

Caffeine—A Drug with a Surprise

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The first reported caffeine consumers in history were the members of the Galla tribe in Ethiopia, who were enjoying coffee 1000 years ago. In 1819 Friedlieb Ferdinand Runge isolated caffeine for the first time as a pure compound from coffee beans. The first total synthesis of caffeine was accomplished by Emil Fischer in 1895. Despite the extensive consumption of caffeinated nutrients in our daily lives over the last 1000 years, caffeine received only scant attention by scientists. Large portions of the textbook knowledge were based on common experiences with that particular drug. The speculative nature of these half-truths about caffeine were recently corrected by different sources.^[1] Caffeine (**1**) is one of the most frequently consumed alkaloidal compounds and is omnipresent in many plants. The traditional significant sources of caffeine in our daily lives are coffee, black tea, and cocoa. The alkaloid is also an ingredient of cola beverages and energy drinks.^[2] Many analgesics sold over the counter contain caffeine.^[3] Caffeine is currently gathering increasing attention because of its wide range of applications and the potential of new analytical tools.

The extensive consumption of caffeinated beverages can be attributed to their stimulating effects. After a long time of speculation concerning the low concentrations of caffeine on the

mechanism of action, a Swedish–American research group was able to prove why caffeine gives, despite its low affinity to the receptors, a good buzz. The efficacy of action is caused by a feedback loop in the nerve cells. As already known from previous investigations in mice, caffeine binds and inhibits the adenosine A_{2A} receptor, which is important for voluntary movements. Inhibition causes a preferential phosphorylation of a particular threonine residue of a protein (DARPP-32). A key player in the signaling cascade is protein kinase A; when the adenosine A_{2A} receptor is blocked the activity of the kinase A to dephosphorylate DARPP-32 is drastically reduced, which leads to an increased DARPP-32 level, thereby amplifying the initial effect of caffeine. Mice that lack DARPP-32 were only slightly affected by caffeine.^[4]

A caffeine-containing diet is a widespread practice for many endurance athletes. How caffeine intake causes a substantial improvement of endurance performance was not scientifically clear. However, two recent studies have shed light on this particular area. In conjunction with a carbohydrate-rich diet, an intake of caffeine leads to a clear improvement of endurance performance (riding a cycle ergometer).

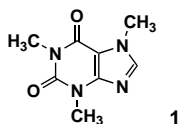
The Australian study reports an increase in performance of around 3% by a single dose of caffeine as well as by multiple smaller intakes. The researchers have also taken a look at cola

beverages, which are held in high esteem by many athletes. A remarkable effect was obtained after increasing the concentration to fourfold that of commercial products. A caffeine intake of 6 mg kg⁻¹ for the tested individuals led to good results.^[5]

An American research group investigated in this context the use of caffeine and habituation to it. An increased performance was found in all of the 21 persons involved. Regular users of caffeine experienced a less stimulating effect and the time to exhaustion was much shorter than for individuals who were considered as non-users. Caffeine produced a significant rise in oxygen consumption after 15 minutes of exercise in all cases.^[6]

Since caffeine is not appropriate for a permanent increase in performance, nonregular users will find the best energetic boost or kick in a cup of coffee or black tea. For the frequent consumers of coffee, who scarcely experiences the stimulating effect of coffee, it might be of some consolation that caffeine in coffee probably substantially lowers the risk of clinical type 2 diabetes. A study of 17000 Dutch people indicated there was a significant decrease in the risk of diabetes when more than seven cups coffee were consumed per day.^[7] It is important to mention the irritants in coffee, such as the chlorogenic acids, which cause adverse effects on the state of health.

Caffeine even offers some unexpected perspectives for amateur gardeners. The drug can be used as an efficient repellent for slugs and snails. Researchers from Hawaii accidentally found that



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surfaces of cabbage leaves heavily disturb the appetite of these gluttonous molluscs. Higher concentrations of caffeine led to uncoordinated writhing, while further increased levels of caffeine killed the critters. The up-take of the alkaloidal compound by the mucous layer of the slug probably happens very fast and initiates a couple of physiological responses. However, the good solubility of caffeine in water means that an application for deterring slugs and snails in an outdoor trial will be challenging, but represents a remarkable alternative to the commercially used metaldehyde treatments. Amelioration by mixing with an appropriate agricultural polymer, which could increase the water resistance of the applied drug, offers the prospect of controlled release.^[8]

The extensive and diverse consumption of caffeine requires further analytical tools to be developed for enhanced product safety. Many naturally occurring materials, especially those containing electron-rich aromatic moieties, have a certain affinity to caffeine. The polyphenolic ingredients of black tea are typical representatives which mask the caffeine and considerably obstruct the analysis. Therefore, several concepts for the selective recognition of this particular drug were developed. Artificial receptors and adaptamers often

prefer the demethylated derivatives of caffeine.^[9] Only a few systems are actually known which recognize and bind caffeine with high affinity and selectivity. The methyl groups at the hypoxanthin structure often prevent the formation of a successful hydrogen-bonding pattern. Molecular imprinting of polymers offers new possibilities.^[10] A combination of adsorption on silanes and a quartz microbalance was used for the detection of caffeine in aqueous media, but yielded results which are still not satisfactory for an analytical application.^[11]

Recently, several research groups accomplished the synthesis of artificial caffeine receptors.^[12] All the systems described, however, were only investigated in organic solvents; a significant selectivity and high affinity for the target molecule in aqueous media will be of particular interest for a promising application in caffeine detection. Important scientific progress is expected in the near future in this field. Although caffeine was isolated from coffee beans for the first time 183 years ago by Runge, it still has some surprises in store.

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