Caffeine

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INTRODUCTION

In a civilised society, the ritual of "going for coffee and a chat" is almost religiously observed. In fact, in industrialised countries coffee is one of the most widely used non-alcoholic beverages. Caffeine is an important component of this drink and has been frequently described as the most widely used drug in the world. A 150ml cup of coffee contains about 60-120mg of caffeine.[1]

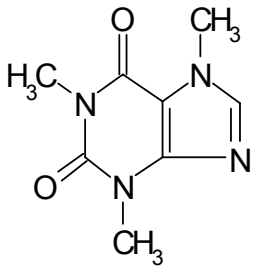
Caffeine is consumed in numerous other forms including tea, soft drinks, cocoa and chocolate. Also, it is found in several medications including over-the-counter cold and allergy medicines, analgesics, appetite suppressants, and stimulants. Therefore, it appears that caffeine has been part of the typical daily diet for many hundreds, if not thousands of years. Other factors that may influence our consumption of caffeine containing beverages include personality traits as well as environmental stressors.

PHARMACOLOGICAL PROPERTIES OF METHYLXANTHINES

Caffeine is an alkaloid and belongs to the methylxanthine group of compounds, of which theophylline and theobromine are also important members. These compounds have different biochemical effects and are present in different ratios in different plant extracts. Caffeine is by far the most popular drug in the group (Figure 1).

Caffeine is readily absorbed from the gastrointestinal tract (GIT) and rapidly distributed in all the body fluids. Ingestion with food does not appear to affect its absorption.[1] In most patients, the drug obeys first-order kinetics within a therapeutic range. At higher concentrations, zero-order kinetics becomes evident as the enzymes involved in its metabolism are saturated.[2] The half-life of caffeine is approximately 3.5 hours, although in overdose this can increase up to 9 hours.[3] The half-life is prolonged by factors such as being pregnant, being on oral contraceptives and having liver disease.[4] Smoking and hepatic microsomal enzyme inducers, like phenobarbital, reduce the half-life of caffeine.[3] Caffeine is excreted in the urine as 1-methyluric acid, 1-methylxanthine and an acetylated uracil derivative.[4] Both genetic and environmental factors influence the considerable inter-individual variability that exists in the rate of caffeine elimination.

Figure 1.
Caffeine: 1,3,7-trimethylxanthine



The methylxanthines have effects on the central nervous system (CNS), kidney, cardiovascular system, and skeletal and smooth muscle (see below). Gastrointestinal disorders, tremor, headache and insomnia are among a number of adverse effects that can occur. Methylxanthines can induce palpitations and even cardiac arrhythmias.[4]

Caffeine is a non-selective antagonist of adenosine at both A1 and A2 adenosine cell surface receptors. A1 receptor stimulation inhibits the release of noradrenaline at the sympathetic smooth muscle junction, whereas A2 receptors have a direct vasodilatory effect.[5] Methylxanthines can be shown, in vitro at high concentrations, to inhibit the enzyme phosphodiesterase causing a hydrolysis of cyclic nucleotides. This inhibition leads to higher concentrations of intracellular cAMP. This effect could explain the cardiac stimulation and smooth muscle relaxation produced by methylxanthines, but the topic remains somewhat controversial. Methylxanthines also have direct and indirect effects on intracellular calcium concentrations. This uncoupling of intracellular calcium increases with muscle contractile elements.[2]

PHYSIOLOGICAL EFFECTS OF METHYLXANTHINES

At low to moderate doses, methylxanthines can affect the CNS causing a mild cortical arousal with increased alertness and deferral of fatigue. In unusually sensitive individuals, the caffeine contained in a single beverage is sufficient to cause nervousness and insomnia. At very high doses, medullary centres are stimulated, and focal and generalised convulsions may occur. Methylxanthines can also impact the musculoskletal system demonstrated by an increase in the strength of isolated skeletal muscle contractions in vitro. They have potent effects on the contractility of the diaphragm and they reduce diaphragmatic

fatigue in both normal subjects and in those with a chronic obstructive pulmonary disorder (COPD). The methylxanthines can also have a relaxation effect on various types of smooth muscle, consequently producing a major therapeutic action of bronchodilation. Another important physiological effect of methylxanthines is an increase in the production of urine. It is suggested that this effect is related to the increase in both renal blood flow, especially in the medulla, and the glomerular filtration rate.[5]

THE CARDIOVASCULAR EFFECTS OF CAFFEINE

Caffeine can affect the cardiovascular system through a variety of mechanisms (Table 1).[2,5] The findings of caffeine's effects on the cardiovascular system are confounding and many are inconsistent among studies.

For example, the administration of 250-300 mg of caffeine to methylxanthine-naive individuals may produce small decreases in heart rate but such doses usually have no effect on those who drink caffeine regularly. The caffeine-induced lowering of heart rate may be a refractory bradycardic response to pressor action or a direct effect on the cardiac or sino-atrial node (SAN). There is controversy as to whether circulating catecholamines or plasma-renin activity increases significantly in caffeine-naive subjects, however, it is generally agreed that little change occurs in chronically exposed individuals.[2,5] In unusually sensitive individuals consumption of a few cups of coffee may result in arrhythmias, but in most people parenteral administration of higher doses of methylxanthines produces only sinus tachycardia and increased cardiac output.

SHORT TERM VASCULAR EFFECTS OF CAFFEINE

After acute intake of caffeine, increased systolic and diastolic blood pressure levels have been detected.[5] Acute intake of caffeine increases vascular resistance, indicating a vasoconstrictor effect. It seems that caffeine plays an active role in this vasoconstriction effect since regular coffee intake has a tendency to increases blood pressure, whereas regular intake of decaffeinated coffee appears to have little or no effect.[6] A 200-250 mg dose of caffeine (2-3 cups of coffee) increases systolic blood pressure by 3-14 mmHg and diastolic blood pressure by 4-13 mmHg in normotensive subjects.[5] The pressor effect correlates with increases in plasma caffeine concentrations. Caffeine-induced increases in blood pressure may last for 4 hours or longer.

Table 1: Important Mechanisms Effecting Cardiovascular System

Antagonistic effects on adenosine receptors
Inhibition of phosphodiesterase (increase in cyclic nucleotides)
Activation of the sympathetic nervous system (release of catecholamines from the adrenal medulla)
Stimulation of adrenal cortex (release of corticosteroids)
Renal effects (diuresis, natriuresis, activation of the renin-angiotensin-aldosterone system)

Hypertensive or hypertension-prone subjects seem to have a more pronounced acute pressor response to caffeine than normotensive subjects.[7,8] Also, individuals experiencing mental and physical stress appear to exhibit the pressor effect of caffeine, which suggests that the response is additive or enhanced. It has also been suggested that the pressor effect of caffeine is stronger in older subjects than in the young.[9] Finally, people who do not normally consume caffeine tend to experience a stronger pressor effect with acute caffeine intake than frequent consumers of caffeine. The degree of blood pressure response associated with a single dose of caffeine seems to be inversely related to the plasma caffeine concentration at the time of administration.[5]

CHRONIC CAFFEINE INTAKE AND BLOOD PRESSURE

The evidence for long-term effects on blood pressure is inconclusive to say the least. Some long-term studies have shown that caffeine induces persistent pressor effects in habitual consumers, often as much as 6mmHg. It has been found that changing from caffeinated to decaffeinated coffee results in a slight fall (2-5mmHg) in blood pressure[5]. A Brazilian study found that the hypertensive effect of caffeine disappeared with chronic use in young adults.[7] However, many other epidemiological studies reported that chronic caffeine consumption or abstinence from caffeine was not accompanied by significant changes in blood pressure.

A large study, of male self-defence officials in Japan, found that habitual coffee drinkers in the group had lower blood pressure than non-drinkers regardless of alcohol use, cigarette smoking, obesity and glucose intolerance.[6] Another study found that regular consumption of coffee appears to be positively associated with an increased risk of thromboembolic stroke in middle-aged hypertensive

men.[5] A study of 45,589 American men between the ages of 40-75 years without any history of cardiovascular disease were assessed to determine the relationship of coffee consumption with the risk of myocardial infarction and the possible risk of stroke.[10] In this case, the findings indicated that the use of caffeinated coffee and the total intake of caffeine did not significantly increase the risk of coronary heart disease or stroke.

TOLERANCE TO CAFFEINE

The development of tolerance may explain the failure to detect an increase in blood pressure caused by repeated administration of caffeine.[5] After regular intake of caffeine, the pressor response has been reported to decrease within a few days. However, in some studies caffeine was still able to elevate blood pressure during habitual consumption, suggesting that tolerance may only play a partial role in the pressor reponse. Also, the pressor response to caffeine may be regained after a relatively short period of abstinence. For example, caffeine ingested after an abstinence of 10-12 hours was shown to increase blood pressure in regular coffee drinkers. A pressor response to a second cup of coffee of the day has also been observed. It is possible that there are people at either end of the spectrum: those who have a higher sensitivity to caffeine and those with lesser susceptibility to the development of tolerance.

One study was carried out to determine the blood pressure response during exercise between individuals who regularly consumed caffeine and those who did not consume caffeine. Caffeine consumption resulted in significant increases in both systolic and diastolic blood pressures at rest and during exercise. No differences were observed between those who were habitual consumers and those who regularly abstain from caffeine.[8]

It is interesting to note that chronic caffeine users who become tolerant to the effects of caffeine may be seen to experience withdrawal in its absence. Typically this abstinence syndrome takes the form of headaches, increased sleepiness and decreased alertness.[1] The psychiatric literature describes associations of caffeine use with a syndrome of anxiety, depression, and even psychosis.[11] Recently, a caffeine dependence syndrome has been characterised by withdrawal, tolerance, and failure to control use despite the knowledge that it is likely to be contributing to an existing physical or psychological problem.[12] Several studies have also suggested possible associations with osteoporosis ulcers and cancer.[13,14,15,16]

POSSIBLE ROLE OF CAFFEINE IN HYPOERTENSON

Five hypertension risk groups (optimal BP, normal BP, high-normal BP, stage 1 hypertension, diagnosed hypertension) were the focus of a study on the acute effects of caffeine.[17] The study indicated that, while all groups exhibited increases in both systolic and diastolic blood pressures, the strongest response to caffeine was among the diagnosed hypertension group, followed by the stage 1 and high-normal groups and then by the normal and optimal groups.

The effects of caffeine on blood pressure and cortisol secretion were examined during a period of elevated work stress in male medical students.[18] These groups consisted of individuals with high and low risk factors for hypertension and were regular consumers of coffee.[8,19] The study found that stress and caffeine resulted in additive increases in blood pressure. Therefore, it has been recommended that individuals at high risk for hypertension should refrain from the use of caffeinated products, especially during periods of heightened stress.[19]

The effects of rest and exercise in relation to caffeine intake and the affect on pressor regulation in men at risk of hypertension were investigated.[19] Conclusions drawn from this study indicated that restriction of caffeine before exercise could benefit persons who are at risk for hypertension or who have an unusual sensitivity to caffeine.

In hypertensive subjects the combination of coffee and smoking produced a stronger and more sustained pressor response than each stimulus alone.[5] Moreover, in a cross-sectional observational study using 24-hour ambulatory blood pressure monitoring, moderate smokers and coffee drinkers with mild hypertension had significantly higher daytime blood pressure than non-smokers and those who did not drink coffee. This suggests that the effect might recur throughout the day, despite the increased caffeine catabolism in smokers.[5]

Mahmud and Feely have found that caffeine acutely stiffens the aorta and impedes the function of the peripheral vascular arteries.[20] This may be an important vascular mechanism for the hypertensive effect of caffeine.

SUMMARY AND CONCLUSION

Caffeine has variable effects on the cardiovascular system depending upon the usage (acute or chronic) and the disposition of the individual. The factors that affect individ-

ual disposition include: age, pregnancy, hypertension-status, burden of stress, smoking status, and caffeine tolerance. In general, acute intake of caffeine increases systolic and diastolic blood pressure levels. The pressor effect correlates with increases in plasma caffeine concentrations, and has been enhanced during times of mental and physical stress. Those who are caffeine-naive tend to experience a stronger pressor effect with acute caffeine intake than habitual consumers.

The information available regarding the effects of chronic caffeine intake on blood pressure was inconclusive. Whereas some long-term studies suggest that caffeine induces a persistent pressor effect in the habitual consumer, other studies suggest chronic caffeine consumption is not accompanied by significant changes in blood pressure.

One study concluded that consumption of coffee appeared to be positively associated with an increased risk of thromboembolic stroke in middle-aged hypertensive men. Another study indicated that the use of regular coffee and the total intake of caffeine did not appreciably increase the risk of coronary heart disease or stroke.

Hypertensive or hypertension-prone subjects seem to have a more pronounced pressor response to caffeine than normotensive subjects. Studies concluded that restriction of caffeine, before exercise and during times of heightened stress, could benefit persons with risk for hypertension or unusual sensitivity to caffeine. The combination of coffee and smoking in hypertensive subjects produces a stronger and more sustained pressor response than each stimulus alone.

Although some of the information available regarding the long-term vascular effects of caffeine is conflicting, the overall conclusion would be that anyone who smokes or has risk factors for hypertension should try to avoid caffeine products as much as possible.

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