

Pharmacologic Food Reactions

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KEY CONCEPTS

- Naturally occurring or added food substances can result in pharmacologic or drug-like activity.
- Pharmacologic food reactions tend to be dose dependent.
- Pharmacologic food reactions can be mistaken for food allergy.
- Concomitant medications may alter the propensity to elicit pharmacologic food reactions.

Many foods contain a variety of either naturally occurring or added components that have pharmacologic or drug-like activity [1]. When consumed in moderation, however, only a small number of substances have been identified that account for the majority of clinically apparent adverse pharmacologic reactions to foods. This chapter focuses on the most common substances implicated in pharmacologic reactions to foods and discusses their mechanisms and strategies for prevention and treatment.

Pharmacologic food reactions have been defined as adverse reactions to foods or food additives that result from naturally derived or added chemicals that produce drug-like or pharmacologic effects in the host [2]. Unlike type I allergic food reactions, which affect only a selected group of atopic patients, pharmacologic food reactions can potentially be elicited in a wider, more diverse group of individuals. The dose or quantity of food necessary to elicit a clinically apparent reaction typically varies among individuals and even in the same individual over time. Pharmacologic food reactions depend on metabolic differences, concurrent medication usage, food freshness, and food preparation.

Vasoactive amines

The vasoactive amines include dopamine, histamine, norepinephrine, phenylethylamine, serotonin, tryptamine, and tyramine. All of these low-molecular-weight molecules are synthesized by decarboxylation of naturally occurring amino acids. The role of biogenic amines as a cause of adverse reactions to foods has recently been called into question [3]. It is true that dietary amines do not appear to elicit clinical

symptoms when ingested in moderate quantities. However, when circumstances arise that result in excessive intake of a biogenic amine or inhibition of metabolic processing to inactive products, clinical consequences will be seen.

Histamine

The diamine histamine is perhaps the best known vasoactive amine. Because of histamine's significant contribution to the pathophysiology of atopic disease, histamine-induced pharmacologic food reactions are frequently confused with food-allergic reactions.

Synthesis

Histamine is synthesized in nature by the decarboxylation of its amino acid precursor histidine. This synthesis is catalyzed by the enzyme histidine decarboxylase and other enzymes that are widely distributed in nature. The most important example of histamine causing pharmacologic effects by ingestion of food is scombroid fish poisoning which will be discussed further [4,5].

Physiologic effects

Histamine mediates its effects on tissues through H1 and H2 receptors. The subsequent tissue responses to histamine, summarized in Table 35.1, can present following any type I hypersensitivity. A clinically similar physiologic response can be noted in non-IgE-dependent pharmacologic food reactions in which histamine is either present in the food ingested or released from tissue stores due to some intrinsic histamine-releasing ability of the food ingested. The IgE- and non-IgE-dependent histamine-mediated events both occur within minutes of ingestion of the culpable food, and are clinically indistinguishable.

Adverse responses to histamine, including abdominal cramping, flushing, headache, palpitations, and hypotension,

Table 35.1 Physiologic responses elicited by histamine

Responses mediated by H1 receptors
Smooth muscle contraction
Increased vascular permeability
Mucous gland secretion
Responses mediated by H2 receptors
Gastric acid secretion
Inhibition of basophile histamine release
Inhibition of lymphokine release
Responses mediated by H1 and H2 receptors
Vasodilation
Hypotension
Flush
Headache
Tachycardia

appear to be roughly dose dependent. Ingestion of 25–50mg of histamine may precipitate headache, whereas 100–150mg may induce flushing [6]. These values are only rough estimates, however, and scombroid toxicity has been described with ingestion of as little as 2.5mg of histamine [7].

Metabolism

The duration of histamine’s effect depends on its metabolism. In normal physiology, conversion of histamine to its major inactive metabolites by either histamine methyltransferase or diamine oxidase (DAO) generally occurs rapidly [8,9]. Figure 35.1 shows the two routes of histamine metabolism. Prolonged binding of histamine from normal dietary sources to H1 and H2 receptors is uncommon, and symptoms rarely occur with such incidental ingestions. When large ingestions of histamine occur (e.g. scombroid poisoning), however, the metabolic capacity is temporarily exceeded and a multitude of histamine-mediated effects are observed. Experimental administration of large oral quantities of histamine yields similar clinical responses [10].

Although methylation appears to be the primary route for metabolism of histamine administered by both the oral and intravenous routes, DAO is important as well. DAO is present in the intestinal mucosa in almost all mammalian species examined [11]. Ingestion of a histamine-containing meal along with ingestion of drugs that inhibit DAO can produce histamine-induced symptoms. Isoniazid is a potent DAO inhibitor and, when combined with a histamine-containing meal, has resulted in severe histamine-induced symptoms [12,13,21]. *In vitro* experiments have shown a number of drugs (e.g. chloraquine, pentamidine, clavulanic acid, dobutamine, pancuronium, imipenem, and others) to be potent human intestinal mucosal DAO inhibitors. The *in vivo* clinical relevance of these findings remains uncertain [14].

Histamine-containing foods

Certain foods are generally accepted as having higher histamine content than others [15,16]. Three cheeses (Parmesan,

Blue, and Roquefort), two vegetables (spinach and eggplant), two red wines (Chianti and Burgundy), yeast extract, and scombroid fish have histamine content adequate to raise postprandial 24-hour urinary histamine levels [15]. For this reason, dietary histamine restrictions are recommended for patients undergoing 24-hour urinary histamine determinations.

The histamine content in red wines is commonly cited as one of the possible causes of wine intolerance. The symptoms most often reported by susceptible individuals include flushing of the face, headache, nasal congestion, and/or respiratory distress. A French study, however, found no significant difference in the occurrence of adverse reactions in wine-intolerant individuals who underwent two double-blind provocation tests, one with a wine poor in histamine (0.4mg/l) and one with a wine rich in histamine (13.8mg/l) [17]. The histamine-rich wine also contained higher levels of other biogenic amines including tyramine, ethylamine, putrescine, and phenylethylamine [17]. This suggests that the histamine content of wine may not be directly linked to adverse reactions to wines. It is also interesting to note that fermented cheeses contain amounts of histamine that are much greater than those found in wines, yet signs typical of intolerance to histamine have rarely been reported after ingestion of cheeses [18].

Several symptoms generally attributed to monosodium glutamate (MSG) resemble those associated with histamine toxicity. Using a radio enzymatic assay technique, the histamine content of several common Asian dishes, condiments, and basic ingredients was measured. Although the amount of histamine in individual food portions was determined to fall below the level generally thought necessary to induce symptoms, consumption of multiple portions could result in ingestion of enough histamine to produce symptoms [18].

Scombroid poisoning

Histamine poisoning from ingestion of foods with high histamine content is well documented. The prototype for this kind of histamine toxicity is scombroid poisoning. Marine bacteria such as *Morganella morganii*, *Klebsiella pneumoniae*, and *Photobacterium phosphoreum* generate histamine from histadine through a chemical reaction involving histadine decarboxylase. In a recent publication this gene was cloned from *P. phosphoreum* and sequenced [19]. Improperly refrigerated scombroid fish (e.g. tuna, mackerel, skipjack, and bonito) and non-scombroid fish (e.g. mahimahi, bluefish, amberjack, herring, sardines, marlin, and anchovies) develop an enriched histamine content through this bacterial action. Laboratory confirmation of scombroid is established by sampling the muscle of the suspected meal and finding a histamine level over 50ppm [20]. Since the last edition of this text two additional reports of outbreaks of scombroid poisoning have been reported. Ninety-four cases occurred at a kindergarten as a result of spoiled sailfish and the other as a result of saury fish paste in six patients on a TB ward who were

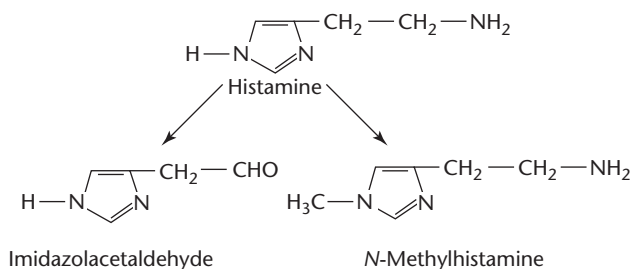


Figure 35.1 Histamine metabolism.

concomitantly taking isoniazid [21,22]. The US Food and Drug Administration (FDA) recognizes the issue of scombroid poisoning as a continuing problem and has conducted a study to base recommendations regarding fish handling to prevent histamine formation. Mahimahi, skipjack, and yellowfin tuna were tested for the formation of histamine after storage. At 26°C, over 12 hours of incubation was required before a histamine concentration of 50ppm was reached, however at 35°C 50ppm of histamine was formed by 9 hours [23].

Ingestion of such fish causes a clinical picture bearing strong resemblance to anaphylaxis. Symptoms generally begin within an hour of ingestion and include flushing, sweating, nausea, vomiting, abdominal cramps, diarrhea, headache, palpitations, urticaria, dizziness, a metallic, sharp, or peppery taste, and, in severe cases, hypotension and bronchospasm [7,24]. Outbreaks of scombroid poisoning continue to appear in the literature. The US FDA has established a hazard concentration for histamine poisoning of greater than 450µg per 100g of tuna [24]. Levels from 2.5 to 250mg of histamine per 100g of fish have been reported in most cases of scombroid poisoning. Treatment is supportive and includes H1 and H2 receptor blockade. Improper warming between the time that the fish is caught and when it is prepared can lead to histamine production sufficient to cause poisoning. Scombroid poisoning can be prevented only by proper handling and refrigeration of fish [23,25,26].

Histamine-releasing foods

Some foods without significant histamine content may contain substances capable of triggering degranulation of tissue mast cells (MCs), with resultant histamine release. Substances thought to be responsible for this histamine-releasing activity include enzymes in foods, such as trypsin, and other agents from both animal and vegetable sources, such as peptone. Foods with this unproven intrinsic histamine-releasing capacity include egg whites, crustaceans, chocolate, strawberries, ethanol, tomatoes, and citrus fruits [27].

Monoamines

Synthesis

Naturally occurring amino acids are converted into vasoactive monoamines by a number of microorganisms that

possess amino acid decarboxylases necessary for this conversion. For example, tyrosine is the precursor for both dopamine and tyramine, phenylalanine is the precursor for phenylethylamine, and tryptophan is the precursor for serotonin. Amine production by these microorganisms varies depending on a variety of different conditions, including pH, temperature, and sodium chloride content [27].

Metabolism

The vasoactive monoamines are metabolized by the enzyme monoamine oxidase (MAO), which includes two subtypes: MAO-A and MAO-B. The genes for both MAO-A and MAO-B have been mapped to the short arm of the X chromosome (Xp11.23) [28], and appear to be derived from a duplication of a common ancestral gene [29]. MAO is found in a variety of tissues, where it is localized to the outer membrane of mitochondria. It catalyzes the oxidative deamination of a variety of neurotransmitters as well as the monoamines of dietary significance. Dopamine and tyramine can be metabolized by both MAO-A and MAO-B. The polar amines (serotonin, epinephrine, and norepinephrine) are metabolized primarily by MAO-A, whereas the non-polar amine phenylethylamine metabolizes primarily by MAO-B [30].

Patients with rare deletions in their MAO-A gene have increased levels of serotonin, epinephrine, and norepinephrine detectable in their urine, whereas MAO-B deficient subjects have increased urinary phenylethylamine levels [31]. Although no studies have examined pharmacologic food reactions in these individuals, it is interesting to note that the MAO-A deficient individuals clinically have problems with impaired impulse control, including a propensity toward stress-induced aggression. MAO-B deficient individuals do not seem to have clinically apparent disturbances in their behavior [31]. Although the reasons for these clinical differences are not known, it may be that raised serotonin levels in MAO-A deficient individuals have a disruptive effect on the developing brain [31].

Specific monoamines

Tyramine

Many fermented foods contain tyramine derived from the bacterial decarboxylation of tyrosine. Foods with particularly high levels of tyramine include Camembert and Cheddar cheeses, yeast extract, wine (especially Chianti), pickled herring, fermented bean curd, fermented soybean, soy sauces, miso soup, and chicken liver. Smaller but still detectable amounts are present in avocados, bananas, figs, red plums, eggplant, and tomato [32–34].

Although tyramine exerts an indirect sympathomimetic effect by releasing endogenous norepinephrine [35], dietary tyramine usually does not cause detectable clinical effects. However, it is suggested to be responsible for adverse clinical

effects involving migraine headache and the hypertensive crisis experienced by patients receiving concurrent treatment with MAO inhibitors. Foods and beverages containing tyramine have been linked to headache in some patients with food-induced migraine. In one study employing double-blind, placebo-controlled (DBPC) challenges in 45 patients with food-induced migraine, 75 (80%) of 94 tyramine (125mg) challenges evoked a migraine, whereas only 5 (8%) of 60 placebo challenges were followed by migraine [36]. Several other studies, however, have failed to demonstrate a relationship between migraines and tyramine [37,38]. Two trials have examined the effect of a low tyramine diet on the frequency of migraine headaches in pediatric and adult populations. Neither study was able to find a difference in headache indices between high tyramine and regular diets [39]. Although dietary tyramine has not been proven to cause migraines, it is possible that there is a subgroup of migraine patients that are hypersensitive to the effects of dietary tyramine because of a deficiency in MAO and conjugating enzymes [40].

As noted earlier, ingestion of foods and beverages containing large quantities of tyramine can lead to headache and hypertensive crisis in patients being treated with MAO inhibitors [33]. Normally, MAO found in the gastrointestinal (GI) tract and liver readily metabolizes dietary monoamines prior to their release into the systemic circulation. When MAO inhibitors block MAO function, however, exogenous dietary monoamines are absorbed and release endogenous norepinephrine. The resulting pressor effect is linked to palpitations, severe headache, and hypertensive crisis. These episodes can be averted by avoiding foods rich in tyramine and other monoamines. Treatment involves slow intravenous administration of the α -adrenergic antagonist phentolamine, which is given until blood pressure stabilizes.

Dopamine

Dopamine exerts both an indirect sympathomimetic effect, by releasing endogenous norepinephrine, and a direct sympathomimetic effect, by interacting with α and β -1 adrenergic receptors. Although tyramine in foods and beverages accounts for the majority of MAO inhibitor-associated hypertensive crises, dopamine present in fava beans or broad beans can also precipitate such a crisis. Avoidance of those foods is recommended for patients taking MAO inhibitors [33].

Phenylethylamine

Like the other monoamines, phenylethylamine may be found in several fermented foods and beverages, especially Gouda and Stilton cheeses and red wine. Unlike the other monoamines, however, phenylethylamine is also found in chocolate [32,41].

Several mechanisms have been implicated in producing phenylethylamine's action [42,43]. It appears likely

that phenylethylamine, like tyramine, exerts primarily an indirect sympathomimetic effect by releasing endogenous norepinephrine. Consequently, phenylethylamine has been implicated in both food-induced migraine [44] and MAO inhibitor-associated hypertensive crisis [44].

Serotonin (5-hydroxytryptamine)

Serotonin is found in highest concentrations ($>3.0\mu\text{g/g}$) in certain fruits, vegetables, and nuts, including banana, kiwi, pineapple, plantain, plum, tomato, walnuts, and hickory nuts [32,45]. Serotonin is present in moderate amounts ($0.1\text{--}3.0\mu\text{g/g}$) in avocados, dates, grapefruit, cantaloupe, honeydew melon, black olives, broccoli, eggplant, figs, spinach, and cauliflower [45]. The only non-plant foods with significant amounts of serotonin are certain mollusks, especially octopus [32].

Serotonin acts on at least two distinct receptors and a variety of cell types. Its actions are complex and exhibit wide species and receptor variability. Two major effects attributed to serotonin are skeletal muscle vasodilation with flushing and both intracranial and extracranial vasoconstriction. Although these effects are often seen with endogenous serotonin production from carcinoid tumors, dietary serotonin does not appear to produce any immediate clinical symptoms, even in patients concurrently taking MAO inhibitors. In fact, oral feeding of serotonin equivalent to as many as 30 bananas failed to elicit clinical symptoms [46]. The urinary excretion of the major metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), increases following ingestion of large amounts of serotonin. In this circumstance, a false diagnosis of carcinoid tumor may be entertained. Consequently, patients collecting 24-hour urine for 5-HIAA measurement should avoid serotonin-containing foods.

Methylxanthines

The three dietary methylxanthines are caffeine, theophylline, and theobromine. All are methylated derivatives of xanthine, which is a dioxypurine. Theobromine is extremely weak physiologically when compared to beverages and foods that contain caffeine. Theophylline is present in only very small amounts in these foods and beverages, and theobromine is only present in significant amounts in chocolate products. Consequently, caffeine accounts for most of the adverse responses from dietary methylxanthine consumption. This section will, therefore, focus on dietary caffeine and its effects.

Physiologic effects

By far the most common physiologic effect of the methylxanthines involves stimulation of the central nervous system (CNS). The methylxanthines also exert effects on the cardiovascular, respiratory, GI, renal, and musculoskeletal systems [47]. These effects are outlined in Table 35.2.

Mechanism of action

The mechanism of action of the methylxanthines has been studied in various systems [47], and at least three have been suggested. Initial investigations focused on the ability of these agents to inhibit the enzyme phosphodiesterase. In many systems, however, it appears that under physiologic conditions this mechanism plays a minor role at best. In the CNS, the methylxanthines appear to act as adenosine antagonists, producing excitation by blocking adenosine's inhibitory effects. In addition, caffeine has been shown to compete for excitation by blocking adenosine's inhibitory effects. Finally, caffeine has been shown to compete for binding at the benzodiazepine site of central chloride channels, causing excitation by limiting activation of these channels [48].

Absorption, distribution, and metabolism

The three dietary methylxanthines are readily absorbed from the GI tract and distributed throughout body water. They are extensively metabolized in the liver, primarily to uric acid derivatives that are, in turn, excreted in the urine. Females taking oral contraceptives have significantly slower rates of catabolism of caffeine than females not taking oral

contraceptives and males [47]. In addition, fluoroquinolones impair caffeine and theophylline metabolism, resulting in increased serum concentrations [49].

Methylxanthine-containing foods

The methylxanthine content of foods and beverages has been widely studied via high-performance liquid chromatography (HPLC) [47,50]. Rough estimates of the quantities of the methylxanthines are given in Table 35.3. These values may fluctuate widely, depending on the variety of foods and their preparation. For example, Robusta coffee blends yield higher caffeine content in general than Arabica blends [47]. Furthermore, brewing times and methods can alter the caffeine content by 100% in certain teas and coffees [47].

Adverse effects of caffeine

As noted, caffeine exerts pharmacologic effects on a variety of organ systems. Consequently, adverse pharmacologic reactions to caffeine-containing foods and beverages are manifested in many ways. Large quantities of coffee and tea are known to produce clinical symptoms that mimic anxiety, and panic disorders [51]. In a blinded, placebo-controlled trial of caffeine consumption in patients diagnosed as having panic disorder or agoraphobia with panic attacks and in normal controls, caffeine produced significantly greater increases in subject-related anxiety, nervousness, fear, nausea, palpitations, restlessness, and tremors in patients compared with controls [52]. Furthermore, these effects were correlated with plasma caffeine levels and were reported to resemble those experienced during panic attacks. The only somatic effect that differed significantly from baseline in the normal controls was an increase in tremors [52]. In addition, caffeine abstinence has been reported to reduce the frequency of panic attacks in this patient population [53]. A central adenosine receptor dysfunction in patients with panic attacks has been proposed as an explanation for their increased sensitivity to caffeine [54].

Two cases of caffeine-induced urticaria reported in the literature were diagnosed by DBPC [55,56]. Although the mechanism remains obscure, both cases were inhibited

Table 35.2 Some physiologic effects of the methylxanthines

Central nervous system:	
Psychostimulation (anxiety, insomnia)	
Cardiovascular:	
Increased contractility, blood pressure, pulse; increased cerebrovascular resistance	
Respiratory:	
Relaxation of respiratory smooth muscle; increased diaphragm contractility	
Renal:	
Diuretic effect	
Gastrointestinal:	
Decreased lower esophageal sphincter pressure; increased gastric secretion, nausea	
Skeletal muscle:	
Increased contractility	

Table 35.3 Methylxanthine content of food and beverages

	Theophylline (mg)	Caffeine (mg)	Theobromine (mg)
Coffee (1 cup)	100–150	80–175	N/A
Cola (12 oz)	40	36–100	N/A
Tea (1 cup)	30–40	20–90	1
Cocoa (1 cup)	4	6–11	13
Milk chocolate (1 oz)	6	6–10	44–60
Baking chocolate (1 oz)	35	25–47	390–450

Source: USDA nutrient database for standard reference, release 14 (2001).

by pre-treatment with terfenadine, suggesting mediator release and H1 receptor stimulation in the pathogenesis of the reactions.

Capsaicin

The genus *Capsicum* encompasses many species, including chili peppers, red peppers, paprika, Tabasco pepper, and Louisiana long pepper. Capsicum peppers have been used for centuries by cultures around the world to enhance the flavor of relatively bland foodstuffs, as well as for its medicinal and irritant properties. Although more than 100 volatile compounds are present in capsicum oleoresin, capsaicin is the most important biologically active compound and is used most frequently for its pharmacotherapeutic benefits [57]. About 70% of the irritant effect of these foods that accounts for their “hot” sensation derives from their capsaicin content [58].

Capsaicin's initial irritant action is mediated by release of the neurosecretory compound substance P from nociceptive nerve fibers. Substance P depolarizes neurons to produce vascular dilation, smooth muscle stimulation, and pain. Repeated exposure to capsaicin results in blockage of substance P synthesis, diminishing the neurons' ability to transmit pain. This process is the basis on which capsaicin creams are used for painful conditions such as rheumatoid arthritis, osteoarthritis, diabetic neuropathy, postherpetic neuralgia, postmastectomy pain syndrome, and reflex sympathetic dystrophy [57].

The most common adverse effect associated with capsaicin is the “burning” oral sensation associated with its ingestion. In this instance, capsaicin binds strongly through its lipophilic side chain to the lipoproteins of oral mucosal receptors. To hinder this strong interaction and “cool the burn,” a lipophilic phosphoprotein such as casein (present in milk, nuts, chocolate, and some beans) is more effective than cold water [59]. A case of plasma cell gingivitis has also been attributed to oral exposure to capsaicin [60].

Adverse pharmacologic effects associated with capsaicin have also been reported in several tissues following exposure by different routes. Gastric installation has been shown to cause significant increases in gastric acid and pepsin secretion, as well as mucosal microbleeding and exfoliation [61]. Nausea vomiting, abdominal pain, and perforated viscus with peritonitis have been reported following ingestion of multiple peppers at a single sitting [62,63]. Inhalation has been reported to result in cough in occupationally exposed capsicum-processing workers [64] and in laryngospasm [65]. Involvement with the eyes causes pain, tearing, erythema, and blepharospasm; this effect has led to use of “pepper sprays” to ward off would-be attackers. Both acute and chronic dermatologic manifestations can also occur when handling capsicum. Possible acute effects include skin irritation, erythema, and burning pain without vesiculation.

In chronic exposures, severe dermatitis with vesiculation can occur [66].

Ethanol

Ethanol, the most widely abused pharmacologic substance in the world, exerts diverse effects on several body systems. The most prominent effects of ethanol consumed in moderate amounts involve the CNS. Ethanol can also act as a peripheral vasodilator and diuretic. It exerts its effects on the brain by dissolving in neuronal plasma membranes, thereby altering the movement of chloride and calcium ions involved in regulation of electrical signals and neurotransmitter release. Ethanol's diuretic effect is thought to relate to its ability to inhibit posterior pituitary secretion of antidiuretic hormone [67]. Both the diuretic and CNS effects of ethanol are well known and not commonly mistaken for allergic reactions. The histamine-releasing ability of ethanol was discussed earlier. Consequently, this section will focus on other responses to ethanol that depend on its peripheral vasodilator properties, sometimes mistaken for ethanol “allergy.”

The mechanism of ethanol-induced peripheral vasodilation remains incompletely understood. Both direct effects – possibly mediated through increases in nitric oxide synthase activity [68,69] – and centrally mediated effects [70] have been suggested. Both normal individuals and those with metabolic deficiencies can experience ethanol's vasodilator effects. In normal subjects, nasal congestion with increases in upper airway resistance [71] and mild cutaneous flushing reactions have been noted within minutes of ethanol ingestion. Alcohol sensitivity is a symptom complex that can consist of cutaneous flushing, tachycardia, hypotension, somnolence, nausea, and vomiting. This response is thought to be mediated by increased levels of acetaldehyde resulting from diminished or inhibited aldehyde dehydrogenase (ALDH) enzymatic activity. It can occur following ethanol interaction with disulfuram, metronidazole, griseofulvin, quinacrine, hypoglycemic sulfonylureas, phenothiazines, or phenylbutazone in normal individuals or in individuals deficient in one of the mitochondrial isoenzymes of ALDH, designated ALDH2.

ALDH2 deficiency is common in certain Asian groups (affecting about 50% of Chinese, Japanese, and Koreans) and has been reported to protect against alcoholism [72,73]. It appears only rarely among non-Asian ethnic groups. The inactive ALDH2 allele is dominant, so that both homozygotes and heterozygotes exhibit ALDH2 deficiency and alcohol sensitivity. Affected individuals experience symptoms to varying degrees within minutes of ingestion, responding with elevations in serum cortisone [74]. Extreme cases of ethanol sensitivity presenting with coma have been reported [75]. Treatment is supportive. A cutaneous ethanol patch test has been suggested as a more reliable indicator of the ALDH2 phenotype than self-reported ethanol-induced flushing [76].

Myristicin

The spice nutmeg is derived from the dried fruit of the nutmeg tree (*Myristica fragrans*). Taken in moderation as a flavoring for foods, nutmeg is innocuous. Consumption of large quantities can precipitate psychosis, however. The active ingredient in nutmeg thought to be responsible for this adverse effect is myristicin. Structurally, myristicin is similar to mescaline (Fig. 35.2) [77]. It has been proposed that myristicin may be metabolized *in vivo* to an amphetamine-like compound with effects similar to those of lysergic acid diethylamide (LSD) [78]. It remains unclear whether myristicin or one or more metabolites accounts for its psychoactive properties, as synthetic myristicin does not always precipitate hallucination [79]. Some investigators questioned nutmeg's psychoactive properties and have reviewed various medicinal uses of this spice [80]. One tablespoon of grated nutmeg (roughly 7 g) contains about 2% myristicin by weight [81]. Symptoms generally appear 3–8 hours after ingesting more than one tablespoon. The most prominent effects involve the CNS and cardiovascular system. Apprehension, fear of impending death, anxiety, and visual hallucinations accompanied by regular tachycardia are common [82,83]. Patients may also experience palpitations, nausea, vomiting, and chest pressure. Because dry mouth, fever, cutaneous flushing, and blurred vision can occur, acute nutmeg intoxication is sometimes mistaken for anticholinergic intoxication. One differentiating physical examination feature is that myristicin usually, although not always, causes miosis rather than mydriasis [84,85].

Treatment for acute nutmeg intoxication is supportive. Emesis induction of an unknown ingestion is controversial. Many patients ingesting a toxic quantity of nutmeg are nauseated and will vomit spontaneously. Activated charcoal with sorbitol may decrease the systemic absorption, thereby mitigating the duration and severity of symptoms. Various psychotropics have also been employed, including diazepam and haloperidol for anxious and hallucinogenic features [35,84].

Psoralen

Psoralens are naturally occurring compounds belonging to a group of compounds known as furocoumarins. Furocoumarins are tricyclic hydrocarbons consisting of a furan ring condensed on benzopyrone (Fig. 35.2) [86]. Synthetic psoralens are used commonly for the treatment of certain dermatologic diseases, including psoriasis. In PUVA (psoralen + ultraviolet A radiation) therapy patients receive psoralen with the addition of UVA light which causes the photoaddition of psoralen to pyrimidine bases of DNA, resulting in a cross-linking between DNA strands [86]. PUVA-induced cross-linking of DNA is thought to mediate the observed antiproliferative effects of psoralen on psoriasis. Sunlight with addition of psoralen also leads to the generation of

reactive oxygen species, free radicals that can damage cell membranes, cytoplasmic constituents, and cell nuclei, resulting in a photodermatitis [86]. Naturally occurring psoralens have been found to be present in celery, parsley, limes, lemons, and parsnips. Celery field workers and handlers frequently develop photosensitization problems as a result of celery furanocoumarins [87]. Photocontact dermatitis of the skin has also been demonstrated to occur following external contact with the fig tree (*Ficus carica*) in conjunction with exposure to the sun. Contact with the fig leaf sap and shoot sap is required in fig-induced photodermatitis; the fruit sap does not contain significant amounts of psoralen [88].

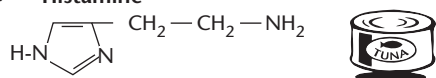
Patients exposed to food psoralens typically develop clinical symptoms within 24 hours of skin contact with furocoumarins. The initial presentation usually includes sunburn, linear bullae, and/or blisters, which may persist for up to 1 week. Hyperpigmentation usually follows and may remain for several weeks to months [89]. In children, phytophotodermatitis may be confused with child abuse [89]. Awareness of this condition in pediatric patients may prevent an unpleasant situation when questioning parents or caretakers, as well as unnecessary diagnostic procedures. Most cases of photodermatitis do not require treatment. Marked pain and discomfort may be treated with cool, moistened dressings for several days. Topical corticosteroids may also be used, and in severe cases the use of systemic steroids has been recommended [89]. The use of aspirin and other prostaglandin inhibitors has been proposed but there is no scientific evidence that this therapy is helpful [89]. The prognosis is usually excellent, although severe, life-threatening burns occur rarely.

Solanine and chaconine

α -solanine and α -chaconine are general terms used to describe the glycosidic alkaloids present in the common potato (*Solanum tuberosum*). Structurally, these glycoalkaloids are complex molecules consisting of three sugars attached to a nitrogen-containing steroidal skeleton (Fig. 35.2) [90,91]. Potato plant synthesis of glycoalkaloids is thought to be a defense mechanism against fungus growth on potatoes; the compound α -solanine has been shown to be fungitoxic and is synthesized at cut (wound) surfaces [91]. The production of α -solanine is also stimulated by mechanical injury, exposure to light in the field (green potatoes) or in the marketplace and with aging of the potato [91]. In addition to its fungicidal properties glycoalkaloids are also moderate inhibitors of specific and non-specific cholinesterases. The highest total glycoalkaloid levels in the potato plant are present in the foliage, blossoms, and sprouts, followed by the peel, potato sprouts, and the tuber flesh. The US Department of Agriculture (USDA) potato-breeding program has an accepted guideline for glycoalkaloid content in commercial potatoes at below 200 $\mu\text{g/g}$ fresh weight [91]. Unfortunately,

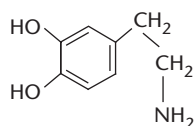
Vasoactive amines:

Diamines: Histamine



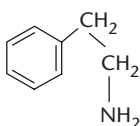
Monoamines:

Dopamine



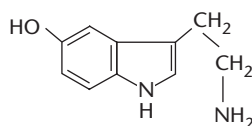
Fava beans

Phenylethylamine



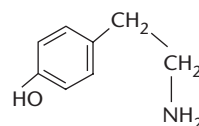
Red wine

Serotonin



Bananas

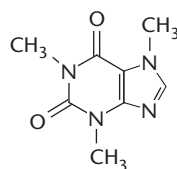
Tyramine



Cheddar cheese

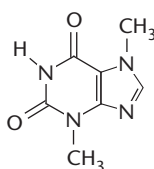
Methylxanthines:

Caffeine



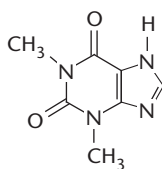
Coffee

Theobromine



Chocolate

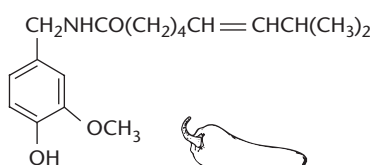
Theophylline



Tea

Others:

Capsaicin



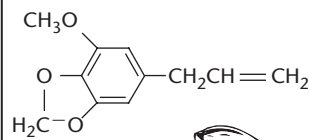
Chili pepper

Ethanol



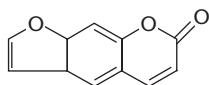
Martini

Myristicin



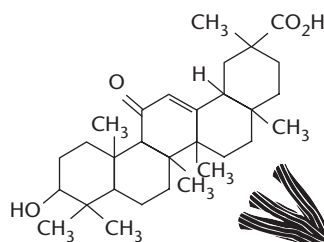
Nutmeg

Psoralen

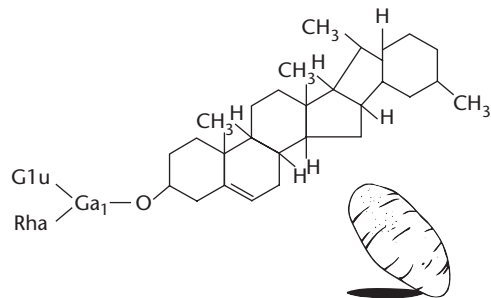


Celery

Glycyrrhetic acid



Licorice

 α -solanine

Potato

Figure 35.2 Endogenous substances responsible for pharmacologic food reactions (vasoactive amines and others).

the level of glycoalkaloid under certain weather conditions can rise to far above that level. Several outbreaks of illness have been traced to the consumption of potatoes with glycoalkaloid contents ranging from 100 to 400 µg/g [91].

The symptoms of glycoalkaloid poisoning may occur 2–20 hours after a meal. They can include vomiting, diarrhea, and severe abdominal pain, and more severe cases present with neurologic symptoms, including headaches, dizziness, drowsiness, confusion, visual disturbances, dilated pupils, and weakness, sometimes followed by unconsciousness. The vital signs include fever, rapid weak pulse, low blood pressure, and rapid respiration – not unlike the vitals seen in patients experiencing anaphylaxis [92]. Recovery from glycoalkaloid poisoning is usually complete, but coma and death have been reported in cases of severe poisoning. Pharmacokinetic differences in inter-individual metabolism have been demonstrated, suggesting that some subjects may be more susceptible than others to the adverse effects of glycoalkaloids [93].

Baking, boiling, or microwaving does not affect the α-solanine content of potatoes. The contents are only slightly reduced by frying. Fried potato peels are a source of large quantities of solanine. In one study, fried potato peels had glycoalkaloid levels that ranged from 1390 to 450 µg/g, which is more than 7 times the upper safety limit [91].

Treatment of glycoalkaloid poisoning is mostly supportive once a history of potato consumption has been obtained. The best way to avoid poisoning is to avoid excessive potato consumption, especially the eating of potato peels. One simple test of glycoalkaloid levels is to chew a small piece of the raw peel. Potato skins with levels of total glycoalkaloid higher than 100 µg/g of tuber cause a slow developing, hot burning, persistent irritation of the sides of the tongue and back of the mouth. Potato skins that contain more than 200 µg/g give an immediate burning sensation [91].

Glycyrrhetic acid

Glycyrrhetic acid is the pharmacologically active constituent of licorice that is extracted from the sweet root of the plant *Glycyrrhiza glabra* (Fig. 35.2) [94]. The use of licorice dates back to at least 1000 BC when stores of the root were placed in the tombs of Egyptian pharaohs. Its therapeutic activity for a wide variety of ailments was extolled in the writings of the ancient Greeks, Romans, and Chinese [95]. More recently licorice has been shown to have the pharmacologic properties of a gastric mucosal protectant, and anti-inflammatory agent [95]. The largest consumer of licorice in the United States is the tobacco industry for use as a conditioning and flavoring agent. Licorice cures tobacco and thus has been used for a century in cigars, pipe tobacco, cigarettes, and chewing tobacco [96].

When licorice is ingested habitually or in excess, patients develop symptoms that share most of the clinical and

biochemical features of primary hyperaldosteronism. Clinical manifestations include those of sodium retention (pulmonary and peripheral edema, breathlessness, and hypertension) and hypokalemia (cardiac dysrhythmias, polyuria due to nephrogenic diabetes insipidus, proximal myopathy, lethargy, paresthesias, muscle cramps, headaches, and tetany) [94,97]. Biochemical markers for excessive activation of mineralocorticoid receptors in the distal renal tubules include hypokalemic alkalosis and suppression of plasma renin activity [94]. It is thought that glycyrrhetic acid acts by inhibiting renal 11-β-hydroxysteroid dehydrogenase activity thereby diminishing the conversion of cortisol to cortisone and resulting in high renal levels of cortisol [98]. Because cortisol binds to mineralocorticoid receptors with the same affinity as aldosterone, there is a resulting hypermineralocorticoid effect of cortisol [98].

Treatment of patients with licorice-induced hypermineralocorticoidism includes the administration of spironolactone, which acts as a competitive inhibitor of mineralocorticoid receptors. Since most sodium is reabsorbed in the proximal renal tubules, concomitant administration of a thiazide diuretic, which blocks reabsorption of sodium proximal to the distal portion of the nephron, is required for maximal diuretic effect. The suppression of 11-β-hydroxysteroid dehydrogenase activity, as well as many of the changes in electrolyte balance, may persist for almost 2 weeks after licorice intake is discontinued. The prolonged suppression of 11-β-hydroxysteroid dehydrogenase activity appears to be due to the continued action of glycyrrhetic acid, because as urinary glycyrrhetic acid levels fall, the suppression of 11-β-hydroxysteroid dehydrogenase activity is reversed [97]. Unfortunately it takes 2–4 months following cessation of licorice consumption for the function of the renin–aldosterone system to return completely to normal [98].

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