Reference:
Smit, H.J. & Rogers, P.J. (2001). Potentially psychoactive constituents of cocoa-containing products. In M. M. Hetherington (Ed.), Food cravings and addiction (pp. 325-349). Leatherhead: Leatherhead Food RA Publishing.

POTENTIALLY PSYCHOACTIVE CONSTITUENTS OF COCOA-CONTAINING PRODUCTS

Hendrik J. Smit and Peter J. Rogers

Department of Experimental Psychology, University of Bristol,
8 Woodland Road, Bristol, BS8 1TN, UK

Food craving: attitudes and physiology

In a recent review we argued for a primarily attitudinal rather than physiological explanation of (self-reported) food craving and food "addiction" (1). We proposed that attitudes towards frequently craved foods such as chocolate can be highly ambivalent. Chocolate is "nice but naughty": it is highly liked, but nutritionally suspect.[1] In other words, chocolate is perceived as an indulgence, a treat not a staple food, and therefore a food that should be eaten with restraint. Paradoxically, though, attempts to resist the desire to eat chocolate can increase the salience of and thoughts about chocolate (cf 2), intensifying this desire sufficiently for it to be labelled a craving. This, perhaps together with the need to provide a reason for why resisting eating chocolate is difficult and sometimes fails, can in turn lead the individual to an explanation in terms of addiction (e.g., "chocoholism"). According to this view, chocolate is the most frequently craved food because it is the food that people most often try to resist eating. In contrast to craving, moreishness ("causing a desire for more") occurs during rather than preceding an eating episode. Nevertheless, restraint is again an essential feature, because moreishness is experienced when the eater attempts to limit consumption before appetite for the food has been satiated (1, 3).

One of the competing explanations for chocolate craving and "addiction" is that cocoa-containing products contain psychoactive or mood-altering compounds (1, 4). This idea was recently given renewed impetus by a widely reported article published in Nature (5) claiming to find "brain cannabinoids in chocolate". The purpose of the present chapter is to examine in detail these speculations about potentially psychoactive constituents of chocolate in the light of what is known about the concentrations of these substances in the products that are most widely eaten, and their likely effects on the brain when administered orally.

[1] "Naughty but nice" was a slogan devised by the author Salman Rushdie as part of a 1970s UK advertising campaign for cream cakes.

Caffeine

Caffeine (1,3,7-trimethylxanthine) occurs naturally in a variety of agriculturally significant plants, including the coffee bean, cola nut, tea, and the cocoa bean (6). Table 1 provides an overview of the occurrence of caffeine in some beverages, foods, food ingredients and medicines.

The physiological effects of caffeine have been extensively researched. Caffeine acts primarily to block competitively adenosine receptors; causing, for example, increases in blood pressure, renin and catecholamine release, and increased urine output, lipolysis, respiration, and intestinal peristalsis (7, 8). After oral administration, absorption of caffeine is rapid and complete. In the presence of sugar, uptake is slower but still complete (9), and typically the maximum blood plasma concentration (peak plasma time) is reached within an hour (7). Mumford et al. (10) found a peak plasma time of 30 minutes after oral administration of 72 mg caffeine, and participants in this study reported onset of subjective effects between 10-45 minutes (mean 21 minutes) after dosing.

Consumption of excessive amounts (> 1 g /d) of caffeine can result in caffeinism, the symptoms of which are: tachycardia, dyspepsia (disturbed digestion, decreased appetite, oppressive feeling in the stomach and unpleasant taste), irritability and insomnia (8). Other authors have described the symptoms following intake of high doses of caffeine as "a variety of unpleasant subjective states including anxiety, dysphoria and depression" (11), "signs and symptoms indistinguishable from those of anxiety neurosis", and nervousness, irritability, tremulousness, occasional muscle twitching, insomnia and sensory disturbances (6).

Caffeine is widely known as a psychostimulant, and many studies have found that caffeine in amounts consumed in coffee and tea can increase feelings of energy (more alert, less tired, etc.) and improve some other aspects of mood, and can enhance psychomotor and cognitive performance (reviewed in 7, 12). Unfortunately, it is not clear from this research whether there is a real benefit of caffeine consumption, or whether such effects are mainly due to the reversal of negative effects of caffeine withdrawal, which occur even after overnight caffeine abstinence (13). Fatigue and headache, for example, are well-recognised consequences of caffeine withdrawal. Related to this, though, is evidence that 70-100 mg caffeine can (negatively) reinforce flavour preferences (14, 15), which helps to explain the very widespread popularity of caffeine-containing drinks. Although we are not aware of any studies showing reinforcing effects of doses of caffeine in the range of 8-30 mg (i.e., 0.1-0.4 mg/kg), these amounts of caffeine do have significant, albeit mild, psychostimulant effects (1). Therefore, caffeine reinforcement could conceivably contribute to the development of preferences for chocolate.

It remains the case, nonetheless, that coffee, tea and cola are much more important dietary sources of caffeine than is chocolate. The amount of caffeine present in a cup of instant coffee is similar to that contained in seven 50 g bars of milk chocolate or two 50 g bars of dark chocolate (calculated from Table 1). In other words, chocolate is far from being a unique or substantial source of caffeine.

Theobromine

In contrast to caffeine, its metabolite theobromine (3,7-dimethylxanthine) is found in unusually high amounts in chocolate and cocoa products (Table 2).

Compared with caffeine or theophylline, the action of theobromine on the central nervous system is considered weak or even virtually absent (16). Tarka (6) describes theobromine as having, on the other hand, the strongest effect of all three of these methylxanthines on the coronary vessels (with caffeine having the weakest effect). Theobromine is generally considered a diuretic, a heart muscle stimulant, a vasodilator and a smooth muscle relaxant (17). The Merck Index (18) places theobromine in the therapeutic categories "diuretic", "bronchodilator", and "cardiotonic". Although it has been used to treat arteriosclerosis and some peripheral vascular diseases (8), there is no current therapeutic use of theobromine (6).

In a study comparing the subjective effects of theobromine and caffeine, Mumford et al. (19) found that four of their seven volunteers could discriminate theobromine from placebo at a dose of 560 mg. For one participant the discriminable dose was as low as 100 mg. The basis for the discrimination involved changes in mood and behaviour, including feeling more energetic, and having increased motivation to work. Caffeine had similar effects, but stronger and at lower doses. There was no significant group effect of theobromine for any of the mood measures included in the study. The onset of the subjective effects of theobromine was reported to be 35 (15-60) minutes after oral ingestion, and subjective ratings of "magnitude of drug effect" peaked between 1 and 2 hours after administration (19), whereas its peak plasma time was on average 2.6 hours (10). Therefore, although chocolate can contain relatively high concentrations of theobromine, this methylxanthine is a weak central nervous system stimulant and has only minor subjective effects.

Biogenic amines

Biogenic amines are formed by decarboxylation of amino acids. Cocoa and cocoa products contain fairly high concentrations of biogenic amines (e.g., phenylethylamine, tyramine, tryptamine and serotonin), and their precursors (phenylalanine, tyrosine and tryptophan). Biogenic amine concentrations in cocoa increase during fermentation of the cocoa beans, and decrease with roasting and alkalisation (20).

For healthy people, the amount of biogenic amines in foods is irrelevant, since the amines are inactivated by the monoamine oxidase (MAO) in the mucosa of the small intestine, and in the liver and kidneys (21). Because of the endogenous abundance of MAO, "even the intraduodenal injection of amines in the absence of enzyme inhibition would be unlikely to lead to their absorption and appearance in systemic blood unless the amount was sufficiently large to swamp the deaminating mechanisms" (22). The amount of amines in foods only becomes meaningful in people treated with drugs containing MAO inhibitors (21) and in people with an MAO deficiency, as has been suggested for migraine sufferers (22). If the amine oxidation is inhibited, symptoms such as headaches, increased blood pressure or even a life threatening "amino shock" can occur (21). If anything, these adverse effects would presumably lead to the avoidance of chocolate.

Phenylethylamine

Phenylethylamine (PEA) is the basic molecule of the phenylethylamine family, which includes the stimulant and hallucinogenic substances amphetamine, mescaline, dopamine, adrenaline and noradrenaline (23). The Merck Index describes endogenous PEA as "related structurally and pharmacologically to amphetamine" (18). Although the name "phenylethylamine" has also been used to refer to its entire family (e.g., 24), it is the basic structure (2- or ß-phenylethylamine) that is referred to here. Some cheeses, red wines, but especially chocolate "contain large amounts of phenylethylamine" according to the British Food Manufacturing Industries Research Association (cited in 25). According to this organisation, chocolate contains at least 3 mg PEA per 2 ounce (56.7 g) bar. More recent research has not revealed such high figures, and even suggests PEA is present in chocolate in very small amounts (Table 3).

Endogenously, PEA has been found in the nervous tissue of most, if not all, animal species researched. In the mammalian brain, it has been detected in minute quantities (single nanograms per gram of nervous tissue). PEA is synthesised by decarboxylation of phenylalanine by the enzyme aromatic L-amino acid decarboxylase, almost certainly in dopaminergic neurones, and is rapidly metabolised by monoamine oxidase type B (MAO-B). It appears to co-exist in the brain with dopamine, and is proposed to be a modulator of catecholamine neurotransmission (26).

Although in the past, researchers have linked a depletion of endogenous PEA with depression, and an excess with mania, the evidence is mixed and inconclusive (27). Liebowitz and Klein (28) identified an affective disorder involving atypical depression and attention-seeking behaviour, which they named "hysteroid dysphoria" and linked to an abnormal regulation of PEA. Without referring to any published evidence, the authors mention that the production of PEA is "stimulated by positive life events", and that "depressed, hysteroid dysphorics often binge on chocolate, which is loaded with phenylethylamine".

In popular writing PEA has been associated with romance, love, and sex. For example, PEA has been claimed to be an essential element in the euphoric feelings we experience when we are in love. "When scientists injected some mice with PEA, they jumped about and squealed with a kind of mouse exuberance and exhilaration animal behaviourists call "popcorn behaviour". When rhesus monkeys are injected with PEA they smack their lips and make pleasure calls, much as they do when they are courting another monkey. Baboons injected with PEA will press a lever in their cage more than 160 times in three hours when pressing that lever will give them PEA-laced food that maintains their high PEA level of euphoria" (29, after 30; see also 31). Shulgin and Shulgin (32), however, could not replicate any of these effects in tests on human beings. Assisted by close friends and colleagues, these authors acted as guinea pigs in their own experiments, in which they assessed the effects of numerous synthesised amphetamines, administered (usually orally) in various doses. PEA was the only substance they found not to show any subjective effects. It was administered in oral doses of 200 to 1600 mg, and intravenously in doses of 25 and 50 mg. These latter findings contradict what we suggest is the "PEA myth" of chocolate. That is, the idea that people eat chocolate to feel more "sexy" or "sensual" because eating chocolate raises endogenous PEA, is simply a myth which is attractive to the popular media, but which has not been seriously proposed or supported in the recent peer-reviewed scientific literature.

Tyramine

Tyramine can be detected in many foods, but is found in chocolate in relatively small amounts (Table 4).

Intravenously injected tyramine releases noradrenaline from the sympathetic nervous system and can lead to various physiological reactions, including increased blood pressure, dilation of the pupils, lacrimation, salivation and increased respiration (33). However, we found no published evidence suggesting positive effects of tyramine on mood or behaviour.

On the other hand, tyramine has been implicated in triggering migraine headaches in migraine sufferers, and it also appears to be responsible for the so-called "cheese reaction". In the late fifties and sixties, monoamine-oxidase inhibitors prescribed for depression and hypertension were found to make patients receiving these drugs very sensitive to the toxic action of tyramine, known to be present in cheese. Symptoms are hypertensive crisis and severe headache, sometimes leading to intracranial bleeding and even cardiac failure (33). The amounts of tyramine in cheese are much greater than the amounts present in chocolate (Table 4).

Serotonin

Serotonin (5-HT; 5-hydroxytryptamine) is formed by decarboxylation of 5–hydroxytryptophan. It has been identified in a variety of foods, some of which are shown in Table 5. There have been claims that bananas, pineapples and tomatoes contain especially high concentrations of serotonin (e.g., 23); however, this could not be confirmed from the literature we obtained, which indicated that walnuts have relatively the highest concentration of serotonin identified in food. Compared with walnuts, chocolate contains only a small amount of serotonin.

Serotonin is a neurotransmitter in both the central and peripheral nervous systems, and plays an important role in the regulation of mood and behaviour (34,35,36,37,38). However, because orally ingested serotonin is deaminised by monoamine oxidase (see above), consumption of foods containing serotonin will not directly affect brain levels of serotonin.

Tryptophan

Tryptophan is an essential amino acid, meaning that foods are normally its only natural source (8). Although other foods, especially peanuts, cheese and certain meat products, contain far more tryptophan than chocolate, it is present in chocolate in significant amounts (Table 6).

Tryptophan is a precursor of the neurotransmitter serotonin (39), and oral administration of amounts of tryptophan in the order of 1.5 to 5 grams has been shown to induce feelings of drowsiness and fatigue, decrease sleep latency, and reduce appetite including rated hunger and actual food intake (reviewed in 40, 41, 42, 43). Daily intakes of tryptophan from dietary sources are typically in the range of 1 to 1.5 g (40).

Tryptophan in larger pharmacological doses can also be an effective antidepressant, both when given alone and in combination with other treatments. Mild or moderately depressed

people appear to benefit most from treatment with tryptophan, although it is less potent than standard antidepressant drugs (40). This would be consistent with the view that a deficit in serotonergic activity is important as a vulnerability factor, but is not the proximate cause of depression (37). Tryptophan has also been found to improve depressive symptoms in Seasonal Affective Disorder and Premenstrual Syndrome (43, 44). Another research strategy has been to measure the effects of administering amino acid mixtures devoid of tryptophan. The results have shown that a lowering of mood following tryptophan depletion is most likely to occur in individuals with high baseline depression scores or who have a family history of depression (45; and reviewed in 35, 36, 46). Taken together, these studies of tryptophan and tryptophan depletion add significantly to the evidence indicating a role for serotonin in the aetiology of depression.

The pharmacological manipulation of tryptophan intakes, however, is not evidence for an influence on mood of the tryptophan content of typical diets. Crucially, significant alterations in brain levels of serotonin, and consequently any serotonergically-mediated effects on mood and behaviour, would not be expected to occur when tryptophan is consumed along with the other amino acid constituents of protein-containing foods (35, 36, 38, 39). In other words, it is very unlikely that tryptophan is responsible for any mood changes that might follow the consumption of chocolate.

Magnesium

The main sources of dietary magnesium are whole grains, green vegetables, meat, nuts (47), soya beans and chocolate (48). Although according to Seelig (49) and Rozin et al. (50) cocoa has one of the highest magnesium levels of all foods listed, this argument cannot be sustained when the calculations are adjusted for serving size (see Table 7).

Magnesium is a co-factor in more than 300 enzymatic reactions, including those involving ATP formation (51) and the synthesis of fatty acids (52). It is an important factor in bone structure (48), and affects protein and carbohydrate metabolism, muscle functioning and the cardiovascular system (47). Some authors have suggested that the recommended daily amount (RDA) for magnesium of 4.5 mg/kg is too low, and should be 6-8 mg/kg (49).

Gibson (48) states that dietary factors are unimportant in the development of magnesium deficiency and that dietary magnesium depletions are rare. This, however, seems to contradict large-scale dietary surveys in the USA, which indicate that the average American diet is deficient in magnesium-rich foods (low in green vegetables, fish, whole grains and nuts, but providing relatively high amounts of magnesium inhibiting elements such as fat, sugar, salt, vitamin D, inorganic phosphate, proteins, and supplementary calcium and fibre) (49). Indeed, magnesium depletion is rarely seen in areas where green leafy vegetables form a significant portion of the diet (53).

Premenstrual tension has been strongly associated with magnesium deficiency, and magnesium therapy has been claimed to have a beneficial effect for premenstrual tension, especially when it is combined with vitamin B6 (54). Moreover, it has been reported that women aged 50 years and over who were on a hormone replacement, developed sudden cravings for chocolate when they entered their monthly 10-day period of progesterone administration. These cravings became less intense when they were given a daily amount of 100 mg magnesium (in 55, and A. Weil personal communication). Subclinical magnesium

deficiency can occur in pregnancy and lactation; whereas severe depletion is associated with clinical disorders, for example, gastrointestinal disorders, severe burns, alcoholism (48), starvation, digitalis toxicity, and excessive sweating (51), and can result in arterial and cardiac lesions, blood coagulation and thrombosis (49). Alcoholism is most often the cause of symptomatic hypomagnesium (47).

Chocolate has the potential to contribute significantly to the dietary intake of magnesium, and to even counteract magnesium deficiency. Other foods, however, contain similar or larger amounts of magnesium. Furthermore, despite speculations concerning changes in mood and food preference associated with the menstrual cycle (e.g., 34, 56), there appears to be no reliable evidence showing that magnesium-deficient people display an increased craving or liking for chocolate.

Anandamide

Separating a presumed lipid-soluble endogenous animal brain cannabinoid, Devane et al. (57) isolated and purified one substance, an N-acylethanol-amine, which they named anandamide. It bound to the cannabinoid receptor, and its sensitivity assessed by its ability to inhibit twitch responses in mouse vasa deferentia suggested a potency "relatively close to that of Δ^9-THC", the main psychoactive compound in cannabis (reviewed in 58). The latter authors also pointed out that anandamide is relatively unstable: it was found to hydrolyse rapidly. Di Tomaso et al. (5), however, found that this reaction is inhibited by at least two other N-acyl-ethanolamines, which were found to co-exist with anandamide in chocolate. Furthermore, they detected these substances in both cocoa powder and chocolate, but not in white chocolate or coffee. This suggests that in chocolate they are confined to the cocoa solids, and not to any added soy lecithin, milk powder or sugar (but see 59).

Although not substantiated with any research or literature, di Tomaso et al. (5) suggest that anandamides present in food might "heighten sensitivity and produce euphoria" and in doing so, intensify the oro-sensory effects of chocolate. However, Δ^9-THC, one of the most psychoactively potent natural cannabinoids, was found to produce a perceived "high" at doses of 18.77 micro-g/kg body weight (= 1.3 mg for a 70 kg person) in human volunteers (60). Using an anandamide concentration of 0.05 micro-g/g chocolate (5), and making the generous assumption of an anandamide uptake of 100%, a plasma concentration of 18.77 micro-g/kg body weight could be achieved in an adult after ingestion of some 25 kg of chocolate. Clearly, consumption in a single sitting of such an amount of chocolate is impossible. Furthermore, other results show that amounts of anandamide several orders of magnitude higher than those present in cocoa products are required to produce significant cannabimimetic behavioural effects in mice (59). These calculations and subsequent results therefore contradict di Tomaso's et al. (5) suggestion that their findings "point to an unexpected link between non-drug craving and the endogenous cannabinoid system" (page 678).

Further considerations and conclusions

Of course, this review of the psychoactive effects of various minor constituents of chocolate is not exhaustive; nor realistically could it ever be, since even very extensive chemical analysis might fail to identify a crucial compound. Also, we have not discussed the possibility that interactions between two or more constituents will produce effects not predicted from their individual actions (see e.g., 61). In any case, identifying a compound in a food is only a first step towards demonstrating that this can have psychoactive effects as consumed in everyday life, and that in turn these effects play a role in influencing consumption of the food. As described earlier, recent research on caffeine has demonstrated significant preference-reinforcing effects, at least at the levels of caffeine found in coffee and tea (14, 15), but this method has not yet been applied widely in the investigation of other psychopharmacologically active constituents of foods and drinks. Furthermore, it is perhaps significant that, while regular caffeine consumers do become mildly dependent on caffeine (withdrawal results in fatigue and headache), people tend not to describe cravings for caffeine-containing drinks. We suggest that this is because the urge to consume, for example, tea or coffee is rarely resisted (1). Indeed, even when caffeine intake is reduced due to changes in daily routines, such as occurs at weekends, it appears that the "need" for caffeine is often not recognised (12).

A different way to attack the problem is simply to test the mood and psychostimulant effects of, for example, cocoa powder in double-blind, placebo-controlled studies. Cocoa powder is assumed to contain most if not all of the potentially psychoactive compounds present in chocolate (4). Results from a series of such double-blind, placebo-controlled studies showed small but significant alerting effects of cocoa powder at a dose level equivalent to a typical serving of dark chocolate (62). A full report on these studies is currently in preparation. A similar but less direct approach was taken by Michener and Rozin (4). They provided chocolate "cravers" (individuals who reported having a craving for chocolate at least once per week) with sealed boxes containing either a bar of milk chocolate, a bar of white chocolate, capsules containing cocoa (and therefore many of the presumed psychoactive ingredients of chocolate), placebo capsules, white chocolate plus cocoa capsules, or nothing. These participants consumed, in random order, the contents of one of these boxes when they experienced a craving for chocolate, and just before, just after and 90 minutes after doing this they rated the intensity of that craving. The results showed that only consumption of chocolate itself, either white or milk chocolate, substantially reduced the craving, suggesting that there is "no role for pharmacological effects in the satisfaction of chocolate craving" (4, page 419).

Finally, another observation is that the most widely consumed chocolate is milk chocolate and chocolate-covered confectionery (63). This is also true for self-reported chocolate "addicts" (64). Compared with dark chocolate, these contain a lower amount of cocoa solids, and therefore a lower concentration of many of the potentially psychoactive compounds unique to chocolate.

Based on the evidence discussed above, we agree with other investigators (4, 6, 49, 64, 65, 66) that there is little support for the suggestion that experiences arising from eating chocolate, including its effects on mood, are related to the activity of psychoactive minor constituents. Instead, it is far more plausible to suggest that liking and appetite for chocolate are due mainly to the oro-sensory and post-ingestive effects of its principal constituents sugar

and fat (3, 4, 65), and that chocolate craving and "addiction" are ultimately manifestations of a culturally determined ambivalence towards chocolate (1, 3).

References

1. Rogers P.J., Smit H.J. Food craving and food "addiction": A critical review of the evidence from a biopsychosocial perspective. Pharmacology, Biochemistry and Behavior, 2000, 66, 3-14.
2. Wegner D.M. Ironic processes of mental control. Psychological Review, 1994, 101, 34-52.
3. Rogers PJ. Mechanisms of moreishness and food craving, in Pleasure: The Politics and the Reality. Ed. Warburton D.M. Chichester, Wiley. 1994, 38-49.
4. Michener W., Rozin P. Pharmacological versus sensory factors in the satiation of chocolate craving. Physiology and Behavior 1994, 56, 419-422.
5. di Tomaso E., Beltramo M., Piomelli D. Brain cannabinoids in chocolate. Nature, 1996, 382, 677-678.
6. Tarka S.M. The toxicology of cocoa and methylxanthines: a review of the literature. CRC Critical Reviews of Toxicology, 1982, 9, 275-312.
7. James J.E. Caffeine and Health. London, Academic Press. 1991.
8. Landau S.I. International Dictionary of Medicine and Biology. New York, Wiley. 1986.
9. Yesair D.W., Branfman A.R., Callahan M.M. Human disposition and some biochemical aspects of methylxanthines, in The Methylxanthine Beverages and Foods: Chemistry, Consumption and Health Effects. Ed. Spiller G.A. New York, Alan R. Liss. 1984, 215-233.
10. Mumford G.K., Benowitz N.L., Evans S.M., Kaminski B.J., Preston K.L., Sannerud C.A., Silverman K., Griffiths R.R. Absorption rate of methylxanthines following capsules, cola and chocolate. European Journal of Clinical Pharmacology, 1996, 51, 319-325.
11. Mumford G.K., Holtzman G. Qualitative differences in the discriminative stimulus effects of low and high doses of caffeine in the rat. Journal of Pharmacology and Experimental Therapeutics, 1991, 258, 857-865.
12. Rogers P.J., Dernoncourt C. Regular caffeine consumption: A balance of adverse and beneficial effects for mood and psychomotor performance. Pharmacology Biochemistry and Behavior, 1998, 59, 1039-1045.
13. Rogers P.J. Why we drink caffeine-containing beverages, and the equivocal benefits of regular caffeine intake for mood and cognitive performance, in Caffeinated Beverages: Health Benefits, Physiological Effects, and Chemistry. Eds. Parliament, T.H., Ho, C.-T., Schieberle, P. ACS Symposium Series No. 754. Washington DC, American Chemical Society. 2000, 37-45.
14. Rogers P.J., Richardson N. J., Elliman, N.A. Overnight caffeine abstinence and negative reinforcement of preference for caffeine-containing drinks. Psychopharmacology, 1995, 120, 457-462.
15. Yeomans M.R., Spetch H., Rogers P.J. Conditioned flavour preference negatively reinforced by caffeine in human volunteers. Psychopharmacology, 1998, 137, 401-409.
16. Czok G. Zur Frage der biologischen Wirksamkeit von Methylxanthinen in Kakaoprodukten. Zeitschr. Ern. wiss. 1974, 13, 165-171.
17. Stavric B. Methylxanthines: Toxicity to humans. 3: Theobromine, paraxanthine and the combined effects of methylxanthines. Food Chemistry and Toxicology, 1988, 26, 725-733.
18. Merck & Co. The Merck Index: An encyclopedia of Chemicals, Drugs, and Biologicals: 12th Edition. Whitehouse Station, NJ, Merck & Co. Inc. 1996.
19. Mumford G.K., Evans S.M., Kaminski B.J., Preston K., Sannerud C.A., Silverman K., Griffiths R.R. Discriminative stimulus and subjective effects of theobromine and caffeine in humans. Psychopharmacology, 1994, 115, 1-8.
20. Ziegleder G., Stojacic E., Stumpf B. Vorkommen von beta-Phenylethylamin und seinen Derivaten in Kakao und Kakaoerzeugnissen. Z. Lebensm. Unters. Forsch. 1992, 195, 235-238.
21. Askar A., Morad M.M. Lebensmittelvergiftung. I: Toxine in Natürlichen Lebensmitteln. Alimenta, 1980, 19, 59-66.
22. Marley E., Blackwell B. Interactions of monoamine oxidase inhibitors, amines, and foodstuffs. Advances in Pharmacology and Chemotherapy, 1970, 8, 185-239.
23. Passmore R., Robson J.S. A Companion to Medical Studies in Three Volumes. Volume 2: Pharmacology, Microbiology, General Pathology and Related Subjects, 2nd edition. Oxford, Blackwell. 1970.
24. Morgan J.P. Phenylpropanolamine: Risks, Benefits and Controversies (Clinical Pharmacology and Therapeutics Series, Volume 5). New York, Praeger. 1985.
25. Sandler M., Youdim M.B.H., Hanington E. A phenylethylamine oxidising defect in migraine. Nature, 1974, 250, 335-337.
26. Paterson I.A., Juorio A.V., Boulton A.A. 2-Phenylethylamine: a modulator of catecholamine transmission in the mammalian central nervous system? Journal of Neurochemistry, 1990, 55, 1827-1837.

27. Davis B.A., Boulton A.A. The trace amines and their acidic metabolites in depression - an overview. Progress in Neuropsychopharmacology and Biological Psychiatry, 1994, 18, 17-45.
28. Liebowitz M.R., Klein D.F. Hysteroid Dysphoria. Psychiatric Clinics of North America, 1979, 2, 555-575.
29. Kohl J.V., Francoeur R.T. The Scent of Eros. New York, Continuum. 1995.
30. Liebowitz M.R. The Chemistry of Love. Boston, Little Brown. 1983.
31. Crenshaw T.L. Why we love and lust: how our sex hormones influence our relationships. London, Harper Collins. 1996.
32. Shulgin A., Shulgin A. PIHKAL: A Chemical Love Story. Berkeley, CA, Transform Press. 1991.
33. Joosten H.N.L.J. The biogenic amine contents of Dutch cheese and their toxicological significance. Netherlands Milk and Dairy Journal, 1988, 42, 25-42.
34. Wurtman R.J., Wurtman J.J. Carbohydrates and depression. Scientific American, 1989, 260, 50-57.
35. Young S.N. Some effects of dietary components (amino acids, carbohydrate, folic acid) on brain serotonin synthesis, mood and behaviour. Canadian Journal of Physiology and Pharmacology, 1991, 69, 893-903.
36. Young S.N. The use of diet and dietary components in the study of factors controlling affect in humans: A review. Journal of Psychiatry and Neuroscience, 1993, 18, 235-244.
37. Maes M., Meltzer H.Y. The serotonin hypothesis of major depression, in Psychopharmacology: The Fourth Generation of Progress. Eds. Bloom F.E, Kupfer D.J. New York, Raven Press. 1995, 933-944.
38. Rogers P.J. Food, mood and appetite. Nutrition Research Reviews, 1995, 8, 243-269.
39. Wurtman R.J., Hefti F., Melamed E. Precursor control of neurotransmitter synthesis. Pharmacological Reviews, 1981, 32, 315-335.
40. Young S.N. The clinical psychopharmacology of tryptophan, in Nutrition and the Brain: Volume 7. Eds. Wurtman R.J., Wurtman J.J. New York, Raven Press. 1986, 49-88.
41. Spring B., Chiodo J., Bowen D.J. Carbohydrates, tryptophan, and behavior: A methodological Review. Psychological Bulletin, 1987, 102, 234-256.
42. Hill A.J., Blundell J.E. Role of amino acids in appetite control in man, in Amino Acids in Health and Disease. Ed. Heuther G. Berlin, Springer-Verlag. 1988, 239-248.
43. Steinberg S., Annable L., Young S.N., Bélanger M-C. Tryptophan in the treatment of late luteal phase dyphoric disorder: A pilot study. Journal of Psychiatry and Neuroscience, 1986, 19, 114-119.
44. McGrath R.E., Buckwald B., Resnick E.V. The effect of L-tryptophan on seasonal affective disorder. Journal of Clinical Psychiatry, 1990, 51, 162-163.
45. Young S.N., Smith S.E., Pihl R.O., Finn P.. Tryptophan depletion causes a rapid lowering of mood in normal males. Psychopharmacology, 1985, 87, 173-177.
46. Benkelfat C., Ellenbogen M.A., Dean P., Palmour R.M., Young S.N. Mood-lowering effect of tryptophan depletion. Archives of General Psychiatry, 1994, 51, 687-697.
47. Terry, J. The other electrolytes: magnesium, calcium, and phosphorus. Journal of Intravenous Nursing, 1991, 14, 167-176.
48. Gibson R.S. Assessment of calcium, phosphorus, and magnesium status, in Principles of Nutritional Assessment. Oxford, Oxford University Press. 1990, 487-510.
49. Seelig M. Cardiovascular consequences of magnesium deficiency and loss: pathogenesis, prevalence and manifestations - magnesium and chloride loss in refractory potassium repletion. American Journal of Cardiology, 1989, 63, 4G-21G.
50. Rozin P., Levine E., Stoess C. Chocolate craving and liking. Appetite, 1991, 17, 199-212.
51. Reinhart R.A. Magnesium metabolism. Wis. Medical Journal, 1990, 89, 579-583.
52. Shils M.E. Magnesium, in Modern Nutrition in Health and Disease, 8th edition. Eds. Shils M.E., Olson J.A., Shike M. Philadelphia, Lea & Febinger. 1994, 164-184.
53. Beal A., Walker A.F. Dietary mineral supplementation and bioavailability, in Nutrition and the Consumer: Issues in Nutrition and Toxicology, Volume 1. Eds. Walker A.F., Rolls B.A. London, Elsevier Applied Science. 1992, 127-160.
54. Abraham G.E. Premenstrual tension. Current Problems in Obstetrics and Gynecology, 1980, 3, 1-39.
55. Roach, M. More reasons to love chocolate. New Woman, February 1989, 135-136.
56. Bancroft J., Cook A., Williamson, L. Food craving, mood and the menstrual cycle. Psychological Medicine, 1988, 18, 855-860.
57. Devane W.A., Hanus L., Breuer A., Pertwee R.G., Stevenson L.A., Griffin G., Gibson D., Mandelbaum A., Etinger A., Mechoulam R. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science, 1992, 258, 1946-1949.
58. Mechoulam R., Fride E. The unpaved road to the endogenous brain cannabinoid ligands, the anandamides, in Cannabinoid Receptors. Ed. Pertwee R.G. London, Academic Press. 1995, 233-258.
59. Di Marzo V., Sepe N., De Petrocellis L., Berger A., Crozier G., Fride E., Mechoulam R. Trick or treat from food endocannabinoids? Nature, 1998, 396, 636.

60. Perez-Reyes M., Timmons M.C., Davis K.H., Wall E.M. A comparison of the pharmacological activity in man of intravenously administered Δ^9-tetrahydrocannabinol, cannabinol, and cannabidiol. Experientia, 1973, 29, 1368-1369.
61. Beltramo M., Piomelli, D. Reply to Di Marzo et al. Nature, 1998, 396, 636-637.
62. Smit H. 1998. The liking for chocolate: attitudes, mood and psychopharmacological effects. PhD thesis, University of Reading, UK.
63. BCCCA. BCCCA Statistical Yearbook 1997. London, Biscuit Cake Chocolate and Confectionery Alliance. 1997.
64. Hetherington M.M., Macdairmid J.I. "Chocolate addiction": A preliminary study of its description and its relationship to problem eating. Appetite, 1993, 21, 233-246.
65. Max B. This and that: chocolate addiction, the dual pharmacogenetics of asparagus eaters and the arithmetic of freedom. Trends in Pharmacological Science, 1989, 10, 390-393.
66. Gibson E.L., Desmond E. Chocolate craving and hunger state: Implications for the acquisition and expression of appetite and food choice. Appetite 1999, 32, 219-240.
67. MAFF. Survey of Caffeine and Other Methylxanthines in Energy Drinks and Other Caffeine-containing Products: Food Surveillance Information Sheet 103. London, Ministry of Agriculture Fisheries and Food. 1997.
68. Barone J.J., Roberts H.R. Caffeine consumption. Food Chemistry and Toxicology, 1996, 34, 119-129.
69. Shively C.A., Tarka S.M. Methylxanthine composition and consumption patterns of cocoa and chocolate products, in The Metylxanthine Beverages and Foods: Chemistry, Consumption and Health Effects. Ed. Spiller G.A. New York, Alan R. Liss. 1984, 149-178.
70. Zoumas B.L., Kreiser W.R., Martin R.A. Theobromine and caffeine content of chocolate products. Journal of Food Science, 1980, 45, 314-316.
71. Souci S.W., Fachmann W., Kraut H. Food Composition and Nutrition Tables 1981/1982, 2nd edition. Stuttgart, Wissenschaftliche Verlagsgesellschaft mbH. 1981.
72. MAFF. Food Portion Sizes, 2nd edition. London, Ministry of Agriculture Fisheries and Food, HMSO. 1988.
73. Koehler P.E., Eitenmiller R.R. High pressure liquid chromatographic analysis of tyramine, phenylethylamine and tryptamine in sausage, cheese and chocolate. Journal of Food Science, 1978, 43, 1245-1247.
74. Hurst W.J., Toomey P.B. High-performance liquid chromatographic determination of four biogenic amines in chocolate. Analyst, 1981, 106, 394-402.
75. Ingles D.L., Back J.F., Gallimore D., Tindale R., Shaw K.J. Estimation of biogenic amines in foods. Journal of the Science of Food and Agriculture, 1985, 36, 402-406.
76. ten Brink B., Damink C., Joosten J.M.L.J., Huis in 't Veld J.H.J. Occurrence and formation of biologically active amines in foods. International Journal of Food Microbiology, 1990, 11, 73-84.
77. Baker G.B., Wong J.T.F., Coutts R.T., Pasutto F.M. Simultaneous extraction and quantitation of several bioactive amines in cheese and chocolate. Journal of Chromatography, 1987, 392, 317-331.
78. Smith T.A. Amines in food. Food Chemistry, 1981, 6, 169-200.
79. Paul A.A., Southgate D.A.T., Russell J. First Supplement to McCance and Widdowson's The Composition of Foods. Amsterdam, Elsevier/North-Holland Biomedical Press. 1980.
80. NEVO. NEVO Tabel: Nederlands Voedingsstoffenbestand 1989/90. Zeist, The Netherlands, Stichting NEVO. 1989.
81. Paul A.A., Southgate D.A.T. McCance and Widdowson's The Composition of Foods, 4th edition. Amsterdam, Elsevier/North-Holland Biomedical Press. 1978.
82. Souci S.W., Fachmann W., Kraut H. Food Composition and Nutrition Tables 1986/1987, 3rd edition. Stuttgart, Wissenschaftliche Verlagsgesellschaft mbH. 1986.

Table 1 Caffeine content of various products

Product	Portion size [6]	Number of samples	Concentration (mg per portion)
Coffee (filter, percol.)	7.6 g/200 ml	8	105 (61-126) [1]
Coffee (instant)	1.6 g/200 ml	16	58 (42-68) [1]
Tea (regular, bag)	230 ml	NA	46 [1]
Cola drinks	can (330 ml)	32	23 (11-70) [1] [4]
Energy drinks	can or bottle,250 or 330 ml	26	63 (0.2-115) [1]
Medicines	tablet or capsule	NA	15-200 [2]
Chocolate, milk	50 g	4	8.4 (5.5-11) [1]
Chocolate, dark	50 g	2	27 (17-36) [1]
Cocoa powder	10 g [5]	8	21 (8-35) [3]

NA, not available

[1] (ref. 67), figures re-calculated using comments in Annex C of this reference where appropriate

[2] (ref. 68)

[3] (refs. 69, 70)

[4] Dried kola nut contains 2.0 % caffeine (ref. 71)

[5] equivalent to two heaped teaspoonfuls to make, for example, one cup of hot chocolate (ref. 72)

[6] (ref. 72)

Table 2 Theobromine content of various products

Product	Portion size [4]	Number of samples	Concentration (mg per portion)
Coffee (filter, percol.)	7.6 g/200 ml	8	0.3 (0.3-0.3) [1]
Coffee (instant)	1.6 g/200 ml	16	0.2 (0.1-0.5) [1]
Tea (regular, bag)	230 ml	14	3.1 (1.4-4.4) [1]
Cola drinks	can (330 ml)	32	ND [3]
Energy drinks	can or bottle,250 or 330 ml	26	0.1 (ND-1.6) [1]
Chocolate, milk	50 g	4	95 (65-160) [1]
Chocolate, dark	50 g	2	378 (237-519) [1]
Cocoa powder	10 g	8	189 (146-266) [2]

ND, not detected

[1] (ref. 67), figures re-calculated using comments in Annex C of this reference where appropriate

[2] (refs. 69, 70)

[3] Dried kola nut contains 0.05 % theobromine (ref. 71)

[4] (ref. 72)

Table 3 Phenylethylamine content of various products

Product	Portion size [7]	Number of samples	Concentration (mg per portion)
Danish Blue cheese	100 g	1	2.5 [3]
Cheddar cheese	100 g	22	2.1 (ND-30.3) [1]
Dutch cheese	100 g	8	0.9 (0-4.6) [5]
Fermented sausage	100 g	14/13	1.4 (0.5-4.5) [5] 7.1 (ND-69.6) [1]
Marmite	4 g	1	ND [3]
Chocolate, milk	50 g	4/6/10	0.08 (ND-0.33) [2] ND [1 4]
Chocolate, dark	50 g	8/1/1/10	0.03 (0.01-0.11) [4] 0.10 [2] ND [1 3]
Cocoa powder	10 g	12/1	0.01 (0.003-0.03) [4] 0.2 [6]

ND, not detected
[1] (ref. 73)
[2] (ref. 74)
[3] (ref. 75)
[4] (ref. 20)
[5] (ref. 76)
[6] (ref. 77)
[7] (ref. 72)

Table 4 Tyramine content of various products

Product	Portion size [7]	Number of samples	Concentration (mg per portion)
Danish Blue cheese	100 g	1	62.5 [3]
Cheddar cheese	100 g	22/1	19.2 (ND-112) [1] 6.2 [6]
Dutch cheese	100 g	8	13.8 (0-62.5) [5]
Fermented sausage	100 g	14/13	11 (4-31) [5] 11.2 (ND-37.4) [1]
Marmite	4 g	1	0.4 [3]
Chocolate, milk	50 g	4/6/10	0.33 (0.19-0.60) [2] 0.02 (0.01-0.03) [4] ND [1]
Chocolate, dark	50 g	8/1/1/10	0.03 (0.01-0.11) [4] 0.19 [2] ND [3] [1]
Cocoa powder	10 g	12	0.01 (0.003-0.03) [4]

[1] (ref. 73)
[2] (ref. 74)
[3] (ref. 75)
[4] (ref. 20)
[5] (ref. 76)
[6] (ref. 77)
[7] (ref. 72)
ND, not detected

Table 5 Serotonin content of various products

Product	Portion size [4]	Number of samples	Concentration (mg per portion)
Pineapple	125 g	not reported	2.4-8.1 [3]
Avocado	130 g	not reported	1.2 [3]
Walnuts	25 g	not reported	13.8 [3]
Chocolate, milk	50 g	4	0.52 (0.05-1.36) [1]
Chocolate, dark	50 g	1	0.43 [1]
Cocoa powder	10 g	1	0.6 [2]

[1] (ref. 74)
[2] (ref. 77)
[3] (ref. 78)
[4] (ref. 72)

Table 6 Tryptophan content of various products

Product	Portion size [1)]	Concentration [2)] (mg per portion)
Cheese (ripened: Stilton, Cheddar, Edam, etc.)	100 g	300-500
Peanuts	50 g	320
Peanut butter	10 g	38
Crisps	100 g	90
Meat & Fish	100 g	100-400
Chocolate, milk	50 g	80
Chocolate, dark	50 g	34
Cocoa powder	10 g	30

Numbers of samples used for analysis not reported

[1)] (ref. 72)

[2)] All data from (ref. 79)

Table 7 Magnesium content of various products

Product	Portion size [6]	Concentration (mg per portion)
Grain and grain products	100 g	60-420 [4]
Rolled oats	50 g	69.5 (56.5-75) [5]
Soya beans (whole corn)	100 g	247 (210-284) [5]
Haricot beans	100 g	132 (130-134) [5]
Shellfish	100 g	34-414 [4]
Sole (fish)	100 g	73 (51-94) [5]
Shrimps	80 g	54 (34-74) [5]
Cashew nuts	40 g	107 [5]
Roasted peanuts	25 g	45.5 (36-59.3) [5]
Fruit gums	50 g	55 [2]
Chocolate, milk	50 g	27.5 [1) 2)] 43 (31-52) [3] 52 [5]
Chocolate, dark	50 g	50 [1) 2) 3) 5)]
Cocoa powder	10 g	52.0 [2] 41.4 (37.0-45.7) [5]

Number of samples unknown for most references

1) (ref. 80)
2) (ref. 81)
3) (ref. 82)
4) (ref. 49)
5) (ref. 71)
6) (ref. 72)