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Caffeine at High Altitude: Java at Base Camp

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Introduction

A survey of high altitude destination resort web sites finds that most recommend avoiding caffeine at high altitude. Reducing or avoiding caffeine at high altitude is also a common admonition in visitors' guides in Colorado and other places. Why does caffeine use at high altitude have a bad reputation? Is it a carry-over from a minority opinion on its use in general (Lovett, 2005)? Does scientific evidence support this? Does caffeine affect acclimatization, the development of high altitude headache and acute mountain sickness, or exercise performance at altitude? A review of the scant literature suggests that, if anything, caffeine is likely to be helpful at altitude, rather than detrimental.

Caffeine is a xanthine alkaloid, an adenosine receptor blocker and psychoactive stimulant. The German Friedrich Runge discovered caffeine in 1819. He coined the term kaffein, a chemical compound in coffee, which in English became caffeine. Caffeine is found in varying quantities in some plants, where it acts as a natural pesticide. Humans ingest caffeine from the cherries of the coffee plant and the leaves of the tea bush, as well as from various foods and drinks containing products derived from the kola nut and cacao plant. Humans have apparently ingested caffeine since the Stone Age. Beverages containing caffeine, such as coffee, tea, soft drinks, and energy drinks, are popular today, making caffeine the world's most widely consumed psychoactive substance; it is legal and unregulated in nearly all jurisdictions. Throughout the world, it is estimated that 80% of adults consume caffeine daily, and 90% in North America (Table 1).

Pharmacodynamics and Metabolism of Caffeine at High Altitude

Is the biology of caffeine the same at low and high altitude? A change in the pharmacodynamics of caffeine could alter its effects. In healthy adults at sea level, caffeine's half-life is approximately 4.9 h. (In women taking oral contraceptives, this increases to 5 to 10 h, and in pregnant women the half-life is roughly 9 to 11 h.) Caffeine is metabolized in the liver by the cytochrome P450 oxidase enzyme system, specifically CYP1A2. Jürgens and colleagues (2002) studied CYP enzyme activity at baseline and 24 and 96 h after a stay at 4559 m in 12 subjects. They found no significant change in the metabolic ratio of caffeine and only minor changes in other substance metabolic ratios; they concluded that altitude hypoxia had no clinically significant effects on CYP enzymes in humans. Kamimori and colleagues (1995a) studied micro swine after 21-day exposure to 4600 m. Caffeine clearance nearly doubled and, consistent with Jürgens and colleagues, there was no change in the ratio of primary metabolites. They concluded that the increase in caffeine clearance was owing to increased hepatic blood flow. These same investigators (Kamimori et al., 1995b) then studied the issue in eight males after 16 days at 4300 m. Compared to sea level, the half-life of caffeine decreased from 6.7 to 4.7 h, the area under the curve (AUC) decreased by 32%, and clearance increased 36%. They also reported an increase in the AUC ratio of metabolites to caffeine, suggesting that either metabolite formation or elimination was increased at high altitude. These studies taken together indicate that high altitude hypoxia appears to hasten the clearance of caffeine and decrease the area under the curve, in part because of increased hepatic blood flow and, perhaps, a change in metabolism. Caffeine may thus be expected to have a shorter duration of action at high altitude compared to low altitude.

The metabolites of caffeine contribute to caffeine's effects. Paraxanthine is responsible for an increase in the lipolysis process, which releases glycerol and fatty acids into the blood to be used as fuel by the muscles. Theobromine is a vasodilator that increases the amount of oxygen and nutrient flow to

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Caffeine Content of Select Common Foods and Drugs

Product	*Serving size*	*Caffeine per serving (mg)*
Caffeine tablets	1 tablet	100–200
Excedrin tablet	1 tablet	65
Dark chocolate bar (45% cacao content)	1 bar (43 g)	31
Light chocolate bar (11% cacao content)	1 bar (43 g)	10
Percolated coffee	207 mL (7 oz)	80–135
Drip coffee	207 mL (7 oz)	115–175
Decaffeinated coffee	207 mL (7 oz)	5–15
Espresso	44–60 mL (1.5–2 oz)	100
Tall coffee	360 mL (12 oz)	240
Black tea	177 mL (6 oz)	50
Green tea	177 mL (6 oz)	30
Coca-Cola	355 mL (12 fl oz)	34
Red Bull	250 mL (8.2 fl oz)	80

the brain and muscles. Theophylline is a smooth-muscle relaxant that chiefly affects bronchioles and acts as a chronotrope and inotrope to increase heart rate and efficiency. All three of these compounds are much weaker than caffeine. In addition, infusions from coffee and tea plants contain other substances with biological actions, such as theobromine in chocolate and polyphenols in tea and coffee. In fact, research suggests that the polyphenols in coffee can counteract some of the effects of caffeine, making caffeine tablets, for example, a superior choice to coffee for exercise improvement.

Clinical Effects

Does caffeine lead to dehydration?

One reason tourist literature recommends avoidance of caffeine is because of its feared diuretic effect. The layperson seems to exaggerate the importance of dehydration at high altitude, and there is a mistaken belief that dehydration can lead to AMS. While symptoms of dehydration are similar to AMS, no compelling evidence suggests that dehydration contributes to AMS. Nonetheless, many apparently think that caffeine should be avoided for fear of dehydration leading to AMS. Caffeine, in fact, does have diuretic properties, but only in sufficient doses in subjects without tolerance for it. Regular users develop a strong tolerance to this effect, and studies in athletes and nonathletes at low altitude have generally failed to support the common notion that ordinary consumption of caffeinated beverages contributes significantly to dehydration (Armstrong et al., 2005; Millard-Stafford et al., 2007). Supporting this, a clinical study conducted at Everest base camp (5345 m) in 13 subjects used a crossover experimental design with two 24-h dietary interventions (Scott et al., 2004). Ingested fluid volume was the same, but for one intervention the fluid was mostly black tea. No other source of caffeine was allowed. Urine volume was identical in the tea and no-tea groups, as were other markers of hydration status. However, the tea drinkers reported less fatigue. Unfortunately, neither ingested dose nor blood levels of caffeine were measured. The authors emphasized that even in an environment of cold and altitude, where diuresis is stimulated, caffeinated tea did not increase diuresis, while it did improve mood. (Scott et al., 2004).

Does caffeine depress ventilation?

One measure of a drug's safety at altitude is its effect on ventilation. Clearly, caffeine stimulates ventilation rather than depresses it, and therefore caffeine might actually be helpful. Although no studies have addressed whether caffeine facilitates acclimatization to altitude, there are good physiologic studies suggesting that it might. Caffeine has long been documented as a respiratory stimulant. D'Urzo and colleagues (1990) found that caffeine increased hypoxic ventilatory response (HVR, +135%), hypercapnic ventilatory response (HCVR, +28%), and the ventilatory response to exercise (+14%). In addition, caffeine increased both resting ventilation (41%) and metabolic rate. However, they administered a large dose of 650 mg and to only 7 subjects. It is likely that smaller doses would have similar but less robust effects on ventilation. Although caffeine had only a small effect on respiratory muscle fatigue at sea level (Lanigan et al., 1993), its effect could be more pronounced at altitude, where ventilation is markedly increased from sea level and muscle fatigue is relatively more important. Caffeine has been used for decades in neonates for treatment of apnea (Comer et al., 2001; Chardon et al., 2004). At 4 mg/kg/day, it apparently works by increasing the effectiveness of chemoreceptor activity. Caffeine also stimulates ventilation in athletes with exercise-induced hypoxemia. Chapman and Stager (2008) administered 7 mg/kg to 7 adults and, although ventilation increased at all levels of exercise, there was no change in desaturation or in HVR and HCVR with caffeine, in contrast to the work of D'Urzo. Whether caffeine might increase ventilation sufficiently to speed acclimatization to altitude and thus prevent or ameliorate AMS is untested, but deserves investigation.

What effect might caffeine have on the cerebral circulation at high altitude?

Hypoxia increases brain adenosine, which increases cerebral blood flow through A2A and A2B receptors located on vascular smooth muscle. By counteracting adenosine, caffeine reduces resting cerebral blood flow between 22% and 30% at sea level acutely, and less so in those with chronic use (Addicott et al., 2009). Caffeine also decreases the ratio of CBF:$CMRO_2$ (cerebral blood flow to cerebral metabolic rate for oxygen) (Chen and Parrish, 2009). Many recent studies have investigated the effect of caffeine on BOLD responses (blood oxygen dependent MRI) (Rack-Gomer et al., 2009) and functional MRI responses and CBF changes (Haase et al., 2005; Sigmon et al., 2009), and one animal study has suggested an effect on cerebrospinal fluid formation (Han et al., 2009). All these documented actions are theoretically beneficial for the high altitude brain, since vasodilation and overperfusion would be minimized without sacrificing oxygenation and metabolism. None of these studies, however, has addressed these issues during acute or chronic hypoxia. Research designed to answer the question of the effects of caffeine on brain physiology at altitude would be enlightening.

Could caffeine help prevent or treat AMS?

Similar to caffeine's successful use for headaches at low altitude, owing to its cerebral vasoconstriction properties, it is likely that caffeine will help prevent or treat altitude headaches and therefore AMS because of its ability to reduce cerebrovasodilation in response to hypoxia. In addition to the

studies cited above, research has suggested that another adenosine blocker closely related to caffeine, theophylline, may indeed help to prevent AMS, improve sleep at high altitude, and reduce episodes of oxygen desaturation (Fischer et al., 2000; Fischer et al., 2004; Küpper et al., 2008). To the extent that these effects are owing to mechanisms in common with caffeine, then caffeine would also help prevent AMS. These studies did not control for caffeine habituation. Thus, whether these possible benefits would apply to both caffeine-habituated and caffeine-naive persons is unknown, but a trial of caffeine for AMS prevention in both populations would be worthwhile.

What effect might caffeine have on sleep at altitude?

Disrupted sleep is a very common complaint in newcomers to high altitude. Caffeine promotes wakefulness and can interfere with sleep at low altitude, and it likely does the same at high altitude. It is interesting that theophylline promotes sleep at high altitude, but this agent apparently does not encourage wakefulness as does caffeine. To the extent that caffeine may help prevent AMS, it could improve sleep. But until further information is available, the clinician might be wise to recommend avoiding caffeine in the late afternoon or evening, especially in nonhabitual users, to avoid caffeine-induced insomnia, which could aggravate altitude-associated insomnia.

Could caffeine counteract high altitude lassitude?

Caffeine is a psychostimulant, also related to its adenosine receptor-blocking properties (Barry et al., 2005; McClellan et al., 2007). Since altitude exposure commonly causes fatigue or lassitude, caffeine could be an antidote for this effect. In the Everest tea study(Scott et al., 2006), there was indeed a decrease in fatigue with tea drinking. Whether the mechanism is a general increase in alertness, documented with caffeine at low altitude, or a specific interruption in pathologic processes at altitude, the net effect may be to counteract the neurocognitive effects of hypoxia. At low altitude, 200 mg of caffeine was found comparable to 200 mg of modafinil in alleviating the nocturnal decline in cognitive performance (Dagan and Doljansky, 2006). A number of studies have shown comparable effectiveness between caffeine (600 mg), dextroamphetamine (20 mg), and modafinil (200 mg), with some differences in duration, side effects, and different effects on specific cognitive functions (Huck et al., 2008; Killgore et al., 2008; Killgore et al., 2009). Although amphetamine, a dopamine agonist, was shown to improve cognition and mood at high altitude (Dill et al., 1940), there has been a surprising lack of attention since then to the issue of neurocognitive decline and possible neurocognitive enhancers at high altitude. Indeed, mountaineers clearly suffer risks from these deficits, and a systematic study of caffeine and other stimulant drugs to counteract altitude hypoxia is long overdue.

Does caffeine impair exercise?

Perhaps caution regarding caffeine at altitude owes its concern to caffeine's effect on exercise. A large body of evidence demonstrates that caffeine can improve exercise performance at low altitudes. Despite differences in dose, differences with pure caffeine (caffeine citrate) versus caffeine-containing foods and liquids, elite versus recreational subjects, and so on, hundreds of studies support the use of caffeine to improve performance. The mechanisms are thought to be both central, with reduced perceived exertion (Demura et al., 2007), and peripheral, with increased muscular force from changes in calcium utilization. This issue has received numerous recent reviews (e.g., Graham, 2001; Burke, 2008; Tarnopolsky, 2008). Burke states that a moderate dose of 3 mg/kg is adequate for performance benefits, and perhaps even 1 mg/kg (Kolata, 2009). Would the effect of caffeine on performance be different at high altitude? Could caffeine help ameliorate the exercise impairment caused by hypoxia? In contrast to low altitude, the study of caffeine and exercise at high altitude is limited. Berglund and Hemmingsson (1982) studied cross-country skiers and found improved race times with caffeine: faster by 1.7% at 300 m and 3.2% at 2900 m. The latter corresponded to a decrease of 152 sec in a 21 km race, a substantial improvement. Fulco and colleagues (1994) studied 8 males with submaximal endurance tests to exhaustion, using placebo or caffeine drinks (4 mg/kg) 1 h before the test. The subjects exercised at sea level, after 1 h at 4300 m, and after 2 weeks at 4300 m. Caffeine provided little improvement at sea level, but a 54% improvement with acute hypoxia and 24% improvement with chronic hypoxia. These two studies are insufficient to allow comparison to the low altitude studies. However, they do suggest that caffeine might confer more benefit to performance at high altitude than at low altitude and certainly do not suggest that caffeine might impair exercise.

How does caffeine affect pulmonary circulation at high altitude?

Caffeine is known to be a competitive inhibitor of the enzyme cAMP-phosphodiesterase (cAMP-PDE), which converts cyclic AMP (cAMP) in cells to its noncyclic form, thus allowing cAMP to build up in cells. This raises the theoretical question of whether caffeine might influence hypoxic pulmonary vasoconstriction by promoting relaxation of the pulmonary arterial smooth-muscle cells. Indeed, a recent study using pulmonary arterial rings in vitro showed attenuation of smooth-muscle activity owing to caffeine, which was attributed to its effect on calcium signaling and ryanodine receptors (Zheng et al., 2008). Although the concentration of caffeine was far above blood levels of caffeine in usual human use, there is at least no evidence that caffeine might cause an increase in hypoxic pulmonary vasoconstriction and therefore no reason to suspect that it might contribute to the development of high altitude pulmonary edema.

How does caffeine affect coronary circulation?

Because coffee consumption has been found to blunt dipyridamole-induced hyperemia through adenosine A2 receptor antagonism, caffeinated foods or beverages must be avoided before pharmacologic radionuclide stress perfusion imaging. Namdar and colleagues (2006) investigated whether caffeine might impair exercise-induced increases in cardiac blood flow. They studied the acute effect of 200 mg of caffeine on myocardial blood flow (MBF) at rest and exercise in 10 subjects during normoxia and when breathing 12.5% oxygen, simulating a 4500 m altitude. Myocardial flow reserve (MFR) was calculated as the ratio of hyperemic to resting MBF. Caffeine reduced MFR by 22% at normoxia and 39% at hypoxia. The results were questioned by McLellan (2006), who pointed out the limitations of the study design owing to possible order effect. In addition, the clinical implications of the study are unclear, since acute hypoxia of this magnitude is unrealistic in a

mountain environment for most visitors to resorts, skiers and trekkers. Although mountaineers can get to over 4000 m in 1 day, this is still less stressful than the immediate onset of comparable hypoxemia. Perhaps more importantly, although the subjects were habitual coffee drinkers, coffee was withheld for 36 h before the study. Thus, the subjects had upregulated adenosine receptors, and the action of acute caffeine may have been exaggerated and not applicable in a nonwithdrawal state. One wonders, however, if the combination of coronary artery disease and caffeine at high altitude would reduce MBF even more. A more recent study did suggest that this is the case (Namdar et al., 2009); but until clinical assessment shows decreased exercise performance, ECG changes, symptoms, ventricular wall motion, or other negative outcomes, these data remain interesting but not compelling.

Cessation of Caffeine Intake

Recommending cessation of caffeine intake to those who habitually use it makes the withdrawal syndrome very likely. Adenosine receptors are upregulated in habitual caffeine users. As a result, the increased effects of adenosine owing to caffeine withdrawal cause cerebral vasodilation with resultant headache and nausea. In addition, the increase in brain adenosine on ascent to altitude, coupled with increased receptors owing to habituation, could cause even worse vasodilation than in caffeine-naive persons. Cessation of caffeine may also cause feelings of fatigue and drowsiness, anxiety, irritability, inability to concentrate, and diminished motivation to initiate or to complete daily tasks; in extreme cases it may cause mild depression. Together, these effects have come to be known as a "crash," and the symptoms and their timing (12 to 24 h) mimic acute mountain sickness. Withdrawal symptoms may last for 1 to 5 days, representing the time required for the number of adenosine receptors in the brain to revert to normal levels, uninfluenced by caffeine consumption. Thus, contrary to helping people, the recommendation to cease caffeine at high altitude is more likely to be harmful. The most effective treatment of caffeine withdrawal is a combination of both an analgesic and a small amount of caffeine. One can only guess at how many cases of caffeine withdrawal are misdiagnosed as AMS and at what role caffeine withdrawal might play in promoting AMS.

Summary

In summary, contrary to conventional wisdom, caffeine use at high altitude seems to be not only safe but likely beneficial. Fears of dehydration from caffeine are exaggerated. Its effect on ventilation and cerebral circulation and its action as a psychostimulant are likely to be helpful at altitude. Whether caffeine may prevent or ameliorate AMS deserves study. Caffeine may also help exercise performance at high altitude. Importantly, habitual caffeine users should not discontinue caffeine because of travel to altitude; the symptoms of withdrawal are very similar to acute mountain sickness and can be misdiagnosed as AMS. The issue of altitude, coronary artery disease, and caffeine in exercising patients deserves further study.

Disclosures

The author has no conflicts of interest or financial ties to disclose.

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