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SHORT COMMUNICATION

Histamine intolerance: a metabolic disease?

H. G. Schwelberger

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Abstract
Objective To evaluate the evidence regarding the disease concept of histamine intolerance as a state of inadequate histamine inactivation.
Methods Keyword-based systematic screening of the scientific literature and of public websites focusing on diagnostic and therapeutic procedures.
Results Histamine intolerance is commonly diagnosed based solely on subjective reporting of symptoms instead of following systematic diagnostic procedures based on objective laboratory and physical parameters. The only effective long-term therapy is avoidance of histamine-containing food.
Conclusions The concept of histamine intolerance as a metabolic disease is in need of more experimental and clinical evidence and affected patients will benefit from a clear, evidence-based diagnostic and therapeutic regime.

Keywords Histamine intolerance · Histamine metabolism · Diamine oxidase · Histamine N-methyltransferase · Diagnosis · Therapy

Introduction

Histamine intolerance describes a state where the catabolic capacity for endogenously released or exogenously administered histamine is insufficient leading to histamine mediated adverse reactions [1, 2]. Specifically, the terms histamine intolerance or enteral histaminosis are used to explain a variety of symptoms that appear to be caused by dietary histamine upon ingestion of food with a high histamine content, such as fish, cheese, meat products, and alcoholic beverages [3, 4]. The hype about this disease concept in the media and on numerous websites, especially in Central Europe, called for a critical evaluation of the current evidence regarding diagnostic procedures and therapeutic strategies.

Materials and methods

Scientific journal articles published on histamine intolerance were retrieved by a comprehensive medical subject heading and keyword search of the PubMed database (http://www.ncbi.nlm.nih.gov/sites/entrez?db=PubMed) and evaluated for diagnostic and therapeutic approaches used. Additionally, the information presented on public websites retrieved by a Google search on "histamine intolerance" was screened for comprehensibility, accuracy, scientific foundation, and citation of sources.

Results and discussion

Histamine intolerance is thought to be caused mainly by ingestion of food containing high amounts of histamine by people with low intestinal histamine inactivation or inhibition of this activity by other food constituents or drugs, which leads to resorption of histamine in amounts sufficient for causing adverse reactions [1, 2]. Evaluation of more than 200 scientific journal articles and over 30 patient oriented websites dealing with this disease concept

H. G. Schwelberger (✉)
Molecular Biology Laboratory, Department of Visceral, Transplant and Thoracic Surgery, Medical University Innsbruck, Schöpfstraße 41, 6020 Innsbruck, Austria
e-mail: hubert.schwelberger@i-med.ac.at

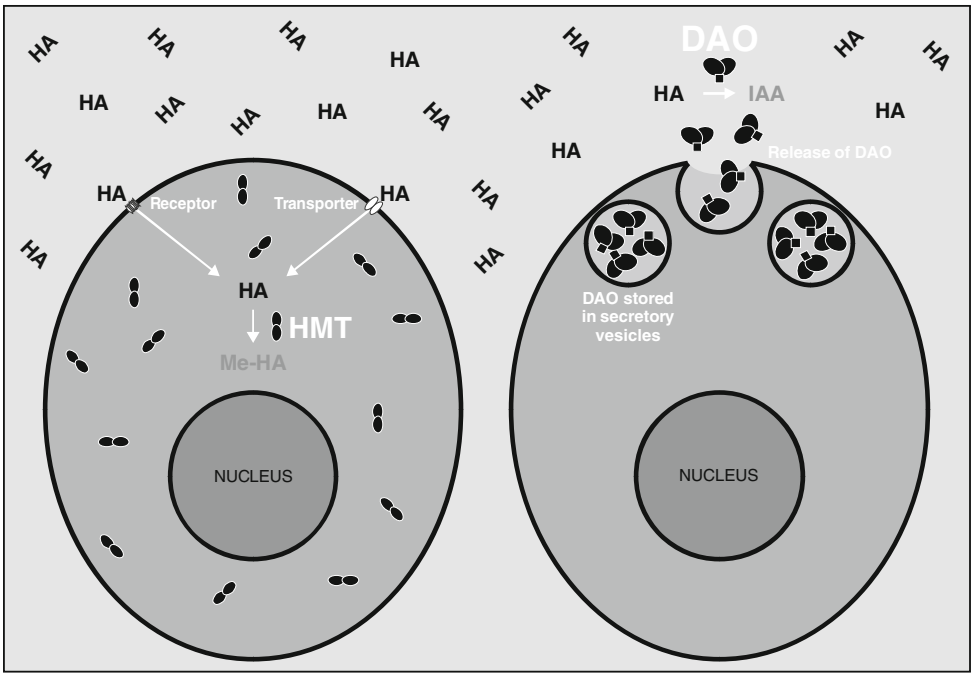

Fig. 1 Histamine (HA) is inactivated inside cells by histamine *N*-methyltransferase (HMT) yielding N^4-methylhistamine (Me-HA) and extracellularly by diamine oxidase (DAO) yielding imidazole acetaldehyde (IAA)

revealed that a lot more is being alleged and stated than is actually substantiated by scientific evidence.

Histamine present in food is usually associated with other pharmacologically active biogenic amines and is produced from the amino acid L-histidine by microorganisms possessing histidine decarboxylase activity in the course of food processing or spoilage [4]. For histamine to cause adverse reactions and symptoms it has to be resorbed in the intestine and transported via the bloodstream without being inactivated by the enzymes, diamine oxidase (DAO) and histamine N-methyltransferase (HMT), present in intestinal epithelial cells (Fig. 1). HMT is a cytosolic enzyme that inactivates histamine by methylation of the imidazole ring forming N^4-methylhistamine, which requires transport of histamine into the cell either by receptor mediated endocytosis or by specific transporters [5]. DAO is a secretory enzyme acting extracellularly that oxidatively deaminates the primary amino group of histamine yielding imidazole acetaldehyde and animal studies suggested that DAO forms the primary barrier for intestinal histamine resorption [6].

The major problem with the diagnosis of histamine intolerance is the variety of tests currently in use, ranging from the red wine provocation test to plasma DAO determination [1]. Adequate diagnosis of histamine intolerance (Fig. 2) should start with carefully recording symptoms

Fig. 2 Diagnosis and therapy of histamine intolerance

Diagnosis of histamine intolerance

- **Association of food consumption and symptoms (diet diary)**
- **Identification of food causing symptoms**
- **Determination of histamine content of symptom causing food**
- **Exclusion of other causes (allergic, metabolic, toxic)**
- **Double-blind, placebo-controlled oral histamine provocation in combination with determination of plasma histamine concentration and objective physical parameters (heart rate, blood pressure, erythema)**
- **Determination of DAO and HMT content and activity in intestinal mucosa (not in peripheral blood plasma)**
- **Analysis of DAO and HMT genetic polymorphisms**

Therapy of histamine intolerance

- **Histamine receptor antagonists**
- **Avoidance of histamine containing food (histamine content?)**
- **Avoidance of histamine releasing substances (endogenous histamine release)**
- **Avoidance of substances inhibiting DAO and HMT**
- **DAO substitution (encapsulated pig kidney DAO)**

after food consumption, identification of causative foodstuffs and determination of their histamine content. This will also be useful to either exclude or identify causes other than histamine. Definitive diagnosis necessitates double-blind, placebo-controlled oral histamine provocation with determination of plasma histamine concentrations and objective physical parameters. In proof of the concept, measurement of intestinal DAO and HMT activities is required and could be complemented by analysis of DAO and HMT gene polymorphisms to identify a possible genetic predisposition [7].

It is clear that therapy of histamine intolerance (Fig. 2) is useless without a firm diagnosis. Treatment with histamine H_1 and H_2 receptor antagonists is warranted only when uptake of high amounts of histamine occurs as in fish poisoning [8] but not for long-term therapy. The only effective therapy of confirmed histamine intolerance is avoidance of histamine containing food, which is difficult as the histamine content is usually not specified by producers and must be inferred from general recommendations [1]. Additionally, substances should be avoided that can either lead to endogenous histamine release or inhibit the activities of DAO and HMT. Controlled trials demonstrating the efficacy of DAO substitution with encapsulated pig kidney enzyme are still lacking. Even if the concept of histamine intolerance as a metabolic disease is in need of further experimental and clinical evidence, therapeutically any diet that improves the condition and does not lead to malnutrition will be beneficial for the patient.

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