Psycho- and Vasoactive Compounds in Food Substances[1]

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A number of biogenic amines that participate in mammalian physiology are also found to occur in food substances. The origin and potential toxicity of these compounds are reviewed. The presence of psychoactive substances in food and plant products is also examined.

The presence of substances in foods and plant products that are physiologically active in man is well known and is the basis for much of therapeutic medicine. While many of these active substances serve normal roles in mammalian physiology, they can also cause unnatural or toxic effects when consumed in quantity. In the current report this subject will be presented in two parts. First, the presence of physiologically active or toxic amines in substances that are commonly used as foods for their nutritive value will be examined. Second, the food or plant materials that are used primarily for their physiologic effect will be discussed.

AMINES IN FOODS

The presence of a number of neurohumoral agents and their analogs in food substances is now well established. Although animal tissues contain these amines, the concentration in unprocessed animal products is too small to be of significance. Some of the amines are natural plant products and are present in foods derived from certain plants in relatively high concentrations. They are also present in foods which either intentionally or unintentionally are subject to bacterial fermentative processes. Many microorganisms contain amino acid decarboxylases and therefore can produce a variety of amines from natural amino acids. The structures of a number of physiologically active phenylethylamines and indolealkylamines are shown in Figures 1 and 2.

These compounds are in general vasoactive and can cause modification of blood pressure when infused into the peripheral circulation of animals or man. Some of these amines also serve as neurotransmitters. In general, these compounds are rapidly inactivated *in vivo via* oxidative deamination by monoamine oxidase and seldom cause physiologic effects when consumed orally. With the introduction into our society of a variety of pharmaceutical agents to regulate physiologic and psychologic activity, the possibility of potentiating the effect of amines became a significant hazard.

A unique series of letters appeared in *The Lancet* in the early 1960's (reviewed by Blackwell *et al.*, 1967). These letters led to the conclusion that several deaths of individuals receiving drugs that inhibit the enzyme, monoamine oxidase, were the result of hypertensive crises and were temporally related to the consumption of cheese. It was found that some cheeses contain high concentrations of tyramine. This amine causes intense pressor responses in man because it releases norepinephrine. Inhibition of its normally rapid oxidation *in vivo* obviously potentiates its effect. Our laboratory (Horwitz *et al.*, 1964) then showed that synthetic tyramine and tyramine occurring naturally in cheese were equipotent in producing pressor responses in man.

The presence of tyramine in foods is usually the result of bacterial fermentative processes, although in several instances tyramine appears to be an endogenous plant material. Some common foods that contain tyramine are listed in Table I. There is wide variation in tyramine content of foods when the amines are of bacterial origin.

Although the absolute content varies widely, cheeses generally contain significant amounts of tyramine and therefore pose a threat when consumed in combination with a drug that inhibits monoamine oxidase. Several instances have also been reported where meats, particularly aged fish or stored liver, had high amounts of tyramine.

Table II lists some fruits that are commonly eaten that contain significant amounts of serotonin. There is no indication that consumption of normal amounts of these foods is harmful. It should be noted, however, that the diagnostic procedure for the carcinoid syndrome involves examination of the urine for metabolites of serotonin. Therefore, foods containing serotonin should be withheld from patients prior to such testing. It has also been suggested that the prevalence of right-sided heart lesions in certain parts of Africa may be related to the fact that bananas and plantains, rich in serotonin, constitute a major portion of the diet of these people (Foy and Parratt, 1962). Similar lesions have been observed in patients with the carcinoid syndrome (Sjoerdsma, 1963). The tumors in these individuals produce large amounts of serotonin. However, a correlation between serotonin and this lesion has not been unequivocally demonstrated.

A number of other vasoactive amines have also been detected in foods. Citrus fruits contain tyramine and a series of compounds related to tyramine (*N*-methyl- and *N,N*-dimethyltyramine, octopamine, and synephrine) (Wheaton and Stewart, 1969). The level of these amines appears not to be toxic, although fruit juices can contain up to 25 μg/ml of tyramine and 280 μg/ml of synephrine (Wheaton and Stewart, 1965), which could be potentially dangerous to a person receiving a monoamine oxidase inhibitor. Norepinephrine and dopamine are also present in bananas (Udenfriend *et al.*, 1959), although the amine resides largely in the peel (dopamine, 700 μg/g; norepinephrine, 122 μg/g). Significant levels of histamine (up to 3 mg/g) have been reported in several foods (Blackwell *et al.*, 1965). Asatoor *et al.* (1963) detected phenylethylamine, tryptamine, isoamylamine, putrescine, and cadaverine in cheese. It is likely that any food subject to bacterial action may contain any of these amines in varying amounts. Under normal conditions, however, none of these products represent a health hazard and in fact the short-chain alkyl amines may contribute to the odor and flavor of food.

AMINES AND RELATED COMPOUNDS THAT AFFECT THE CENTRAL NERVOUS SYSTEM

Foods and plant products contain many substances that affect the central nervous system and can be considered to be psychoactive. These plant products are usually only consumed for their physiologic effect.

Perhaps the three most widely used compounds are caffeine, ethanol, and nicotine. Caffeine and other methylxanthines (Figure 3) are considered stimulants and are consumed in substantial quantities in coffee, tea, and many soft drinks. It has been estimated that a cup of coffee contains 100 to 150 mg of caffeine, and that about

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[1] The material in this presentation is taken largely from a recent literature review (Lovenberg, 1973).

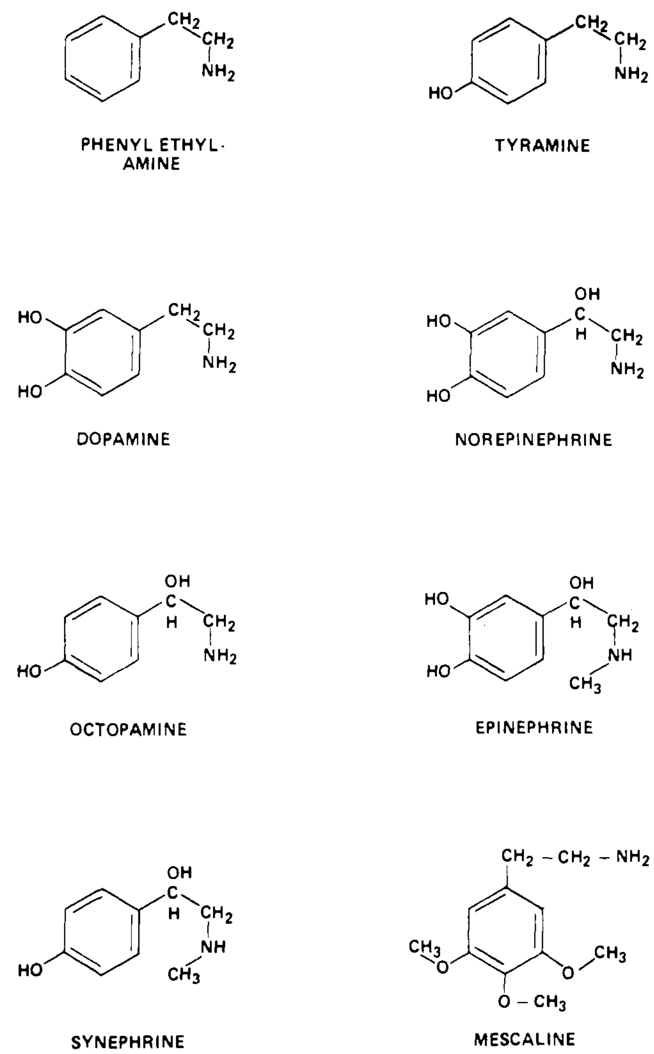


Figure 1. Phenylethylamines in foods.

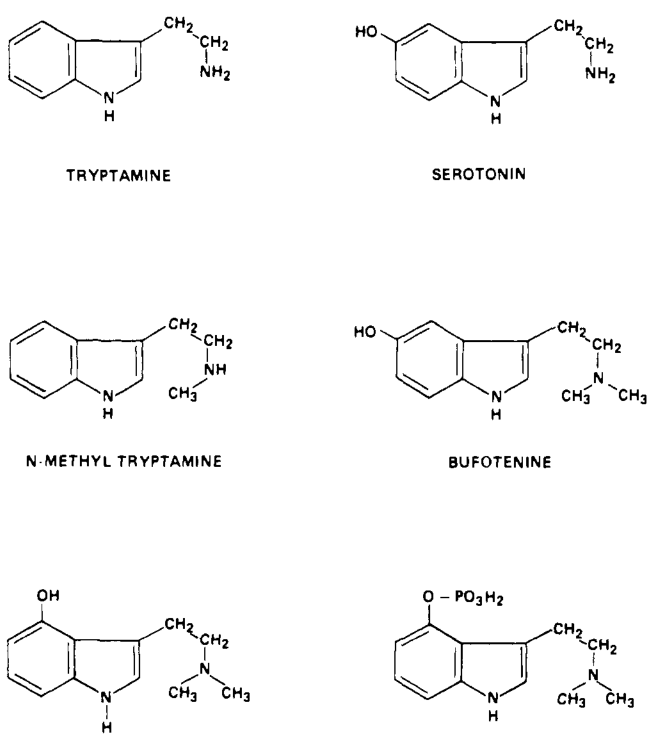


Figure 2. Indolealkylamines.

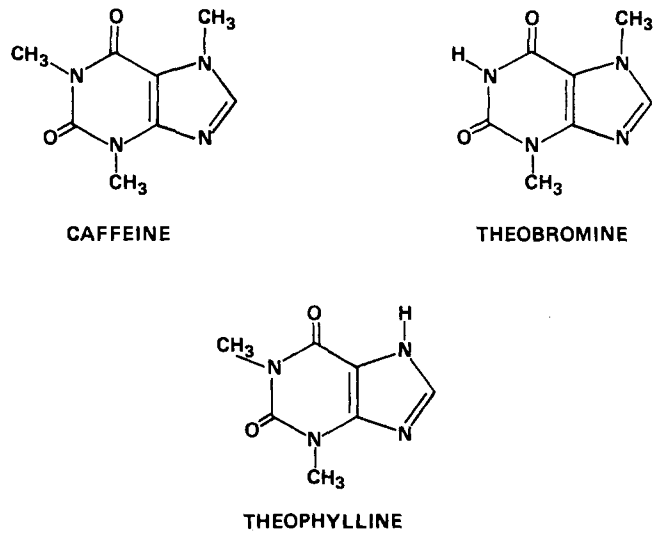


Figure 3. Methylxanthines.

Table I. Tyramine in Foods

	μg/g or ml
Natural plant products	
Banana peel[a]	65
Banana pulp[a]	7
Red plum[a]	6
Avocado[a]	23
Orange[b]	10
Aged or fermented foods	
Cheeses[c,d]	0–2200
Beer and ale[c,d]	2–10
Wine[c,d]	0–25
Marmite or yeast[c,d]	0–2250

[a] Udenfriend *et al.* (1959). [b] Wheaton and Stewart (1969). [c] Sen (1969). [d] Horwitz *et al.* (1964).

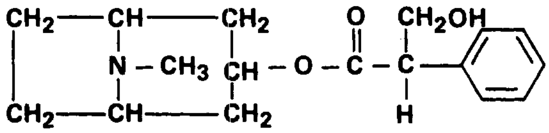
Table II. The Quantity of Serotonin in Some Plant Foods

	Serotonin, μg/g or ml
Banana peel[a]	50–100
Banana pulp[a]	28
Plantain pulp[a]	45
Tomato[a]	12
Red plum[a]	10
Avocado[a]	10
Pineapple juice[b]	25–35
Pineapple[b]	20
Passion fruit[c]	10–40
Pawpaw[c]	10–20

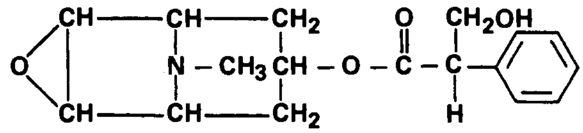
[a] Udenfriend *et al.* (1959). [b] Foy and Parratt (1961). [c] Foy and Parratt (1960).

7,000,000 kg of caffeine are consumed annually in the United States (Goth, 1968). Nicotine, present in tobacco, is also a stimulant in small quantities but extremely toxic in large doses. Ethanol, on the other hand, is a central nervous system depressant. Large quantities of alcoholic beverages are consumed in this country and alcoholism is one of our major social problems.

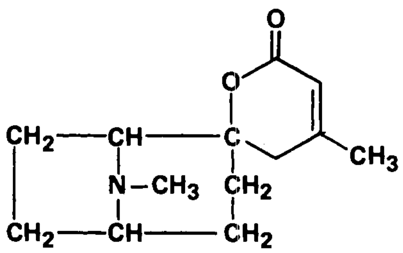
Tropane alkaloids (Figure 4) are a group of compounds that are used medicinally, but constitute a hazard with regard to accidental poisoning. Scopolamine is used clinically in small doses, but in larger doses can cause central nervous system stimulation and hallucinations. This compound is present in jimsonweed and has caused toxicity in individuals who either intentionally consumed the plant



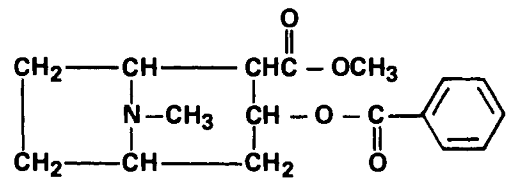
ATROPINE



SCOPOLAMINE



DIOSCORINE



COCAINE

Figure 4. Tropane alkaloids.

for its psychogenic effects or accidentally ate the plant (Hoffer and Osmond, 1967; Jacobziner and Raybin, 1961).

Atropine is a potent inhibitor of cholinergic systems and is found in the leaves and berries of purple nightshade, jimsonweed, and henbane. Although this tropane alkaloid is also used clinically in small doses, toxicity occurs following the ingestion of the above plants and as few as three berries from purple nightshade can cause death in children. A similar alkaloid, dioscorine, is present in yams (Pinder, 1951). Although this compound causes severe depression of the central nervous system, it probably would not constitute a hazard unless yams were a major component of the diet.

Cocaine, an alkaloid present in the leaves of the coca plant, has been used as a local anesthetic and is a powerful stimulant of the central nervous system. This compound is dangerous and addictive, although used widely for its psychogenic effect. Its use for nonmedicinal purposes is illegal and it has become one of our major drug problems.

A number of plant substances are used almost exclusively to alter one's psychological state. These psychoactive substances produce a gradation of responses ranging from mild euphoria to hallucinations and psychotic behavior. The rather widespread use of such compounds without medical supervision constitutes the "national drug problem" and is the subject of intense interest. While numerous books have been devoted to this subject, *e.g.*, Hoffer and Osmond (1967), only a superficial survey of the major natural psychoactive substances will be attempted here.

The most widely used of the plant substances in this country is the common hemp or marihuana. The leaves and dried flowering tops contain a group of tetrahydrocannabinols which appear to be responsible for the euphoric effect obtained upon smoking or ingestion. These compounds do not appear to be physically addictive, although the toxicology of repeated usage has not been adequately established. Catnip, known to cause euphoric responses in cats, has recently been observed to cause an effect in man similar to that of marihuana (Jackson and Reed, 1969). The active ingredient of catnip may be nepetalactone, which is the principal volatile compound in catnip oil (McElvain and Eisenbraun, 1955). The common spice nutmeg is psychoactive when consumed in excess and has been used by numerous prisoners for its psychic effects (Weiss, 1960). It has also been rumored to be an abortifacient. A review of reported cases indicates that it is uneffective in this regard (Green, 1959). The active agent in nutmeg appears to be the organic compound myristicin.

A much more serious problem resides in the opiates such as morphine, codeine, and heroin, which are derived largely from the poppy plant. Extracts of these plants or purified compounds can be eaten, smoked, or injected for their euphoric effects. These alkaloids are very dangerous because they are both physically and psychologically addictive.

Finally, it should be noted that numerous compounds containing an indole nucleus have very pronounced effects on the psyche. These observations led to the speculation that serotonergic neurons and systems are important components of the psychic activity of the central nervous system. Many indole-containing plant substances have been used for centuries by primitive cultures to achieve "religious" experiences. A well-known example is the magic mushroom of Mexico. This strain of mushroom, *Psilocybe mexicana*, contains psilocin and psilocybin (Figure 2), which are hallucinogenic agents. Other *N,N*-dimethylindoles such as *N,N*-dimethyltryptamine and bufotenine are the hallucinogens in various South American snuffs (Fish and Horning, 1956; Hofmann, 1962; Stromberg, 1954).

A number of more complex alkaloids containing an indole nucleus are psychoactive compounds. Some classic scientific observations by Albert Hofmann three decades ago focused considerable interest on man's potential ability to alter his mental state. Hofmann, who was working on the chemistry of alkaloids from the Ergot fungus, achieved the chemical synthesis of lysergic acid. After preparing the diethylamide derivative (LSD), he felt a strange dreamlike intoxication. He later intentionally consumed 250 μg of pure LSD and recorded the intense physiologic and psychotropic effects of the drug. LSD is one of the most potent psychotogenic substances known, with as little as 20 μg causing hallucinations in man. The seeds of the common morning glory contain lysergic acid amide and have been eaten by youthful drug experimenters in this country (Ingram, 1964). The Aztec Indians, however, have recognized the hallucinogenic properties of the morning glory seeds for centuries and have used them in their religious ceremonies. The lysergic acid derivatives are now considered dangerous, possibly causing permanent brain damage, and their use is illegal.

CONCLUSIONS

In the past several decades great strides have been made in man's understanding of his physiological mechanisms. During this time an increasing awareness of the potential of chemical substances to alter physiologic and psychologic states has emerged. While this awareness has provided the basis for development of pharmaceutical agents to treat disease, it has also led to experimentation with potentially dangerous drugs by the general population. It is clear that many compounds which are greatly beneficial to man when prescribed under controlled conditions are very dangerous when consumed in unknown quantities in plant or food substances. In addition to direct toxicity, we have the problem that food substances not toxic to untreated humans may become toxic when eaten by individuals receiving certain pharmaceutical agents. A classic example of this situation is the toxicity of cheese containing substantial amounts of tyramine as discussed above. An increasingly important aspect of drug evaluation, therefore, is knowing if the compound interacts with other drugs or with constituents of common foods.

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Toxic Proteins Produced by *Clostridium botulinum*

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The chemical, physical, and biological properties of *Clostridium botulinum* toxins are reviewed. Highly purified toxins in acidic solutions behave as simple proteins with molecular weights 200,000 to 900,000. These proteins are the most toxic substances known and cause botulism in man and animals. As found in culture, the molecule is a complex of at least two simple proteins: one the neurotoxin, molecular weight about 150,000, and the other nontoxic of high molecular weight. The complex is produced in foods under anaerobic conditions. It is quite stable under acidic conditions at room temperature. Alkaline conditions cause dissociation of the proteins. The separated neurotoxin is much less stable, particularly to the digestive enzymes. All of these toxins are readily destroyed by heating to 100°. They are good antigens and can be toxoided for safe immunization of man and animals.

The spore-forming bacterium, *Clostridium botulinum,* found in many soils throughout the world, produces a series of toxins that have caused food poisoning in man and animals from time immemorial. The poisoning, now called botulism, was not recognized as being caused by a food-borne microbial toxin until the discoveries of Professor Van Ermengem of the University of Ghent about the end of the 19th Century (Dolman, 1964). Eight immunologically distinct toxins are now recognized and are designated types A, B, C_1, C_2, D, E, F, and G. As far as we know, all of these toxins are simple proteins and the most toxic substances known to man. The organism normally produces the toxins in foods that are canned or preserved under anaerobic conditions. Generally, a strain of *C. botulinum* produces one toxin and is classified according to the toxin it produces. The types of toxins and the organisms producing them are illustrated in Table I.

Toxin types A, B, E, and to some extent F, have caused most of the cases of botulism in man, and types C_1, C_2, D, and E have caused most of the cases of botulism in the domestic and wild animal populations of the world. Botulism from types A and B in the United States has usually resulted from contaminated canned vegetables and fruits. In Europe contaminated meat and fish products are relatively more common causes of botulism, and in Japan and some parts of Russia practically all cases are from contaminated fish products. Type E botulism occurs mainly from contaminated foods of marine origin, but fresh water fish have been involved also. This particular type of organism is found along many marine coasts of the world and in the Great Lakes of the United States. About 90% of all cases of botulism in man have resulted from the toxin formed in improperly sterilized home-processed

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