

Monoamine Oxidase Inhibitors, Dietary Tyramine and Drug Interactions

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Monoamine Oxidase Inhibitors, Dietary Tyramine and Drug Interactions

Summary

Key Facts

- For those who already follow healthy eating (and drinking) amounts and patterns a low tyramine diet involves almost no changes at all
- Only rotten foods, or those prepared using 'fermenting' techniques have high tyramine
- The possible high blood pressure reaction is proportional to the amount of the tyramine-containing food eaten
- There is no food or drink that is so strong (i.e. high in tyramine) that a small amount (i.e. 100 grams or less) is likely to be risky
- Some specialised aged Belgian-type beers (Lambic) can have high tyramine, with some having around 50 mg/L. Since they may be drunk on an empty stomach they could be risky
- Most modern cheese is safe (in healthy sized portions) but some aged cheeses can have rather higher tyramine concentrations, so care and awareness is needed
- If a reaction ever did occur, and you attend hospital when you get symptoms, the chance of coming to harm is very remote
- The symptoms of a reaction are: a thumping forceful heartbeat (usually a **slower** pulse rate), paleness (pallor), rapid onset severe headache, tightness in the chest. Pulse may drop as low as 40 beats per minute
- The risk of harm from blood pressure reactions with foods and MAOIs has previously been greatly exaggerated
- Remember to check compatibility of any medications you get, including over-the-counter (non-Doctor scripts) drugs.

General Summary

Interactions between monoamine oxidase inhibitors and other drugs are now understood much more clearly than in the past. These interactions are not as widespread or as difficult to deal with as many people think, and as many texts indicate. In my opinion, such problems with MAOIs are less than with the SSRIs, especially fluoxetine, which has multiple potentially problematic interactions. However, it is relevant to appreciate that many standard texts do

contain incorrect information that can cause confusion. The references and details herein may help to clarify these issues.

There is now more quality data on the tyramine levels in foods, and how much tyramine is likely to constitute a problem. Some previous opinions and advice have been based on old data and have over-extrapolated from minimal information. This paper surveys more original data on tyramine than any paper previously published.

All levels are given as mg of tyramine per kilogram or litre: so if you live in a non-metric area, then get smart and think metric: it is unhelpful and confusing to work in standard servings/standard drinks or oz./pints.

Although a small proportion of people may get a significant blood pressure increases with only 10 mg of tyramine a majority of people need to have 50 mg or more (in a meal) to get a serious blood pressure increase (i.e. 60 mm Hg or more). For a detailed analysis of the evidence relating to tyramine dose and blood pressure see (1) and www.psychotropic.com. It is easy to work out how much tyramine is in 100 grams of any of these foods. Learn what 100 grams looks like, and what sensible food portion sizes are: if you eat 1 kg beef steaks, or half a kilo of cheese, chocolate etc. then you will need to adjust to avoid trouble (and to become healthy). Some people will need to consult a dietician for explanations of how to eat sensibly. Also see website information like

<http://www.win.niddk.nih.gov/publications/PDFs/justenough.pdf>

For those who already follow healthy eating amounts and patterns the low tyramine diet involves almost no changes at all. This is because healthy amounts of cheese are around what is safe tyramine-wise: i.e. 100 grams of cheese in a meal is a large portion, and very few cheeses contain more than 25 mg of tyramine in 100 grams (i.e. 250 mg/kg). So a typical 50 gram portion (12.5 mg tyramine) is very unlikely to cause a blood pressure reaction.

It is important to realise that even if excessive tyramine is taken, serious consequences are most unlikely providing appropriate action is taken. That will usually mean monitoring blood pressure for a few hours and possibly having medication to lower it (in hospital) if it goes over about 180 - 200 mm Hg and there is clear evidence of harmful consequences.

Storage of foods below 5°C is a crucial factor, and some domestic fridges fail the test. It is vital to check your fridge temperature with an accurate thermometer.

Introduction

These drugs all belong to a group that are similar and are called Mono-Amine Oxidase Inhibitors (MAOIs). The enzyme MAO has two sub-types, A and B. This information is most relevant for irreversible MAO-A inhibitors (the most common are tranylcypromine & phenelzine) and less important for various other types of MAOI. This document covers diet (both food and drink) and also drug interactions for those on MAOIs. It is intended to inform and assist both doctors and those taking MAOIs.

Persons on these drugs may be advised to keep some means of identifying the fact that they are on MAOIs readily available. Similar steps as may be taken with insulin dependent diabetes and those suffering epilepsy are appropriate; this is in case of accidents or emergencies. This may be kept on the person (medical alert bracelet, handbag or wallet), and also in the car (glove box) as well as at home.

Information such as that contained in here should be given to any person supplying treatment, or advising on any aspect of treatment, any dentist or medical practitioner, and including 'herbalists', 'naturopaths' etc. Generally, advice on MAOIs should come from specialist psychopharmacologists. Most information on the internet is inaccurate, even that on sites of educational institutes. Be clear, this is authoritative information; I have published many recent papers on the pharmacology of MAOIs and TCAs and their interactions etc., besides having a lot of first-hand practical experience (1-9).

Note Anyone can use Google Scholar, and the National Library of Medicine (PubMed), to find references, mostly with abstracts. If you follow links to journal websites it is surprising how often you can get full-text papers too.

The Mechanism of Tyramine Formation

Amino Acids

Tyrosine is the amino acid precursor for the amine tyramine. Amino acids are the building blocks of proteins. [Wikipedia] "Twenty-two amino acids are encoded by the standard genetic code and are called proteinogenic or standard amino acids; eight are generally regarded as essential for humans: **phenylalanine**, valine, threonine, tryptophan, isoleucine, methionine, leucine, and lysine. Additionally, cysteine (or sulphur-containing amino acids), **tyrosine** (or aromatic amino acids), histidine and arginine are required by infants and

growing children. The amino acids arginine, cysteine, glycine, glutamine, histidine, proline, serine and **tyrosine** are considered conditionally essential, meaning they are not normally required in the diet, but must be supplied exogenously to specific populations that do not synthesize them in adequate amounts.”

Vertebrate tissues contain ~ 5 – 20 mg/kg of most of the amino acids.

Tyramine formation requires the availability of the amino acid precursors, tyrosine or phenylalanine, the presence of micro-organisms with amino acid decarboxylase enzymes, and favourable conditions for their growth and decarboxylating activity, in order for tyramine, and other **biogenic amines (BA)**, to accumulate in foods.

Tyramine’s precursors, but little or no actual tyramine, are present at up to 20 mg per kg in animal protein sources, but generally lower in plants (see below for exceptions). That is why fresh properly stored foods are always safe. Animal protein can accumulate tyramine if left to go off, but few people in western society would accept green rotten smelly meat. Game birds that have been hung for lengthy periods may be risky, but these will only be encountered in private houses because health regulations do not permit such practices in restaurants etc. Some chefs will bend the rules a little but that is unlikely to be sufficient to cause major problems.

Histamine, putrescine, cadaverine, tyramine, tryptamine, 2-phenylethylamine, spermine and spermidine are the most important biogenic amines (BA) in foods (10), that is why smell is a helpful guide for what to avoid. The smell of putrescine is the key, being the origin of the word putrid. A little of the decaying smell of these biogenic amines is what gives some foods that certain something that gourmets develop a taste for.

The following list gives an indication of likely tyramine levels for relevant substances as indicated by currently available research. It may be used as a guide. It is a lot to do with ‘freshness’ (i.e. time and storage conditions) for fish and meat, whether tyramine is present depends on the type of micro-organism causing the spoilage (e.g. see (11)). Older estimations of tyramine levels may sometimes be inaccurate because the isolation of primary amines from complex food matrices is not easy, and usually a derivatization procedure needs to be applied to enable HPLC or GC determinations.

Storage below 5°C is the crucial factor, and some domestic fridges fail the test. It is vital to check fridge temperature with an accurate thermometer.

People who have aberrant eating habits may get into trouble, e.g. chocolate is safe, but only assuming you agree that eating no more than 100 grams is sensible eating, eating a kilo could possibly be

risky because of excess tyramine, among other things: anyone who eats like that could get in trouble with various foods.

Tyramine in Foods and Beverages

Avoiding the few risky foods and beverages that do exist is easy and necessary whilst taking MAOIs. Only a few foods can build up the degree of excess tyramine that can make the blood pressure (BP) go dangerously high. The seriousness of any BP reaction is in proportion to the amount of tyramine that is consumed. It is a strictly dose-related effect, that is why it is safe to 'test' small quantities of some foods e.g. your favourite local cheese.

MAOIs themselves lower blood pressure. The interaction between tyramine & MAOIs is what raises blood pressure, i.e. produces hypertension. Deaths from tyramine/MAOI induced hypertension are extremely rare, probably rarer than serious reactions to many modern drugs, or to bleeding secondary to SSRIs (12), or being struck by lightning. It is not logical or reasonable to describe MAOIs as 'dangerous'. The opinion has been well argued that the dangerousness idea was much encouraged and spread by pharmaceutical company representatives over-enthusiastically extolling the virtues of newer drugs (13). I agree.

Tyramine only accumulates in significant quantities when the amino-acids tyrosine and phenylalanine are converted to tyramine by decarboxylase enzymes possessed by some, not all, micro-organisms. The only foods that have enough tyramine in them to cause significant reactions are those that have been subjected to the action of these particular types of micro-organisms. However, modern food hygiene standards are such as to make that increasingly rare, because such amines are monitored as part of food hygiene control audits. Also, special starter cultures have been developed that minimise the proliferation of undesirable bacteria (cf. yoghurt, below).

The BP reaction can only occur if a relatively large amount of tyramine is eaten or drunk (see list below), i.e. for most people about 25 mg of tyramine. Since it is only rarely encountered foods that are very occasionally high (1000 mg per kg is exceptionally high) that means one would need to consume 25 grams of such a food; and that is an extreme example of an exceptionally high tyramine level. Most foods with elevated tyramine (like matured cheeses) actually have about 250 mg per kg, quantities of up to 100 grams of such as cheese is likely to be OK. So, it is obvious that there is no cause for worry if, as an example, a little grated parmesan cheese on a salad has been eaten.

What are the symptoms of a reaction?

A reaction consists of a thumping heartbeat and a progressive increase in blood pressure (BP). The heart rate (pulse) usually becomes **slower** (14, 15), in response to the increase in BP, not usually, as many sources state, faster. If blood pressure goes up to approximately 180 mm Hg or more quite rapid onset of severe headache is usual (although headache is not a reliable indicator of high BP). Tightness in the chest, paleness (pallor) may occur. **The increase in BP is proportional to the amount of tyramine ingested.** Symptoms usually start soon after eating, maybe within 30 minutes, usually within one hour. Any symptoms/headache starting more than two hours after eating is less likely to be due to a high blood pressure reaction. Duration of reaction is ~ 1 – 2 hours (16). If such a reaction occurs, and nothing is done about it, i.e. getting medical help, then there is a *small* chance that a ‘stroke’ (cerebral bleed or haemorrhage) would occur, which could be very serious.

First, the tyramine champions

One soy sauce clocked in at **6,000 mg/kg** (17).

An Italian goat cheese at ~ **2,000 mg/kg** (18)

And, there is a French cheese called ‘crotte du diable’ (translates as ‘Devil’s turds’), and various rotten fish brews (best consumed on isolated Scandinavian mountain tops), that I am sure would be contestants, but I cannot find any data! I doubt that anyone could find a lab technician brave enough to endure them.

Milk Products

Milk and yoghurt

In France, the regulations are strict. To be called yoghurt milk must be fermented by *Lactobacillus bulgaricus* and *Streptococcus thermophilus* (no decarboxylase activity, so no tyramine), via starter cultures. Bacteria have to be at least at 10,000,000 CFU/g till the end of shelf-life. That means it is virtually impossible for tyramine producing bacteria to gain a footing: so yoghurt likewise has none. Novella-Rodriguez, 5 samples no tyramine (19).

Cho, Korea, Yoghurt, 8 samples, no tyramine to a max of 4 mg/kg (20).

Cheeses

Mature cheeses

It is likely that the higher levels of 1,000 – 2,000 mg/kg found in older assays will be much less common now. Food regulations have driven widespread use of starter cultures. These contain no bugs with decarboxylase activity and greatly minimise the chance of contaminant tyramine (or other biogenic amines).

Matured 'artisanal' cheeses can develop high levels (~ 1,000 mg/kg) of tyramine, e.g. Stilton, Cheddar, Parmigiano, Manchego, Compté, Brie and Camembert; the older and smellier it is the more tyramine it probably contains. A twenty-five gram serving of such a really strong cheese would have 25 mg of tyramine, and could possibly raise the BP to a measurable, but not to a dangerous, extent.

Contrary to what one might think from the paucity of data in the medical literature there have been thousands of tyramine estimations performed from cheeses all over the world: a small selection of studies with extensive and varied sampling is given here to illustrate this.

Most commercial 'supermarket' cheeses are low in tyramine (<100 mg/kg) because budget prices do not pay for long warehouse aging. First, the champion Italian goat cheese (18) at ~ 2,000 mg/kg, very high indeed. It is remotely possible only 5 grams of this could be dangerous. But such specimens are increasingly rare as practices are improving.

Portuguese traditional cheese, Terrincho (21), 29 cheeses from five batches, dairy farms located throughout the region: all < 100 mg/kg. Blue cheese, Czech (22, 23): the mean and median being 380 mg/kg and 289 mg/kg, respectively) and, different cheeses (vats) varied widely, from 10 mg/kg, to 875 mg/kg; and 20 samples of blue cheeses obtained from Spanish retail stores average 14 mg/kg, but with a range from 0 to 1585 mg/kg.

Dutch-type semi-hard cheeses mostly < 50 mg/kg, max 250 (24, 25).

Brie and Camembert styles: there seem to be no recent assays, all I can find is older papers (26, 27) Camembert 15 samples 100 – 1800 mg/kg, Brie 260 mg/kg. I suspect they are less now because of starter cultures.

Compté (5 months old) 1,300 mg/kg.

Non-matured cheeses

Fresh non-matured, i.e. unripened/unaged, cheese styles, and yoghurt, are always safe because milk itself has no tyramine, e.g. curd styles, fromage frais, mascarpone, cream, ricotta, cottage cheeses,

bocconcini. Tyramine is only present as a result of the action of certain micro-organisms on the proteins in milk. The amount is proportional to the degree of 'contamination' and length of time of ripening: that is why most modern supermarket cheeses have low (< 100 mg/kg) levels of tyramine (it costs money to keep cheeses maturing in temperature-controlled warehouses).

Unripened cheeses 10 samples (19) < 0.5 mg/kg.

Goats cheese (28) 'frais' styles, usually ~ 20 mg per Kg, but aged goats cheeses will be higher, max 70 mg per Kg (28).

And the Italian goat cheese (Robiola di Roccaverano) 2,067 mg/kg **for tyramine**, Bonetta(29).

Fermented Sauces – Vegetable

Marmite

Marmite is made from residual brewer's yeast and the first production facility was near the Bass beer brewery in Burton on Trent: production started in 1902. It has relatively high amounts of biogenic amines ~ 320 mg/kg of tyramine (30). One would need to take 30 mls to get 10 mg tyramine, which is more than is usually consumed. Vegemite was produced under licence in New Zealand post war, initially to the same formula, but changes were made after various Company take-overs.

Marmite-like spreads are somewhat similar to soy sauce, 'tofu' and 'miso' which are also made by 'fermentation' of brews containing non-animal proteins, so small amounts can be safely eaten.

Soy sauce, Miso and Sufu etc

Soy sauce is made from steamed soybeans, roast wheat and Koji fungus, the 'Moromi' mash may then ferment for as much as 2 years after which it is filtered and pasteurised. Soya beans have no tyramine, it is produced slowly during the fermentation reaching typical levels of ~150 mg per kilo (litre) after many months. Miso is very similar.

Miso, 5 samples tyramine ~ 20 mg/kg (20).

Japanese soy sauce: Maximum 940 mg per litre (approx 1 mg per ml).

Most samples measured have ranged between 10-200 mg per litre (31). Maximum tyramine levels in the past may have been as high as 1000 mg per litre (but those may be spurious values), so 25 mls would have contained 25 mg of tyramine. But that is unusual, most supermarket Soy sauces actually have much less (like 100 mg per litre).

Yongmeia (32)21), **40 samples** of Chinese soy, mostly less than 200 mg/litre (20 of the 40 were < 100 mg/kg). 'The total content for the five biogenic amines in these samples was 497 mg/L with a range from 41.7 to 1357 mg/L. The levels for each of the five amines were **0–673 mg/L for tyramine**, 0–592 mg/L for histamine, 0–550 mg/L for cadaverine, 0–486 mg/L for spermidine and 0–145 mg/L for spermine'.

Stute (17), **23 samples** soy, all low < 200, except one clocked a staggering 6,000 mg/kg (dead rat in the vat I suspect).

Other soy derived products like 'miso' soup and Sufu (20, 33) generally have similar levels. Miso, 5 samples < 25 mg/kg (20), and soy sauce < 50 mg/kg (20). Sufu Taiwan, histamine 150 mg/kg (34), and Miso 40 samples tyramine all < 10 mg/kg (35).

Fermented Sauces – Animal

Fish Sauces

In Classical Roman cooking fish sauce was called garum or liquamen. They are ubiquitous now, but deeply rooted in Far Eastern cuisine: seafood, often anchovy, allowed to ferment ~ 140 - 200 days. Names: Nuoc-Mam (Vietnam), Nam-Pla (Thailand), Budu (Malaysia), or Patis (Philippines) ketjap-ikan (Indonesia), ngapi (Burma), ishiru or shottsuru (Japan), colombo-cure (India Pakistan), yeesu (China), aekjeot (Korea). For more see Wikipedia, and for a recent reviews refs (17, 20, 36). NB Cho is in Korean, but the tables of values are readable.

They will, like everything, vary a bit with producer and hygiene quality, but seem usually to be OK, 200 – 500 mg/kg (bearing in mind its is, like soy sauce, a condiment, so if used in modest amounts (no more than ~ 20 grams) will be safe (37).

Korean fermented fish products < 50 mg/kg (20), liquid fish sauce made from a variety of things, scallop, squid etc average 350, max (anchovy) 600 mg/kg (20).

Stute (17), **45 commercial fish sauces** from the Far East, most < 200 mg/kg, maximum 588 mg/kg for tyramine.

Worcestershire sauce is fermented and contains anchovies. There seems to be no specific data on tyramine content, but it is reasonable to assume it will be similar to other fish sauces, probably lower. It is used in small quantities and is unlikely to add any significant tyramine load to a meal.

Meat and Fish Products

Meat products are safe, but if they are not fresh, i.e. if they have been subject to decomposition by micro-organisms, then they could be risky. Fresh liver has no tyramine (38), but if stored badly or past its 'use by' date when purchased, and then kept in a domestic fridge that is not cold enough, may become risky (39). The Hedberg paper is a great illustration of observation and investigation and a unique exception to my comments about lack of BP observations.

Aged beef can have significant tyramine levels, stored at +4°C for 21 days, 60 mg/kg, and after 36 days 120 mg/kg (40). Such meat is usually only available in the restaurant trade (at a high price!), but such a steak could contribute to a significant tyramine intake as part of a gourmet meal. However, there are no reports of reactions with beef in 50 years.

Ordinary commercial supermarket beef is not usually aged and levels are like to be < 10 mg/kg. Galgano, 7 mg/kg after 8 days at +4°C (41).

Similarly, liver pate (and similar meat or fish pastes) are safe **if freshly made and properly refrigerated** (i.e. *below* 4°C), especially because such foods are normally consumed in very small portions. I have found no specific modern data, yet, but the lessons enumerated herein tell us what is likely. Liver (42) has no tyramine, but once processed and contaminated with bugs it would be an ideal culture medium, so any laxity in storage time and temperature will result in a steady increase in tyramine. I would guess at levels of 100 – 500 mg/kg in badly stored product after a week or two.

Meat

Fresh Meats

For a review of polyamines in meat (and vegetables) see refs (43-45).

Chicken, refrigerated for 20 days at a temperature of +4±1°C in a domestic refrigerator. One day - 3 mg/kg, 20 days - 15 mg/kg (46, 47). Moreira found well stored product < 5 mg/kg. Red and white meat (40), refrigerated for 30 days +4±1°C max 30 mg/kg.

Beef (48): stored at -18°C for 178 days, tyramine max <4 mg/kg.

Fresh Kidneys (49) and Liver (42), no tyramine.

Dry cured Ham

As with all dry cured meat products only low levels of tyramine are expected, Lorenzo found < 5 mg/kg (50), which agrees with (51). So 'Parma ham', prosciutto, copa etc will all be safe.

Fermented Sausages

In their paper, 'Biogenic amines in dry fermented sausages: a review' Suzzi reviewed 20 studies from all over Europe (52) and found tyramine was usually below 200 mg/kg, very few samples were higher (51). Suzzi (52) '*In the several reports concerning the Spanish dry fermented sausages Chorizo, Fuet, Sobrasada and Salsichon tyramine was generally detected at the higher concentration (exceeding 600 mg/kg in some sausages with mean values of about 200 mg/kg).*'

Levels of tyramine depend, as would be expected, on the hygienic quality of the meat used, those produced with frozen meat have maximum levels of about 100 mg/kg.

In Spanish fermented sausages Chorizo, Fuet, Sobrasada and Salsichon tyramine was detected at up to 600 mg/kg in some sausages, with mean values of about 200 mg/kg (53).

French sausages, both artisanal and industrial, had tyramine maxima of 270 mg/kg (52, 54).

Things (i.e. hygiene and low temperature processing) are improving steadily, more recent surveys all finding lower levels (55-57).

Latorre-Moratalla et al is a good recent review: it found average of 150 mg/kg, max < 200 mg/kg. The study received financial support from the European community project: Assessment and improvement of safety of traditional dry sausages from producers to consumers (QLK1 CT-2002-02240, Website: www.clermont.inra.fr/tradisausage/). It is a good example of the efforts being made to monitor and improve hygiene standards.

Preparations of Stock Cubes, Powders, Bouillon, etc

These are not prepared by fermentation but are flavoured extracts and reductions. They are most unlikely to be high in tyramine. Populin tested broths (homemade or canned products from the market), soups (ready-to-eat soups, condensed soups and creams), soup bases (bouillon cubes, pastes and granulated powders), sauces and salad dressings. From the European and US markets (30). They found none exceeded 10 mg/kg.

Fish

Fresh Fish

Tyramine and histamine go in parallel and many regulations limit histamine to between 50 and 200 mg per kg, the FDA limit is 50 mg/kg. Histamine itself causes Scombroidosis (58). **Freshness and handling is everything**, and quality control and screening of imported produce have been a powerful force for improving hygiene world wide. Fresh fish usually has 2 – 5 mg per kg tyramine (59).

Whole and filleted trout kept on ice for up to 18 days, max at 18 days was 7 mg/kg (11, 60). Frozen fish 1 mg/kg (61).

Herring, fresh, stored on ice (i.e. $\sim 2^{\circ}\text{C}$) < 5 mg/kg (62).

Trout fillets < 7 mg/kg after 20 days at $+4^{\circ}\text{C}$ (60).

Shelf life of chilled fresh and frozen/thawed salmon (59, 63) max 40 mg/kg at end of shelf life.

And, especially re histamine, see (64).

Smoked Fish

Smoked salmon (65) dry-salted, traditional smoking, sliced, vacuum-packed stored nine days at 4°C and 19 at 8°C contained no tyramine.

Cold smoked salmon < 20 mg/kg (66).

Dried Fish

Dried salted Tuna roe 90 mg/kg (67).

Canned Fish

Some canned samples reach 10 mg/kg, but that seems rare (68). Max 70 mg/kg (69)

Canned fish: re histamine (some were $>$ FDA limit of 50 mg/kg), one was 1,000 mg/kg of histamine! see (70, 71).

The Norwegians have their rakfisk (fermented fish), and the Swedish fermented herrings (Surströmming), Icelanders fermented shark (Hákarl or kæstur hákarl), and I dare say on the Kamchatka peninsula they fester something similar, perhaps an unmentionable part of a brown bear buried in peat for months. I can find no tyramine data on these. But if you have read this far without knowing already that they are obviously to be avoided then ... well, I can't help you any more.

Fish Sauces

See 'Fermented Sauces' above.

Malaysian "budu" and "cincalok"

Malaysian local appetisers "budu" and "cincalok" (37) up to 450 mg/kg.

Vegetables

Vegetables generally have lower amine levels, but can increase with spoilage. And plants do produce an extra-ordinary range of amines, many are part of the ancient battle where plants very successfully manipulate the behaviour of animals (e.g. opioids, tannins, nicotine

etc) to enhance their own survival. Many of these compounds are more common in a greater variety of plants than a casual reading of the literature would lead one to suppose. Their concentration varies greatly depending on many factors like variety, tissue and stage of growth etc.

Useful reviews are: (72, 73).

In summary, it would seem **normal servings** of unprocessed vegetables, fruits etc are most unlikely to have any significant adverse effects via histamine, tyramine or L-Dopa.

L-DOPA

Dopamine is present in many plants and may play a role in repelling pathogens. It is the precursor of the quinones that cause browning when they polymerise into melanin (e.g. bananas). Some legumes contain significant amounts of L-DOPA in some tissues, at some stages of growth, including *Vicia faba* L. varieties (aka fava beans, broad beans) and *Mucuna pruriens* (Cowhage, itching powder) (74-79). Varieties of these plants are being genetically engineered to try to find a suitable dietary source for L-DOPA because it may be better than pharmaceutical L-DOPA (absorption, more even plasma levels). Various preparations are being sold on the internet. A search for 'mucuna aphrodisiac' or 'mucuna parkinson' returns many thousands of hits.

Maximum concentrations of 10-20 mg/g (dry weight) have been found in *Vicia faba* (74), equivalent to a wet weight of approximately 100 mg kg⁻¹. However, the edible beans are lower.

Since L-Dopa is a dopamine precursor, not a releaser, i.e. not an indirectly acting sympathomimetic like amphetamine is, it is likely to have an effect more analogous to L-tryptophan with MAOIs (i.e. mild potentiation only). L-tryptophan does not cause serious problems with serotonin toxicity, and nor would one expect L-Dopa to do so with BP.

Despite the warnings on interactions with medicinal L-Dopa, and the early papers often quoted, e.g. (80) the evidence for **serious** hypertension (see below for discussion) with L-DOPA and MAOIs seems poor.

Such amounts of L-Dopa may potentiate or precipitate small blood pressure increases, but, in my opinion, it is very unlikely that a significant blood pressure elevation would result unless huge amounts of such foods are ingested, see (81).

Spinach

Tyramine in spinach (82) was < 5 mg/kg, but histamine can be higher ~ 50 – 100 mg/kg.

Fava beans

Fava beans (*Vicia Faba*, aka broad beans) tyramine 10 mg/kg (83), & L-Dopa, but at low levels, probably not sufficient to have any effect in normal portions. See 'L-Dopa'.

Bananas

Bananas can have significant dopamine, up to 400 mg/kg in the pulp, about 1,500 mg/kg in the skin (84), but little tyramine (85, 86). The first report of dopamine was in 1958 (87). Large amounts of banana (20 per day) have been shown to increase plasma dopamine levels (81). This may be via release of endogenous DA, and or via L-Dopa or other precursors/releasers. So, although DA cannot cross the blood brain barrier brain (or only to a limited extent (88)), plasma DA may be elevated, and raised peripheral DA may raise BP by vaso-constriction. As with all plants, levels will vary greatly according to variety, part of plant, stage of ripeness etc. and it is clear levels are much higher in the skin (1,000 mg/kg) than the pulp (84), at only 2 mg/kg (89) and (90-92).

Banana may inhibit the adsorption of medicinal L-Dopa (93, 94). It would seem doubtful that bananas in usual quantities would have any significant effect.

Sauerkraut

Sauerkraut: review (43), **more than 100 samples from 7 countries**, almost all < 200 mg/kg, but a couple from Czech Rep. were 400 – 900 mg/kg.

Tyramine level was 50 mg/kg in one canned sauerkraut other samples < 12 mg/kg. A spinach sample showed the highest histamine content 20 mg/kg (83).

Korean 'kimchi' cabbage average 50 mg/kg, max 120 mg/kg (20).

From (73, 85) Spinach 2 mg/kg. Histamine levels were 100 mg/kg.

Miscellaneous

Any food source that contains protein can theoretically, if allowed to rot, accumulate high tyramine levels. Various interesting and strange things are eaten around the world, so a little common sense is needed.

Chocolate

Chocolate does involve a slight, sort-of-fermentation, stage. Somewhat variable levels of amines have been reported: tyramine from 9 to 70 mg/kg (95-97).

Pastore (98) found 1 mg/kg for tyramine (10 mg/kg for dopamine, 2 mg/kg for serotonin, 1 mg/kg for histamine, 3 mg/kg for 2-phenylethylamine).

From (85) Chocolate 0.3, Spinach 2, Hazelnut 1.8, Banana 1, Potato 2 mg/kg.

In my opinion, we can say it is completely safe in usual quantities.

Other non-serious, non-dangerous interactions

Many plant derived substances (alkaloids), e.g. 'herbs' and 'foods' like coffee, and tea contain various compounds that act as 'drugs', stimulants like caffeine, b-phenylethylamine, methylamine, trimethylamine (see Strolin Benedetti & Tipton (99)). These affect everyone but may have an exaggerated effect in those taking various sorts of antidepressant drugs, including MAOIs; they should be taken in moderation and avoided if they precipitate symptoms such as tremor, anxiety, jitteriness, palpitations, agitation, poor sleep etc.

Wine and Beer

Wine and beer in moderation (two drinks in 2 hours) are definitely safe. Modern hygienic production methods have made excessive tyramine levels extremely rare (there is now extensive regulation and documentation of this, see below for details). Badly made or stored drinks may be risky, so take care with 'home-made' wines or beers. Bottled beer is safe; a little caution is warranted with 'live' beers which may be available from 'boutique' producers. They can be distinguished by the sediment (of dead yeast) in the bottom and they are cloudy if shaken. Also 'keg' or 'tap' beers, although they do not have tyramine whilst in keg, may very rarely get significant tyramine levels, possibly because the pipes are not kept clean (pipe runs can be very long, and not chilled, so the residue is in a dirty state, and can be risky if you get the first stagnant sample). Modern commercial wines do not contain significant tyramine.

Tyramine in liquids taken on an **empty stomach** should be regarded as a special case, because tyramine will be absorbed much more rapidly (100, 101). One small (330 mls) glass of some 'live' beers could, in *rare* instances, have about 10 mg of tyramine; this might be sufficient to cause a reaction in a minority of cases when taken on an empty stomach, e.g. see (102) and (14).

Wine

Wine does not usually contain significant levels of tyramine.

Recent major reviews covering many hundreds of different wines of all types: tyramine all < 5 mg/L (103-107).

Aged wines, all < 5 mg/L (108).

30 different wines including fortified wines (Port and Madeira) max 5 mg/L (109). Wines 200 samples, histamine average 1.2 mg/L (110) and 300 samples max tyramine < 5 mg/L (111, 112).

USA wines, max tyramine 3 mg/L (107).

Marcobal, 61 different Spanish wines including aged Rioja Gran Reserva wines (113). Tyramine range 0–11.32 mg/L, Average 1.40 ± 2.35 mg/L. Only 34 of 61 wines had detectable tyramine.

Vinegars

Ordinary vinegars low, but: Chinese rice wine (old) 400 mg/L, Sherry vinegar 15 mg/L, Italian Balsamic ~ 15 mg/kg (114).

Beers

Standards, and awareness of brewing hygiene issues, have increased since some of the older results, but some caution is still warranted: it would seem very likely that all standard commercial and modern beers all over the world will be safe, but some low volume ‘artisan’ and ‘boutique’ ones are risky on occasion (see Lambic below).

For a review see (115), although a great majority are low (2 – 8 mg/L) a very few are up to 30 – 50 mg/L.

Tang (116) looked at 18 beers all brewed in China, some European under licence, values mostly 3 – 5 (max 7) mg/L.

Spanish beer < 2 mg/L (117).

17 domestic Turkish and 13 imported beers were evaluated (118) and all were < 2 mg/L.

Ken Shulman’s group (119) looked at a total of **98 beer samples** (79 different brands of beer) 15 years ago, they analysed by HPLC for tyramine: Quote:

‘All of the bottled beers analysed had safe tyramine concentrations (< or = 10 mg/liter; range, 0 to 3.16 mg/liter) and, thus, do not require restriction in patients receiving MAOIs. Therefore, the consumption of canned or bottled beer, including dealcoholized beer, in moderation (fewer than four bottles or cans; 1.5 litres within a 4-hour period) appears to be safe and does not require restriction in patients receiving MAOIs. Only 4 of 98 beer samples studied were found to have a dangerous (> 10 mg/liter) tyramine concentration, one of which was the index beer. The tyramine concentration in these four beers ranged from 26.34 to 112.91 mg/liter. All four of these beers were tap beers produced by bottom fermentation (lagers) and brewed by a secondary fermentation process. ... Therefore, to err on the side of caution, it is recommended that patients on irreversible MAOIs avoid beers on tap’.

This was probably an influential paper, but subsequent results do not quite support all the conclusions.

For instance, some Belgian beers do have high tyramine. Loret et al (120), considered a large number of these Belgian beers: the types covered four different brewing processes; low or bottom fermentation (LF, 18 samples), top fermentation (TF, 36 samples), top fermentation followed by a secondary fermentation into bottle (TF+ BSF, 184 samples), and spontaneous fermentation (SF, 42 samples).

They found 21 samples out of 220 that exceeded 10 mg/L of either histamine or tyramine, these 21 had a **mean tyramine of 28 mg/L**, and the maximum was nearly **70 mg/L**. They developed a “Beer biogenic amine index” (BAI) that would allow assessment of the quality of the production process. Since the work was financed in part by the Belgian Brewer Confederation we may assume they are trying to improve things because of EC regulations and a recommended limit of 10 mg/L.

Older results (1996) from a large number of samples did show some high levels, even though averages are low (mostly below 5 mg/L), out of **180 samples** several reached high levels. **Lambic Gueuze was almost 70 mg/L** and there were a few 30s and 50s (121).

Belgian Lambic beer is an old style (see Wikipedia for information) allowed to spontaneously ferment with wild airborne yeasts and then aged for 1 – 3 years, breweries locate their open fermenters in well-ventilated attic roofs. The general category is spontaneously fermented beers (SF beers) which are obviously likely to have more tyramine. One recent assay of SF Belgian beer had only 20 mg/Litre of tyramine, which may reflect improved standards (120). Gueuze is an aged unflavoured Lambic style. A good example of why dirty farmhouse styles of anything are more likely to have contaminant strains that have decarboxylase activity, and thus potential for tyramine production, especially if a rat/sparrow/cockroach falls in the open fermenter.

MAOIs: Interactions with Other Drugs

The MAOI tranylcypromine (Parnate) does not interact with other drugs any more frequently than SSRIs. Tranylcypromine has no significant **pharmacokinetic** interactions at all, but phenelzine has many. The potentially dangerous interactions are **pharmacodynamic** ones

1. Serotonin syndrome, caused by SRIs + MAOIs

2. Blood pressure elevation, caused by tyramine in food, or by the other 'indirectly acting sympathomimetic amines' (releasers) pseudoephedrine and phenylephrine (in some cold remedies).

These are clearly understood interactions that are straightforward to avoid. I have published several review papers that provide the background knowledge to understand all these interactions which will be helpful for those unsure of the latest data (bearing in mind that standard and reputable texts are still somewhat behind in much of this information). See especially the reviews- (1-4, 6-9, 122-125).

Cough and cold remedies available over-the-counter (OTC) must be checked, they may contain the releasers pseudoephedrine and phenylephrine which are dangerous (much more so than L-DOPA). Directly acting adrenergic agents are not dangerous e.g. adrenaline. The anti-histamines brompheniramine and chlorpheniramine are best avoided because they have, possibly significant, SRI potency. All other anti-histamines are safe (126).

Analgesics (pain killers) that are **safe** to take with MAOIs-- Aspirin and Paracetamol and all the 'NSAIDs' (anti-inflammatory drugs used for arthritis), such as: ibuprofen, mefenamic acid, naproxen, indomethacin, phenylbutazone etc. and the newer 'COX2' drugs.

All anti-anxiety drugs (benzodiazepines) like diazepam, oxazepam and temazepam are safe.

Stronger analgesics (narcotics / opioids, like morphine)

- Safe: codeine, oxycodone, buprenorphine and morphine.

Risky analgesics

The risk with opioid (narcotic) analgesics is that of serotonin toxicity (ST) or 'serotonin syndrome', which is quite different to the hypertensive reaction with tyramine (127). Do please note that many supposedly authoritative current texts (e.g. Physicians Desk Reference, British National Formulary, Australian Medicines Handbook) still contain serious inaccuracies: these are explained in detail in my review (9), which is the only recent comprehensive review on this topic. The analgesics that are dangerous are dangerous because they are serotonin reuptake inhibitors. Pethidine (aka meperidine) and tramadol, especially, must not be given to anyone on MAOIs. Dextromethorphan, (dextro)propoxyphene and pentazocine are also best avoided.

Antidepressant drugs

Any antidepressant drug that works as a serotonin reuptake inhibitor (SRI) is potentially dangerous (possibly even fatal) if combined with

any MAOI, even the newer 'RIMAs' like moclobemide (3, 122). If people have been taking any serotonin reuptake inhibitor type drug including:-- **sertraline, fluoxetine, paroxetine, fluvoxamine, citalopram, escitalopram, clomipramine or imipramine, or SNRIs like milnacipran, venlafaxine, desvenlafaxine, duloxetine or sibutramine** recently then specialist advice may be needed before starting any MAOI or a RIMA like moclobemide.

NB It is usually stated that all TCAs pose a risk, but that is not correct, it is **only clomipramine and imipramine** that are sufficiently potent as serotonin reuptake inhibitors to precipitate ST; all other TCAs like nortriptyline, amitriptyline, dothiepin, desipramine, doxepin are quite safe (as are selective NRIs like reboxetine and atomoxetine).

On ceasing other antidepressants to start MAOIs, washout intervals varying between one and five weeks may be required. No washout is required for TCAs (other than clomipramine and imipramine), or mirtazapine, mianserin, trazodone or reboxetine, because they are safe taken together with MAOIs.

Fluoxetine

If the SSRI fluoxetine has been taken (Prozac and other names) within the previous two months caution is required and specialist advice may be needed before starting various drugs, but particularly any MAOIs including moclobemide. This is because fluoxetine has a very long elimination half-life in some people (it takes a long time to get out of the system).

Ceasing treatment

This advice should be followed for a minimum of two weeks (six weeks in some situations) after ceasing MAOIs (between one and three days in the case of moclobemide).

Medical Treatment of High BP Resulting from Tyramine Ingestion

If excessive tyramine is ingested in cheese etc. blood pressure will rise within about half an hour. Current evidence suggests that elevated BP without other symptoms (of 'end organ' damage) does not require treatment, and should not be treated. This is because rapid BP reduction may do more harm than the short term BP elevation (usually less than 2 hours) caused by tyramine. Rapid control (i.e. within 1-2 hours) of hypertension that does not also exhibit definite end organ damage may result in adverse effects (128-130). Usually, treatment should only be initiated when there is

definite evidence of *acute and rapidly evolving end organ damage*. Several recent reviews make strong statements about premature treatment in the absence of end organ damage: e.g. Flanigan “*Often the urgency is more in the mind of the treating physician than in the body of the patient ... The compulsive need to treat reaches the pathological in some physicians, especially during the early years in their careers*”. **Treatment should not be initiated by psychiatrists:** on the rare occasions where it is required it is best initiated after admission to a critical care setting (2).

It is noteworthy that pain and anxiety both exacerbate hypertension, so remaining calm and using a benzodiazepine (which usually lowers BP to a significant extent (131)), whilst instituting measures to assess any possible developing end organ damage, is probably the most important step. The most appropriate hypotensive agent will depend on the particular end organ affected (brain, heart, lungs, kidneys).

Note: sub-lingual nifedipine is now considered contra-indicated because it has an unpredictable effect: it should rarely, or never, be given to patients to self-administer. This exemplifies why psychiatrists should refer such cases and not attempt management themselves.

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