Methylxanthines

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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 derivatives 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

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