The Pivotal Role of Histamine in the Symptoms of Food Intolerance

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Histamine in Food Allergy

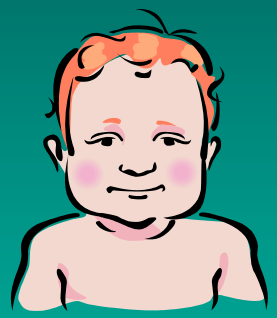
- Traditionally, allergy is defined as a Type I hypersensitivity (IgE-mediated) reaction
- Histamine is the most important inflammatory mediator in IgE-mediated reactions
- Principally released from mast cells
- Also released by degranulation of other granulocytes especially basophils

Histamine in Non-IgE-mediated Reactions

- IgG-mediated reactions also release histamine
  - Food-specific antibody-antigen complex formed
  - Activates complement cascade
  - Production of anaphylatoxins (C3a; C5a)
  - Action of anaphylatoxins on mast cells releases histamine and other inflammatory mediators
- Reaction is delayed in onset (up to 8 hours) compared to IgE-mediated immediate reaction

Action of Histamine in Allergy

- Vasodilation: widening of blood vessels
  - **May cause slight drop in blood pressure**
  - **Increase in heart rate**
- Erythema
  - **Flushing, reddening**
- Increased vascular permeability
  - **Fluid moves from blood vessels into tissues**
  - **Causes swelling**
- Pruritus
  - **Histamine is the main cause of itching**



Examples of Symptoms of Food Allergy

- Urticaria and angioedema
- Rhinoconjunctivitis and rhinorrhea
- Headaches
- Symptoms in the oral cavity
- Digestive tract disturbances: abdominal pain, diarrhea, nausea, vomiting

➔ ***Similar symptoms can be caused by histamine intolerance***

Food Allergy and Food Intolerance: What is the Difference?

- Definitions:
- Food Allergy:
  - **A response of the immune system involving antigen consisting of protein or a molecule linked to a protein**
- Food Intolerance
  - **A non-immunologically mediated event, usually triggered by small molecular weight chemical substances, and biologically active components of foods**

Characteristics of Food Allergy and Food Intolerance

- Food allergy:
  - **Requires a "sensitizing event" that primes the immune system for future response**
  - **Reaction is not dose-dependent**
  - **Allergic potential is an inherited characteristic (is idiosyncratic)**
- Food Intolerance
  - **Does not require "priming"**
  - **Event is dose-dependent**
  - **Reaction is not always idiosyncratic**

Histamine Intolerance

- Histamine is a biologically active derivative of an amino acid (histidine)
- Is present in many foods and beverages
- High doses are toxic to all humans: levels of >2.7 mg/kg body weight cause “histamine poisoning”
- Individual tolerance determines reactivity to small quantities

Individual Intolerance of Histamine

- Cause is most likely a defect in the catabolism of histamine
- In humans, enzymatic inactivation of histamine occurs by two pathways:
  - Diamine oxidase (DAO)
  - Histamine N-methyl transferase (HMT)

Theory of Histamine Excess

- Histamine from dietary sources and from the activity of intestinal micro-organisms will normally be catabolized before gaining access to circulation
- If enzyme activity is reduced, histamine will gain access to blood and augment the level of plasma histamine from endogenous sources

Histamine-restricted Diet: Case studies - Subject #1

- Female aged 24 years; cashier and student
- Presenting Sx:
  - Recurrent urticaria on neck, midsection, back, arms: Hives occur on various body surfaces several times a week; present for several years
  - Dermatographia and pressure urticaria (water in shower)
  - Frequent headaches: occur almost daily

Histamine-restricted Diet: Case studies - Subject #1

- Other relevant data:
  - Seasonal rhinoconjunctivitis
  - "Borderline asthmatic" (especially in smoky environment)
  - Skin-test positive to: dust, grasses, trees, feathers
  - Respiratory tract Sx improved when living in a home with hard-wood floors

Histamine-restricted Diet: Case studies - Subject #1

- Outcome of histamine-restricted diet:
  - Urticaria and pruritus completely cleared up
  - Patient experienced only one headache during the diet trial - following consumption of tomato soup
  - Consumption of Tylenol for control of headaches reduced from daily to only once (after above episode)

Histamine-restricted Diet: Case studies - Subject #2

- Female, age 29 years. Case room nurse
- Presenting Sx:
  - Urticaria
  - Frequent diarrhea and vomiting after eating certain meals since childhood, and more severely since her latest pregnancy
  - Migraine headaches
  - “Panic attacks”

Histamine-restricted Diet: Case studies - Subject #2

- **Other relevant data:**
  - **Skin-testing in childhood resulted in "whole arm swelled to an enormous size"**
  - **All reactions have worsened since the birth of her daughter 1 year ago**
  - **"Panic attacks" becoming debilitating**
- **Outcome of histamine-restricted diet:**
  - **Significant improvement in all symptoms**
  - **Complete remission of symptoms associated with "panic attack"**

Indicators of Possible Histamine Intolerance

- Skin tests:
  - **"Mildly positive" to multiple allergens**
  - **Large reaction wheal to histamine control**
- Dermatographia
- Unusually sensitive to alcoholic beverages
- Sensitive to fermented foods, especially Oriental food, cheese, vinegar
- Sensitive to benzoate-containing foods, especially cinnamon, green and black tea
- Positive family history

Reduced Histamine Catabolism

- Indicators of reduced histamine metabolism have been suggested to be:
  - Elevated plasma histamine (>2 ng/ml)
  - Reduced DAO activity (<0.7 nkat/L)
- Reduced histamine catabolism, combined with IgE-mediated histamine release suggested to result in increased severity of allergy
  - may be a critical factor in anaphylaxis

Occurrence of DAO and HMT

- DAO occurs predominantly in:
  - **intestinal mucosa - kidney**
  - **placenta - thymus**
- HMT occurs more widely, in:
  - **brain - spleen**
  - **stomach - kidney**
  - **lung - thymus**

Function of HMT and DAO

- HMT primarily functions at the level of histamine receptors:
  - **It terminates the biological activity of histamine in a wide range of organs**
- The primary function of DAO seems the elimination of excess histamine
  - **This is effectively achieved in controlling the amount of histamine entering the body from the digestive tract**

Catabolism of Histamine

- Histamine from exogenous sources is catabolised differently from endogenous histamine
  - Exogenous histamine is metabolised predominantly via oxidative deamination by DAO
  - Endogenous histamine is metabolised more via ring N-methylation by histamine N-methyltransferase

Catabolism of Histamine (continued)

- The two systems produce different end-products:
- DAO: imidazole compounds:
  - imidazole-acetaldehyde
  - imidazole acetic acid
- HMT: N-methylated products:
  - N-methylhistamine
  - N-methylimidazole acetic acid

Biological Activity of Histamine Breakdown Products

- Biological activity of histamine metabolites is largely unknown
- It appears that the methylated products of HMT activity are inert
- In lab experiments imidazoleacetic acid (from DAO activity) has been reported to have behavioral effects in rats and mice
- Most do not accumulate, but are excreted in urine

Catabolism of Histamine (continued)

- The contribution of the two enzyme systems to histamine breakdown varies between tissues:
  - DAO tends to predominate in the intestine
  - HMT predominates in the brain
- However, inhibition of one pathway may switch the degradation to the other, even in the same organ

Fate of Histamine in the Body

- Histamine in the blood stream is rapidly cleared
  - **May arise from mast cells and basophils**
  - **In research studies radiolabelled histamine injected intravenously**
  - **Degradation products can be detected and measured in urine**
- 99% of histamine given orally is prevented from reaching the circulation

Level of Histamine Metabolites in Urine

- Seems to be greatly influenced by:
  - Level of histamine in food
  - Activity of bacteria in the large bowel (caecum and colon)
  - Possibly activity of bacteria in the vagina
- These are exogenous sources
- The level of endogenous histamine may be fairly stable, except when an allergic reaction causes increased release of histamine

Exogenous Sources of Histamine

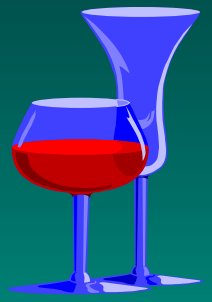
- Amines are produced from amino acids by decarboxylation
- Result from metabolism of animal, plant, and microorganisms
- Are present in most animal and plant foods in small quantities
- Histamine is produced by decarboxylation of histidine

Histidine Decarboxylase

- Histidine decarboxylase is produced by a range of micro-organisms
- These species are used in manufacture of fermented foods, such as:
  - **Cheese**
  - **Fermented sausages (Salami; Bologna; Pepperoni, etc)**
  - **Fermented vegetables (sauerkraut)**
  - **Fermented soy (miso and soy sauce)**

Other Food Sources of Histamine

- Fermented beverages
  - Wine
  - Beer, ale, lager, etc



- Fruits:
  - Citrus - Stone fruits - Dates
  - Berries - Pineapple - Currants

- Vegetables
  - Tomato - Eggplant - Soy bean
  - Spinach - Pumpkin - Red bean
  - Olives

Other Food Sources of Histamine

- Several species of bacteria in the gut of fish and shellfish produce histidine decarboxylase
  - **When fish dies bacteria degrade its protein**
  - **Bacteria can multiply every 20 minutes**
  - **Histamine content of ungutted fish can double every 20 minutes**
- Shellfish are not gutted before consumption
- Left-over meats may be colonized by histidine decarboxylase-producing bacteria

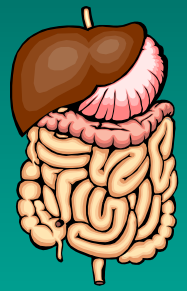
Other Food Sources of Histamine

- Some food additives appear to release histamine:
  - **Tartrazine and other azo dyes**
  - **Sulphites**
  - **Benzoates**

- Some foods contain natural benzoates:
  - **Cinnamon - Tea - Berries**
- Egg white (ovalbumin) has been implicated in histamine release by an unknown mechanism

Histidine decarboxylase and the Resident Micro-flora

- Many bacterial species that colonize the large bowel of humans produce histidine decarboxylase
- Convert histidine in non-digested food material to histamine



- This is an additional source of exogenous histamine
- If not catabolised by DAO in situ, histamine will enter the blood circulation

Inhibitors of DAO and HMT

- **Drugs that inhibit enzymes involved in histamine breakdown result in histamine excess:**
  - **HMT inhibitors:**
    - Antimalarial drugs (4-aminoquinoline derivatives)
    - Anticancer drugs (pyrimidine analogs)
  - **DAO inhibitors:**
    - Copper-chelating agents (cyanides; carbamates)
    - Carbonyl group reagents (aminoguanidine; semicarbazide)

Histamine Degrading Bacteria

- Certain species of bacteria produce diamine oxidase:
  - Lactobacillus sp. - Sarcina sp.
  - Leuconostoc sp. - E.coli faecium sp.
- Capable of degrading food sources of histamine
- May reduce total histamine load
- Possible role in probiotics?