Pharmacology & Therapeutics 178 (2017) 148–156

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

The clinical pharmacology of non-sedating antihistamines

Kazuhiko Yanai [a,b], Takeo Yoshikawa [a,*], Ai Yanai [a], Tadaho Nakamura [c], Tomomitsu Iida [a], Rob Leurs [d], Manabu Tashiro [b]

[a] Department of Pharmacology, Tohoku University School of Medicine, Sendai 980-8575, Japan
[b] Cyclotron and Radioisotope Center, Tohoku University, Sendai 980-8578, Japan
[c] Department of Pharmacology, Tohoku Medical and Pharmaceutical University, Sendai 981-8558, Japan
[d] Amsterdam Institute of Molecules, Medicines and Systems, Department of Medicinal Chemistry, Vrije Universiteit Amsterdam, The Netherlands

ARTICLE INFO

Available online 27 April 2017

Keywords:
Histamine
Non-sedating antihistamines
PET
Histamine H1 receptor occupancy
CNS
Carnosine
Histidine
Sedation
Impaired performance
P-glycoprotein

ABSTRACT

We previously reported on brain H_1 receptor occupancy measurements of antihistamines in human brain using [^{11}C]doxepin and positron emission tomography (PET). We proposed the use of brain H_1 receptor occupancy to classify antihistamines objectively into three categories of sedating, less-sedating, and non-sedating antihistamines according to their sedative effects. Non-sedating antihistamines are recommended for the treatment of allergies such as pollinosis and atopic dermatitis because of their low penetration into the central nervous system. Physicians and pharmacists are responsible for fully educating patients about the risks of sedating antihistamines from pharmacological points of view. If a sedating antihistamine must be prescribed, its sedative effects should be thoroughly considered before choosing the drug. Non-sedating antihistamines should be preferentially used whenever possible as most antihistamines are equally efficacious, while adverse effects of sedating antihistamines can be serious. This review summarizes the pharmacological properties of clinically useful non-sedating antihistamines from the perspective of histamine function in the CNS.

Contents

1. Introduction . . . 148
2. Histamine as a "good" substance . . . 149
3. Development of non-sedating antihistamines . . . 150
4. PET evaluation of sedating action of antihistamines . . . 151
5. P-glycoprotein inhibitors and multidrug-resistance genes (MDR) gene expression . . . 153
6. Clinical pharmacology of non-sedating antihistamines . . . 154
7. Conclusion. . . . 155
Author disclosure . . . 155
Acknowledgments. . . . 155
References . . . 155

1. Introduction

Since histamine activity was discovered in 1910 by Sir Henry Dale, a Nobel Prize winner in physiology or medicine 1936, a great number of researchers have investigated the physiological and pathological activities of histamine. Furthermore, Daniel Bovet and Sir James W. Black, who developed H1 and H2 receptor antagonists, received the Nobel Prize in physiology or medicine in 1957 and 1988, respectively, for making a significant contribution to mankind. As part of recent progress in the study of histamine, H3 and H4 receptors have been actively investigated (Brioni, Esbenshade, Garrison, Bitner, & Cowart, 2011; Passani & Blandina, 2011). To aid this research, genetic knockout mice have been created for H1–H4 receptors, histidine decarboxylase (HDC), and histamine *N*-methyltransferase (HNMT). X-ray analysis of the H1 receptor has been also reported. While histamine was considered detrimental as an allergy-causing substance, recent studies have demonstrated that

* Corresponding author at: Department of Pharmacology, Tohoku University School of Medicine, 2-1 Seiryo-cho, Aoba-Ku, Sendai 980-8575, Japan.
E-mail address: tyoshikawa@med.tohoku.ac.jp (T. Yoshikawa).

http://dx.doi.org/10.1016/j.pharmthera.2017.04.004
0163-7258/

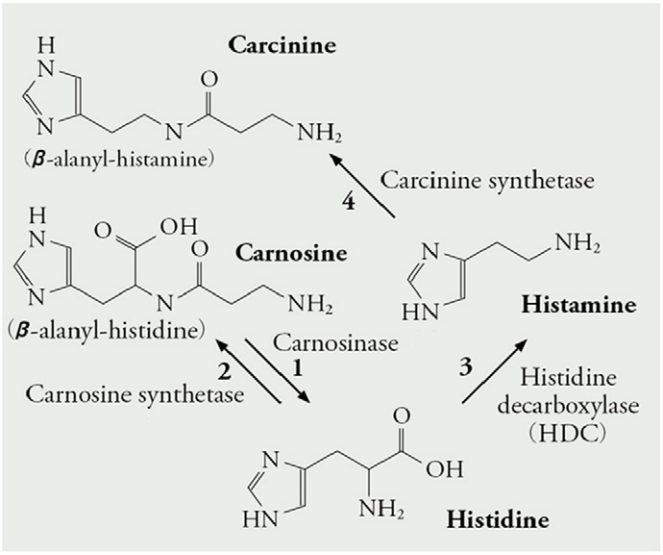

Fig. 1. Carnosine–histidine–histamine pathway. The decarboxylation of L-histidine, one of essential amino acids, is catalyzed by histidine decarboxylase (HDC), a pyridoxal phosphate-containing enzyme (3). The dipeptide, carnosine, is synthesized by carnosine synthetase (2) and degraded by carnosinase (1). Histamine is an important neurotransmitter in the eye of *Dorsophila*, and it is inactivated by carcinine synthetase (4), which converts to carcinine, a β-alanyl derivative (Chaturvedi, Luan, Guo, & Li, 2016). Carcinine synthetase does not exist in humans, and the function of carcinine is poorly understood at present in humans.

physiological activities of histamine are often beneficial to the human body. In the central nervous system, in particular, histamine plays an important role in maintaining wakefulness and suppressing appetite. Accordingly, the guidelines for pollinosis, atopic dermatitis, and other allergic disease now recommend non-sedating antihistamines with lesser penetrability into the central nervous system.

2. Histamine as a "good" substance

Histamine is a biogenic amine synthesized from the amino acid L-histidine by histidine decarboxylase (HDC). The various biological functions occur via four G protein–coupled receptor (GPCR) subtypes: H_1 receptor, H_2 receptor, H_3 receptor, and H_4 receptor (Panula et al., 2015). The main histamine-producing cells are histaminergic neurons, the cell bodies of which lie in the hypothalamic tuberomammillary nucleus, gastric enterochromaffin-like (ECL) cells, mast cells, and basophils (Falus, Grossman, & Darvas, 2004). Gastric ECL cells release histamine upon stimulation by gastrin and acetylcholine. Through the effect of histamine on histamine H_2 receptors, gastric acid is secreted from parietal cells. Mast cells and basophils store histamine within granules, and degranulation occurs upon stimulation by an antigen in a sensitized state. Meanwhile, histamine contained in foods is also important. In relation to food-derived histamine, histamine food poisoning has long been recognized in humans (Sarkadi, 2004; Visciano, Schirone, Tofalo, & Suzzi, 2014). Upon proliferation of HDC-producing bacteria, considerable amounts of histamine may be synthesized from histidine contained in fish. The symptoms of histamine food poisoning include urticaria, hypotension, nausea, vomiting, abdominal pain, diarrhea, headache, facial flush, and skin eruptions. The majority of symptoms develop within one hour of eating. On the other hand, exogenously administered histamine is sometimes beneficial for us. Histamine itself has been approved for use in European countries and Israel to prevent relapse in acute myeloid leukemia. In accordance with this, mice with histamine deficiency due to genetic disruption of HDC showed a high rate of colon and skin carcinogenesis. The absence of histamine formation caused accumulation of immature myeloid cells, which was accompanied by an increased susceptibility to chemically induced cancer (Yang et al., 2011).

The amount of histidine contained in fish meat is greater than that of any other essential amino acid (http://wholefoodcatalog.info/). In the living body, levels of carnosine, histidine, and histamine are considered to be interactively and closely correlated (Fig. 1). Carnosine, an imidazole dipeptide, has recently drawn attention for therapeutic potential in stress- and age-related disorders (Babizhayev, 2014; Boldyrev, Aldini, & Derave, 2013; Cararo, Streck, Schuck, & Ferreira Gda, 2015; Hipkiss, 2015). In addition to being synthesized from L-histidine by HDC, histaminergic neurons, in particular, contain carnosinase, and histamine can be efficiently synthesized from carnosine (Otani, Okumura, Nagai, & Okumura, 2008). During exercise, carnosine is synthesized from histidine and β-alanine in muscle (Blancquaert, Everaert, & Derave, 2015; Hoffman, Stout, Harris, & Moran, 2015). It has been proposed that after being released from muscle, carnosine can stimulate central histaminergic neurons as shown in Fig. 2. Exercise is very effective in preventing dementia, as demonstrated by a number of epidemiological studies; however, the molecular mechanism underlying this phenomenon is unknown. Carnosine is efficiently incorporated into histamine neurons in the brain and reported to reduce the cytotoxicity owing to amyloid β protein and suppresses its deposition (Corona et al., 2011). The activities of carnosine and histidine, both of which have the same imidazole skeleton, are as follows: antioxidant, metal chelating (Ca^{2+}, Zn^{2+}, and Cu^{2+}) inside and outside the cell, pH buffering activity (Boldyrev et al., 2013; Swietach, Leem, Spitzer, & Vaughan-Jones, 2014), and histamine neuron-activating effects (Shen et al., 2007).

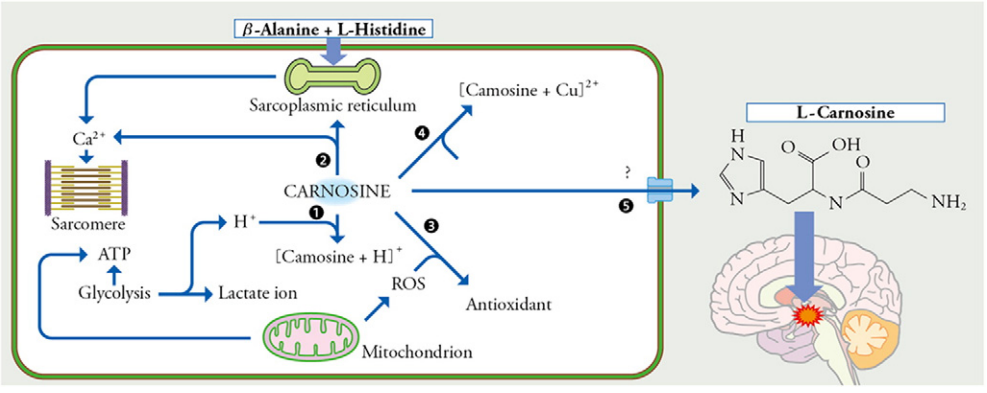

Fig. 2. Synthesis of carnosine in the muscle and its activities. Carnosine (β-alanyl-L-histidine) is a dipeptide produced in muscle by condensation of histidine and β-alanine (an amino acid that is not a constituent of protein). When β-alanine is ingested, carnosine is synthesized in the muscle (Blancquaert et al., 2015), and (1) buffering of intracellular H^+ in muscle, (2 & 4) chelating of intracellular Ca^{2+} and Cu^{2+}, and (3) antioxidative action against reactive oxygen species (ROS) occur. Carnosine can be released from muscle into the circulation, and it can activate the histaminergic neuron system, which is very similar to histidine-induced actions.