Caffeine chronicles

This natural high may be the most widely used "herbal remedy"; as purified drug it is in a host of medications.

BY MARK S. LESNEY

In the endless quest to fine-tune the proliferating forms of drug delivery, few pharmacologists have come up with anything more attractive than the feel and fragrance, the taste and temperature, of a steaming cup of hot coffee or tea, the sweet chill of an icy cola, or the fulsome delicacy of a high-quality chocolate bar. But at the heart of every one of these is a natural drug, and to aficionados and "addicts" they are only the means to an end—the delivery of caffeine. Caffeine's use as a stimulant and cultural "glue" dates back to the dawn of recorded civilization. And, although the beginnings of its function as a therapeutic agent are almost equally shrouded in history, the pharmacological basis of caffeine's effects (both good and ill) is a product of modern science.

Caffeine in natural products such as coffee, tea, and chocolate is used for a wide variety of physiological and psychological reasons. It acts as a stimulant, increases heart rate and blood pressure, improves reaction times, and creates wakefulness and a generalized sense of alertness. In terms of psychological effect, it has been variously touted as a creativity, memory, and concentration booster. Vast numbers of people rely on their morning cuppa to get going.

Perhaps one of the most famous users of caffeine for both wakefulness and its purported benefits to the intellect (to the point of his consuming dry coffee powder to receive its effects in an era before NoDoz was available) was the 19th century French novelist Honoré de Balzac, who commented: "It brutalizes [the] beautiful stomach linings. . . . sparks shoot all the way up to the brain. From that moment on everything becomes agitated. Ideas quick-march into motion like battalions of a grand army to its legendary fighting ground. . . . the paper is spread with ink—for the nightly labor begins and ends with torrents of this black water" (*1*). Balzac noted, as have most modern users (or abusers) of caffeine, the quintessential tendency to become tolerant of ever-increasing doses of the drug—hence his moving from liquid to solid dosage forms.

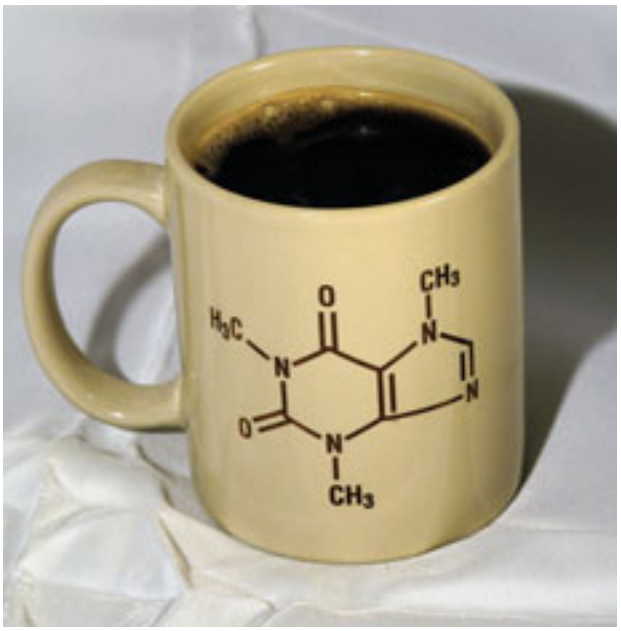

Figure 1. The caffeine molecule.

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Adenosine of the sleep?

Caffeine is 1,3,7-trimethylxanthine (Figure 1), one of a family of alkaloids that also contains the similar-acting compounds theophylline and theobromine. These companion chemicals are found in coffee, tea, cocoa, and a few other plant species.

How caffeine and related compounds work is not completely understood, but most current thinking on the "buzz" it provides to wakefulness and intellectual activity involves its direct chemical impact upon the brain. Contrary to intuitive thinking, caffeine does not act to wake people up. Its real effect is to block the action of the natural relaxation compound adenosine. Under normal conditions, as adenosine builds up during the day and binds to membrane proteins (primarily the A2A adenosine receptors) in the brain, loss of concentration and sleepiness occur at some variable threshold point. Caffeine, however, competitively binds with these adenosine receptors in the brain, preventing the sleepiness signal from getting through.

Caffeine physiology is especially interesting in that the chemical acts in a gender-specific manner, more easily metabolized by women than men. Of cultural and physiological interest as well is the fact that caffeine is more readily metabolized by smokers—perhaps a rationale for the almost cliché linkage of smoking to that afterdinner cup.

For those who would take up coffee-drinking as brain food, however, there is unfortunate news—caffeine helps to improve mental performance, but only when other bodily conditions such as fatigue, pain, or sleepiness have diminished it—and then only to unimpeded normal levels, not as a sudden IQ pill. For this reason, the U.S. military has shown significant interest in caffeine as a possible means for improving the performance of soldiers under the unavoidable conditions of fatigue and sleepiness that often occur during extended military campaigns.

Good to the last drug?

Purified caffeine is used to complement a host of medications and is prevalent in over-the-counter pain relief, especially for headaches. Because caffeine increases the oral and rectal absorption of the ergot alka-

loids sometimes used to treat migraines, it is often prescribed in conjunction with such medications. In addition, because caffeine reduces blood flow to the brain, it is valuable as an adjunct to headache relief (*1*).

Despite numerous studies, there is no evidence that caffeine is a human carcinogen. In fact, recent studies have demonstrated that caffeine, topically applied, can protect mice from developing skin cancer (*2*).

Because it is a weak bronchodilator and can decrease lung muscle fatigue, caffeine has been used as a folk remedy for asthma and as an adjunct to some oral prescriptions. Investigating its use led to the discovery that the related alkaloid theophylline is a somewhat more efficient bronchodilator. That compound became one of the first clinical treatments for asthma, though it is currently being supplanted (*www.mtsinai.org/pulmonary/Asthma-Rx.htm*).

One of the most recent and promising research developments regarding caffeine is its potential as a preventive for, and indicator of, possible therapeutic targets for Parkinson's disease. Michael A. Schwarzschild and his colleagues at Massachusetts General Hospital found that, using a mouse model of the disease, caffeine and other A2A receptor antagonists were found to decrease disease-associated neurotoxicity. This provided a mechanistic model for epidemiological studies that showed that Parkinson's sufferers were 4–8 times less likely than control subjects to be heavy coffee drinkers (*3*).

The baneful bean?

Of course no drug is without its side effects and possible toxicities—wasn't it Paracelsus who declared that the poison is in the dose? Caffeine is no exception.

Because caffeine affects both heart rate and blood flow, for those with hypertension and a variety of other heart-related conditions the drug can cause significant problems. A recent study has shown that caffeine coupled to stress can significantly raise blood pressure even in healthy adults and habituated coffee drinkers (*4*).

In addition, caffeine can present other dangers for individuals with certain psychological predilections. According to University of Washington psychiatrist Stephen Dager, "People who are prone to panic attacks tend to be sensitive to caffeine. I frequently evaluate people who have severe panic attacks or anxiety. . . . Before I start thinking about starting them on a medication, I always recommend that these people discontinue caffeinated products" (*http://depts.washington.edu/uweek/archives/2002.06.JUN_06/hs_f.html*).

But the psychological effects are definitely not all bad, as recent research demonstrates that caffeine users are less prone to suicide (*5*).

And, significantly, because of its effects on calcium uptake and use, caffeine can also be a problem for individuals, predominately women, who are prone to osteoporosis (*6*). This effect is eliminated in women who consume the equivalent of a glass of milk daily—a plus for latte drinkers.

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Caffeine addiction is also an authentic phenomenon following the typical pattern of other addictive substances, including increased dosage tolerance, decreased effectiveness, and physiological and psychological symptoms (primarily headache and excessive fatigue, sometimes nausea) upon withdrawal. This addiction tolerance is the key reason why nonusers can achieve a significant "buzz" and a full night of insomnia with a single cup of coffee, whereas true caffeine "junkies" (the author of this piece and the aforementioned Balzac to name just two) need a half pot of joe just to keep them from dozing off.

Coffee, tea, or baby & me?

Perhaps some of the most troublesome of the public fears regarding caffeine are a result of often confusing research results on the chemical's effects on reproductive health and on fetuses and nursing infants. Original laboratory studies on caffeine-treated pregnant rats raised significant fears of birth defects. But the levels required were equivalent to over 70 cups of coffee a day. Epidemiological research has shown no effect from the caffeine found in moderate coffee consumption (no more than three cups a day) on the rate of either miscarriages or birth defects. Similarly, caffeine's effects on sperm motility do not seem to be problematic except for excessive consumers and men with other fertility problems.

Caffeine easily passes from mother to developing fetus; since the fetus has less ability to break down the compound easily, frequently newborns are born with a coffee "buzz" inherited from heavily consuming mothers. And since caffeine readily passes into all bodily fluids, mothers' milk can act as a caffeine-delivery system to nursing infants—generally with no ill effects other than increased wakefulness and fussiness in the child. For these reasons, however, it is recommended that pregnant women and nursing mothers drink no more than three cups of coffee daily (Center for the Evaluation of Risks to Human Reproduction; *http://cerhr.niehs.nih.gov/genpub/topics/caffeine-ccae.html*).

So, happily for those who are addicted to their daily dose of coffee, tea, or chocolate, caffeine appears to indeed be "Generally Regarded as Safe", as its FDA status since 1958 would have it. Individuals with health conditions such as hypertension, male infertility, panic attacks, osteoporosis, and pregnancy, and those who are nursing, should be wary of the drug, or at least aware of the potential effects consuming it may have on their conditions. But for the vast majority of individuals, the morning "cuppa" can be considered a not-so-guilty pleasure after all.

References

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