



METHYLXANTHINES

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1. INTRODUCTION

Caffeine, theobromine and theophylline are chemical compounds with closely related structures and similar pharmacological properties. They are all members of the class of compounds known as methylxanthines which are mild stimulants. They occur in many common food plants such as coffee, tea, cocoa, maté and cola. From time to time, they have been linked with a range of conditions including heart disease and high blood pressure. Some people are concerned that children may be consuming excessive amounts. As a result of this interest, a vast amount of research has been carried out, mainly on caffeine with less on theobromine. Caffeine is the compound that is consumed in the largest quantities, although intakes average only 2.4 to 4.5 mg per day in typical Europeans.

2. OCCURRENCE

Though Methylxanthines occur in as many as 60 plant species, major dietary sources are coffee, tea, cocoa, cola and maté, all of which have been consumed for many years. Vast number of analyses^{1,2,3} carried out in recent years demonstrate that it is difficult to give typical figures for methylxanthine contents on foods. This is because they vary according to the origin of the raw material and the amount in the product. Typically, espresso coffee contains about 100 mg caffeine and filter coffee 60 mg.

A cup of English tea and 330 ml of a cola drink both contain about 40 mg caffeine, although tea can contain up to 90 mg. It also contains a very small quantity of theophylline. A 50 g block of plain chocolate has about 30 mg of caffeine and 250 mg of theobromine. However, it should not be assumed that these products are just delivery systems for the methylxanthines. They are all complex mixtures and other ingredients in either the raw material or the finished product definitely affect both their taste and physiological effect.

3. ABSORPTION AND METABOLISM

Methylxanthines are rapidly and completely absorbed by man. Detailed studies have been carried out for caffeine which is detected in the bloodstream as little as 5 minutes after consumption and reaches a peak after about 20 minutes⁴. Exact rate depends on the source of caffeine, cola beverages giving slower figures than tea or coffee. Methylxanthines are metabolised by the liver.

Caffeine level is halved in 2.5 to 4.5 hours but theobromine is slower, taking between 6 and 10 hours. A number of factors influence the rate. Late stages of pregnancy and obesity slow it down whereas smoking accelerates it. Interestingly there is a positive correlation between smoking and coffee consumption⁵.

It is important to note that the mechanism of metabolism of methylxanthines differ from species to species. Therefore, it is necessary to take this into account when extrapolating rodent data to man.

4. PHYSIOLOGICAL EFFECTS

4.1 Central Nervous System

The fact that large doses of caffeine can increase wakefulness is well known but the evidence that caffeine increases mental alertness is equivocal. Theophylline is less active and theobromine almost without effect⁵. Individuals can get used to high caffeine consumption though there are cases where excessive consumption by sensitive individuals has produced symptoms which together have been called « caffeinism ». These symptoms, such as restlessness, insomnia, rambling of thought and speech, intestinal complaints and irregular heart beat can be caused by a number of other agents. Where the cause is caffeine they cease when consumption of caffeine containing drinks is reduced, although there is sometimes a period of withdrawal symptoms such as headaches⁵.

4.2 Cardiovascular System

Research has shown that moderate intakes of caffeine do not affect cardiovascular function or blood pressure in healthy individuals⁶. Some early studies did appear to show a relationship between coffee consumption and the risk of heart attack but more recent, better controlled studies have found no evidence of a link. However, individuals suffering from cardiac rhythm abnormalities should take medical advice on their dietary caffeine intake.

4.3 Digestive System

Coffee has been shown to have a number of effects on the digestive system but many of these are shared by decaffeinated coffee and cannot be due to the presence of caffeine. Caffeine, along with other constituents of coffee, does stimulate the secretion of stomach acid but there is no evidence that it is a cause of the development of peptic ulcers.

4.4 Respiratory System

There is some evidence that caffeine, perhaps via a metabolite, has some dilating effect on the bronchial tubes. All methylxanthines, especially theophylline, have been shown to relax the smooth muscle of the bronchi, but it is unlikely that this effect is noticeable when they are consumed as part of food or drink.

It is also known that green coffee can cause allergic symptoms but all the allergens are destroyed during roasting.

4.5 Diuresis

All methylxanthines have a diuretic effect but this is only noticed when they are consumed with large volumes of water, as is the case with coffee.

4.6 Cardiovascular Disease

It has been shown that under certain circumstances coffee can raise blood cholesterol levels. Detailed investigation of this result demonstrated that the effect was a result of the way the drink was prepared and was not affected by caffeine. When coffee grounds are boiled with water for some time, higher levels than usual of two compounds, kahweol and cafestol, are extracted from the grounds. It is these two compounds which give rise to the increase in cholesterol⁷.

4.7 Osteoporosis and Calcium metabolism

Caffeine has been suggested as a contributory factor to osteoporosis and caffeinated beverages in general have been suggested as contributors to the formation of calcium oxalate stones in kidney or bladder. However, recent studies have found neither experimental nor epidemiological evidence to support these claims⁵.

4.8 Sports Performance

There is some evidence that caffeine can have a beneficial effect on performance in sports requiring explosive speed, but results for sports in general are conflicting. The international Olympic Committee permits a maximum urine concentration of 12 µg/ml which is the equivalent of 1 g of caffeine or 8 cups of coffee in a short period of time. Nevertheless, there was a disqualification at the Seoul Olympics as a result of exceeding this limit³.

4.9 Fertility and Reproduction

There have been reports suggesting that high intake of caffeine may be related to length of time taken to conceive but the studies were poorly controlled. Nevertheless, a combination of smoking and high caffeine intake may have this effect. Equally, there were reports of trials in which reduced spermatogenesis and testicular atrophy in rats was caused by caffeine at 0.5%, or theobromine at 0.6%, of the total diet, but it is difficult to relate this to normal caffeine consumption of human males. Despite this lack of evidence, it is general practice to recommend women wishing to become pregnant to restrict their caffeine intake to the equivalent of 2 cups per day. Currently there is no similar advice for men.

Well controlled studies have suggested the 2% of spontaneous abortions could be due to coffee, but not necessarily to caffeine.

4.10 Teragenicity

The possibility that caffeine consumption could damage the unborn child has been raised in the past, largely from experiments with rodents fed very high levels of caffeine, but a thorough review of all the data in 1984⁸ concluded that there was no evidence that moderate consumption presented any such danger to humans. There is, however, a possibility that caffeine may make the effects of other substances, such as tobacco and alcohol, worse. A number of studies have produced no evidence that theobromine is teratogenic.

4.11 Effects on the New-born

There is evidence from experiments with rats that consumption of caffeine by the mother could lead to changes in the brain of the offspring. Also, there is evidence that new born babies show withdrawal symptoms if their mothers have been taking caffeine during pregnancy. However, a long term study has shown no adverse effects on children up to the age of 7⁹. To put this into context it should be noted that the levels of caffeine being consumed by some mothers in trials have been very high - up to 24 cups of coffee or 2 litres of cola per day.

Caffeine appears in the milk of nursing mothers but it is the least readily transferred of the three methylxanthines, theophylline being transferred best. Only low levels are transferred and there is a debate about how well the baby absorbs the methylxanthines. The evidence suggests that less than 10% is absorbed, although it will take a long time to be cleared from the baby's system.

4.12 Fibrocystic Breast Disease

This disease involves the formation of benign lumps in the breasts. It was suggested in the 1970's that there might be link between caffeine consumption and the formation of these lumps. A study by the National Cancer Institute of America showed no evidence of a link with this disease or with other benign tumours^{10,11}.

4.13 Cancer

Caffeine and coffee has been extensively studied to see if there is any correlation with the formation of cancers. Most of these studies have been done with rats and mice, but epidemiological studies have been done on humans. These studies were reviewed in 1991 by International Agency for Research on Cancer (IARC) who concluded that there is inadequate evidence for caffeine being carcinogenic in either humans or experimental animals. A further review in 1994 concluded that, in the doses normally consumed by man, caffeine does not have any potential genotoxic, mutagenic or carcinogenic effect.

Those few studies that have been carried out on theobromine or cocoa powder lead to the same conclusion, that these materials are not carcinogenic.

5. IOCCC POSITION

Man has been consuming substances containing methylxanthines for thousands of years. Extensive research has concluded that there is no evidence that these substances, at levels usually consumed, have any ill effects on humans. In particular, chocolate forms a small and enjoyable part of the diet of most consumers and the presence of small quantities of methylxanthines will cause no harmful effects.

REFERENCES

1. Clifford M.N. The composition of green and roasted coffee beans **in** : Coffee : Botany, biochemistry and production of beans and beverage. Clifford M.N. and Willson K. C. Eds., Chapman and Hall, London 1985.
2. Macrae R. Nitrogenous substances **in** : Coffee 1 : Chemistry. Clarke R.J. and Macrae R. Eds., Elsevier Applied Science Publishers Ltd. London 1985
3. Debry G. Caffeine **in** Coffee and Health. Debry G. Ed., John Libbey Eurotext, Paris 1994
4. Marks V., Kelly J.F. Absorption of caffeine from tea, coffee and Cocoa-cola. Lancet 1973, i, 827
5. Marks V. Physiological and clinical effects of tea **in** : Willson K.C. and Clifford M.N. Tea : Cultivation to consumption. Chapman and Hall, London 1992
6. Bättig K. The physiological effects of coffee consumption **in** : Coffee : Botany, biochemistry and production of beans and beverage. Clifford M.N. and Willson K.C. Eds., Chapman and Hall, London 1985
7. Salvaggio A., Periti M., Miano., Quaglia G., Marzorati G. Coffee and cholesterol, and Italian study. Am. J. Epidemiology, 1981, 124, 603-611
8. Dews P., Grimes H.C., Neims A., Wilson J., Wurtman R., Report on the Fourth International Caffeine Workshop, Athens 1982. Food Chem. Toxicol., 22, 1984, 163-169.
9. Barr H.M., Streissguth A.P., Caffeine use during pregnancy and child outcome : a seven year prospective study. Neurotoxicol. Teratol. 13,1991,441-448.
10. McDonald A.D., Armstrong B.G.& Sloan M., Cigarette, alcohol and coffee consumption and congenital defects. American Journal of Public Health 1986, 82, 91-93.
11. Schairer C., Brinton L., Hoover R., Methylxanthines and benign breast disease. American Journal of Epidemiology, 1986, 124, 603-611

BIBLIOGRAPHY

1. Clarke R.J. and Macrae R. Coffee 1 : Chemistry. Elsevier Applied Science Publishers Ltd. London 1985
2. Clarke R.J. and Macrae R. Coffee 3 : Physiology. Elsevier Applied Science Publishers Ltd London 1988.
3. Clifford M.N. and Willson K.C. Coffee : Botany, Biochemistry and production of beans

and beverage. Chapman and Hall London 1985

4. Debry G. Coffee and Health John Libbey Eurotext Paris 1994
5. IARC Monographs on the Evaluation of Carcinogenic Risk to Humans. Volume 51 : Coffe, Tea, Maté, Methylxanthines and Methylglyoxal. Lyon : International Agency for Research on Cancer 1991
6. Willson K.C. and Clifford M.N. Tea : Cultivation to consumption. Champan and Hall, London 1992

