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Bertil B. Fredholm
Editor

Methylxanthines

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Dedication to Klaus Starke

This volume of the *Handbook of Experimental Pharmacology* was one of the last that Klaus Starke initiated as Editor-in-Chief. We dedicate this 200th volume in the series to him.

Klaus was born in 1937. Since his father was an apothecary, it was natural for him to study pharmacy, but he also graduated in medicine. He combined the two, and devoted himself to pharmacology, where he has left a very important mark. Despite calls from many other universities, he remained in Freiburg from 1977. He was one of the scientists who simultaneously realized that neurotransmitters can regulate their own release via presynaptic receptors. This discovery has been extremely important in our understanding of the fine-tuning of neuronal activity. The pharmacology of these presynaptic receptors was recently summarized in volume 184 of the handbook, which was edited by Klaus together with Thomas Südhof. Klaus is deeply respected internationally for his solid science. He is a member of the Academia Europea, the Heidelberger Akademie der Wissenschaften, and the National German Academy "Deutsche Akademie der Naturforscher Leopoldina." He received the Ernst Jung-Preis and the Wilhelm Feldberg-Preis.

In addition to his scientific accomplishments, Klaus has influenced and shaped German pharmacology by his teaching and his dedicated work on numerous committees and in grant-awarding agencies. He has also been deeply involved in many pharmacology journals. The extreme care he took with each manuscript submitted to *Naunyn-Schmiedeberg's Archives of Pharmacology* during his period as managing editor is very memorable to all of us who benefited from his penetrating, but benevolent editing. This devoted attention to both detail and strategic goals was brought by him to the *Handbook of Experimental Pharmacology*. He had, for example, several excellent suggestions on how to organize this volume and he even suggested that we include two poems. One of them was used in the introduction to this volume. The other is printed below. It shows his interests in cultural activities outside pharmacology.

Given the care with which Klaus always dealt with everything, it is with some trepidation that we submit this volume to his scrutiny.

Bertil Fredholm
Volume Editor

Franz Hofmann
Editor-in-Chief

For lo! the Board with Cups and Spoons is crown'd,
The Berries crackle, and the Mill turns round;
On shining Altars of *Japan* they raise
The silver Lamp, and fiery Spirits blaze:
From silver Spouts the grateful Liquors glide,
And *China's* earth receives the smoking Tyde.
At once they gratify their Scent and Taste,
While frequent Cups prolong the rich Repast...
Coffee (which makes the Politician wise,
And see through all things with his half-shut Eyes)
Sent up in Vapours to the *Baron's* Brain
New Stratagems, the radiant Lock to gain.

Alexander Pope (1688–1744) *The Rape of the Lock*

Preface

Methylxanthines are doubtless the most widely consumed of all pharmacologically active agents. The reason for this is, of course, that caffeine-containing beverages are consumed on a daily basis by the majority of humans. The human use of coffee and tea was limited until surprisingly recently. Now the global use means that coffee and tea are very important products commercially. Indeed, the sale of tea and coffee has been an important source of national income and for a long time provided the main source of income of the greatest nation in the world at the time, China.

Methylxanthines are found in several plants, from many parts of the world. Coffee beans were probably discovered in Africa, tea leaves in East Asia, mate and cocoa in South America, but it is also found in some 100 other plant species. To make these compounds the plants have developed sophisticated enzymatic machinery. The reason for the investment in methylxanthine synthesis is possibly because methylxanthines can act as a chemical defense, and hence because methylxanthines can have toxic effects. Caffeine is taken up well and distributed throughout the body and elimination depends on a series of enzymatic steps. These differ between species and ages of the same species, including man.

At the beginning of human use of both coffee and tea, the focus was on the medicinal effects, which were both lauded as beneficial and deplored as being detrimental. Now the major interest is perhaps in the public health consequences of the widespread use. Over the years, considerable effort has been spent in population studies to elucidate the risks of caffeine use. One of the surprising things in recent years has been the realization that the evidence for health benefits in, e.g., Parkinson's disease and type II diabetes, has been easier to document than that for possible detrimental effects in, e.g., cardiovascular disease. There are also some possibilities to use methylxanthines or derivatives as drugs. While this is good news, the bad news is that we are still not clear how these effects are brought about. There have been concerns that caffeine may be a major reproductive hazard, but provided that women limit their intake, this may not be a real concern.

Methylxanthines were early shown to cause muscle contractions in high doses, an effect we now know is due to mobilization of intracellular caffeine. In somewhat lower doses, caffeine and theophylline were found to prevent the enzymatic hydrolysis of cyclic AMP. At still lower doses, they block the actions of adenosine at its receptors. All these actions, and some others, contribute to give methylxanthines a complex pharmacological profile, where utmost care must be taken with dosing.

In this volume of the *Handbook of Experimental Pharmacology*, well-known experts describe the facts alluded to above in detail with a focus on caffeine and theophylline. A special chapter is devoted to theobromine, an active component of chocolate, the actions of which are less well characterized. We also present the pharmacology of one xanthine derivative, propentofylline, as an example of a xanthine that has gone through extensive development for a novel therapeutic area.

The powerful effects caffeine exerts on the nervous system are covered. The ability of methylxanthines to influence the physiological processes involved in sleep and the pathophysiological processes involved in pain are described as largely secondary to adenosine antagonism. Methylxanthines can provoke epileptic seizures, and prevent neurodegenerative disease, but the possible mechanisms, involving actions on one or more adenosine receptors, on both neuronal and nonneuronal cells have not yet been fully elucidated. There are interesting therapeutic possibilities, and novel xanthine derivates are being examined. The fact that caffeine-containing beverages have so rapidly established themselves in a variety of cultural settings raises the possibility that caffeine may actually be a dependence-producing drug. Indeed, there are important interactions with some of the neural systems involved in dependence, but caffeine is not a typical drug of addiction, despite the fact that in the famous coffee cantata of Bach (see below) the heroine is almost willing to forego the pleasures of sex for coffee.

It has also been well known for a long time that caffeine (and some of its metabolites) can influence respiration and can be used to treat asthma, that there are increases in cardiac activity and blood pressure, and that methylxanthines have marked renal effects. In all these instances, a major explanation for the effects is blockade of the actions of endogenous adenosine. This is also the reason why methylxanthines can influence cells of the immune system, an action with therapeutic implications, which has been realized for a much shorter time. By contrast, there is evidence that the metabolic effects of coffee and tea may not be entirely explained by adenosine receptor blockade, or by the caffeine content for that matter.

It has been a pleasure to work with world experts in a common effort to produce an up-to-date and authoritative account of the pharmacology of methylxanthines. We have aimed to give more than just a description of facts or findings, and instead to present ideas, concepts, and open questions.

> "Ei! wie schmeckt der Coffee süße,
> Lieblicher als tausend Küsse,
> Milder als Muskatenwein.
> Coffee, Coffee muß ich haben,
> Und wenn jemand mich will laben,
> Ach, so schenkt mir Coffee ein!"
> Lieschens Aria (fourth movement) from Bach's Coffee Cantata BWV 211, "Schweigt stille, plaudert nicht."

Stockholm Bertil Fredholm

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Notes on the History of Caffeine Use

Bertil B. Fredholm

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Abstract As behooves something so deeply entrenched in culture, the historical origins of the use of methylxanthines are unknown and dressed in myth. This is true for coffee as well as tea, and for both it is interesting to note that their common use is really very recent. For coffee we know that its use became more widespread in the fifteenth and sixteenth centuries, and in Europe this occurred in the eighteenth and nineteenth centuries. The use of tea became more common during the Ming Dynasty in China and during the eighteenth century in Britain. Coffee was mostly an upper-class drink in Arabia, and remained a relative luxury in Europe until quite recently. The use of other methylxanthine-containing beverages, such as maté, is even less well known. It is interesting to note that before these drinks were commonly used on a daily basis they were used for medicinal purposes, indicating that their pharmacological actions had long been noted.

Keywords Cocoa · Coffee · Maté · Tea

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1 Mythological Origins[1]

The coffee bush grows wild in many parts of Africa and it may also have been indigenous in Arabia. There is, however, little solid evidence that people had knowledge that the coffee bush could yield a useful drink before Islamic times. Solid evidence is replaced by good mythological stories. One myth is that the archangel Gabriel offered coffee brewed in heaven to Muhammad when he was overcome by sleepiness. A sip of this heavenly coffee was sufficient to make him so vigorous that he could "unhorse 40 men and make 40 women happy." A more often told myth is about an Ethiopian (sometimes Arabian) goatherd, Kaldi, who observed that his goats became very agitated, indeed dancing, when they ate the berries of a certain bush. Having tried them himself, he informed the abbot of a local (perhaps Sufi) monastery, and from there the conquest of the earth was supposed to start. The story of Kaldi appears to occur first in a book by a Maronite professor of oriental languages, Antoine Faustus Nairon, but local sources for the legend are lacking (Nairon 1617). There are also other stories involving the role of the civet cat in spreading the coffee bush, which has been exploited to market very, very expensive kopi luwak coffee (Mair and Hoh 2009), where beans have passed through the gastrointestinal tract of the animal. In a manuscript published in Paris in 1699 by Antoine Galland, the so-called Abd-el-Kadir manuscript, a sheik Omar is credited with the discovery in AD 1258 during his banishment to a mountainous region near Ousab. There he detected a bush with white flowers and red berries and being famished, he cooked a soup of the berries and leaves and was very invigorated. The brew was also able to heal all illness in the surrounding villages.

The history of tea is similarly clouded in myth and national pride (Mair and Hoh 2009) – the Chinese maintain that tea has "always" been part of Chinese culture. A variant of "always" is the story that the nonhistorical second emperor Shen Nung discovered tea when tea leaves blew into his cup of hot water in 2737 BC. The credibility of this is reduced by the "fact" that this emperor was born with the head of a bull and body of a man: he spoke after 3 days, walked within a week, and could plow a field at age three. Many Chinese associate the widespread use of tea with the introduction and spread of Buddhism. According to one account, a Buddhist monk named Gan Lu brought tea back with him when he returned from a pilgrimage to India during the first century. He is supposed to have planted seven "fairy tea trees." They are still shown to tourists on Mt Mengding in Sichuan.

Another, pretty grim, story says tea sprang from the eyelids of Bodhidharma, the first patriarch of Zen. He had sailed from India to China but after he arrived he merely sat down facing a wall at the Shaolin Temple and did not stir for 9 years. Unsurprisingly, the determined saint once drowsed off, so far forgetting himself that his eyes closed momentarily. Without hesitation he sliced off his eyelids to make sure they would never

[1]The author is heavily indebted to some excellent earlier treatises and the reader is referred to these for references (Ukers 1922; Weinberg and Bealer 2001; Elgklou 1993; Mair and Hoh 2009).

again close and interrupt his wakefulness. Where they fell the compassionate deity Quan Yin caused tea plants to grow to serve Bodhidharma and all who came after him as an aid on the path to enlightenment. The story may have gained particular popularity in Japan, because the Japanese characters for tea leaf and eyelid are the same.

2 Early History of Coffee

It seems clear that coffee beans were first eaten as such; later they were ground up and mixed with fat paste as a stimulating travel snack. Only around AD 1000 did infusions with boiling water start to be used. The word “coffee” derives from *qahva* (or *qahwah*), which is simply a word denoting a drink made from plants. From the initial cultures in Ethiopia, cultivation of coffee bushes soon came to be dominated by Yemen. The city of Mocha became a center – and its name came to denote the drink. Now coffee is grown in 50 different countries around the world (Ukers 1922; Weinberg and Bealer 2001; Elgklou 1993).

Although the Arabs cultivated the plants and prepared drinks from coffee beans, it was only by the fourteenth century that the process of roasting was discovered. And only when this happened did the use of coffee rapidly spread in the Arab world. In the Muslim world the need for a social drink was filled by coffee and the beverage was consumed both at home and in coffee bars. The fact that these coffee houses developed into independent intellectual centers was perceived as a threat to the authorities, and sometimes they were forced to close. Already in the sixteenth century health arguments were used, for example, when Kair Bey, the governor of Mecca, prohibited the use of coffee in 1511. The coffee bars started in the mid sixteenth century in Constantinople, and soon became very popular. They were called *quaweh khaneh* and developed into centers for cultural and intellectual activity. For that reason they also got the name *mekteb-i-irfan* (“the school of the wise”). In Turkey the use of coffee tended to decrease the use of opiates and was promoted by most officials. Since the Arabs controlled a vast territory at the time, the use of coffee spread to Spain, North Africa, India, Turkey, and the Balkans. The permeation into popular culture is revealed by its common use among women, such that a failure to provide sufficient coffee for the wife (or wives) was reason for dissolution of a marriage.

The use of coffee was described in travelogues. The first may have been that of Leonhard Rauwolf (1535–1596) from Augsburg, who published an account in 1582–1583. One particularly well-known description was in *De Plantis Aegypti liber* (Venice, 1592) by Prospero Alpini (1553–1617). He was born in the republic of Venice. After a time in the army, he went to Padua to study medicine, and settled as a physician outside Paduan territory. He traveled to Egypt in 1580 as physician to the Venetian consul in Cairo. He is reputed to have deduced that “the female date-trees or palms do not bear fruit unless the branches of the male and female plants are mixed together; or, as is generally done, unless the dust found in the male sheath or male flowers is sprinkled over the female flowers.” He returned to Padua and became professor of botany. Although *De Plantis Aegypti liber* is his best-known work, an earlier work, *De Medicina Egyptiorum* (Venice, 1591), that describes Egyptian medical practices is said to contain the first account of the coffee plant published in Europe. He used the word *caova* to describe the drink.

Another influential writer was Pietro della Valle (1586–1652), who learned Arabic and traveled widely in Turkey, Egypt, Mesopotamia, and Persia. His name for the drink was *cahve*. He was well connected with the Vatican and this argues that it is probably incorrect that Pope Clemens VIII in 1605 (10 years before della Valle) was given coffee by members of the Curia who wanted him to ban this Muslim drink. He is reputed to have said: "This satanic drink is in truth so good that it would be a pity if only nonbelievers were allowed to drink it. We will fool Satan and baptize it so that it becomes a Christian drink, with no danger for the soul."

According to one story, coffee was introduced to Europe in the seventeenth century. It is said that after their defeat at the gates of Vienna in 1683, the Turks left a large amount of coffee behind, and that the Viennese learned to prepare it and served it with half-moon-shaped cakes. It is, however, well established that coffee was introduced to Europe by Venetian merchants in early 1615. About 10 years later they had learned to roast and grind the imported green beans. The popularity of coffee was promoted by *botteghe del caffé* (coffee shops, originally called *botteghe delle acque e dei giacci*, because all kinds of drinks made with water and ice were served). They were modeled on the Arab establishments and also developed into gradually more sophisticated coffee establishments such as Caffé alla Venezia Trionfante, which opened in 1720. Here was the start of the typical café with newspapers and reviews that developed into cultural and commercial centers. By the mid eighteenth century Venice had more than 200 such establishments. The first Viennese establishment was established by Georg Kolshnitzky (according to legend using the Turkish leftover coffee sacks). In Paris, Café Procope, in rue de l′Ancienne Comédie, was opened in 1686 by the Sicilian Francesco Procopio dei Coltelli. It still exists and was given a name that alluded to hidden secrets in high places by alluding to the Byzantine historian Procopius, whose secret history had just been discovered and published for the first time ever in 1623. The café was a meeting place of the chic elite especially after Comédie Française opened across the street a few years later. It was a famous meeting place of the encyclopedists and the early revolutionaries, but also the literary elite after the political restoration and late nineteenth century met there. The first coffee house in London was apparently opened even earlier, in 1652.

Venice also became the transit port for shipment of coffee to other parts of Europe. By the end of the seventeenth century, the use of coffee in Europe was widespread. For some time the Arab countries maintained their monopoly of supply, but in the seventeenth century plants were smuggled to India and to Amsterdam and from there to the Dutch colonies in the East Indies. However, coffee had been grown outside the Arab countries and Ethiopia before that as small coffee plantations (and there had also been tea plantations of course) founded on Ceylon by the Portuguese in the early sixteenth century. By the beginning of the eighteenth century, Java and Sumatra were the main suppliers. The quality of the

Indonesian coffee was, however, for long inferior to that of the Yemenite coffee – at least if we are to believe Voltaire, who spoke of the ". . . mauvais café de Batavia et des iles" and explicitly preferred the Mocha coffee. One celebrated description of coffee farming is by Karen Blixen (pen name Isak Dinesen), whose book *Out of Africa* (Dinesen 1937) was filmed (albeit not following the book very closely) with Meryl Streep playing the author and Robert Redford playing her husband, Bror. The book starts, "I had a farm in Africa at the foot of the Ngong Hills...," and in it she describes both ups and downs and the hard labor involved: "Coffee-growing is a long job. It does not all come out as you imagine, when, yourself young and hopeful, in the streaming rain, you carry the boxes of your shining young coffee plants from the nurseries...patiently, awaiting coming bounties" (Dinesen 1937; Lorenzetti and Lorenzetti 1999).

The spread of producers allowed coffee to become a mass product. It is culturally very much entrenched and it is relevant that the culture associated with the coffee house has been the subject of much intense research (Ellis 2007). It is beyond the scope of this historical sketch to outline the development of the coffee business as we now see it (Ukers 1922; Weinberg and Bealer 2001; Prendergast 1999). Suffice it to say here that it is remarkable that coffee has in a few hundred years become such an important part of everyday culture throughout the world that it has become one of the commercially most important traded commodities.

3 Early History of Tea

It is commonly stated that tea use was common in China for thousands of years before Christ. This is difficult to verify and there can be no one simple explanation for China's nationwide adoption of the tea habit. Tea is (probably – but it could be other infusions) referred to in old texts from the first centuries BC. A clear unambiguous reference to the tea plant occurs only from AD 750. Alerting and mood-elevating effects are referred to in early literature. Indeed, this early literature mainly refers to the use of tea for medicinal purposes (Mair and Hoh 2009). However, by the Tang Dynasty, and particular Emperor Tai-tsung (627–649), the cultural and ceremonial aspects took a larger part. During this dynasty the famous *Chá Ching* (*The Classic of Tea*) was written as a manual of tea connoisseurship (Lu 1974) by Lu Yu. This developed into a ceremonial use of tea that incorporated aspects of both Taoism and Confucianism. Tea fell somewhat out of favor as a drink during the years of the Mongol Yuan Dynasty and it does not figure in Marco Polo's descriptions of court life[2] (but he did describe how important taxes on tea were for the national economy). Tea clearly was of major importance in trade – in particular

[2]This has, however, also been interpreted as evidence that Marco Polo never visited the imperial court.

the trade of horses for tea, which represented a major part of the foreign/defense policy of China (Mair and Hoh 2009).

Tea use increased in popularity under the Chinese Ming Dynasty (1368–1644), which represented a return to power of the Han people, and it was in this period that tea began to be brewed by steeping cured loose leaves in boiling water. Because it was at this time that the tea was first tried by Europeans, it was this method of making tea that became popular in the West and remains so to this day. Also under the Ming Dynasty different types of teas, including fermented black teas, unfermented green teas, and the semifermented variety that is now known as oolong, were developed. During the Ming Dynasty there were tea houses that apparently functioned much as the coffee houses in Arab countries (Mair and Hoh 2009).

Tea was introduced to Japan around 800 BC and it came with all the ceremonial and quasi-religious overtones. However, it took many centuries until tea use became more popular, and it coincided in time with the spread of the Zen variant of Buddhism. The monk Myoan Eisai is credited with the popularization, including the demonstration for the shogun that tea can help you sober up a bit after too much sake. In Japan the institutions of the tea house and tea garden, as well as the Tea Ceremony, reached full development through a series of Zen monks (Mair and Hoh 2009). Of particular importance was Sen No Rikyu (1522–1591), Tea Master of the powerful political leader Hideyoshi, who incorporated the essence of Zen into the Tea Ceremony, and it is in the form he developed that the Way of Tea (*chado*) is practiced through the Tea Ceremony to this day. This classical ceremony is based on powdered green tea that is intensely whisked. By the mid sixteenth century traditions based on "boiled tea," *sencha*, using intact tea leaves were established (Mair and Hoh 2009). A well-known description of tea use in Japan (with notes on the rest of the world) was written by Okakuzo Kakuzo (2000).

Tea arrived in Europe about the same time as coffee did. The first green tea leaves from China were brought to Amsterdam by the Dutch East India Company and tea was drunk in France by 1636. Tea in Russia was first offered by China as a gift to Czar Michael I in 1618. Tea appeared in Germany by 1657. In Britain tea was apparently first publicly distributed in the 1650s by Thomas Garraway and it was within the confines of his coffee house. Whereas tea never became very popular in mainland Europe (except Russia), by 1730 the use of tea in England had passed the use of coffee. The reason for this could be the strong position of the British East India Company. Despite the fact that tea is an indigenous Indian plant, culture of tea plants began in earnest only after the British rule. In particular, the teas producing the Darjeeling variety were from Chinese plants planted during British rule. The native Assam tea was also being cultivated more systematically, and cultivation was transferred to Ceylon.

Like the Arabs in the case of coffee, the Chinese wanted to monopolize tea trade, and, conversely, many wanted to get plants and grow them. One well-known story is how the Swedish naturalist Carl von Linné (1707–1778) attempted to get tea plants for his botanical garden in Uppsala. The idea was to test if tea could be grown locally and therefore improve the national economy. He made a deal with the Swedish East India Company to have one of his students travel with it and bring home a plant. The student, Pehr Osbeck, managed to collect numerous plants and bring them home, but the one tea plant brought on board that survived most of the sea voyage during the first trip was knocked overboard when the crew fired a salute. He lost a plant on his second trip during a storm off the Cape of Good Hope. The third effort was a plant brought by a director of the East India Company directly to von Linné, but it soon proved not to be the proper plant at all but another species of *Camellia*. The fourth one was the proper thing, but was deemed so valuable that it was left in the commander's safe room – where it was devoured by rats. Finally, one of two plants brought as potted seeds was brought by the wife of the commander of the ship herself after the first one had been destroyed in transit. Finally, in October 1763 von Linné was the first person in Europe to have a tea plant of his own (Mair and Hoh 2009). The plants gradually died and by 1781 only one remained. By now tea is widely used throughout the world (but not very much in Sweden).

Even though coffee was the first methylxanthine-containing drink associated with Muslim countries[3], tea has subsequently become the dominant drink in these parts of the world (Mair and Hoh 2009). In the UK the first such drink was again coffee, but by the nineteenth century there was a switch to tea; in the USA the opposite development is seen. In each of these cases there are interesting political overtones (Mair and Hoh 2009).

4 The History of Cocoa and Maté

These two methylxanthine-containing beverages have Latin American or Central American origins. Cocoa beans were used and the tree was cultured by the Olmec people (1500–400 BC), and was later used by the Maya culture. The Maya recorded their use in writing. After them Toltec and Aztec cultures used it, and via the latter the Spaniards (Hernán Cortés, 1485–1547) came in contact with the drink and its proper preparation. The huge consumption of chocolate by the Montezuma court was recorded by the historiographer Bernal Diaz del Castillo (Ukers 1922; Coe and Coe 1996).

In all probability the cocoa seeds brought by Columbus to King Ferdinand in 1502 were the first plant products containing methylxanthines brought to Europe, and the Spanish royalty was thus prepared when Cortes wrote a exuberant description calling cacao the "drink of goods." Cortés returned to the Americas to set up cocoa plantations for King Charles V in Haiti, Trinidad, and Fernando Po (Weinberg and Bealer 2001; Coe and Coe 1996). The Indians probably mixed vanilla with the cocoa to reduce the bitter taste. In Europe sugar in different forms was added as were milk products. Now, of course, cocoa products are eaten as much as they are drunk (Coe and Coe 1996).

[3]However, tea export from China to muslim countries had been important for a long time.

Maté is prepared from the leaves of a holly (*Ilex paraguariensis*) harvested in pre-Hispanic times along the Paraná–Paraguay river system. It has oval, dark green leaves that are six to eight inches long and white flowers. As with tea, the best product is from young, unopened leaflets. The history of this use is clouded in mystery, but the use is often associated with the Guarani Indians, who have a myth of the maté being a present from a shaman to a traveling chief. It is clear that the Spanish invaders rapidly adopted the practice and saw economic possibilities. Jesuits developed maté into a plantation crop and before 1700 the use had spread along the Andes and the Rio de la Plata. However, the use has never spread much beyond South America.

5 Methylxanthines and Health

As already noted, in the earliest history of methylxanthine use the medicinal effects were important (Ukers 1922; Weinberg and Bealer 2001; Mair and Hoh 2009). For example, in India, where tea is indigenous, tea was long used for medicinal purposes, but its social use was limited. Just as there were overblown claims for the wholesome effects of the drinks made with coffee, tea, or cocoa, there were claims about the negative health consequences. A case in point is an apocryphal experiment of Gustaf III (1746–1792). This Swedish king was reported to be convinced that coffee was dangerous and in order to prove his opinion he is said to have given two condemned twins an alternative to death: they should take part in a long-term experiment. One twin was to drink coffee, the other tea. Reportedly, the experiment was ended when the tea-drinking twin died at age 83. Unfortunately much of the early literature of the health effects is of the same standard and the present author is not a great believer in the usefulness of mining old literature for clues about medicinal herbs in general. Only by the mid nineteenth century did the reports of health effects get a sufficiently scientific basis to be taken seriously. Some of the early literature is cited in relevant chapters of this volume. One very clear example is the reports of the usefulness of coffee in asthma (Salter 1860). There were also early correct reports on the negative effects of high doses of caffeine (Cole 1833). An attitude representative of much later literature is represented by the “discoverer” of homeopathy, Samuel Hahnemann (1755–1843), who found the alerting effects of caffeine to be very beneficial, but warned against its use because it involved the disruption of a natural balance (Hahnemann 1803).

6 The Early Science of Methylxanthines

It was early realized that the effects of coffee were due to some active principle. Prompted by Goethe, the young amateur chemist Friedrich Ferdinand Runge (1795–1865) was able to identify in a rather pure form a substance we call caffeine (Weinberg and Bealer 2001). The chemistry of caffeine and its relatives was clarified by the great Hermann Emil Fischer (1852–1919) in a series of studies that were explicitly cited in his Nobel prize nomination and lecture in 1902. The study of caffeine was also his first major effort, published when he was 29–30 years of age (Fischer 1881a, b, 1882). Using oxidation with moist chlorine, he found that caffeine had a similar heterocyclic skeleton as uric acid. He then found that it was a trimethylxanthine, but he struggled for some time to clarify the structure of xanthine. However, it was only when Fischer turned to a synthetic approach to structure that he finally correctly realized that the xanthine structure proposed by Ludwig Medicus (1847–1915) prior to Fischer was the correct one (Fischer 1897).

Among the dimethylxanthines, theobromine was first identified in 1841. The name derives from the name of the cocoa plant and refers to the name given to it by Cortés, "the food of Gods" (*Theobroma*). Fischer discovered a synthesis in 1882. Theophylline was identified as a minor component in tea in 1888, and a synthetic pathway was devised by Fischer, who also established the structure. Already at the beginning of the twentieth century theophylline was introduced in the clinic, first as a diuretic, later in the treatment of asthma. The third dimethylxanthine, paraxanthine, is not a major component in plants but is the major metabolite of caffeine in several species, including man.

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Distribution, Biosynthesis and Catabolism of Methylxanthines in Plants

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Abstract Methylxanthines and methyluric acids are purine alkaloids that are synthesized in quantity in a limited number of plant species, including tea, coffee and cacao. This review summarizes the pathways, enzymes and related genes of caffeine biosynthesis. The main biosynthetic pathway is a sequence consisting of xanthosine → 7-methylxanthosine → 7-methylxanthine → theobromine → caffeine. Catabolism of caffeine starts with its conversion to theophylline. Typically, this reaction is very slow in caffeine-accumulating plants. Finally, the ecological roles of caffeine and the production of decaffeinated coffee plants are discussed.

Keywords Biosynthesis · Caffeine · Catabolism · Coffee · *N*-Methyltransferase · Tea · Theobromine

1 Introduction

Methylxanthines and methyluric acids (Fig. 1) are secondary plant metabolites derived from purine nucleotides (Ashihara and Crozier 1999a). The most well known methylxanthines are caffeine (1,3,7-trimethylxanthine) and theobromine (3,7-dimethylxanthine), which occur in tea, coffee, cacao and a number of other non-alcoholic beverages of plant origin. Caffeine was isolated from tea and coffee in the early 1820s, but the main biosynthetic and catabolic pathways of caffeine were not fully established until recently, when highly purified caffeine synthase was obtained from tea leaves and a gene encoding the enzyme was cloned (Kato et al. 1999; Kato et al. 2000). In this chapter, the distribution, biosynthesis and catabolism of methylxanthines in plants are described. Furthermore, the roles of methylxanthines *in planta* and production of decaffeinated coffee plants are summarized.

2 Distribution of Methylxanthines in Plants

Methylxanthines have been found in nearly 100 species in 13 orders of the plant kingdom (Ashihara and Suzuki 2004; Ashihara and Crozier 1999a). Compared with other plant alkaloids, such as nicotine, morphine and strychnine, purine alkaloids are distributed widely throughout the plant kingdom although accumulation of high concentrations is restricted to a limited number of species, including *Coffea*

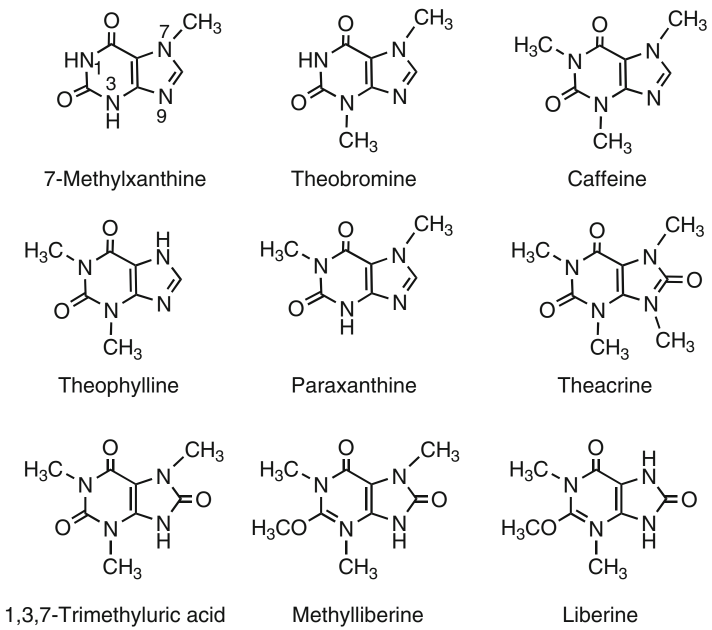

Fig. 1 Structures of purine alkaloids present in plants constituting methylxanthines (7-methylxanthine, theobromine, caffeine, theophylline and paraxanthine) and methyluric acids (theacrine, 1,3,7-trimethyluric acid, methylliberine and liberine)

arabica (coffee), *Camellia sinensis* (tea) and *Theobroma cacao* (cacao). All caffeine-containing plants, except *Scilla maritima*, belong to the Dicotyledoneae. In some species the main methylxanthine is theobromine or methyluric acids, including theacrine (1,3,7,9-tetramethyluric acid), rather than caffeine (Ashihara and Crozier 1999a).

2.1 Coffee and Related **Coffea** *Plants*

The caffeine content of seeds of different *Coffea* species varies from 0.4 to 2.4% dry weight (Mazzafera and Carvalho 1992). Green beans (as opposed to roasted beans, which are used to prepare the beverage) of current commercially cultivated coffee plants contain substantial quantities of caffeine; arabica coffee (*Coffea arabica*) beans usually contain 1.2–1.4% caffeine (Charrier and Berthaud 1975), while robusta coffee (*Coffea canephora*) contains 1.2–3.3% caffeine (Charrier and Berthaud 1975; Mazzafera and Carvalho 1992). There are also several wild coffee species where the green beans contain either no caffeine or extremely low levels of caffeine. Such low-caffeine species include *Mascarocoffea* sp. and *Coffea eugenioides* (Mazzafera and Carvalho 1992; Rakotomalala et al. 1992; Campa et al. 2005).

Caffeine is distributed mainly in the leaves and cotyledons of *Coffea arabica* seedlings, at concentrations ranging from 0.8 to 1.9% dry weight. Essentially, there is no caffeine in roots or in the older brown parts of the shoot (Zheng and Ashihara 2004). Mature leaves of *Coffea liberica*, *Coffea dewevrei* and *Coffea abeokutae* contain the methyluric acids theacrine, liberine [*O*(2),1,9-trimethyluric acid] and methylliberine [*O*(2),1,7,9-tetramethyluric acid] (Fig. 1) (Baumann et al. 1976; Petermann and Baumann 1983). Examples of the purine alkaloid content in the seeds of *Coffea* species are illustrated in Fig. 2a.

2.2 Tea and Related Camellia *Plants*

The caffeine content of young leaves of first flush shoots of *Camellia sinensis*, *Camellia assamica* and *Camellia taliensis* is 2–3% of dry weight, while the level in *Camellia kissi* is less than 0.02%. Unusually, theobromine is the predominant purine alkaloid (5.0–6.8%) in young leaves of a Chinese tea, kekecha (cocoa tea) (*Camellia ptilophylla*) (Ye et al. 1997), and *Camellia irrawadiensis* (less than 0.8%) (Nagata and Sakai 1985). Theacrine and caffeine are the major purine alkaloids in the leaves of another Chinese tea called “kucha” (*Camellia assamica* var. *kucha*). The endogenous levels of theacrine and caffeine in expanding buds and young leaves of kucha are approximately 2.8 and 0.6–2.7%, respectively (Zheng et al. 2002). Some examples of the purine alkaloid content of the leaves of *Camellia* species are shown in Fig. 2b.

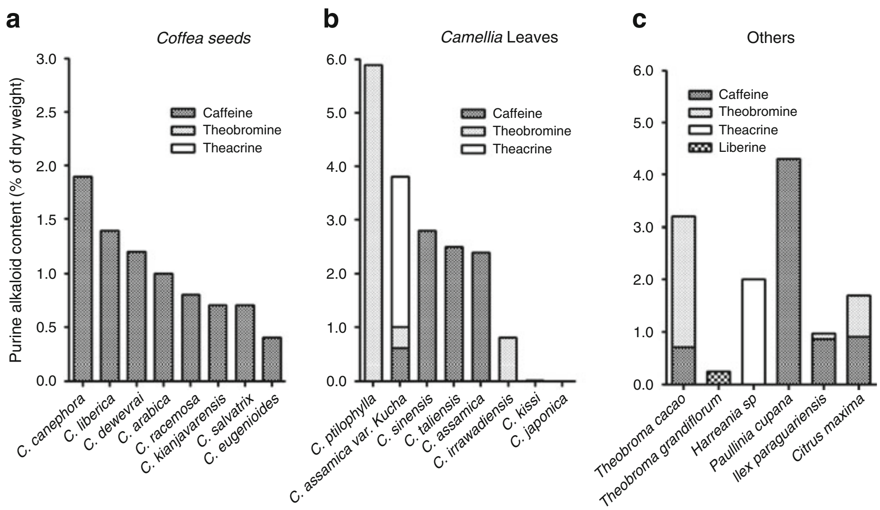

Fig. 2 The methylxanthine and methyluric acid content of selected plant species. **a** Leaves of *Camellia* species, **b** seeds of *Coffea* species and **c** seeds of *Theobroma cacao* (cacao), *Theobroma grandiflorum* (cupu), *Herrania* sp. and *Paullinia cupana* (guarana), leaves of *Ilex paraguariensis* (maté) and anthers of *Citrus maxima* (pomelo). Values were obtained from references cited in the text

2.3 *Cacao and Related* Theobroma *and* Herrania *Plants*

Theobromine is the dominant purine alkaloid in seeds of cacao (*Theobroma cacao*). The cotyledons of mature beans contain 2.2–2.7% on a dry weight basis and 0.6–0.8% caffeine, while shells contain 0.6–0.7% theobromine and 0.5–0.6% caffeine (Senanayake and Wijesekera 1971). Examination of several cacao genotypes representing the three horticultural races Criollo, Forastero and Trinitario revealed considerable variations in the purine alkaloid content of the seed, with slightly higher levels found within the Criollo types (Hammerstone et al. 1994). Roasted seeds of *Theobroma cacao* are used to make cocoa and chocolate products (Duthie and Crozier 2003).

Cupu (*Theobroma grandiflorum*) contains 0.25% liberine in cotyledons and 0.08% in the nut shells (Baumann and Wanner 1980). Hammerstone et al. (1994) reported that theacrine is the principal purine alkaloid in seeds of 11 species of *Theobroma* and nine species of *Herrania*. Quantitative data on purine alkaloid levels in *Theobroma* and *Herrania* species are presented in Fig. 2c.

2.4 *Maté, Guarana and Other Species*

Maté (*Ilex paraguariensis*) leaves are used to make a beverage that is consumed widely in rural areas of Argentina, Paraguay and Brazil. Young maté leaves contain caffeine (0.8–0.9%), theobromine (0.08–0.16%) and theophylline (less than 0.02%). Methylxanthines have been detected in *Paullinia cupana* (guarana), *Paullinia yoco*, *Paullinia pachycarpa*, *Cola* species and *Citrus* species (Baumann et al. 1995; Kretschmar and Baumann 1999; Weckerle et al. 2003). In seeds of guarana, caffeine is located mainly in the cotyledons (4.3%) and testa (1.6%). Citrus flowers can accumulate up to 0.17% methylxanthines on a fresh weight basis; caffeine is the main methylxanthine, but theophylline is also present. Trace quantities of caffeine have also found in the nectar of citrus flowers (Weckerle et al. 2003). Quantitative data of selected samples are shown in Fig. 2c.

3 Methylxanthine Biosynthesis in Plants

Methylxanthines are formed from purine nucleotides in plants. Historically, there have been a number of proposals on the pathways involved in such conversions (see Ashihara and Crozier 1999a). However, data from studies on in situ metabolism of labelled precursors, as well as enzymes and genes have established that the main caffeine biosynthetic pathway is a four-step sequence consisting of three methylations and one nucleosidase reaction starting with xanthosine acting as the initial substrate (Fig. 3). Although the information has been obtained mainly from coffee