Food sources and biomolecular targets of tyramine

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Tyramine is a biogenic trace amine that is generated via the decarboxylation of the amino acid tyrosine. At pico- to nanomolar concentrations, it can influence a multitude of physiological mechanisms, exhibiting neuromodulatory properties as well as cardiovascular and immunological effects. In humans, the diet is the primary source of physiologically relevant tyramine concentrations, which are influenced by a large number of intrinsic and extrinsic factors. Among these factors are the availability of tyrosine in food, the presence of tyramine-producing bacteria, the environmental pH, and the salt content of food. The process of fermentation provides a particularly good source of tyramine in human nutrition. Here, the potential impact of dietary tyramine on human health was assessed by compiling quantitative data on the tyramine content in a variety of foods and then conducting a brief review of the literature on the physiological, cellular, and systemic effects of tyramine. Together, the data sets presented here may allow both the assessment of tyramine concentrations in food and the extrapolation of these concentrations to gauge the physiological and systemic effects in the context of human nutrition.

INTRODUCTION

Tyramine is a biogenic amine generated via the decarboxylation of the amino acid tyrosine in animals, plants, and microorganisms. Together with β-phenylethylamine, tyramine belongs to the group of aromatic biogenic amines and, because it contains a single amine group, is referred to as a monoamine. Tyramine is involved in many physiological processes. For example, it acts as a neuromodulator and is a precursor for the neurotransmitter octopamine. In addition, it has cardiovascular effects and modulates the cellular immune system. At high concentrations, tyramine also elicits toxic effects, induces hypertension and migraine, and may cause allergic reactions. Therefore, reliable data about the tyramine content of foods, and, moreover, detailed information about the mode of action of tyramine and the responsible biomolecular targets, are indispensable. This review summarizes the evidence on (1) the presence of tyramine in a variety of foods, (2) the postprandial physiological and adverse effects of tyramine, and (3) the biomolecular targets of tyramine. It is not intended to be a systematic or comprehensive review of all data available on the factors that affect tyramine levels in food or food model systems. Rather, the intent is to examine the association between tyramine concentrations in food and the physiological effects of tyramine, specifically with regard to biomolecular targets. One limitation of this review is its focus on commercially available foods. However, tyramine concentrations in food model systems are discussed in the text.

FOOD SOURCES

Humans acquire tyramine through endogenous synthesis as well as their diet. A variety of factors influence the tyramine content of food, as reviewed by Gardini et al.[1] These include the availability of free tyrosine as well as

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the presence of tyramine-producing microorganisms and the conditions that support their growth (ie, favorable salt concentration, temperature, and pH). Furthermore, factors affecting the activity of the enzyme tyrosine decarboxylase (eg, temperature, pH) will also affect the tyramine content of food. Consequently, foods that undergo fermentation processes during manufacturing, such as dairy products (eg, cheese), dry-cured sausages (eg, salami), wine, or beer, will have comparatively high amounts of tyramine.[2–6]

FACTORS INFLUENCING TYRAMINE CONTENT OF FOOD

Availability of tyrosine

Certain food-processing methods can lead to high amounts of available amino acids in foods. These amino acids can be subsequently decarboxylated to their respective biogenic amines. One of the most prominent examples of a food with high tyramine concentrations is cheese (Table 1[3,4,7–27]). During the ripening process, casein is hydrolyzed, thereby generating high amounts of free tyrosine and, as a consequence, tyramine.[28–31]

In the case of fermented meats, free amino acids are already present in the raw meat and are additionally released from proteins and peptides by proteases during fermentation.[32] For example, lactic acid bacteria contribute to proteolysis in foods by decreasing the pH, which in turn increases the activity of the endogenous proteases, called cathepsins.[33,34]

Presence of tyramine-producing bacteria

Generally, microorganisms possessing the enzyme tyrosine decarboxylase are responsible for the formation of tyramine in foods. In fermented foods, the tyramine-producing bacteria are mostly gram positive and belong to the genera *Enterococcus*, *Lactobacillus*, *Leuconostoc*, and *Lactococcus*.[35–39] These bacteria can derive from a variety of sources; for example, they can be present in the food prior to fermentation, they can result from contamination during the manufacturing process, or they can be present in the added starter culture.[40–42]

At present, commercial starter cultures are evaluated for their capability to generate biogenic amines in accordance with the strict guidelines of the European Food Safety Authority.[43] The European Food Safety Authority Panel on Biological Hazards has proposed the concept of "Qualified Presumption of Safety," which requires reliable data about the absence of biogenic amine production as a criterion to permit starter cultures to be used in food manufacturing.

Besides using starter cultures that are negative for the presence of amino acid decarboxylase,[44–47] other approaches to reduce biogenic amine formation have been proposed. For example, Leuschner and Hammes[48] described the use of *Brevibacterium linens* as surface inocula in Munster cheese. In that case, the histamine and tyramine content was decreased by 55% to 70% after a 4-week ripening period. Another approach uses adjunct cultures that contain bacteria able to degrade biogenic amines.[49] Ladero et al[50] suggested the use of an *Enterococcus faecalis*–infecting bacteriophage (Q69) as a tool for reducing the tyramine content in cheese, since they could show that Q69 was able to decrease tyramine concentrations in a model cheese by 85%.

Other intrinsic and external factors

Among the many factors influencing the production of tyramine in food, the main ones are temperature, storage time, environmental pH, salt content of the food, and storage conditions (eg, post-ripening technological processes, and packaging methods).

In a multifactorial study using 2 strains of lactic acid bacteria, *Lactobacillus brevis* CECT 4669 and *Enterococcus faecium* BIFI-58, Marcobal et al[51] investigated 5 physicochemical parameters (incubation temperature and time, environmental pH, added tyrosine concentration, and pyridoxal 5′-phosphate supplementation) for their impact on cell growth and tyramine production. High temperatures led to increased tyramine concentrations. Similarly, in a skim-milk model, increasing the temperature from 16° to 44°C led to a pronounced increase in the tyramine content, which the authors attributed to temperature-dependent enhanced cell growth rather than increased enzyme activity.[52] However, Marcobal et al[51] identified tyrosine concentration and incubation time as the main contributors to tyramine production. Recently, decarboxylase-independent thermal formation of biogenic amines was shown for 2-phenylethylamine, 2-methylpropylamine, 2-methylbutylamine, and 3-methylbutylamine in cocoa beans.[53] By comparing the amounts of these amines in unfermented beans, fermented beans, and unfermented roasted beans, the authors could demonstrate that roasting of unfermented beans resulted in up to a 6-fold increase in the respective amine concentration. The roasting process yielded higher concentrations of the amines than the fermentation process. The authors did not include tyramine in their study, yet a similar mechanism is conceivable, since other analyses showed that baking of French fries induced a 2-fold increase in tyramine concentrations (N. Sulzinger, G. Andersen, P. Schieberle, unpublished data, 2016), as shown in Table 1. On the other hand, boiling spinach did not induce an increase of tyramine content (N. Sulzinger, G. Andersen, P. Schieberle, unpublished data, 2016).

Table 1 **Tyramine content of foods**

Food item	Tyramine content (mg/kg)[a]	Reference
Milk and dairy products (except cheese)		
Buttermilk	2.2	Souci et al (2016)[24]
Cow's milk	ND	Novella-Rodriguez et al (2000)[19]
Cream	1.7	Souci et al (2016)[24]
Sour cream	1.4	Souci et al (2016)[24]
Yogurt	1.3	Souci et al (2016)[24]
	ND	Mayr & Schieberle (2012)[4]
	ND	Novella-Rodriguez et al (2000)[19]
Cheese		
Appenzeller cheese	55.0	Souci et al (2016)[24]
Brie cheese	ND–260.0	Souci et al (2016)[24]
Camembert cheese	37.0	Souci et al (2016)[24]
Cheddar cheese	350.0	Souci et al (2016)[24]
	130.0	Tarjan & Janossy (1978)[25]
Edam cheese	310.0	Souci et al (2016)[24]
	13.5	Lange et al (2002)[3]
	25.6	Tarjan & Janossy (1978)[25]
Emmental cheese	42.0	Souci et al (2016)[24]
	128.7	Tarjan & Janossy (1978)[25]
Feta cheese	152.0–246.0	Valsamaki et al (2000)[26]
Gorgonzola cheese	8.0	Lange et al (2002)[3]
Gouda cheese	20.0–670.0	Souci et al (2016)[24]
Gruyère cheese	37.0	Souci et al (2016)[24]
Leerdammer cheese	ND	Mayr & Schieberle (2012)[4]
Parmesan cheese	4.0–290.0	Souci et al (2016)[24]
	3.75	Mayr & Schieberle (2012)[4]
Quark, fresh cheese	2.4	Souci et al (2016)[24]
Roquefort cheese	27.0–1100.0	Souci et al (2016)[24]
	152.0	Lange et al (2002)[3]
Tilsit cheese	32.0	Souci et al (2016)[24]
Meat		
Chicken liver	100.0	Souci et al (2016)[24]
	50.0	Tarjan & Janossy (1978)[25]
Ham, cooked	6.0–108.0	Saccani et al (2005)[21]
Ham, dry cured	7.5	Lange et al (2002)[3]
	4.0–171.0	Saccani et al (2005)[21]
Onion sausage	32.0	Lange et al (2002)[3]
Ox liver	270.0	Souci et al (2016)[24]
Pork, fresh meat	ND–56.0	Saccani et al (2005)[21]
Salami	77.1	Mayr & Schieberle (2012)[4]
	17.0	Lange et al (2002)[3]
Fish and fish products		
Cod	2.0	Lange et al (2002)[3]
Fermented fish sauce	276.0–357.0 (mg/L)	Kirschbaum et al (2000)[13]
Herring	ND	Lange et al (2002)[3]
Herring, Dutch cured	ND–3000.0	Souci et al (2016)[24]
Mackerel	25.8; 27.4[b]	Shakila et al (2001)[22]
Mackerel, in brine	ND	Shakila et al (2001)[22]
Mackerel, salt dried	398.4; 413.8[b]	Shakila et al (2001)[22]
Salmon	ND	Lange et al (2002)[3]
Sardine	16.2; 11.8[b]	Shakila et al (2001)[22]
Sardine, in oil	ND	Shakila et al (2001)[22]
Sardine, salt dried	169.5; 178.1[b]	Shakila et al (2001)[22]
Seer fish	9.4; 10.7[b]	Shakila et al (2001)[22]
Seer fish, salt dried	154.2; 154.1[b]	Shakila et al (2001)[22]
Shrimp	8.8; 12.6[b]	Shakila et al (2001)[22]
Shrimp, salt dried	704.7; 693.2[b]	Shakila et al (2001)[22]
Tuna	0.06	Mayr & Schieberle (2012)[4]
Tuna, in oil	0.72	Souci et al (2016)[24]
	ND; 1.2[b]	Shakila et al (2001)[22]

(continued)

Table 1 **Continued**

Food item	Tyramine content (mg/kg)[a]	Reference
Alcoholic beverages		
Alcohol-free beer	1.2	Souci et al (2016)[24]
	6.16 (mg/L)	Kalač et al (1997)[11]
Pilsner lager beer	1.4	Souci et al (2016)[24]
	6.85 (mg/L)	Kalač et al (1997)[11]
Port wine	0.51 (mg/L)	Cunha et al (2011)[9]
Full beer (Vollbier [Germany])	1.8–12.0	Souci et al (2016)[24]
Red wine	ND–20.0	Souci et al (2016)[24]
	1.93	Mayr & Schieberle (2012)[4]
	0.8–2.6 (mg/L)	Landete et al (2005)[14]
	38.8 (mg/L)	Tarjan & Janossy (1978)[25]
	1.40 (mg/L)	Marcobal et al (2005)[17]
	ND–0.292 (mg/L)	Anlı et al (2004)[7]
	3.1	Lüthy & Schlatter (1983)[16]
White wine	ND–3.0	Souci et al (2016)[24]
	110.8 (mg/L)	Tarjan & Janossy (1978)[25]
	1.2–22.7	Lüthy & Schlatter (1983)[16]
Fruits and fruit products		
Apple	ND	Tarjan & Janossy (1978)[25]
Apple juice	≤ 0.1 (mg/L)	Maxa & Brandes (1993)[18]
Avocado	23.0	Souci et al (2016)[24]
Banana	7.0	Souci et al (2016)[24]
	0.9	Lavizzari et al (2006)[15]
Currant	ND	Tarjan & Janossy (1978)[25]
Currant juice, freshly squeezed	3.26 (mg/L)	Maxa & Brandes (1993)[18]
Grape	691.0	Tarjan & Janossy (1978)[25]
Grape juice	0.04 (mg/L)	Cunha et al (2011)[9]
	≤0.1 (mg/L)	Maxa & Brandes (1993)[18]
Grapefruit juice, freshly squeezed	≤0.1 (mg/L)	Maxa & Brandes (1993)[18]
Hazelnut	1.8	Lavizzari et al (2006)[15]
Orange	10.0	Souci et al (2016)[24]
Orange juice	0.21 (mg/L)	Maxa & Brandes (1993)[18]
Orange juice, freshly squeezed	0.1–0.49 (mg/L)	Maxa & Brandes (1993)[18]
Peach	ND	Tarjan & Janossy (1978)[25]
Pear	ND	Tarjan & Janossy (1978)[25]
Plum	ND–6.0	Souci et al (2016)[24]
	ND	Tarjan & Janossy (1978)[25]
Raspberry	10.0–90.0	Souci et al (2016)[24]
Raspberry juice, freshly squeezed	66.66 (mg/L)	Maxa & Brandes (1993)[18]
Watermelon	460.0	Tarjan & Janossy (1978)[25]
Vegetables and vegetable products		
Beetroot	160.0	Tarjan & Janossy (1978)[25]
Cabbage	670.0	Tarjan & Janossy (1978)[25]
Kohlrabi	930.0	Tarjan & Janossy (1978)[25]
Carrot	0.001	Sulzinger et al (unpublished data, 2016)[c]
	119.0	Tarjan & Janossy (1978)[25]
Carrot juice	0.002	Sulzinger et al. (unpublished data, 2016)[c]
Cauliflower	400.0	Tarjan & Janossy (1978)[25]
Chinese cabbage	1.26	Simon-Sarkadi & Holzapfel (1994)[23]
Cucumber	250.0	Tarjan & Janossy (1978)[25]
Endive	1.60	Simon-Sarkadi & Holzapfel (1994)[23]
Fermented cabbage (sauerkraut, drained)	20.0	Souci et al (2016)[24]
	60.66	Mayr & Schieberle (2012)[4]
	6.0	Lange et al (2002)[3]
Fermented cabbage juice	37.1–73.0 (mg/L)	Kirschbaum et al (2000)[13]
French fried potatoes, baked	1.77	Sulzinger et al. (unpublished data, 2016)[c]
French fried potatoes, raw	0.77	Sulzinger et al. (unpublished data, 2016)[c]
Green pea, frozen	8.7	Kalač et al (2002)[12]
Haricot bean	160.0	Tarjan & Janossy (1978)[25]
Iceberg lettuce	0.94	Simon-Sarkadi & Holzapfel (1994)[23]
Miso	24.6–349.0	Kirschbaum et al (2000)[13]
	ND–49.8	Yen (1986)[27]
Olive	ND	Lange et al (2002)[3]

(continued)

Table 1 **Continued**

Food item	Tyramine content (mg/kg)[a]	Reference
Paprika	266.0	Tarjan & Janossy (1978)[25]
Potato	1.14	Sulzinger et al. (unpublished data, 2016)[c]
	840.0	Tarjan & Janossy (1978)[25]
	2.0	Lavizzari et al (2006)[15]
Radicchio	2.73	Simon-Sarkadi & Holzapfel (1994)[23]
Radish	200.0	Tarjan & Janossy (1978)[25]
Soy sauce	17.7–172.0 (mg/L)	Kirschbaum et al (2000)[13]
	16.1–1699.0 (mg/L)	Yen (1986)[27]
Soybean	9.05	Bartkiene et al (2015)[8]
	ND	Gloria et al (2005)[10]
Soybean, fermented	27.8–416.1	Bartkiene et al (2015)[8]
Spinach	3.78	Sulzinger et al. (unpublished data, 2016)[c]
	286.0	Tarjan & Janossy (1978)[25]
	2.2	Lavizzari et al (2006)[15]
Spinach purée, frozen	10.2	Kalač et al (2002)[12]
Spinach, boiled	2.58	Sulzinger et al. (unpublished data, 2016)[c]
Sufu (fermented tofu)	ND–1125.4	Yen (1986)[27]
Tomato	4.0	Souci et al (2016)[24]
	1.07	Sulzinger et al. (unpublished data, 2016)[c]
	4.0	Lange et al (2002)[3]
	250.0	Tarjan & Janossy (1978)[25]
Tomato ketchup	33.6	Kalač et al (2002)[12]
Tomato purée, concentrated	7.23	Sulzinger et al. (unpublished data, 2016)[c]
	10.4	Kalač et al (2002)[12]
Turnip	ND	Tarjan & Janossy (1978)[25]
Zucchini	0.06	Sulzinger et al. (unpublished data, 2016)[c]
Miscellaneous		
Chocolate	3.11	Mayr & Schieberle (2012)[4]
	0.3	Lavizzari et al (2006)[15]
Coffee, ground	1.26–16.14	Restuccia et al (2015)[20]
Coffee, brewed	0.25–1.89 (mg/L)	Restuccia et al (2015)[20]

Abbreviation: ND, not detectable.

[a] Unless otherwise stated, contents are given as average values in milligram per kilogram. In cases where natural deviations are exceptionally high or results from different cultivars or food items were listed individually in the references, only the variations are shown.

[b] Values given for concentrations determined using 2 different techniques.

[c] Quantified as described in Mayr & Schieberle (2012).[4]

In fact, the tyramine content in raw spinach was slightly higher than in cooked spinach (Table 1), which could be caused by a transfer of tyramine into the cooking water, as described by Ziegler et al.[54]

The addition of 5% sodium chloride to milk inoculated with *E faecalis* strongly reduced the tyramine concentration,[52] owing to the inhibitory effect of sodium chloride on bacterial growth. Moreover, increased sodium concentrations have been shown to decrease decarboxylase activity,[55] as reviewed in Gardini et al[1] and Linares et al.[30]

Acidic pH enhances tyramine production in a variety of bacterial strains, mainly gram-positive bacteria and, in particular, lactic acid bacteria, although this is accompanied by a reduced growth rate of the tyramine producers.[39,51] The decarboxylation of amino acids is a cellular mechanism to counterbalance acidic stress, so it allows the bacteria to survive in an inhospitable environment. At least 2 causative factors underlying this phenomenon have been identified: enhanced transcription of decarboxylase-related gene clusters, and optimum activities of microbial decarboxylases at acidic pH,[55,56] as reviewed by Gardini et al,[1] Linares et al,[30] and Marcobal et al.[57]

Finally, storage conditions of different kinds of foods have a great impact on tyramine concentrations. Prime examples are fish and fish products. As shown in Table 1, fresh fish contains very small amounts of tyramine ($\leq$3 mg/kg). Unfavorable storage conditions, however, lead to a rapid accumulation of tyramine. For example, storage of Indian mackerel at ambient temperature (25°–29°C) led to an increase in the tyramine concentration to 200 mg/kg after 20 hours.[58] Although fish poisoning is generally caused by high amounts of histamine ($\geq$500 mg/kg) and is therefore often referred to as histamine poisoning, other biogenic amines may potentiate the toxic effect of histamine.[59,60] A recent investigation showed that broccoli and radish sprouts also can contain moderately high amounts of tyramine.[61] Whereas the tyramine content of nongerminated seeds was about 2.5 mg/kg of dry matter, tyramine concentrations reached about 17 mg/kg of dry matter in seeds germinated for 5 days.

Postprandial physiological and toxicological effects of tyramine

Tyramine is considered the most toxic biogenic amine. However, its physiological effects differ with respect to cell type and tissue. Normally, tyramine is degraded by monoamine oxidases (MAOs).[62] Monoamine oxidase A and MAO B (Enzyme Commission no. 1.4.3.4), located at the outer mitochondrial membrane, are flavoproteins that dehydrate amines to imines. For tyramine, the imine generated is then hydrolyzed, yielding 4-hydroxyphenylacetaldehyde and ammonia.

The activity of MAOs can be decreased by alcohol intake, medications used to treat depression, or metabolic defects that augment the toxic effects of tyramine. Since cheese was the first food associated with elevated blood pressure in patients treated with MAO inhibitors,[63,64] this phenomenon often is referred to as the "cheese effect." Upon entering noradrenergic nerves, tyramine causes a release of noradrenaline, which leads to, for example, headache, increased respiration, and elevated blood pressure.[65,66] At worst, an increase in blood pressure can cause a stroke, a heart attack, or symptoms of shock. Oral administration of 450 mg of tyramine to healthy individuals elevated systolic blood pressure by 30 mmHg. However, after pretreatment with an MAO inhibitor (tranylcypromine), a similar increase in blood pressure was observed with much lower doses of tyramine (8 mg).[67]

According to the European Food Safety Authority,[43] an intake of 600 mg of tyramine per meal is not likely to cause adverse effects in healthy individuals not taking MAO inhibitors, but individuals taking MAO inhibitors should not consume more than 6 mg of tyramine per meal.

Table 1 shows a general overview of the tyramine content of different food items. The data were collated via PubMed using the search term "tyramine content food." Publications that reported on model systems or other noncommercially available food were not included in the table. In addition, values in the nutrition tables of Souci et al[24] were used. For some foods, there are large variations between individual samples of different origin. Variations may result also from technical limitations of the different methods used, reflecting the numerous factors that influence the tyramine content of food.

Biomolecular Targets

In recent years, exogenous tyramine has attracted attention because of its mostly postprandial effects, which have been demonstrated in various areas of human neurology and health and are mediated by a variety of biological target molecules, for example, receptors or enzymes (Table 2[68–83]).

Tyramine is mostly known for its systemic effects on human health, such as inducing migraine or hypertension. Indeed, overconsumption of tyramine-containing food can lead to severe headache,[84–86] which is one of the main symptoms of the above-mentioned cheese effect.[68] The cheese effect occurs when patients undergoing therapy with MAO inhibitors do not adhere to a tyramine-free diet of nonfermented foods and consume, for example, cheese. Additionally, acute hypertension may be caused by tyramine acting on α and β_1 adrenoceptors in blood vessels and the myocardium, leading to the release of noradrenaline and adrenaline[71,73,83,87] (Table 2). Indeed, experiments with isolated rat hearts demonstrated positive chronotropic effects of tyramine that could be antagonized by the β-blocker propranolol, suggesting a sympathomimetic action of tyramine, presumably by activation of adrenergic receptors[74] (Table 2). Alternatively, tyramine has been shown to function as an allosteric antagonist on the recombinant β-adrenergic receptors ADRB1 and ADRB2.[76] Moreover, it activates trace amine-associated receptor 1 (TAAR1) and cyclic adenosine monophosphate signaling.[70] Indeed, several trace amine-associated receptors (TAARs) were found to be expressed in the rat heart.[88] Taken together, these findings suggest that biogenic amines such as tyramine play a role in modulating cardiovascular activities via TAARs (Table 2).

There is a wealth of evidence for biogenic so-called trace amines to function as physiological neuromodulators in the central nervous system.[89–94] A recent study demonstrated, through a model of blood–brain barrier permeability, that tyramine may reach the central nervous system postprandially, suggesting a need to investigate the neuronal effects of exogenous tyramine.[95] The process of tyramine metabolism has been shown to produce hydrogen peroxide in rats, thereby damaging mitochondria[75,79] (Table 2). This production of hydrogen peroxide has been demonstrated to contribute to the development of Parkinson disease in humans.[96,97] Finally, animal experiments revealed that tyramine may play a role in regulating neural function by reversibly inhibiting dopamine activity. The application of tyramine stimulated subthalamic neurons, presumably via dopamine D_2 receptors[82] (Table 2), and subdued the induction of midbrain dopaminergic cells by dopamine[77] in rat- and mouse-based in vitro models, respectively.

Recent studies show that, beyond having known physiological effects, trace amines in general, and tyramine in particular, are involved in modulating human immunity.[98,99] For example, tyramine, which can be released from activated platelets,[100] appears to be an endogenous, chemotactic TAAR1 ligand for neutrophils.[69] Tyramine was demonstrated to convey cytotoxic activity against B cells expressing TAAR1.[80] In addition, the

Table 2 **Target-specific effects of tyramine in tissues and cells**

Cells/tissue	Putative target molecules[a]	Effect	Reference
Systemic-wide cells/tissue	ND	Migraine	Alkhouli et al (2014)[68]
	α and β_1 adrenoceptors (ADRA1, ADRA2, ADRB1)	Hypertension	Broadley (2010)[71]
		Cheese effect	Finberg & Gillman (2011),[73] Frascarelli et al (2008)[74]
	TAARs		Broadley et al (2013)[83]
Rat intestine mitochondria	Tyramine as a substrate for MAO	Damage by hydrogen peroxide	Valoti et al (1998)[79]
Rat brain mitochondria	Tyramine as a substrate for MAO	Damage by hydrogen peroxide	Hauptmann et al (1996)[75]
Rat subthalamic neurons	Dopamine D_2 receptor (DRD2)	Synaptic signaling	Zhu et al (2007)[82]
Mouse dopaminergic midbrain cells	ND	Depression of dopaminergic neuron activity	Ledonne et al (2010)[77]
SH-SY5Y (human neuroblastoma cell line), DAN-G (human pancreas carcinoma cell line)	ND	Morphine production	Poeaknapo (2005)[78]
HEK293 (human embryonic kidney/adrenal precursor cell)	Recombinant TAAR1	cAMP signaling	Borowsky et al (2001)[70]
HEK293	Recombinant TAAR5	cAMP signaling, activation of reporter genes	Dinter et al (2015)[72]
	Recombinant ADRB1, ADRB2	Allosteric antagonist	Kleinau et al (2011)[76]
White blood cells, neutrophils	Tyramine as a substrate for cytochrome P450 2D6 (CYP2D6)	Morphine production	Zhu et al (2005)[81]
Neutrophils	TAAR1, TAAR2	Chemotaxis	Babusyte et al (2013)[69]
T cells	TAAR1, TAAR2	IL-4 production	Babusyte et al (2013)[69]
B cells	TAAR1, TAAR2	IgE production	Babusyte et al (2013)[69]
	TAAR1	Cytotoxicity	Wasik et al (2012)[80]

Abbreviations: cAMP, cyclic adenosine monophosphate; IgE, immunoglobulin E; IL, interleukin; MAO, monoamine oxidase; ND, not determined; TAAR, trace-amine associated receptor. [a]Abbreviations in parentheses represent official gene symbols.

TAAR1-selective and tyramine-related drugs 3-iodothyronamine and o-phenyl-3-iodotyramine showed greater cytotoxic activity against B cells than tyramine itself.[80] Dinter et al[72] reported 3-iodothyronamine as an inverse agonist of recombinant human TAAR5 (Table 2). Besides exerting agonist activity on TAARs, tyramine can also be a precursor to morphine production[78] in white blood cells in general and in neutrophils in particular, cells that likely express cytochrome P450 2D6 (CYP2D6).[81] This could represent a way for these cells to convey immunosuppressive activity.[101] Moreover, tyramine activates human neutrophil functions such as chemotaxis via TAAR1/TAAR2[69] (Table 2). Finally, tyramine, via TAAR1/TAAR2, regulated the messenger RNA expression of a variety of cytokines and their receptors via both TAAR1/TAAR2–activated interleukin 4 release from human T cells and immunoglobulin E release from B cells[69] (Table 2).

CONCLUSION

The tyramine content of food is influenced by numerous factors, resulting in wide variations in tyramine concentrations. The highest amounts can be found in foods that undergo fermentation, such as Roquefort cheese (up to 1100 mg/kg) or soy sauce (up to 1699 mg/L). Typically, the lowest tyramine content, based on the data available, can be found in fruits and nonfermented dairy products (except cheese), in which concentrations rarely exceed 10 mg/kg.

The physiological effects of tyramine are mediated by a variety of biological target molecules. Tyramine may modulate adrenergic receptors, which triggers hypertension, while its neuro- and immunomodulatory actions are mediated via TAARs. However, for some of the tyramine-related effects described thus far, for instance the induction of migraine, the biomolecular targets have yet to be determined.

In this review, data from the literature regarding the tyramine content of food and the potential for tyramine receptors as biomolecular targets were compiled. To fully understand the mechanisms underlying the postprandial effects of tyramine in human physiology, it is imperative to use food analysis and to examine potential biomolecules targeted by tyramine.

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