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FILE: ▪Coffee
▪Health Effects
▪Drug Interactions

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Re: Health Effects of Coffee

Nolan L. The world's favorite beverage—coffee—and health. *Journal of Herbs, Spices & Medicinal Plants* 2001;8(2/3):119-159.

Coffee is the world's favorite beverage, with an estimated 1.5 billion cups of coffee being drunk every day. This review explores the legend, history, and economics of the drink and summarizes current knowledge on the health effects of coffee/caffeine on the central nervous system (CNS) and cardiovascular system and the effect of caffeine on reproduction, bone loss, and cellular division.

Historians trace coffee's origins to Ethiopia, where it still grows wild in the rain forest. Before its use as a beverage 700 years ago, coffee evolved from food, to wine, and then to medicine. Coffee reached Arabia in the 1200s. During the 1500s, it was introduced to Turkey and appeared in Italy in the early 1600s. It is estimated that coffee came to the Americas in the 1660s and was grown in Brazil in the 1700s.

Coffee is currently produced mostly by underdeveloped countries and consumed by the most developed countries. Coffee plants are divided into three major groups—Brazils, Milds, and Robustas. The Milds include *Coffea arabica* grown outside of Brazil. *Coffea robusta* (*Coffea canephora*) is a different kind of coffee, which is grown almost entirely in Africa.

Biochemistry of Coffee

Caffeine, theophylline, and theobromine are three closely related alkaloids (methylated xanthines) that occur in plants widely distributed throughout the world, including the coffee bean. It is well established that caffeine is a stimulant, but caffeine and related compounds possess other important pharmacological properties that can be used as valuable therapeutic agents. They stimulate the CNS, act on the kidney to produce

diuresis, stimulate cardiac muscle, and relax smooth muscle, most notably the bronchial muscle. However, they vary markedly in the intensity of their actions on various organs.

Caffeine is a powerful CNS stimulant, exciting the CNS at all levels, theophylline is less so, and theobromine is virtually inactive in this respect. Caffeine's main action is believed to produce a more rapid and clearer flow of thought and to alleviate drowsiness and fatigue. These effects may be brought on by the administration of 150-250 mg of caffeine, the amount contained in one or two cups of coffee or tea.

Toxicity of Coffee's Components

The xanthines are relatively nontoxic drugs, with theobromine being the least toxic. Fatal poisonings due to caffeine are extremely rare, but a few have occurred as the result of extremely high intakes of the compound. In animals administered large doses of caffeine, death appears to originate in the CNS, as the animals undergo convulsions followed by respiratory arrest.

Metabolism of Coffee's Components

The methylxanthines are readily absorbed after oral, rectal, or parenteral administration. The absorption rate depends on the preparation used and on the route of administration. Caffeine is rapidly absorbed after ingestion with peak plasma levels after thirty to sixty minutes. Numerous studies have determined the major metabolic pathways for caffeine in man, which have been shown to be different than those in other animal species.

Effects of Methylxanthines on Cellular Metabolism

Early attempts to discover the cellular basis of the pharmacological actions of methylxanthines soon revealed that these compounds have pronounced effects on cellular metabolism. Methylxanthines, particularly theophylline, are competitive inhibitors of cyclic nucleotide phophodiesterase, an enzyme that catalyzes the conversion of cyclic AMP to 5'-AMP. Cyclic AMP (cAMP) concentrations are thus elevated in some tissues following exposure to methylxanthines. The catecholamines secreted by the adrenal glands, such as norepinephrine and dopamine, also increase the concentration of cAMP formation. Thus, both the methylxanthines and the catecholamines would be expected to have particular pharmacological properties that are thought to depend on their common ability to increase the cyclic 3',5'-AMP concentration in the tissues. This shared biochemical mechanism of action of xanthines and catecholamines may account for the fact that the xanthines markedly potentiate the cardiac responses to the catecholamines.

Over the past ten to fifteen years, interest in the behavioral effects of caffeine has led neuropharmacologists to explore the effects of caffeine and other methylxanthines on the release of neurotransmitters. A few more recent studies have explored the possibility that caffeine's effects may be mediated by other mechanisms, such as interaction with adenosine receptors, or affect other transmitters, such as gamma-aminobutyric acid (GABA) and acetylcholine.

Several laboratories have reported that acute administration of caffeine elevates brain levels of serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA). Overall, caffeine's

effects of 5-HT synthesis and turnover appear complex and are the subject of current research. Caffeine has frequently been studied for its effects on catecholamine neurons in the brain. Early reports indicated that caffeine injection enhanced norephinephrine (NE) synthesis and turnover. The precise mechanism by which caffeine stimulated NE neurons in the brain is unknown. One popular hypothesis is that caffeine acts by blocking an adenosine receptor on the NE neurons.

There are several hypotheses suggested for how caffeine elicits a cellular response:

- On or within cells via adenosine receptors (whether by causing neurons to release catecholimines or acetylcholine);
- Within cells via phosphodiesterase inhibition;
- Combination of the above; or
- An as yet unknown mechanism.

Cellular division

Early studies involving the effect of caffeine on cellular division revealed that caffeine inhibited cellular division and caused chromosomal breaks. One of the first studies on human cells revealed that caffeine seemed to act primarily at the time of DNA replication, suggesting that the rate of the cell division cycle was the relevant factor in determining the detrimental effects of caffeine. Breaks and other abnormalities were produced, and the number of breaks was very nearly a linear function of caffeine concentration. From the dose relationship, it was estimated that a concentration of 1 mg/ml would produce a negligible increment in the spontaneous rate of chromosome breakage. From this data, it seems unlikely that caffeine would be a significant mutagen in humans.

The effects of caffeine on congenital malformations in the offspring of mice were also examined. Pregnant mice were given a single intraperitoneal injection of one percent caffeine once during the seventh to fifteenth days of pregnancy. Caffeine administration resulted in embryonic death or malformed fetuses. "Incidence of embryonic death was highest for injections given during the seventh through twelfth days when resorption of all embryos of a litter was sometimes induced."

Drug metabolism

Animal studies have found caffeine to increase the drug-metabolizing enzymes aminopyrine N-demethylase and p-nitroanisole o-demethylase, while theophylline causes a slight decrease. But rats treated with caffeine failed to show an increase in cytochrome P-450, a major drug-metabolizing enzyme.

ATP metabolism

It has been suggested that caffeine does not inhibit the mobilization of energy stores, but does inhibit the processes involved with the restoration of those stores.

Interactions of Caffeine With Drugs That Affect Neural Transmission

All drugs affect neural transmission in one way or another, but some are known to have specific effects on synaptic or neuroeffector junction sites. One line of research has

involved the interaction between caffeine and L-dopa, a precursor of the adrenergic neurotransmitter norepinephrine. In two studies with mice, increased brain-levels of dopamine were associated with caffeine-dopa-induced hyperactivity. Chronic administration of L-dopa is the treatment of choice in the management of Parkinson's disease. Caffeine may alter the therapeutic response to L-dopa, and thus the wide individual variation in response to this treatment of choice in the management of Parkinson's disease and may, in fact, be of value in the treatment of the disease.

Monoamine oxidase inhibitors substantially increase the toxicity of caffeine. They also prevent disappearance of other presumed neurotransmitters that may be involved in caffeine's action. Although caffeine obviously interacts powerfully with many of the drugs that alter neural transmission, the precise nature of caffeine's effects remains unclear.

Coffee/Caffeine and Health

Coffee and caffeine have been studied in relation to causing myocardial infarction, arrhythmias, hypertension, hyperlipidemia, gout, anxiety, fibrocystic breast disease, various cancers, birth defects, and osteoporosis. Despite decades of research on coffee and caffeine and centuries of consumption, there are many misconceptions concerning the potential health risks associated with caffeine or coffee.

Cardiovascular System

Numerous studies have examined caffeine consumption and its effects on blood pressure and serum lipids. The majority of these studies conclude that caffeine has no adverse effect on cardiovascular risk. A number of the studies have shown that any temporary rise in blood pressure due to caffeine consumption is typical to changes produced during routine daily activities. A literature review on the effect of caffeine on cardiac arrhythmias revealed that consumption of up to six cups of coffee a day does not increase the severity of cardiac arrhythmias.

Nervous System

Numerous studies have confirmed that caffeine, in moderate doses, enhances alertness, well-being, energy, motivation, and concentration. Caffeine improves performance on vigilance tasks but the effects on more complex tasks are difficult to analyze. When regular caffeine consumption is reduced or abruptly discontinued, some users experience withdrawal symptoms including headaches, fatigue, or drowsiness. It has been suggested that gradually reducing consumption by ½ cup per day can greatly alleviate withdrawal symptoms. Researchers have also found that consuming caffeine has a positive effect on exercise performance, increasing both energy and endurance.

Reproductive System

Reviews of 26 human studies since 1981 pertaining to the effect of caffeine consumption on reproduction revealed that caffeine, as currently consumed by pregnant women, has no discernable adverse effects on fetuses. Since 1993, various researchers have conducted extensive studies in pregnant women and monitored the amount of caffeine they consumed from conception to birth. The studies accounted for nausea, smoking, alcohol

use, and maternal age; no correlation was found between caffeine consumption of up to 300 mg per day and adverse pregnancy outcomes, including spontaneous miscarriage.

Skeletal System

Caffeine has been shown to mobilize calcium from internal storage sites in cells of skeletal muscle. Because caffeine has been shown to impact calcium excretion, it has been considered a risk factor for osteoporosis, particularly in post-menopausal women. However, in 1994, the National Institutes of Health concluded that caffeine had not been found to affect calcium absorption or excretion significantly, and a tablespoon or two of milk could offset any adverse effect.

Cancer

Most attention on a possible connection between coffee, caffeine, and cancer has focused on three cancer sites: the pancreas, colorectum, and bladder. Despite concern in the 1980s that coffee might be linked to pancreatic cancer, recent updated overviews of coffee and cancer epidemiology provide reassuring information on the absence of any meaningful association of coffee with most common cancers. In addition, animal and in vitro studies suggest that coffee has no carcinogenic effects.

The reviewer concludes that all literature, taken together, suggest that drinking coffee in moderation (three cups per day) is safe. Most of the accusations against coffee have not been confirmed by investigations carried out with proper scientific methodology.

--Densie Webb, Ph.D.

The American Botanical Council has chosen not to include the original article due to the prohibitive reprint fee required by the publisher.