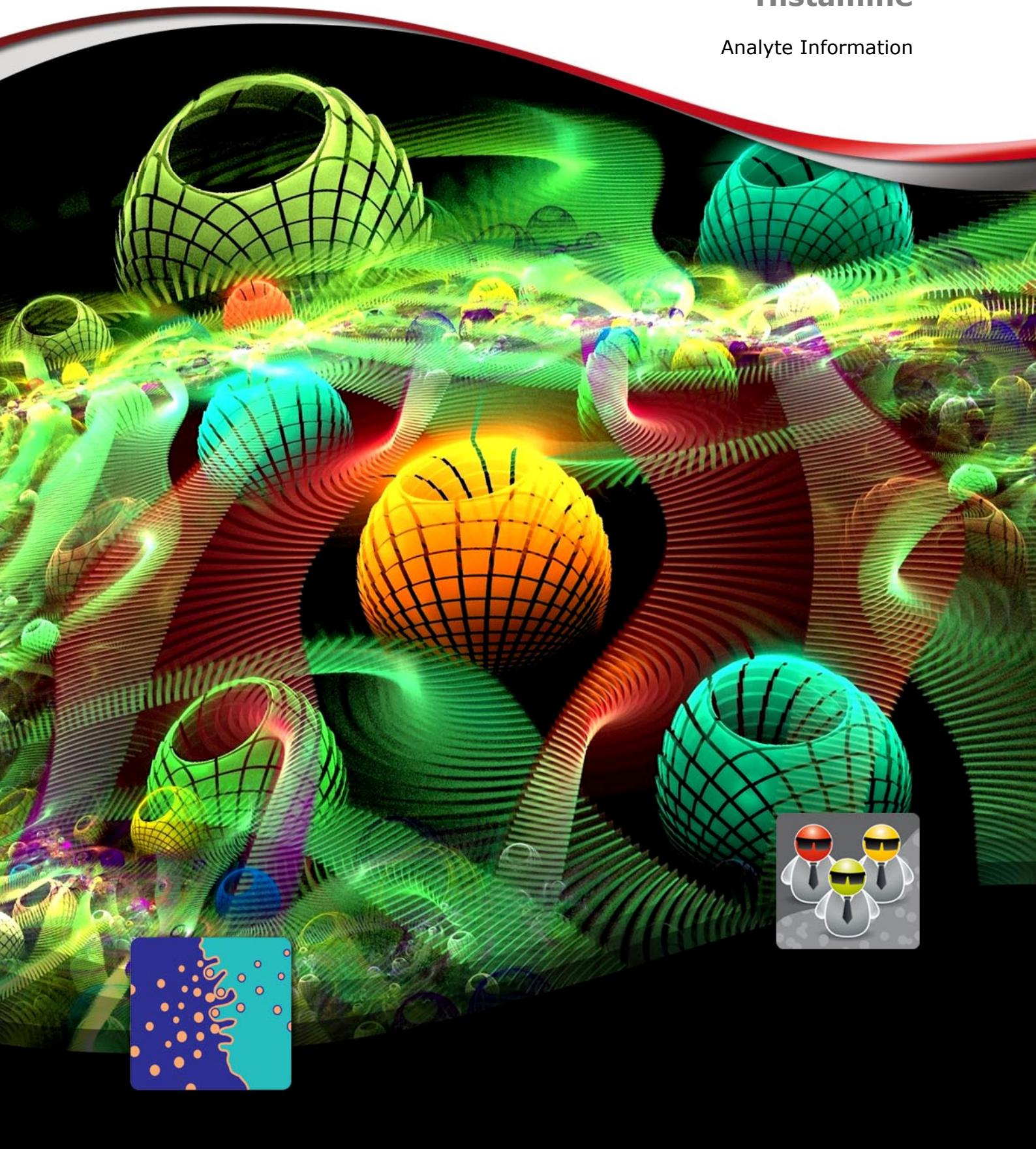
Specialty - allergy

Histamine

Analyte Information

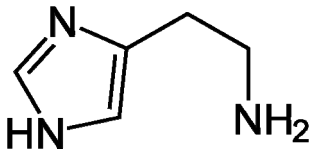


Histamine

Introduction

Histamine (2-(4-imidazolyl) ethylamine) belongs to the group of biogenic amines. Its molecular weight is 111 Da. Its formula is shown in Fig.1.

Fig.1: Histamine



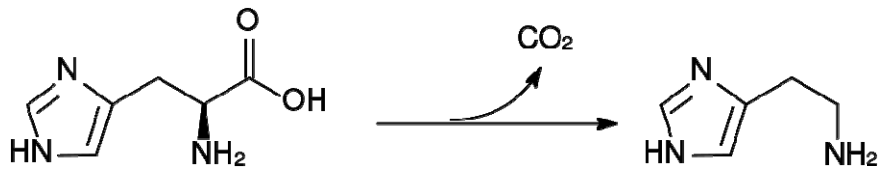
Histamine is involved in local immune responses as well as in regulating physiological functioning in the gut and acting as a neurotransmitter[1].

In this brochure, emphasis is placed on histamine as a key factor in allergic response.

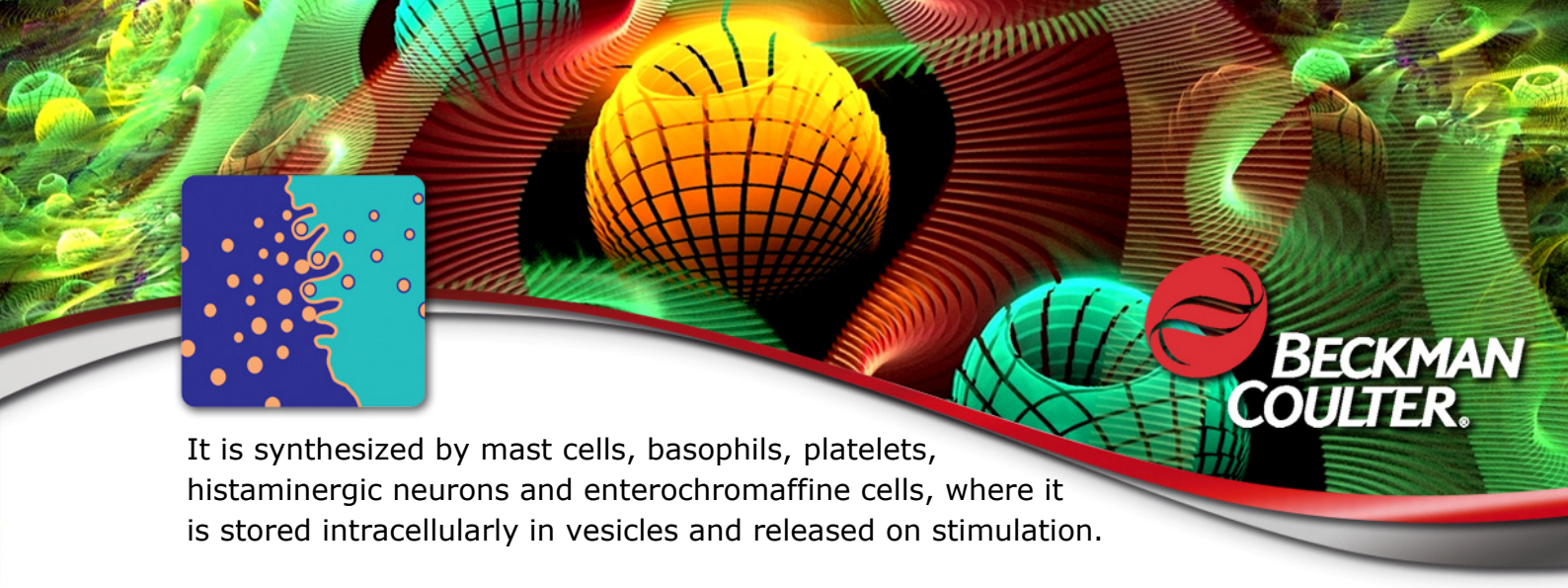
Biosynthesis

Histamine is synthesized by pyridoxal phosphate (vitamin B-6)–containing L-histidine decarboxylase (HDC) from the amino acid histidine (Fig.2).

Fig.2: Biosynthesis of histamine



Histidine **Decarboxylation** **Histamine**



It is synthesized by mast cells, basophils, platelets, histaminergic neurons and enterochromaffine cells, where it is stored intracellularly in vesicles and released on stimulation.

Metabolism

Histamine can be metabolized in two ways: by oxidative deamination by DAO (diamine oxidase, previously known as histaminase) or by ring methylation by histamine-N-methyltransferase (HNMT)[2] (Fig.3). The mehod of catabolization is supposed to depend on the localization of histamine.

The DAO protein is stored in plasma membrane–associated vesicular structures in epithelial cells and is secreted into circulation upon stimulation[3, 4]. It has been proposed that DAO may be responsible for scavenging extracellular histamine (e.g., after ingestion of histamine-rich food).

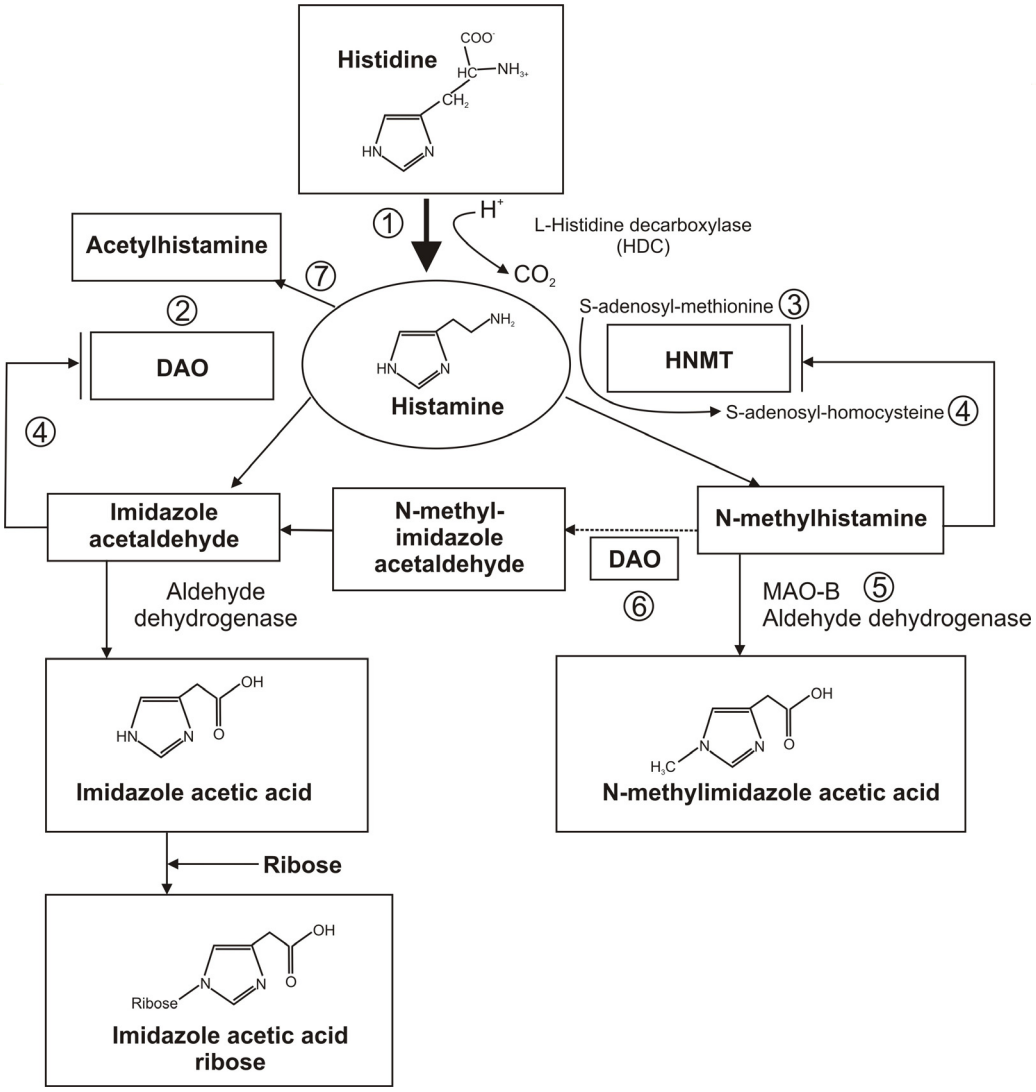
Conversely, HNMT, the second-most important enzyme in inactivation of histamine, is a cytosolic protein[5] which can convert histamine only in the intracellular space of cells[6, 7]. Thus HNMT and DAO do not seem to compete for the substrate, although they have a similar affinity for histamine and are expressed in some overlapping tissues.

HNMT has a slightly higher affinity for histamine than DAO. In mammals, DAO expression is restricted to specific tissues; the highest levels of activity are in the small bowel and colon ascendens[8, 9, 10] and in the placenta and kidney[3, 6].

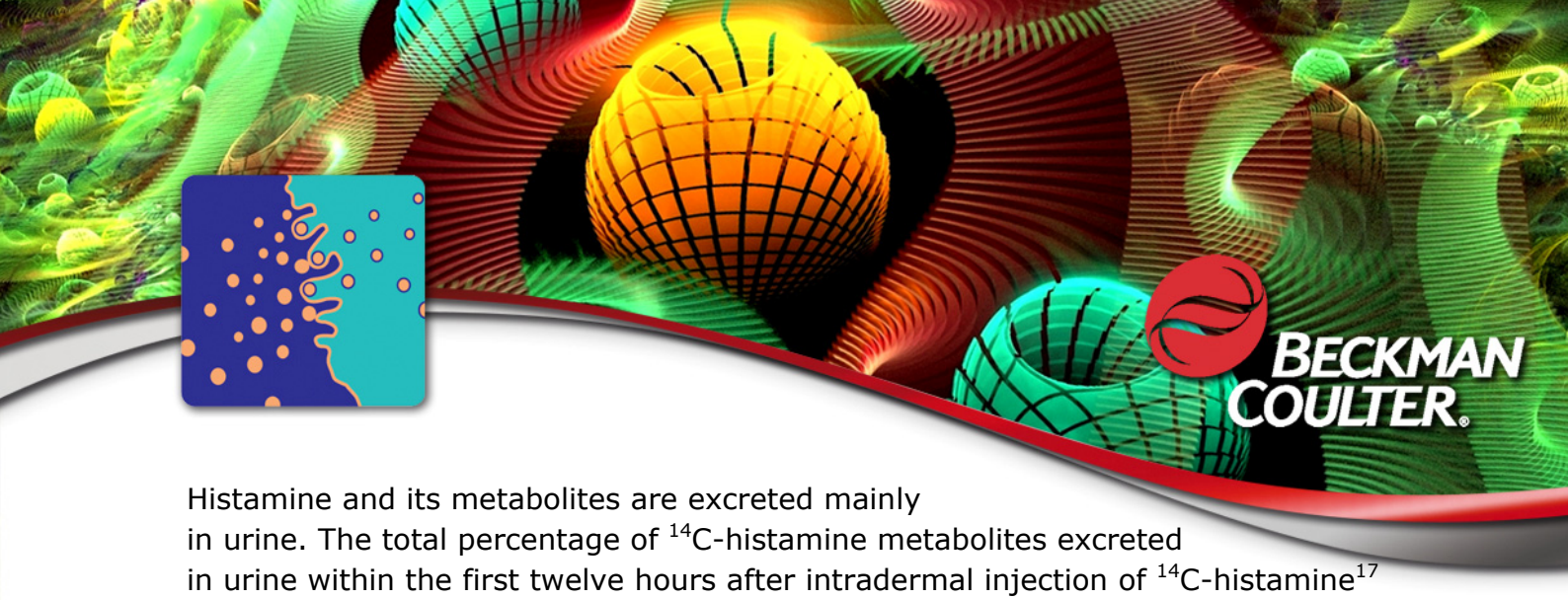
Decreased DAO activity has been discussed as a potential indicator of intestinal mucosa damage in inflammatory and neoplastic diseases[11, 12, 13] and in persons undergoing chemotherapy[14].

HNMT is widely expressed in human tissues; the greatest expression is in kidneys and liver, followed by the spleen, colon, prostate, ovary, spinal cord, bronchi and trachea[15]. HNMT is regarded as the key enzyme for histamine degradation in the bronchial epithelium[16].

Fig. 3: Histamine and histamine intolerance



Summary of histamine metabolism. Histamine is synthesized via the decarboxylation of the amino acid histidine, catalyzed by L-histidine decarboxylase (HDC) (1). Histamine can be metabolized via extracellular oxidative deamination of the primary amino group by diamine oxidase (DAO) (2) or via intracellular methylation of the imidazole ring by histamine-N-methyltransferase (HNMT) (3). Both enzymes can be inhibited by their respective reaction products in a negative feedback loop (4). N-Methylhistamine is oxidatively deaminated to N-methyl-imidazole acetaldehyde by monoamine oxidase B (MAO B) (5) or by DAO (6). Because the methylation pathway takes place in the cytosolic compartment of cells, MAO B (5) has been suggested to catalyze this reaction *in vivo*[14]. The acetylhistamine is minor metabolite (7).



Histamine and its metabolites are excreted mainly in urine. The total percentage of ^{14}C-histamine metabolites excreted in urine within the first twelve hours after intradermal injection of ^{14}C-histamine[17] are as follows:

Metabolite	**%**
Histamine	2 – 3
N-methylhistamine	4 – 8
N-methylimidazole acetic acid	42 – 47
Imidazole acetic acid	9 – 11
Imidazole acetic acid riboside	16 – 23
Acetylhistamine	< 1

Physiological Function

Histamine is a potent mediator of numerous biological reactions. Besides the well-known triggering of degranulation of mast cells by crosslinking of the FcεRI receptor by specific allergens, several other nonimmunologic stimuli may also activate mast cells. These stimuli include neuropeptides, complement factors (i.e., C3a and C5a), cytokines, hyperosmolarity, lipoproteins, adenosine, superoxidases[18], hypoxia, chemical and physical factors (e.g., extreme temperatures, traumas)[19], alcohol and certain food and drugs.

Histamine exerts its effects by binding to target cells of various tissues via its four receptors (H1R, H2R, H3R, and H4R) (Fig.4). It causes smooth muscle cell contraction, vasodilatation, increased vascular permeability and mucus secretion, tachycardia, alterations of blood pressure and arrhythmias; and it stimulates gastric acid secretion and nociceptive nerve fibers. In addition, histamine has been known to play various roles in neurotransmission, immunomodulation, hematopoiesis, wound healing, day-night rhythm, and the regulation of histamine- and polyamine-induced cell proliferation and angiogenesis in tumor models[12,20] and intestinal ischemia[21].

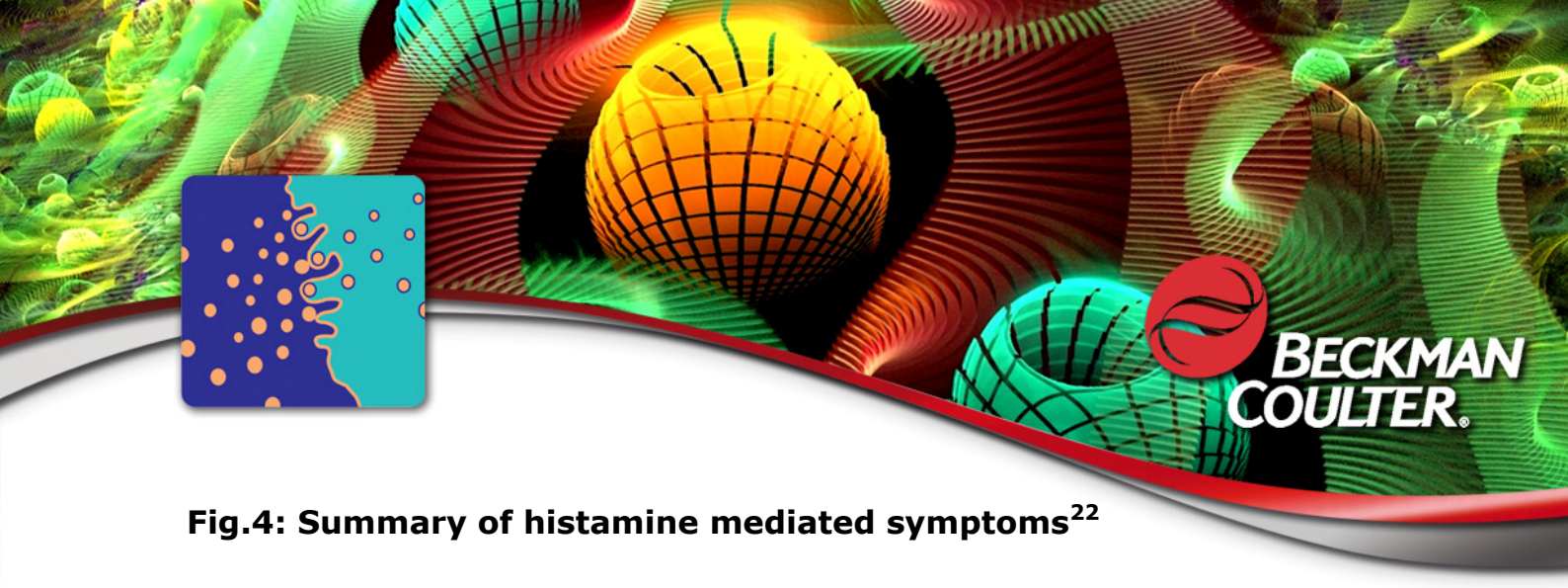
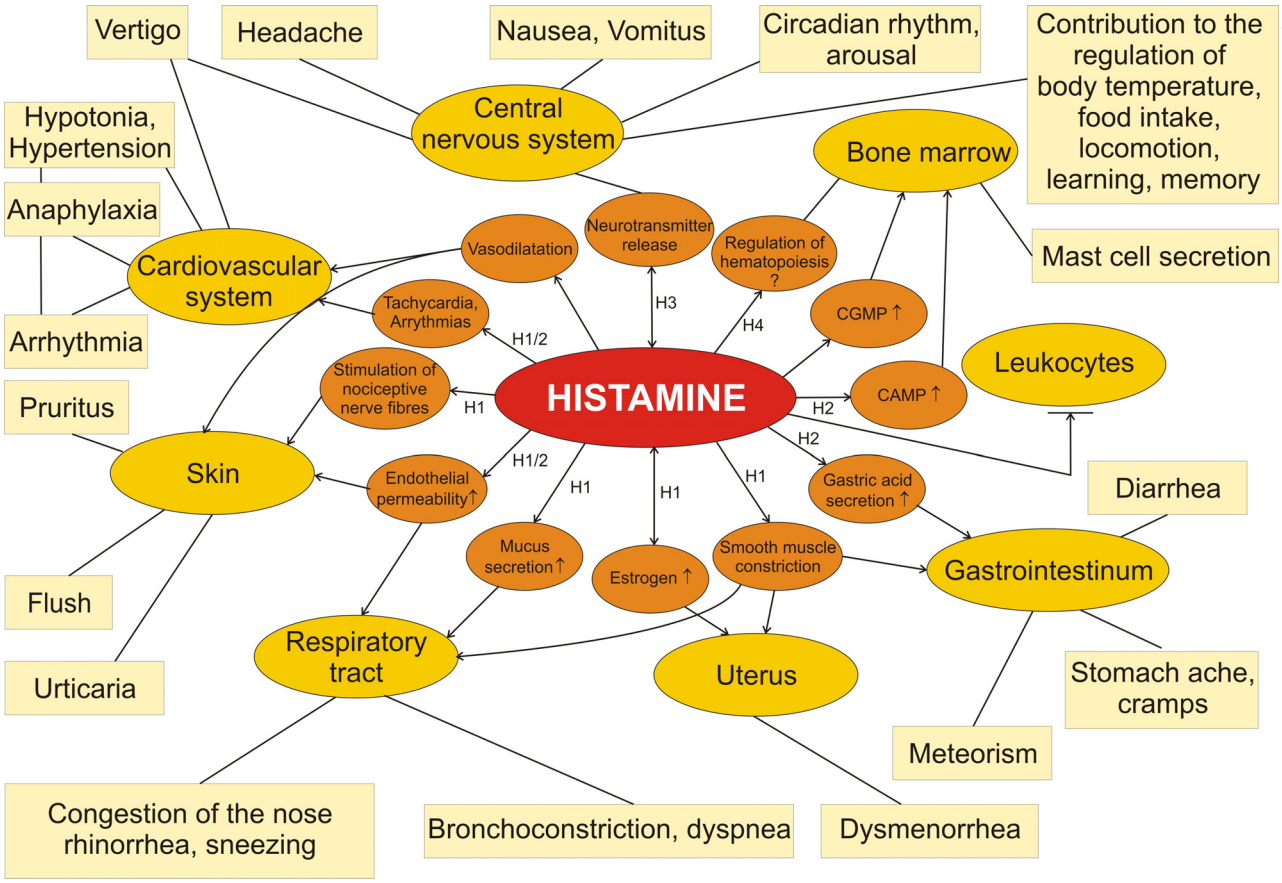


Fig.4: Summary of histamine mediated symptoms[22]

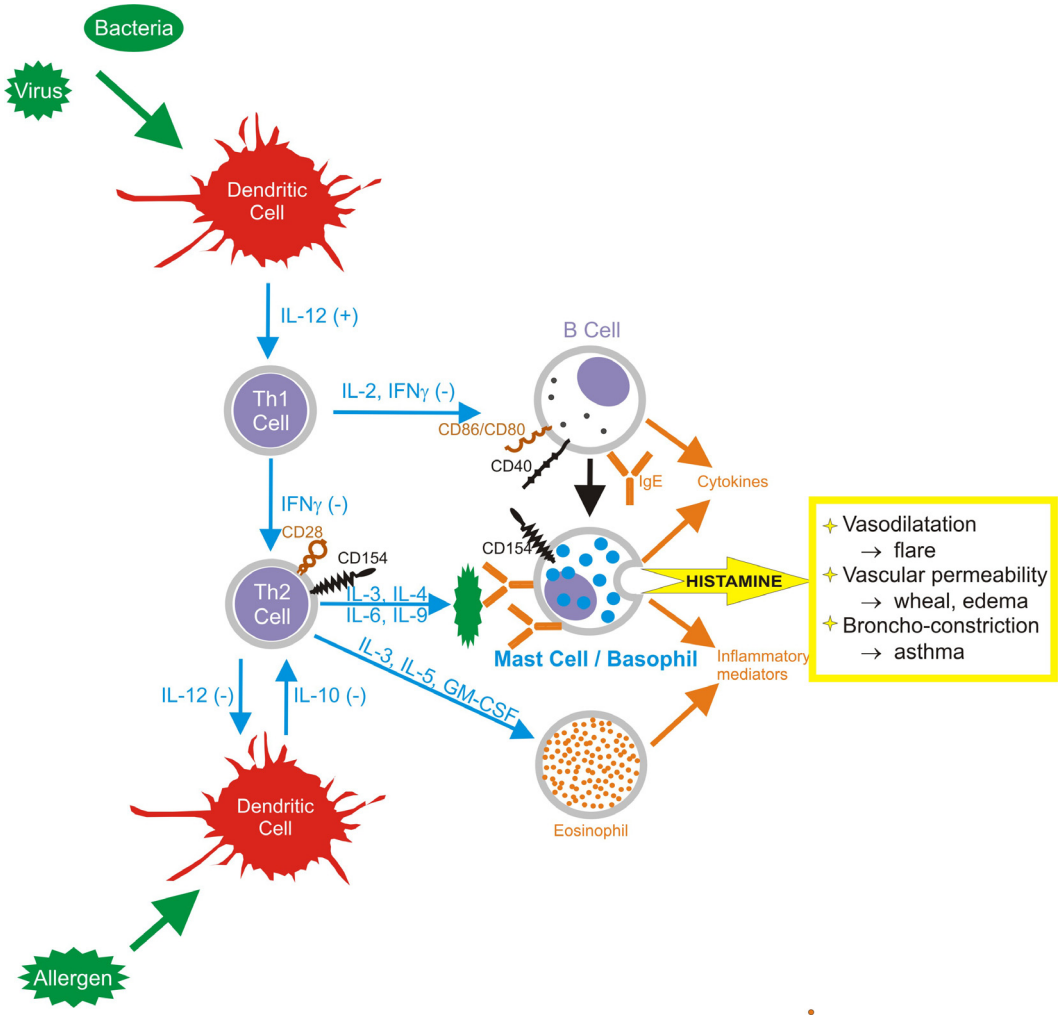


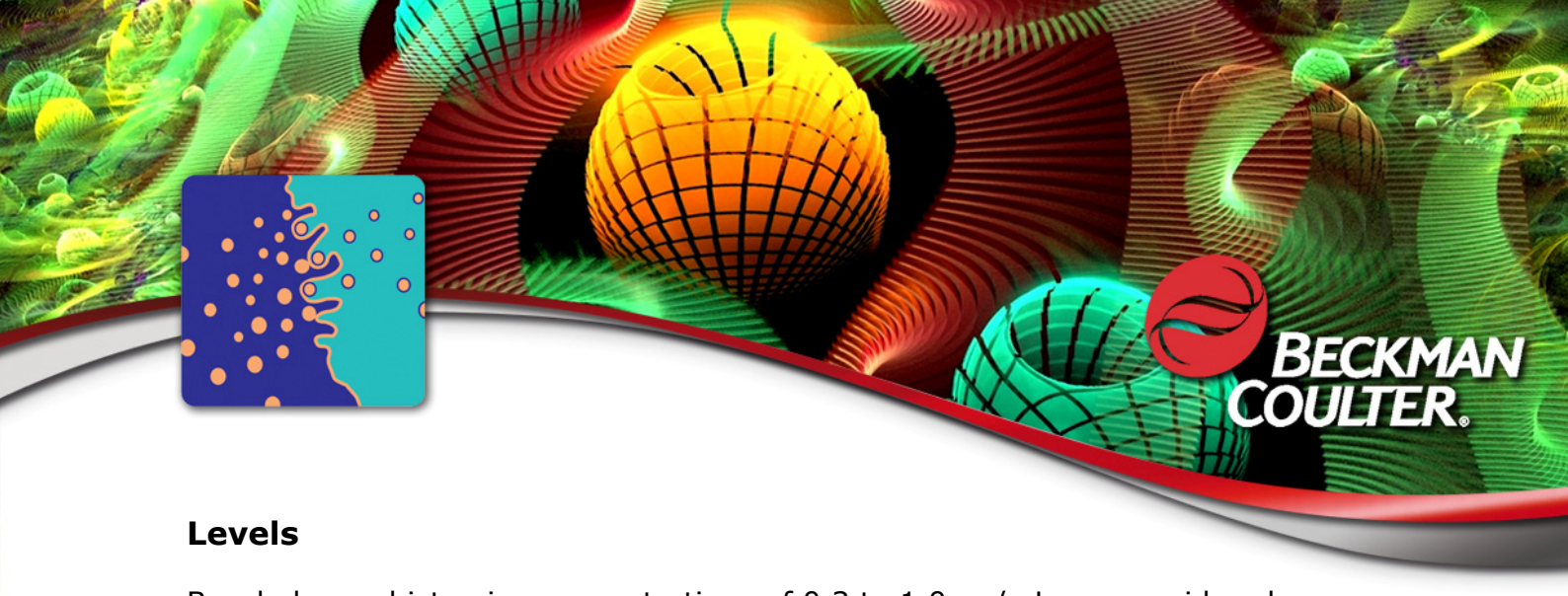
Allergic response

Histamine is a central mediator of allergic response.

Allergens are usually proteins, processed and presented to T cells through antigen-processing cells such as dendritic cells. T helper cells (Th2 type), mast cells, basophils or eosinophils produce proinflammatory cytokines that may induce an allergic response. Many inhalant allergens have enzymatic activities that enhance the allergic response. Exposure of sensitized individuals to the allergen then triggers histamine release in basophil or mast cells by IgE/FcεRI crosslinking. Histamine binds to specific receptors on smooth muscle cells and provokes potent adverse effects (Fig.5).

Fig.5: Summary of allergic response





Levels

Basal plasma histamine concentrations of 0.3 to 1.0 ng/mL are considered normal[23]. Concentrations in excess of the individual histamine tolerance give rise to concentration-dependent histamine-mediated symptoms[24, 25, 26, 27] (Table 2).

Table 2 - Histamine effects according to plasma histamine concentration (ng/mL)

Histamine (ng/mL)	Clinical effect
0 - 1	None
1 – 2	Increase in gastric acid secretion Increase in cardiac heart rate
3 – 5	Tachycardia, headache, flush, urticaria, pruritus
6 – 8	Decrease in arterial pressure
7 – 12	Bronchospasm
~ 100	Cardiac arrest

Diagnostic utility – Possibilities

Allergy testing

Histamine is released from basophils and mast cells as the result of an allergic reaction. Its level increases transiently in the blood as well as in tissue and it exerts a variety of pathological effects which may lead to cardiac arrest. The release of histamine may occur *in vivo* as the result of immediate hypersensitive reaction or may be induced by provocation. This release may be evidenced by plasma or urine measurement.

In vitro, histamine release may be induced by the addition of an allergen to whole blood or to a preparation of leucocytes or mast cells.

Pharmaceutical Industry

Histamine release may be inhibited by drugs. *In vitro* and *in vivo* modulation of histamine release is useful for anti-allergic drug screening and drug efficiency testing.

Histamine is released during adverse hypersensitivity to drugs. The measurement of histamine release during the clinical evaluation of a drug is useful parameter of establishing its harmlessness.

Cosmetology/Dermatology

Histamine and cytokines are crucial in allergenicity testing of cosmetic/dermatologic products. *In vivo* models are progressively transposed into *in vitro* models (mixed skin cell culture).

Research and Clinical Investigations

Significant amounts of histamine and its receptors are found in the mucosa of the stomach. It plays a role in gastric secretions. Histamine and its specific receptors also occur in the central nervous system. Their role in neurological abnormalities is under investigation. Varying levels of histamine have been found in various experimental and pathological conditions in spinal fluid, tears, saliva, nasal secretions, urine, bronchoalveolar lavages and tissues, demonstrating the extensive interest of this molecule in current research.

Veterinary

Histamine is ubiquitous. The use of the histamine release test in isolated cells or in the whole animal permits rapid quantitative exploration of the allergenic potential of a novel substance. Histamine determination is also useful for exploring therapeutic inhibitors of histamine release. All animal models are suitable.

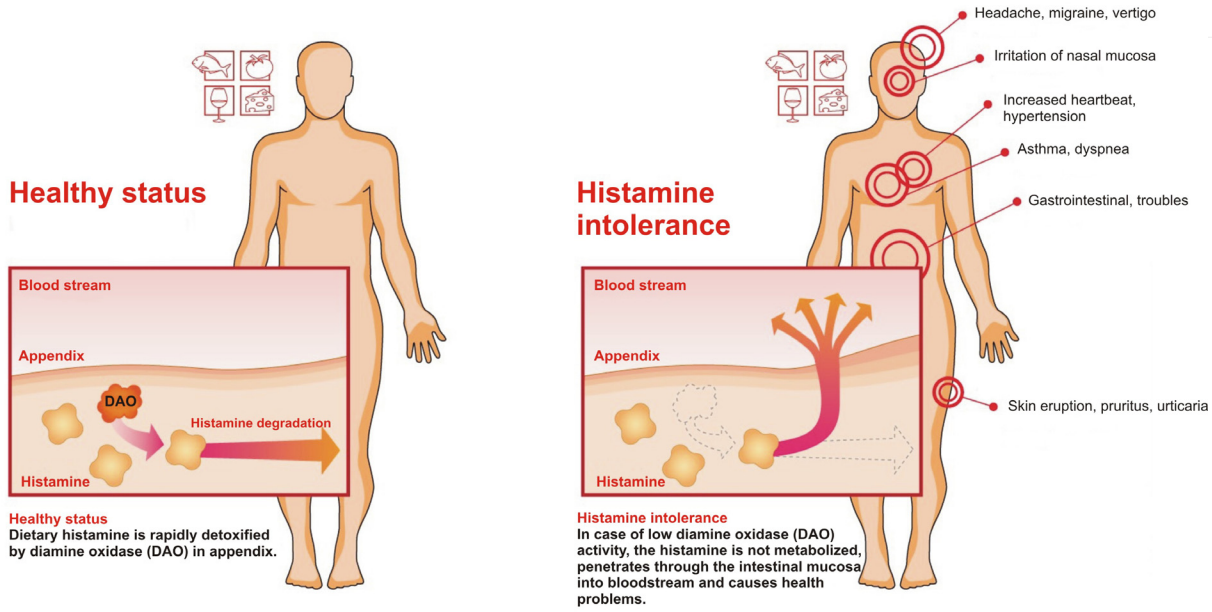
Pets or race horses may also be sensitive to various allergens. The measurement of *in vitro* histamine release in whole blood samples allows the identification of incriminated allergens.

Histamine intolerance[28, 29, 30, 31]

Histamine intolerance results from a disequilibrium between accumulated histamine and capacity for histamine degradation. Histamine is a biogenic amine that occurs to various degrees in many foods. In healthy persons, dietary histamine can be rapidly detoxified by amine oxidases, whereas persons with low amine oxidase activity are at risk of histamine toxicity (Fig.6).

The ingestion of histamine-rich food, alcohol or drugs that release histamine or block DAO may provoke diarrhea, headache, rhinoconjunctival symptoms, asthma, hypotension, arrhythmia, urticaria, pruritus, flushing and other conditions in patients with histamine intolerance. Symptoms can be mitigated by a histamine-free diet and/or antihistaminics.

Fig.6: Histamine intolerance[32]



Source: www.alles-essen.at

Food quality – histamine fish poisoning

Histamine fish poisoning (HFP) is a foodborne chemical intoxication caused by the consumption of spoiled or bacterially contaminated fish. Histamine is the main toxin involved in HFP. Although HFP is not uncomplicated histamine poisoning, the disease is generally associated with high levels of histamine (more than 50 mg per 100g of food) in spoiled fish.

Testing food for histamine levels can help to prevent undesirable events connected with HFP.

More information can be found in the brochure "Histamarine and Histamine Fish Poisoning".

Diagnostic utility – Main applications

In vitro histamine release

This test is most useful in the investigation of *in vitro* release of histamine caused by allergens. The allergen, when added to diluted blood, induces the degranulation of basophils, provided that the basophils carry the IgE specific for the allergen on their surface. The test allows the specific and safe identication of allergens to which the blood donor is sensitive.

Plasma histamine

Histamine is a key factor in allergy. *In vivo* allergic reactions are usually associated with increase in plasma histamine levels. Kinetics of *in vivo* histamine release may be followed by measurement of plasma histamine level increase after introduction of the suspected allergen[33, 34].

Urine histamine

Urine histamine excretion may be a good indicator of *in vivo* mast cell activation and indicates anaphylactic reactions which may have occured in the context of allergies to a medication. Urine histamine levels may also depend on histamine intake originating in the stomach.

Tissue histamine

Intracellular histamine is closely related to the regulation of cell proliferation. It plays a role in tissue repair as well as in cancer. Histamine present in tissues is measured after acid extraction.

References

1. Marieb, E.: Human anatomy & physiology. San Francisco: Benjamin Cummings.. 2001, pp. 414
2. Schwelberger HG.Diamine oxidase(DAO)enzyme and gene. In: Falus A, ed. Histamine: biology and medical aspects. Budapest, Hungary: SpringMed Publishing, 2004:43–52.
3. Schwelberger HG, Hittmair A, Kohlwein SD. Analysis of tissue and subcellular localization of mammalian diamine oxidase by confocal laser scanning fluorescence microscopy. Inflamm Res 1998;47(suppl): S60–1.
4. Schwelberger HG, Bodner E. Purification and characterization of diamine oxidase from porcine kidney and intestine. Biochim Biophys Acta 1997;1340:152– 64.
5. Brown DD, Tomchick R, Axelrod J. The distribution and properties of a histamine-methylating enzyme. J Biol Chem 1959;234:2948 –50.
6. Klocker J, Matzler SA, Huetz GN, Drasche A, Kolbitsch C, Schwelberger HG. Expression of histamine degrading enzymes in porcine tissues. Inflamm Res 2005;54(suppl):S54 –7.
7. Kufner MA, Ulrich P, Raithel M, Schwelberger HG. Determination of histamine degradation capacity in extremely small human colon samples. Inflamm Res 2001; 50 (suppl): S96 –7.
8. Bieganski T, Kusche J, Lorenz W, Hesterberg R, Stahlknecht CD, Feussner KD. Distribution and properties of human intestinal diamine oxidase and its relevance for the histamine catabolism. Biochim Biophys Acta 1983;756:196 –203.
9. Bieganski T. Biochemical, physiological and pathophysiological aspects of intestinal diamine oxidase. Acta Physiol Pol 1983;34:139 –54.
10. Raithel M, Kufner M, Ulrich P, Hahn EG. The involvement of the histamine degradation pathway by diamine oxidase in manifest gastrointestinal allergies. Inflamm Res 1999;48(suppl):S75– 6.
11. Schmidt WU, Sattler J, Hesterberg R, et al. Human intestinal diamine oxidase (DAO) activity in Crohn's disease: a new marker for disease assessment? Agents Actions 1990;30:267–70.
12. Raithel M, Ulrich P, Hochberger J, Hahn EG. Measurement of gut diamine oxidase activity. Diamine oxidase as a new biologic marker of colorectal proliferation? Ann N Y Acad Sci 1998;859:262– 6.
13. Backhaus B, Raithel M, Hahn EG. Nicht-immunologisch induzierte Histaminfreisetzung an vitalen menschlichen Darmschleimhautbiopsien durch Stimulation mit Polyaminen. (Nonimmunologically induced histamine release of biopsies of vital human intestinal mucosa after stimulation with polyamines.) Allergo J 2005;14:41 (abstr) (in German).
14. Tsujikawa T, Uda K, Ihara T, Andoh A, Fujiyama Y, Bamba T. Changes in serum diamine oxidase activity during chemotherapy in patients with hematological malignancies. Cancer Lett 1999;147:195– 8.
15. Schwelberger HG. Histamine N-methyltransferase (HNMT) enzyme and gene. In: Falus A, ed. Histamine: biology and medical aspects. Budapest, Hungary: SpringMed Publishing, 2004:53–9.
16. Yamauchi K, Sekizawa K, Suzuki H, et al. Structure and function of human histamine N-methyltransferase: critical enzyme in histamine metabolism in airway. Am J Physiol 1994;267:L342–9.

17. Nilsson K., Lindell S.E., Schayer R.W., Westling H. Metabolism of 14C-labelled histamine in pregnant and non-pregnant women. Clin.Sci.18, 1959, 313-319.
18. Vlieg-Boerstra BJ, van der HS, Oude Elberink JN, Kluin-Nelemans JC, Dubois AE. Mastocytosis and adverse reactions to biogenic amines and histamine-releasing foods: what is the evidence? Neth J Med 2005;63: 244–9.
19. Ring J. Angewandte Allergologie. (Implemented allergology.) Munich, Germany: Urban & Vogel, 2004 (in German).
20. Kusche J, Bieganski T, Hesterberg R, et al. The influence of carcinoma HISTAMINE AND HISTAMINE INTOLERANCE 1193 Downloaded from www.ajcn.org by on September 2, 2010 growth on diamine oxidase activity in human gastrointestinal tract. Agents Actions 1980;10:110 –3.
21. Kalchmair B, Klocker J, Perkmann R, et al. Alterations in plasma amine oxidase activities in a compartment syndrome model. Inflamm Res 2003;52(suppl)1:S67– 8.
22. Maintz, L; Bieber, T; Novak, N.: Histamine Intolerance in Clinical Practice. Dtsch Arztebl 2006; 103(51-52): A-3477-83
23. Dyer J, Warren K, Merlin S, Metcalfe DD, Kaliner M. Measurement of plasma histamine: description of an improved method and normal values. J Allergy Clin Immunol 1982;70:82–7.
24. 15. Wohrl S, Hemmer W, Focke M, Rappersberger K, Jarisch R. Histamine intolerance-like symptoms in healthy volunteers after oral provocation with liquid histamine. Allergy Asthma Proc 2004;25:305–11.
25. Kaliner M, Shelhamer JH, Ottesen EA. Effects of infused histamine: correlation of plasma histamine levels and symptoms. J Allergy Clin Immunol 1982;69:283–9.
26. Ind PW, Brown MJ, Lhoste FJ, Macquin I, Dollery CT. Concentration effect relationships of infused histamine in normal volunteers. Agents Actions 1982;12:12–6.
27. Lorenz W. Histamine release in man. Agents Actions 1975, 5:402-416.
28. Maintz L, Novak N. Histamine and histamine intolerance. Am J Clin Nutr 2007; 85:1185–96. Printed in USA. © 2007 American Society for Nutrition.
29. Ind PW, Brown MJ, Lhoste FJ, Macquin I, Dollery CT. Concentration effect relationships of infused histamine in normal volunteers. Agents Actions 1982;12:12–6.
30. Bieganski T, Kusche J, Feussner KD, Hesterberg R, Richter H, Lorenz W. Human intestinal diamine oxidase: substrate specificity and comparative inhibitor study. Agents Actions 1980;10:108 –10.
31. Bieganski T, Kusche J, Feussner KD, Hesterberg R, Richter H, Lorenz W. The importance of human intestinal diamine oxidase in the oxidation of histamine and/or putrescine. Arch Immunol Ther Exp (Warsz) 1980;28:901– 6.
32. www.alles-essen.at
33. Bosso JV, Schwartz LB, Stevenson DD. Tryptase and histamine release during aspirin-induced respiratory reactions. J. Allergy Clin. Immunol. 1991, 88:830-837.
34. Helmbauer G, Hauk P, Forster J, Urbanek R, Kaufmehl K, Koller DY. In vivo histamine release during the first minutes after deliberate sting challenges correlates with the severity of allergic symptoms. Pediatr Allergy Immunol 1999, 10: 53-57.