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Review of Intolerance Reactions to Food and Food Additives

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Abstract There is ongoing interest in the community in the area of intolerance reactions to food and food additives. To inform future discussions on this subject, FSANZ initiated a scientific review to give further consideration to key issues underpinning the public debate. This paper provides an overview of the contemporary understanding of food intolerance, and highlights the individual nature of intolerance reactions and the wide range of food chemicals, whether naturally occurring or added to food, which may contribute to intolerance reactions. The clinical manifestations of intolerance described in the literature vary widely, both in relation to the symptoms reported and the substances implicated. Symptoms associated with food intolerance reactions range from mild to severe but the effects are largely transient. The immune system is not involved in these reactions, and therefore these forms of food intolerance are not allergies.

Food substances most commonly associated with intolerance reactions are naturally occurring chemicals such as salicylates and biogenic amines. While some food additives may contribute to intolerance reactions, clinical observations suggest that affected individuals are usually sensitive to several substances, including both natural food chemicals as well as artificial and natural food additives. Food additives, particularly food colours, are perceived to be a major cause of intolerance reactions in the community. However, except for sulphites, clinical evidence of a causal link between food additives and intolerance reactions is limited, and the frequency, severity and spectrum of symptoms are yet to be determined.

In Australia and New Zealand, the approval of food additives follows a rigorous process based on two principles: the additive must fulfil a technological function, and must not pose a safety concern to consumers at the proposed level of use. Approved additives must be declared on the food label. This regulatory approach ensures a high level of safety for all consumers and supports dietary management for individuals affected by food intolerance.

Keywords food intolerance, malabsorption, food additives, food chemicals

1. Introduction

Food is composed of a wide range of chemicals other than the macro and micro nutrients directly required to support life. The human diet therefore contains a variety of chemicals, both naturally present and those

intentionally added to food. Food may also be contaminated with potentially toxic substances, both natural and synthetic, during production or processing. The spectrum of potential adverse reactions to food includes toxic, allergic and intolerance reactions. While the scientific basis and potential burden of toxic and allergic reactions to food is well established, the evidence for a significant burden of food intolerance due to additives in food is less clear.

The term 'food intolerance' has been used for decades in the medical literature to refer to any illness or biochemical or metabolic abnormality caused by the ingestion of any food or dietary component without implying any specific mechanism [1, 2]. As the clinical picture of various types of adverse reactions to food became clearer, diagnostic criteria were established. In contemporary literature, adverse reactions are broadly divided into toxic and non-toxic reactions. A widely accepted terminology scheme is outlined in Figure 1 [3-5].

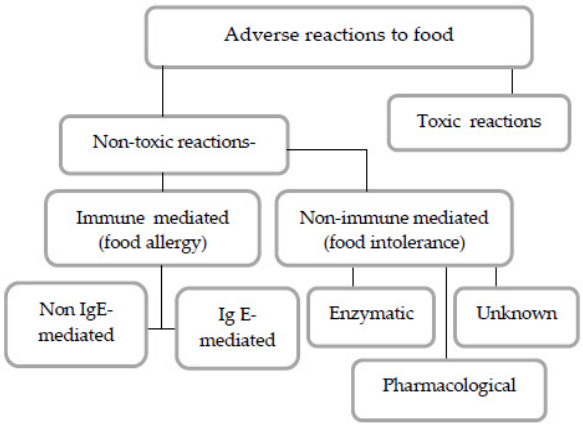

Figure 1. Classification of adverse reactions to food

Toxic compounds may occur naturally within a food – such as toxins in the leaves of the rhubarb plant, or they can be natural and/or anthropogenic contaminants, while some toxins may be introduced during food processing. Toxic reactions will usually occur in any exposed individual provided that the dose is sufficiently high, although individuals in certain age groups, or with specific genetic predispositions, may be more or less adversely affected [4]. By contrast, the occurrence of non-toxic reactions is highly individual, and depends on genetic, epigenetic and environmental factors, and adverse reactions generally do not occur in non-sensitive individuals even at relatively high exposures [2, 6, 8, 67].

Non-toxic reactions may be either immune-mediated or non-immune-mediated. The term 'food allergy' or 'allergic hypersensitivity' refers to adverse reactions that involve the immune system [3, 6, 7, 63]. The term 'food intolerance' is generally used in relation to non-immune-mediated reactions, while the term 'nonallergic hypersensitivity' has been proposed to emphasise the nonallergic nature of some of the well-documented adverse reactions previously referred to as allergies or pseudoallergies (e.g. reactions to aspirin) [63].

In this overview, we summarise information on intolerance reactions to natural food constituents and food additives[1]. Food allergy and coeliac disease are well documented immune-mediated medical conditions and are not discussed in this paper.

2. Food intolerance

This paper largely draws on review articles published in peer-reviewed journals and authoritative textbook chapters in the area of food intolerance. Personal communications from experts in the field are also incorporated where appropriate.

Food intolerances occur through non-immunological reactions to food. The spectrum of food chemicals, the symptoms, and the amount necessary to trigger the symptoms, are peculiar to the individual. Affected individuals are likely to react to several food substances, including both naturally occurring food chemicals and natural and synthetic food additives [8, 9]. The largest class of natural food substances linked to intolerance reactions are salicylates and amines [10, 11]. Symptoms of intolerance reactions to food are reported to affect the skin, gastrointestinal tract, respiratory tract and the central nervous system [7, 8]. There is a wide range of symptoms reportedly associated with intolerance to food and food additives including irritable bowel, headache, migraine, fatigue, behavioural problems, asthma and urticaria [7, 8, 39].

The diagnosis of food chemical intolerance is difficult due to the lack of reliable, scientifically validated blood or skin tests or histopathological examination [7, R. Loblay, personal communication]. A diagnosis typically entails a period of strict dietary elimination of suspect foods or food additives followed by a double-blind placebo-controlled challenge test [7]. However, this diagnostic process requires a high level of commitment from patients and health professionals, and the dietary restrictions can be difficult to maintain for an extended period [12].

The underlying mechanisms of food intolerance may be metabolic or pharmacologic in nature, but for some

[1] The term food additive (as used in the Australia New Zealand Food Standards Code) refers to any substance not normally consumed as a food in itself and not normally used as an ingredient of food, but which is intentionally added to a food to achieve one or more of the technological functions specified in Standard 1.3.1 Schedule 5 .

reported intolerance reactions presumed to be caused by food, the mechanism is unknown [13]. The prevalence of intolerance reactions to food and food additives has not been reliably determined. However, estimates of 5-20% have been cited in the literature although the higher estimates appear only in the older literature and may encompass food allergies and intolerances [7, 27, 66]. Exposure to environmental chemicals, hormonal changes or emotional stress are some of the factors that may aggravate food intolerance reactions [8].

2.1 Enzymatic intolerance

Enzymatic intolerance of dietary carbohydrate and sugars can result from a variety of genetically determined enzyme deficiencies. These are metabolic disorders caused by the inability to digest a particular food or food ingredient.

Lactose intolerance results from lactase deficiency. Lactose is the disaccharide sugar found in milk and some milk products. During digestion, lactose is broken down in the small intestine by the enzyme lactase into two simple sugars, glucose and galactose. Lactase activity is thus vital in babies to obtain full nutritional benefit from both human and animal milk but is genetically programmed to decline after weaning [14]. Nevertheless, lactase activity persists in populations of Northern and Western Europeans and pastoral nomadic tribes where fresh milk forms a significant part of the adult diet [15].

The symptoms of lactose intolerance result from bacterial fermentation of undigested lactose to produce lactic acid, carbon dioxide and hydrogen gas which cause bloating, cramps and diarrhoea [16]. Lactase deficient adults can usually consume some milk but the tolerated amounts vary between people. While some can tolerate a glass of milk (240 ml=11 g lactose), others develop symptoms with just 2–3 g lactose from a chocolate bar [17]. The lactose content of milk, dairy products and processed foods vary widely from 53% by weight in dried skim cow's milk to less than 1% in most cheeses [18, 19]. Secondary lactose intolerance can occur transiently as a result of illness or injury. Lactase production may decrease after an acute gastroenteritis, surgery or injury to the small intestine [20].

Other forms of enzymatic intolerance to food are due to inborn errors of metabolism, including the following:

Galactosaemia is a deficiency in enzymes that are responsible for converting galactose to glucose. Galactose is primarily derived from the lactose content of milk that a newborn receives. The clinical manifestations include failure to thrive, vomiting and liver disease and elimination of galactose from the diet is required [21, 22].

Hereditary Fructose Intolerance is caused by a rare genetic deficiency of the enzyme aldolase B responsible for hepatic metabolism of dietary fructose, the principal sugar in fruit. Symptoms begin in infancy with vomiting and hypoglycaemia after fructose ingestion, and if unrecognized can lead to failure to thrive, and kidney and liver involvement. Lifelong avoidance of fructose is required to prevent the disease [15].

Phenylketonuria is caused by a gene mutation which suppresses the activity of the liver enzyme phenylalanine hydroxylase which results in a reduced rate of conversion of phenylalanine to tyrosine. Approximately 4–5% of amino acids in all food protein are phenylalanine which accumulate in the blood and cause brain toxicity. Restriction of phenylalanine intake throughout life is required for normal physical and mental development [23, 24].

Glucose-6-phosphate dehydrogenase deficiency is the most common enzyme deficiency in the world. Individuals with G6PDH deficiency are susceptible to haemolytic anaemia, or favism, if they consume fava beans (*Vicia faba*). The symptoms result from damage to the erythrocyte membranes caused by vicine and convicine, the naturally occurring oxidants in fava beans. Although G6PDH deficiency affects nearly 400 million people worldwide, favism is relatively uncommon due to the limited consumption of fava beans [64, 65].

2.2 Intolerance due to malabsorption

In addition to food intolerances caused by enzyme deficiencies discussed above, intolerance to dietary sugars can result from deficiencies in transporters such as sodium-dependent glucose transporter (SGLT1). Deficiency of SGLT1 results in glucose/galactose malabsorption [15]. Also, important dietary carbohydrates such as fructose and sorbitol are incompletely absorbed in the normal small intestine. Individuals will have a degree of fructose malabsorption with or without symptoms depending on the amount of fructose consumed. This occurs when the capacity of the gut to transport fructose across the intestinal epithelium, which varies widely within the population, is exceeded. Unabsorbed fructose enters the colon where it is fermented by gut bacteria to short chain fatty acids and gases which lead to abdominal symptoms [25, 26].

Impairments of the digestion and absorption of simple carbohydrates, such as lactose, fructose and sorbitol, are the most common type of food intolerances in the European population [27].

2.3 Pharmacological intolerance

Information available indicates that the largest class of substances that are found in many foods responsible for inducing pharmacological food intolerance are salicylates followed by biogenic amines [4]. Salicylic acid (2-hydroxybenzoic acid) belongs to an extremely diverse group of plant phenolics and is ubiquitously distributed throughout the plant kingdom. The various chemical derivatives of salicylic acid are collectively known as salicylates. Oral administration of acetylsalicylic acid (aspirin) for analgesic purposes, while tolerated by the majority of people, has long been known to cause side effects such as bronchial asthma and rhinitis in some people [28]. The effect is mediated by a deviation of the arachidonic acid metabolic pathway towards excessive leucotriene production which then produces the clinical features [29]. High levels of naturally occurring salicylates are found in many fruits, vegetables, nuts, herbs and spices and wines [30, 31]. The average Australian diet may contain up to 100 mg of naturally occurring salicylates per day, and suggest these amounts may precipitate symptoms when consumed on a daily basis by sensitive individuals [9].

Biogenic amines are organic, basic nitrogenous compounds of low molecular weight generated in the course of metabolism in plants, animals and microorganisms. The biogenic amines are usually formed by decarboxylation of free amino acids or by amination and transamination of aldehydes and ketones. The names of many biogenic amines correspond to the names of their originating amino acids: histamine from histidine, tyramine from tyrosine, beta-phenylethylamine from phenylalanine, tryptamine from tryptophan [32, 33]. Biogenic amines can be expected in all foods that contain protein or free amino acids and are subject to conditions enabling microbial or biochemical activity. Foods likely to contain elevated levels of biogenic amines include fish and fish products, dairy products, meat and meat products, fermented vegetables and soy products, and alcoholic beverages such as wine and beer [32, 34].The consumption of food containing high levels of biogenic amines can have toxic effects resulting in nausea, headaches, respiratory distress, oral burning, and hyper- or hypotension among other symptoms. High levels of biogenic amines, like histamine and tyramine, are usually associated with food spoilage and present a risk to the general population[2].

Histamine toxicity is also referred to as scombroid fish poisoning because of the association of this illness with the consumption of scombroid fish, such as tuna, mackerel, and sardines. This process occurs when fish are not refrigerated properly following capture, bacteria break down the fish flesh and histamine is formed. Histamine is heat resistant and therefore illness can occur even with fish that is properly canned or cooked. Symptoms can appear ten minutes to several hours after the affected fish has been eaten, and may last up to four hours [35].

While high levels of histamine are toxic, moderate levels of ingested histamine may lead to food intolerance in some individuals [32]. The symptoms of histamine intolerance are highly variable and range from typical cutaneous reactions (erythema, pruritus, flush, urticaria), gastrointestinal complaints (colic, diarrhoea), respiratory complaints (nasal obstruction, rhinorrhoea, asthma attacks), cardiovascular responses (hypo- and hypertension, arrhythmias) and headache. About 1% of the total German population of 82 million is considered to be affected by histamine intolerance [27]. Foods with high histamine content include microbially produced foods such as long ripened cheese, pickled cabbage, red wine, and microbially contaminated high protein foods, such as tuna and sausage [33].

In humans, low levels of biogenic amines absorbed from food are rapidly detoxified by the action of amine oxidases. Intolerance reactions may occur if the detoxification process is disturbed, possibly due to insufficient oxidase activity leading to accumulation of biogenic amines in the body [33]. However, the role of dietary amines in food intolerance has been questioned due to the lack of published randomized, double-blind, placebo-controlled studies [36].

2.4 Intolerances of unknown mechanisms - the example of food additives

For many reported intolerance reactions to food constituents, no plausible biological mechanism of action has been proposed. In general, intolerance reactions to food additives fall into this category.

Additives are a diverse group of substances which are used to make food products safe, shelf stable, convenient and appealing. The use of additives is strictly regulated in Australia and New Zealand to ensure the safety of consumers. The Australia New Zealand Food Standards Code (the Code) stipulates the use of food additives to be based on technological need and must be declared on the ingredient list. The Code also lists what additives may be used, in what type of food and in what amount. Food additives are not generally used in all foods where permissions are given or up to the allowable limits.

[2] The Australia New Zealand Food Standards Code (Standard 2.2.3) requires that :the level of histamine in fish or fish products must not exceed 200 mg/kg.

Food additives, particularly food colours, are perceived by some to be a major cause of intolerance reactions in the community. However, the perceived extent of the problem is not supported by medical evidence regarding the role of food additives in intolerance reactions [9, 37, 2, 27]. In addition, public concern about food additives is enhanced by claims founded predominantly on misinformation, speculation and misinterpretation [38].

2.4.1 Symptoms of intolerance reactions to food additives

A review of adverse reactions to food additives lists the various symptoms reported to be possibly caused by food additives [39]. The list includes dermatologic, gastrointestinal, respiratory, musculoskeletal, neurologic and cardiovascular symptoms. However, the authors note that a causal relationship between food additives and these symptoms is not well documented in all cases. Experts in the field suggest that food additives are more likely to provoke symptoms in patients with underlying disorders. For example, exacerbations are more likely to occur in patients with skin conditions, such as chronic urticaria or eczema, than in those with healthy skin [10, 39, 50, R. Loblay, personal communication].

2.4.2 The role of food additives in intolerance reactions

Despite the numerous studies in the area of intolerance to food, most do not establish cause and effect relationship between food additives and various intolerance symptoms [6, 39, 49]. Some clinical experts consider that, rather than playing a primary causal role, food additives are more likely to act as symptoms triggers exacerbating underlying conditions [50, R. Loblay, personal communication]. Food colours in particular are widely claimed to be associated with intolerance reactions.

A review of the role of azo dyes and non-azo dyes in intolerance reactions concluded that although a few well-designed and implemented studies have been conducted, most reports are flawed [51]. The author found little evidence to support the claims of adverse reactions due to food colours. While rare cases of contact dermatitis have been documented, all other claims, including headache provocation, are at least overstated and probably not true. The author concludes that, in fact, these dyes are remarkably safe and the majority of claims against them result from mistaken identity, association or misdirected blame.

Conclusive evidence for the role of food additives in intolerance is generally lacking. A Cochrane review was unable to reach a conclusion on the overall effect of tartrazine, a mono-azo food colour commonly implicated in provoking asthma, due to paucity of data [52]. Also, a recent review of data on tartrazine and monosodium glutamate found no convincing evidence of their role in inducing asthma responses [53]. In contrast to known asthma triggers, such as respiratory infections, exposure to pets, house dust mites or pollen, the effect of food additives is likely to be very small [38]. On the other hand, the role of sulphites in triggering asthma attacks, primarily in patients with underlying severe or uncontrolled asthma, is firmly established based on double blind placebo controlled studies [54, 55]. The strong evidence forms the basis for the mandatory declaration of added sulphites, required in a number of countries including Australia, New Zealand and Canada.

2.4.3 Prevalence of intolerance to food additives

The prevalence of intolerance reactions to food additives is difficult to determine due to the subjective nature of many of the symptoms and lack of reliable biological markers of reactivity. Diagnostic testing is most appropriately performed by dietary elimination and double-blind placebo-controlled challenges. However, there are difficulties in conducting studies of this nature in large population samples to determine prevalence [13, R. Loblay, personal communication]. A further important consideration is whether the dose of food additive used in the clinical testing is relevant to the likely dietary intake of the additive in question [13]. In most clinical studies, the challenge dose is many times higher than the likely daily intake of a normal diet. In the majority of intolerances to food additives, reactions have not been documented with doses within the range of normal dietary intake.

A number of questionnaire-based studies have been conducted to estimate the prevalence of intolerance to food additives. However, it is widely acknowledged in the medical literature that self-reporting of intolerance reactions does not provide reliable information on prevalence in the general population. In all studies, the rate of perception far exceeds the calculated, objectively estimated, prevalence rate [13, 45-48]. This is important to keep in mind when considering claims of high prevalence based on self-reporting. While accurate prevalence data are lacking, estimates of intolerance to additives vary widely from 0.18% in a mixed-age group to 1% in adults and 2% in children, but may be up to 7% in children with underlying allergy [7, 39, 47, 48].

2.4.4 Synthetic versus natural additives

Food additives may be synthetic or natural. For example, synthetic food colours include tartrazine and erythrosine. Natural food colours are generally derived from plant or animal sources. For example, carmine is a dark red colour obtained by aqueous extraction of cochineal, which is derived from the dried bodies of the gravid female insect

Coccus cacti. Carmine is used as a colouring agent in food and cosmetics. Annatto is a natural colour derived from the tree (*Bixa orellana*), a large, fast-growing shrub cultivated in tropical climates. The tree produces large clusters of brown or crimson capsular fruit-containing seeds coated with a thin, highly coloured resinous coating that serves as the raw material for the preparation of the colour annatto.

Some natural food additives have been linked to severe adverse reactions. For example, annatto and carmine have been implicated in IgE-mediated allergic reactions [40]. Both of these natural colours contain protein residues from their plant and animal sources, making allergic sensitisation possible [41-44].

In the United States, the cause of sensitization to carmine appears to be through skin exposure from the use of carmine-containing cosmetics and not from ingestion of carmine-containing foods and beverages. However, once sensitisation has occurred, affected individuals could react to carmine present in foods and beverages.

2.4.5 Effect of food additives on behaviour

The effect of food additives, particularly food colours on children's behaviour, is highly controversial. This issue initially emerged when Dr Benjamin Feingold implicated food colours in the hyperactivity of children [56]. Feingold postulated that some children have a genetic predisposition to hyperactivity. He reported dramatic improvement in the behaviour of 50% of children who followed a diet free of artificial colours, flavours and salicylates. However, subsequent well-controlled studies did not support Feingold's results. In 1982, the US National Institute of Health consensus development panel reviewed all the studies on this issue and concluded that although the Feingold diet is not harmful, it was not influential in controlling hyperactivity in children [56].

The impact of these early events continued to influence the views of parents on the effect of food additives on children's behaviour [57]. A study published in 1987 highlighted the need for paediatricians to manage the increasing clinical problem of parents' anxieties about diet without being dismissive or confrontational. As to why parents tend to attribute behaviour disorders to additives, the author found that many parents in his study said they first learnt of the possible importance of additives through the media. While it is understandably attractive for parents of children with behaviour problems to have a diagnostic labels and an exogenous cause, objective clinical verification is required.

The debate on the effect of food additives on children's learning and behaviour has continued to this day. A critical review of 17 published studies [58] provided very limited support for such a role. The reviewers acknowledged that: '*While striving for evidence-based practice, in certain instances, the practitioner may yield to a harmless management claimed by parents as beneficial. It may be reasonable to agree on the avoidance of a specific food or additive that the family strongly believes to be causing behavioural problems in a child, even if it is a placebo effect'.*

In 2007, a study commissioned by the UK Food Standards Agency on the effect of certain food additives on children's behaviour was published [59]. The study, referred to as the Southampton study, suggested that a mixture of additives (six artificial food colours and a preservative) increased hyperactivity in children from the general population. Further analysis of the data from the Southampton study by expert panels concluded that increases in mean level of hyperactivity observed in this study were small relative to normal inter-individual variation. Experts also concluded that the findings could not be used as a basis for altering the Acceptable Daily Intake (ADI) of the food additives used in the study [60, 61]. The European Parliament has since introduced a new provision that the food colours used in the study (E110, E104, E122, E129, E102 and E124) must be labelled with the statement 'may have an adverse effect on activity and attention of children'.

Recently, the USFDA conducted an evidence-based review of the proposed association between artificial food colours and problem behaviours in children [62]. The review concluded that a causal relationship between artificial food colors and hyperactivity has not been established. The conclusion was upheld by the FDA's Food Advisory Committee at its meeting in March 2011, with a majority of the Committee opposed to adding a warning label to products containing artificial colours.

While further research in this area may help clarify important questions, including on prevalence and mechanism of action, there is a need to acknowledge the limited role that food additives are likely to play in behavior disorders and learning difficulties affecting some children.

3. FSANZ's regulatory approach to food additives

In Australia and New Zealand, food additives are prohibited unless they are specifically approved by FSANZ and included in the Code. Approval of food additives is based on two principles: the additive must fulfil a technological function and must not pose a safety concern to consumers at the proposed level of use. The Code also requires that additives approved for use in

food and beverages must be identified on the label by name or code number.

The pre-market safety assessments of food additives as conducted by FSANZ are consistent with the safety assessments conducted by JECFA (the Joint FAO/WHO Expert Committee on Food Additives). These assessments are generally based on extensive toxicology data from animal studies and, if available, human clinical studies. The assessment determines the ADI, which is the amount of a food additive that can be consumed every day for an entire lifetime without adverse effect. Dietary modelling is performed using the data obtained from a total diet survey to account for all the sources of the food additive. Ultimately, food additive requirements in the Code reflect the scientific information generated by JECFA, the Codex Committee on Food Additives (CCFA) and the Codex General Standard for Food Additives (GSFA).

Maintaining food additives permissions at the lowest levels required to achieve the specified technological function minimises exposure and potential intolerance reactions. The use of food label information to make informed choices, together with appropriate medical and dietary advice, provide an effective tool for consumers to manage intolerance reactions to food additives.

4. Conclusion

The usage of terms in the literature is confusing since food allergy and food intolerance are often used indiscriminately and interchangeably. Generally, food allergies can be distinguished from food intolerances on the basis of the mechanisms involved and the severity of symptoms. Food intolerances due to metabolic disorders, such as enzyme deficiencies, are well documented. Intolerance reactions to food additives are reported but no mechanisms are proposed. Responses are highly individual (including genetic susceptibility and underlying health status) and susceptibility varies even for the same individual at different times. Where intolerance to additives is confirmed, it is most likely to be part of a much wider problem of intolerance to food chemicals in general. Medical specialists suggest that food additives are more likely to cause symptoms in patients with underlying illness.

In most clinical studies of food additives the challenge dose used is many times higher than the likely intake from a normal diet. Therefore, except for sulphites, it is not possible to establish unequivocally a cause and effect link between food additives, at the levels used in food and intolerance reactions. The current labeling requirements for food additives allow consumers to avoid food additives that may be of concern to them.

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