HISTAMINE INTOLERANCE, DIAMINE OXIDASE ACTIVITY, AND PROBIOTICS

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June 2004

Histamine in Allergy

Histamine is an important mediator of the symptoms of allergy. Allergy is a Type I hypersensitivity reaction, involving the production of allergen-specific IgE, which leads to the release of pre-formed inflammatory mediators that are stored within cytoplasmic granules in tissue mast cells, and to a lesser extent from similar granules in blood basophils. Histamine is the most important of these mediators, and is responsible for the symptoms that are typical of an immediate-onset allergic reaction. Defects in histamine catabolism may contribute to the severity of the reaction. When the histamine released from the granulocytes in the process of allergic (or atopic) degranulation is not broken down efficiently, excess will accumulate, theoretically leading to a situation that might critically enhance the adverse effects of the amine. The contribution of defects in histamine pharmacodynamics to anaphylaxis has been assessed in very few studies, but where this has been considered, the results seem to indicate that it might represent an important factor in a condition which can be life-threatening (Hershko et al 2001).

Histamine Intolerance

Varying opinions exist on the significance of biogenic amines in non-immunologically-mediated reactions to foods that may be termed "food intolerance" in contrast to "food allergy" which is a hypersensitivity reaction of the immune system. Because histamine is the most important mediator responsible for the symptoms of "classical allergy" in the Type I (IgE-mediated) hypersensitivity reaction, it is difficult for clinicians to distinguish between reactions due to allergy and those resulting from histamine excess, since the symptoms are the same in both cases. Typical symptoms of food allergy include urticaria, angioedema, rhinitis, asthma, headaches, oral allergy symptoms, and digestive tract complaints such as nausea, flatulence, abdominal cramps and diarrhea (Bischoff and Manns 1998).

Food intolerance, which is not immunologically mediated, is usually triggered by small molecular weight chemical substances and biologically active components of foods, not by food proteins (Bischoff and Manns 1998). Histamine is an important example of a biologically active component that is present in many foods and beverages. Whereas high doses of histamine are toxic for all humans (Taylor 1986), individual tolerance is the important characteristic that determines reactivity to small quantities. Just about everyone who ingests preformed histamine from a contaminated food at a level of more than 2.7 mg/kg body weight will show symptoms of "histamine poisoning" (Moneret-Vautrin 1987), but at lower concentrations only a few sensitive individuals will experience an adverse reaction. It is likely that differences in levels of tolerance are of genetic origin, but tolerance can be reduced by disease and medications.

It is thought that the cause of histamine intolerance is most likely a defect in catabolism of histamine (Lessof et al 1990). In humans, enzymatic inactivation of histamine occurs through the operation of two types of enzymes, diamine oxidase (DAO) and histamine N-methyltransferase (HMT) that have different characteristics (Rangachari 1992). DAO occurs predominantly in the human intestinal mucosa as well as the placenta, kidney and thymus. HMT has a wider distribution, occurring in the stomach, lung, spleen kidney, thymus, and particularly the brain (Rangachari 1992). Both enzymes can be inhibited by a variety of compounds (Beaven et al 1983), many of which are used as medications. Reduced DAO activity has been the subject of several investigations of conditions such as "idiopathic" urticaria and angioedema in which an immunologically-mediated hypersensitivity response (allergy) has been ruled out (Lessof et al 1990; Gotz et al 1996; Wantke et al 1998). Laboratory findings of elevated plasma levels (> 2 ng/ml) of histamine and reduced DAO activity (0.7 nkat/L) have been suggested as indicators of reduced histamine catabolism (Jarisch and Wantke 1996; Bischoff and Manns 1998).

The key to histamine intolerance lies in the way that histamine is metabolised within the human body; specifically, how excess histamine is catabolised. It appears that the degree of histaminosis is directly linked to the amount of histamine breakdown (Maslinski and Fogel 1991; Götz et al 1996; Jarisch and Wantke 1996). The greater the histamine catabolising capacity, the lower the level of plasma histamine.

Catabolism of Histamine

Histamine is an essential mediator of several processes within the body. In particular it acts as an important neurotransmitter in the central nervous system, and plays an essential role in digestive functions, especially in the production of secretions such as gastric acid in the stomach. Histamine for these functions is produced within the body, and is thus endogenous in origin. Histamine also enters the body from exogenous sources in food, or from the activity of the resident micro-organisms in the large bowel that decarboxylate histidine in proteinaceous food residues.

Research indicates that histamine from exogenous sources tends to be catabolised differently from endogenous histamine. The former is metabolised principally via oxidative deamination by diamine oxidase; the latter by ring N-methylation by histamine N-methyltransferase (Sjaastad and Sjaastad 1974). The two systems produce different end-products (Figure 1). This provides a means whereby the fate of histamine from the diet may be studied independently from that of the histamine arising within the body that is designed for participation in many essential body functions.

The contribution of each of the enzymes systems (DAO and HMT) to histamine breakdown seems to vary between tissues. Diamine oxidase activity seems to predominate in the intestine, whereas, N-methyltransferase activity predominates in the brain (Holcslaw et al 1985; Schayer and Reilley 1973). However, there is evidence that inhibition of one pathway may switch the degradation to the other, even within the same organ. Recent research indicates that in tissues where both enzymes occur together (in this case porcine kidney), DAO tends to exhibit a histamine-degrading capacity ten times higher than that of HMT (Huertz and Schwelberger 2003).

When histamine is released from granulocytes such as mast cells and enters the blood stream, it is usually rapidly cleared from circulation. Radiolabelled histamine injected intravenously appears in tissues within minutes and is excreted in urine as metabolites, with only a small fraction being excreted as histamine (Maslinskin and Fogel 1991; Reilley and Schayer 1971). In contrast, 99% of histamine entering the body in the digestive tract is prevented from reaching the circulation (Naranjo 1966) (Figure 1).

The levels of urinary histamine and its metabolites seem to be greatly influenced by the level of histamine consumed in food, by the activity of bacteria in the digestive tract, and possibly in the vagina (Keyzer et al 1983).

Function of Histamine-Catabolising Enzymes

The primary function of histamine-catabolising enzymes appears to be to terminate the biological activity of histamine, most efficiently at the site of its action, namely histamine receptors (Maslinski and Fogel 1991). The wide distribution of histamine N-methyltransferase in tissues, and its location in the cytosol of cells and in red blood cells (Lindahl 1960; Maslinski and Fogel 1991) would indicate such a function. It has been suggested that in contrast, the primary function of diamine oxidase is to control histamine excess.

Exogenous Sources of Histamine

Biogenic amines are catabolic products of amino acids and are a result of both animal and plant metabolism (Finn 1987). In small quantities they are present in almost all foods (Bischoff and Manns 1998). Large quantities result from microbial activities during rotting of foods, and during manufacture of fermented foods such as cheese, wine, vinegar, fermented sausages, soy sauce, and sauerkraut (Halasz et al 1994; Chin et al 1989; Beljaars et al 1998; Diel et al 1997; Vidal-Carou 1989). In addition, undigested food materials passing into the large bowel are acted upon by the resident microbial flora. Many enteric bacterial species produce histidine decarboxylase, and therefore can convert histidine in dietary proteins to histamine within the gut.

Histamine from dietary sources and from the activity of intestinal microorganisms will normally be catabolised by diamine oxidase within the digestive tract before gaining access to circulating blood. However, if the enzymatic activity at this site is reduced, histamine will be transported from the gut lumen into circulation and augment the level of plasma histamine from endogenous sources (Appendix A).

Function of Products of Histamine Catabolism

The biological activity of most of the breakdown products of histamine is currently unknown. A few have been demonstrated to possess biological activity in laboratory animals; for example, imidazoleacetic acid (but not methylimidazole acetic acid) has been reported to have behavioural effects in mice and rats (Roberts and Simonsen

1966). As far as is presently known, the methylated products of histamine catabolism are biologically inert, which would be expected if the main function of HMT is inactivation of histamine at its reaction site within the target cells.

Histamine Intolerance and Diamine Oxidase Activity

Intolerance of histamine may be experienced clinically in several ways:

- As symptoms of histamine excess after consumption of histamine-rich foods and beverages when an allergic aetiology has been ruled out. Symptoms may include:
  - Urticaria
  - Angioedema
  - Erythema
  - Pruritus
  - Headache
  - Rhinitis
  - Hypotension
  - Tachycardia

- Exacerbation of allergy, possibly to the level of systemic anaphylaxis, in the absence of exogenous sources of histamine. The allergens may be encountered by inhalation, contact, injection, or consumed as food

- Exacerbation of allergy, possibly to the level of systemic anaphylaxis, after consumption of histamine-rich foods and beverages.

Diamine oxidase appears to be the enzyme of greatest interest as far as histamine intolerance is concerned. Its presence and activity in the intestine, together with the observation that 99% of exogenous histamine never reaches circulation, would suggest a primary role in providing a barrier to exogenous histamine from entering circulation. In theory DAO is the enzyme involved in reducing histamine excess, and allowing HMT to function in its primary capacity in controlling the activity of endogenous histamine at its reaction sites within cells.

In the event that histamine intolerance is indeed due to a deficiency of diamine oxidase, it would be logical to suggest that if diamine oxidase activity could be increased, the contribution of excess histamine in the above scenarios would be reduced. Clinically, this would be expected to result in a significant reduction in the symptoms of histamine excess in the absence of allergy, and to significantly decreased symptom severity in situations where allergy exists. Importantly, there should be a decrease in the risk of a life-threatening anaphylactic reaction in patients where a combination of allergic sensitisation and diamine oxidase deficiency predisposes to such a condition. At the present time there is no research data that may suggest a mechanism whereby up-regulation of diamine oxidase production or activity in human tissue can be achieved *in situ*.

Prebiotics, Probiotics, and Synbiotics

The last decade has seen an increasing interest by physicians, scientists and the general public in changing the types of micro-organisms that colonise the bowel, with the intention of encouraging the "good bacteria" and eliminating or limiting the "bad" (Gorbach 2000). A thriving industry has developed to manufacture products that contain live micro-organisms within a food that will sustain their growth, in the expectation that they will be delivered to the bowel and there become established and thrive. The environment of the bowel determines precisely which micro-organisms survive therein; factors such as the presence or absence of oxygen (eH), acidity or alkalinity (pH), nutrients in a solid, liquid or gaseous form, interaction with other micro-organisms and their metabolic products, and tolerance by the immune system of the gut, all play a part in determining which species survive and which do not.

Once the microbial flora is established, which usually occurs soon after weaning, it remains more or less unchanged throughout life unless significant modifying events within the gut environment occur. Even if many species succumb to oral antibiotics used in treating an infection, over time the micro-organisms that were present prior to the antibiotic therapy become re-established in more or less the same proportions. However, a number of studies have indicated the possible value of modifying the indigenous micro-flora, especially in situations where the existing microbial activity appears to be detrimental (Bazzocchi et al 2002).

The term "probiotic" was coined in the early 1990s to describe a culture of living micro-organisms within a food that was designed to provide health benefits beyond its inherent nutritional value (Thompson 2001). The types of micro-organisms used in such foods must have certain characteristics to be of any value: they must have a beneficial effect within the bowel and they must be capable of living within the human bowel without causing any harm to the host. In order to colonise the area the micro-organism must be able to survive passage through the hostile environment of the stomach and upper small intestine, resist the effects of intestinal secretions, attach to intestinal cells on reaching the large bowel, and thrive

within its physiological and nutritional milieu. It is thought that probiotic micro-organisms alter the gut microflora by competitively interacting with the existing flora through the production of antimicrobial metabolites, or possibly modulating the local immune response to the indigenous micro-organisms (Thompson 2001; Shanahan 2000).

The micro-organisms most frequently used in probiotics are human strains of lactobacilli, bifidobacteria, and a few enterococci. Given the enormous number of different species resident in the healthy human digestive tract it is probable that many more types of bacteria will be identified as beneficial in the future. At the present time, however, research is being directed towards the saccharolytic[1] strains, which seem to promise the greatest benefit. The strains used in research studies have been identified by genotype characterization, principally 16SW rRNA sequencing. This method of identification of specific strains allows researchers to track the fate of the micro-organism from its source in the food to its presence in faeces. When the strain can be demonstrated in faeces in samples taken at intervals over a significant period of time, it can be assumed that the strain has colonised and is thriving in the bowel (Fasoli et al 2002; Dunne 2001). At the present time probiotic bacteria may be delivered to the bowel via the oral route in yoghurts (bioyoghurts), fermented milks, fortified fruit juice, infant formulae, powders, capsules, tablets and sprays.

However, it is not sufficient to merely deliver the micro-organism to the bowel and allow it to colonise, it is very important to know what the micro-organism does when it gets there. It will not be of any great value if the products of its metabolism are not providing the benefit expected. The micro-organisms may well produce the desired end-products in laboratory culture, but within the complex environment of the bowel it may be a different story. To facilitate the study of how probiotic organisms perform in the mixed bowel culture, researchers have constructed an approximation of the bowel environment in a series of culture vessels that simulate the conditions at successive sites along the bowel in a human colon taken from sudden death victims (De Boever et al 2000). This model has demonstrated that the proximal (ascending colon) on the right tends to support a saccharolytic microflora, while in the distal colon (descending colon) on the left, proteolysis is predominant. In other words, fermentation of carbohydrates predominates as the food material enters the bowel from the small intestine; the type of fermentation changes as the food material moves along, until at the distal end the breakdown of proteins and peptides is the principal activity. It is significant that the distal end of the colon tends to be the site of more disease than the proximal, which seems to suggest that saccharolytic fermentation is beneficial, while proteolysis can be detrimental to health. Hence, it is thought that the development of saccharolytic strains of bacteria for probiotics might reduce the numbers of the potentially more harmful proteolytic strains. Preliminary clinical trials on IBS patients seem to indicate that while lactobacilli, bifidobacteria and *Streptococcus thermophilus* delivered in a probiotic preparation did become established within in the colon of the test subjects. However, there was no measurable decrease in enterococci, coliforms, *Bacteroides* and *Clostridium perfringens* (the "less desirable" bacteria), whose numbers did not change (Brigidi et al 2001).

Micro-organisms act on the substrate available and produce end-products depending upon the enzymes that they are able to produce and the environment in which they are growing. The substrate and environment can be readily manipulated in the laboratory where most microbiological studies have been conducted. However, within the complex environment of the bowel it is not so easy to achieve the desired end-products. In order to ensure that the desirable micro-organisms survive in the colon, and that they produce the end-products that will of greatest benefit, current research is being focused on not only the appropriate selection of the strains of micro-organisms to be incorporated into the probiotic food, but also the substrate that will yield the desired end-products. The term "prebiotic" has been coined for the substrate; "synbiotic" refers to the combination of the specific microbial strain with its specifically designed prebiotic. Hopefully, this new research will yield the desirable result of allowing colonic colonization by the beneficial micro-organism, ensure that it produces the end-product required, and eventually lead to a decrease in the undesirable strains as a more healthy environment becomes established as a result of increasing numbers of the probiotic strains.

Probiotics Designed for Specific Functions

Probiotic micro-organisms are now being investigated for their possible use as therapeutic agents with a more targeted role than merely changing the colonic environment to one that is considered more beneficial to health (i.e. from one that is predominantly proteolytic to a more saccharolytic milieu). For example, it has been known for some time that yoghurts containing live bacterial cultures of bacteria such as lactobacilli, bifidobacteria and *Streptococcus thermophilus*, assist in reducing the symptoms of lactose intolerance. The beneficial effects are due to the production of the enzyme beta-galactosidase (lactase) by the bacteria in the yoghurt, which breaks down lactose, and the fermented milk itself delays gastrointestinal transit, thus allowing a longer period of time in which both the human and microbial lactase enzyme can act on the milk sugar lactose. It has been suggested that lactose tolerance in people who are deficient in lactase may be improved by continued ingestion of small quantities of milk. There is no evidence that this will improve or affect the production of lactase in the brush border cells of the small intestine in any way, but it seems that the continued presence of lactose in the colon contributes to the establishment and multiplication of bacteria capable of

[1] Saccharolytic: able to chemically split sugars (also Proteolytic: able to chemically split proteins; Lipolytic: able to chemically split lipids (fats))

synthesizing the beta-galactosidase enzyme over time. Thus, when lactose reaches the colon undigested, large numbers of the resident micro-flora will break down the lactose, which will therefore not cause the osmotic imbalance within the colon that is the cause of much of the distress of lactose intolerance (de Vrese et al 2001).

Another example of targeted probiotics is the release of natural antioxidants such as hydroxycinnamic acids from food plants where they occur as conjugated hydroxycinnamates, by the action of esterases produced by colonic bacteria (Couteau et al 2001). Conjugated hydroxycinnamates are present as compounds such as caffeic acid, ferulic acid, p-coumaric acids and chlorogenic acid in coffee, fruits, vegetables, and cereals, but the free hydroxycinnamates are not available to human cells until the ester linkage is broken by colonic bacteria. Human enzymes are not able to break this linkage. Free hydroxycinnamates are antioxidants and nitrite scavengers, and as such have been demonstrated to inhibit chemically-induced carcinogenesis in rats (Tanaka et al 1993). It is postulated that free hydroxycinnamates, released by specific strains of colonic bacteria such as *E.coli*, *Bifidobacterium* and *Lactobacillus* species, might have similar beneficial effects in humans (Couteau et al 2001).

There are an increasing number of reports of clinical trials that indicate the value of pro- and prebiotics in the treatment of a variety of gastrointestinal disorders, including IBS and chronic diarrhoea (Dunne 2001). There are, however, few clinical trials of the use of probiotics in the management of other conditions, although the idea that they may be of value has been suggested (Isolauri 2001). A recent review (Vanderhoof and Young 2003) examining the role of gut microflora in allergic disease suggested that providing *Lactobacillus rhamnosus* strain GG in an extensively hydrolysed infant formula might effect a significant improvement in allergic disease in infants. However, the mechanism whereby members of the human microflora might positively influence the development and/or expression of allergy remains to be elucidated (Laiho K et al 2002). The possibility that certain colonic bacteria might modulate the immune system of the gut has been suggested (Isolauri et al 2001), and a variety of immunological mechanisms whereby this might be achieved have been proposed, all of which remain to be investigated.

A targeted approach to modulating the expression of allergy in the digestive tract might yield information about the way that the indigenous microflora influences this condition. Since histamine is one of the most important, if not the most significant single mediator of allergy symptoms, a reduction in the amount of histamine absorbed from the digestive tract should lead to a decrease in the severity of symptoms that arise from excess histamine in the body.

Focus of the Proposed Research: Diamine oxidase activity

If active diamine oxidase could be supplied to the human digestive tract from a probiotic source, it may be possible to reduce the level of histamine entering the body from the digestive tract. Some preliminary research indicates that certain strains of bacteria, such as species of *Lactobacillus*, *Leuconostoc*, *Escherichia faecium, Weisella* and *Sarcina* (Figure 3) can produce diamine oxidase (Dapkevicius et al 2000; Leuschner et al 1998). It is possible that there may be other micro-organisms capable of synthesising the enzyme, which could be exploited in the production of a probiotic food able to deliver the deficient enzyme to the human gut.

Human diamine oxidase: Characteristics

Copper-containing amine oxidases (CAOs) catalyse the two-electron oxidative deamination of primary amines to the corresponding aldehyde, using dioxygen as the oxidant (Elmore et al 2002). Aldehyde, ammonia, and hydrogen peroxide are the products of the reaction.

Copper-containing amine oxidases are widespread in nature, occurring in bacteria, fungi, plants and animals. The enzymes are homodimers, and range is size from 140 to 200 kDa. There are two active sites per dimer (Elmore et al 2002).

There are three known classes of copper-containing amine oxidases:

1. Semicarbazide-sensitive amine oxidase, which is found tightly associated with tissues, and acts on monoamine substrates
2. Plasma amine oxidases (also known as serum amine oxidases, or benzylamine oxidases) that are soluble and found in blood plasma, act on a wide range of monoamines, diamines and aromatic amines. They are thought to be synthesised in the liver.
3. Diamine oxidases (DAOs) that display a distinct substrate specificity for diamines. They are soluble, and are distinct from the plasma and membrane-bound CAOs in their sequence homology.

It is the latter group that are of interest in probiotics as they are found in bacteria, fungi, plants, animals and humans.

The structure of five copper amine oxidases have been characterised by X-ray crystallography: from *Escherichia coli*, *Arthrobacter globiformis*, *Hansenula polymorpha* (previously *Pichia angusta*), *Pisum sativum* (pea seedling), and human kidney (Elmore et al 2002).

Copper-Associated Diamine Oxidase Gene

Search of the NCBI gene catalogue (http://www.ncbi.nim.nih.gov) for copper-associated diamine oxidase reveals that the gene sequence has been delineated in a variety of prokaryotes and eukaryotes.

Bacteria showing gene homology with the human enzyme include:
- Enterobacteria: *E.coli, E.coli K12*, and *Klebsiella aerogenes*
- Cyanobacteria: *Trichodesmium erythraeum* and *Nostoc* species
- Gram-positive bacteria: *Arthrobacter* species and *Deinococcus radiodurans*

Plants showing gene homology with the enzyme include the Eudicots:
- Mouse-ear cress (*Arabidopsis thaliana*)
- Garbanzo beans (*Cicer arietinum*)
- Garden pea (*Pisum sativum*)
- Indian mustard (*Brassica juncea*)
- Lentils (*Lens culinaris*)
- Japanese rice (*Oryza sativa*)
- Soybeans (*Glycine max*)

Fungi exhibiting the gene include the Ascomycetes:
- *Neurospora crassa*
- *Schizosaccharomyces pombe*
- *Pichia angusta*
- *Pichia pastoris*
- *Aspergillus oryzae*
- *Aspergillus niger*
- *Podospora anserine*
- *Kluyveromyces marxianus*

Mammals in which the gene has been sequenced include:
- *Homo sapiens* (human)
- *Mus musculus* (mouse)
- *Rattus norvegicus* (brown rat)
- *Cavia porcellus* (guinea pig)
- *Bos taurus* (bovine)

Although the presence of the enzyme in strains of *Lactobacillus*, *Leuconostoc*, *Escherichia faecium, Weisella* and *Sarcina* has been suggested (Dapkevicius et al 2000; Leuschner et al 1998) the gene sequence coding for the enzyme has not yet been identified in these micro-organisms.

Requirements for Probiotic Micro-organisms

In order to reduce the amount of histamine passing into the body through the epithelium of the digestive tract, sufficient active diamine oxidase must be available to catabolise histamine from a variety of sources, principally undegraded histamine, and the products of microbial catabolism of histidine, in undigested food material, body cells and secretions. A probiotic that is designed to increase the concentration of DAO must possess a number of essential characteristics: It should
- Express the gene coding for the enzyme
- Have been demonstrated to synthesise the enzyme in culture
- Be non-pathogenic, causing no harm to the host
- Be capable of establishment within the normal microflora of the large bowel
- Be demonstrated to increase the amount of diamine oxidase within the large bowel after colonisation

Achievement of these conditions can be visualised in the following stages:
1. Appropriate micro-organisms will be cultured and the gene sequence of CA-DAO characterised
2. The cultured micro-organisms will be assessed for the expression of the gene in the form of active DAO, using putrescine as a substrate (Elmore et al 2002). The enzyme will be concentrated on a gel filtration column and enzyme activity measured spectrophotometrically.
3. A suitable low-allergenic consumable substrate will be developed as a prebiotic food in order to deliver the probiotic micro-organism to the human colon and allow its colonisation
4. Clinical trials will be designed to test the efficacy of the synbiotic in reducing food allergy in sensitised individuals.

Figure 1

Catabolism of Histamine

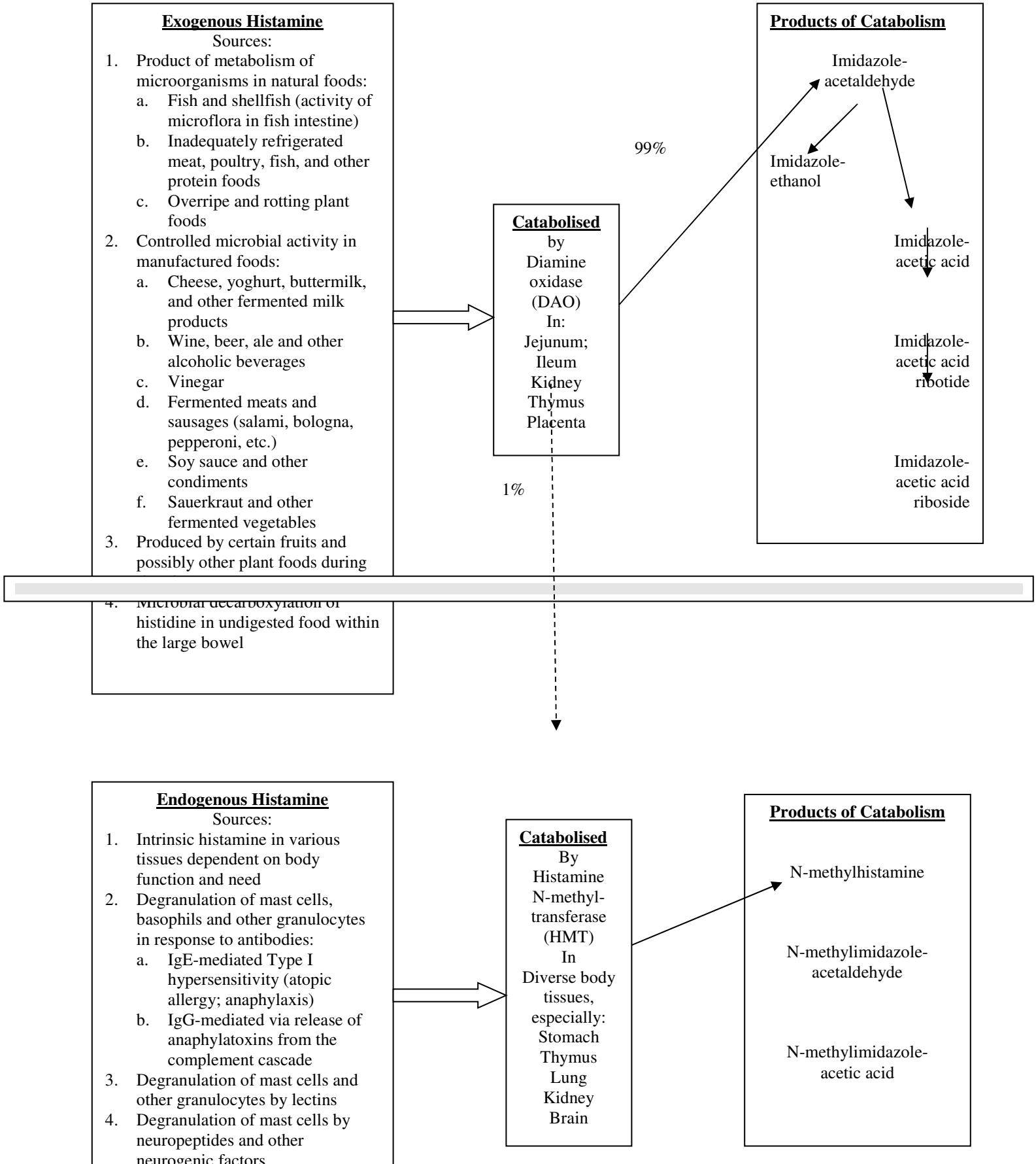
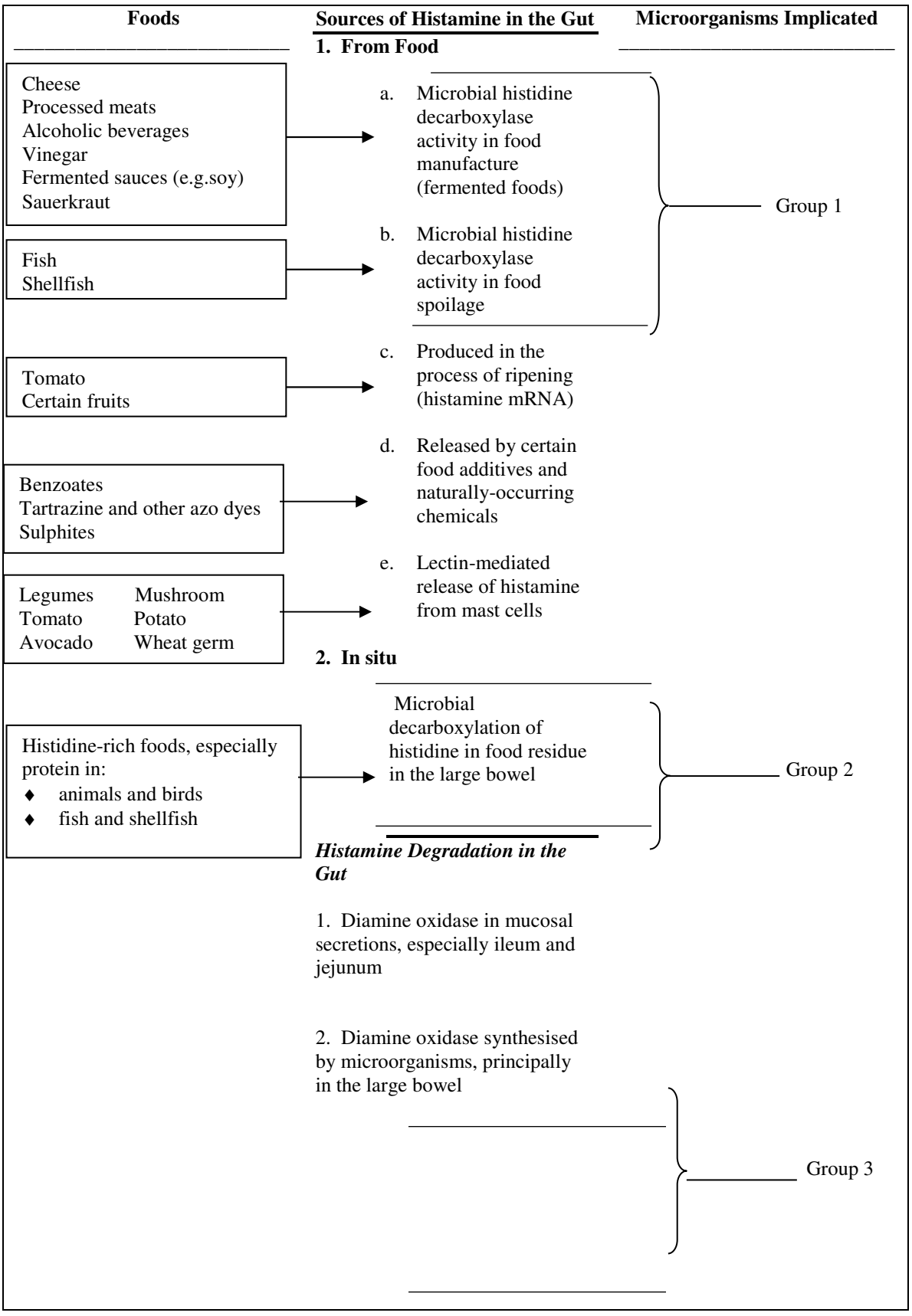


Figure 2

Microorganisms Capable of Metabolising Histamine



Group 1
Histamine - producers (Histidine decarboxylase producers) (Taylor et al 1978)

Aeromonas hydrophila

Bacillus cereus
Bacillus subtilis

Brevibacterium linens

Citrobacter diversus
Cirtobacter freundii
Citrobacter sp.

Clostridium perfringens

Enterobacter aerogenes
Enterobacter cloacae
Enterobacter liquefaciens (aka Serratia liquefaciens)
Enterobacter sp.

Escherichia coli
Escherichia intermedia

Hafnia alvei (aka Enterobacter alvei)

Klebsiella pneumoniae
Klebsiella sp.

Lactobacillus brevis
Lactobacillu buchneri
Lactobacillus fermentum
Lactobacillus sp.

Pediococcus cerevisiae

Proteus mirabilis
Proteus morgani
Proteus rettgeri
Proteus vulgarisi
Proteus sp.
Providencia alcalifaciens

Pseudomonas aeruginosa
Pseudomonas fluorescens
Pseudomonas reptilivora
Pseudomonas sp.
Salmonella arizonae
Salmonella cholerasuis
Salmonella enteritidis
Salmonella paratyphi-A
Salmonella schottmuelleri
Salmonella typhi
Salmonella typhimurium
Salmonella sp.
Serratia marcescens
Serratia sp.
Shigella boydii

Shigella dysenteriae
Shigella flexneri
Shigella sonnei
Shigella sp.

Staphylococcus aureus
Streptococcus bovis
Streptococcus faecalis
Streptococcus faecalis subsp. Liquefaciens
Streptococcus faecium
Streptococcus sp.

Group 2
Histamine-producers isolated from digestive tract (saliva; stomach contents; intestinal tract; feces)

Escherichia coli

Lactobacillus sp.
Proteus morganii
Proteus sp.

Pseudomonas reptilivora

Streptococcus sp.

Group 3
Microorganisms capable of degrading histamine
(diamine oxidase producers) (Dapkevecius et al 2000; Leuscher et al 1998)

Lactobacillus curvatus
Lactobacillus sakei
Lactobacillus sp.
Weisella hellenica
Leuconostoc mesenteroides
Leuconostoc sp.
Escherichia faecium sp.group
Sarcina lutea

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