ISBN 0387258078. [Google Scholar].

Hashemipetroudi S.H., Nematzadeh, G., Ahmadian G., Yamchi A., Kuhlmann M.(2018). Assessment of DNA contamination in RNA samples based on ribosomal DNA. J. Vis. Exp. 22, 55451. [Google Scholar] [CrossRef].

Hill S..J, Ganellin C..R, Timmerman H., Schwartz J..C, Shankley N..P, Young J.M., Schunack W., Levi R., Haas H.L. (1997). "International Union of Pharmacology. XIII. Classification of histamine receptors". Pharmacol. Rev. 49 (3): 253–78. PMID 9311023.

Hofstra C.L., Desai P.J., Thurmond R.L., Fung-Leung W.P. (2003). "Histamine H4 receptor mediates chemotaxis and calcium mobilization of mast cells". J. Pharmacol. Exp. Ther. 305 (3): 1212–21. doi:10.1124/jpet.102.046581. PMID 12626656.

Hogg J.C., Paré P.D., Boucher R.C., Michoud M.C.(1979). The pathophysiology of asthma. Can. Med. Assoc. 121:409–414. [PMC free article] [PubMed] [Google Scholar].

Keppel Hesselink J.M. (2015). "The terms 'autacoid', 'hormone' and 'chalone' and how they have shifted with time". Autonomic & Autacoid Pharmacology. 35 (4): 51–8. doi:10.1111/aap.12037. PMID 27028114.

Maier T., Güell M., Serrano L.(2009). Correlation of mRNA and protein in complex biological samples. FEBS Lett. 2009, 583, 3966–3973. [Google Scholar] [CrossRef].

Marieb E.(2001). Human anatomy & physiology. San Francisco: Benjamin Cummings. pp. 414. ISBN 0-8053-4989-8.

Michel M.C., Wieland T., Tsujimoto, G.(2009). How reliable are G-protein-coupled receptor antibodies? Naunyn Schmiedebergs Arch. Pharmacol. 2009, 379, 385–388. [Google Scholar] [CrossRef] [PubMe].

Mickleborough T.D.(2010). "Salt Intake, Asthma, and Exercise-Induced Bronchoconstriction: A Review". The Physician and Sportsmedicine. 38 (1): 118–131. doi:10.3810/psm.2010.04.1769. PMID 20424409. S2CID 5761664.

Nieto-Alamilla G., Márquez-Gómez R., García-Gálvez A.M., Morales-Figueroa G.E., Arias-Montaño J.A. (2016). "The Histamine H3 Receptor: Structure, Pharmacology, and Function". Molecular Pharmacology. 90 (5): 649–673. doi:10.1124/mol.116.104752. PMID 27563055.

Rafferty P., Beasley R., Holgate S.T.(1987). The contribution of histamine to immediate bronchoconstriction provoked by inhaled allergen and adenosine 5′ monophosphate in atopic asthma. Am. Rev. Respir. Dis. 136:369–373. doi: 10.1164/ajrccm/136.2.369. [PubMed] [CrossRef] [Google Scholar]..

Schirmer B., Neumann D.(2021). The Function of the Histamine H4 Receptor in Inflammatory and Inflammation-Associated Diseases of the Gut. Institute of Pharmacology, Hannover Medical School, D-30625 Hannover, GermanyAuthor to whom correspondence should be addressed. Academic Editors: Paul Chazot and Ilona Obara. Int. J. Mol. Sci. 2021, 22(11), 6116; https://doi.org/10.3390/ijms22116116 nReceived: 26 April 2021 / Revised: 31 May 2021 / Accepted: 3 June 2021 / Published: 6 June 2021.

Thangam E.B., Jemima E.A., Singh H., Baig M.S., Khan M., Mathias C.B., Church M.K., Saluja R. (2018). The Role of Histamine and histamine receptors in Mast cell-

mediated allergy and inflammation: The Hunt for New therapeutic Targets. Front. Immunol. 9:1–9. doi: 10.3389/fimmu.2018.01873. [PMC free article] [PubMed] [CrossRef] [Google Scholar].

Vuckovic D, Pawliszyn J (2011). "Systematic evaluation of solid-phase microextraction coatings for untargeted metabolomic profiling of biological fluids by liquid chromatography-mass spectrometry". Analytical Chemistry. 83 (6): 1944–54. doi:10.1021/ac102614v. PMID 21332182.

White M.V. (1990). The role of histamine in allergic diseases. J. Allergy Clin. Immunol. 86:599–605. doi: 10.1016/S0091-6749(05)80223-4. [PubMed] [CrossRef] [Google Scholar].

Yoshikawa T., Yanai K.(2017). Histamine Clearance through Polyspecific Transporters in the Brain. Handb. Exp. Pharmacol. 241:173–187. [PubMed] [Google Scholar].