Adverse effects of caffeine after a single dose and after repeated doses consumed within a day

Anders Sjödin
Copenhagen University (Denmark)
Chair of EFSA's WG on caffeine

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OVERVIEW

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1. Blood pressure, endothelial function, arterial compliance
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HYDRATION STATUS AND BODY TEMPERATURE

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2. Perceived exertion during exercise
3. Subjective perception of alcohol intoxication

CARDIOVASCULAR SYSTEM

1. Blood pressure, endothelial function, arterial compliance

Caffeine: single doses

- Many human intervention studies available
- 80-300 mg caffeine = acute increase in BP
- Endothelial function and arterial compliance change accordingly
- Transient effect (peak at 60-90 min)
- Observed in caffeine abstainers and habitual caffeine consumers
- Baseline plasma caffeine, baseline BP and caffeine dose may affect the size of the effect
- Several plausible mechanisms

CARDIOVASCULAR SYSTEM

1. Blood pressure

Caffeine: repeated doses

- Two human intervention studies available
- Both in habitual caffeine consumers
- Only 250 mg doses (2 or 3) given 4 hours apart were tested (500-750 mg/day)
- Significant increase in daytime BP, which remains significantly elevated up to 9-12 hours following consumption of the last dose (caffeine accumulation in plasma through the day)
- Effect depends on habitual caffeine consumption (lower in high caffeine consumers)

CARDIOVASCULAR SYSTEM

1. Blood pressure

Caffeine and physical exercise

- Three (small, 14-22 subjects) human intervention studies on caffeine supplementation (4-6 mg/kg bw), 45-60 min before resistance training
- Mostly men, lower doses not tested
- Heterogeneous designs, difficult to compare
- Suggest an additive effect of caffeine and resistance training on BP (mostly SBP) during exercise
- Caffeine could attenuate the decrease in BP observed after resistance training
- Size of the effect may depend on baseline BP

CARDIOVASCULAR SYSTEM

1. Blood pressure

Caffeine and other components of "energy drinks"

- Only two (small) studies designed to investigate the acute effects of "energy drinks" on BP beyond what could be expected from caffeine alone

Study 1: 4 repeated caffeine doses (80 mg each =320 mg) about 4 h apart; 12 subjects, 9 completed; no blinding = higher increase in 24-h BP with "energy drink" than with the same amount of caffeine

Study 2: single doses of 320 mg and 240 mg caffeine, 19 subjects = caffeine in "energy drink" did not increase BP more than caffeine alone.

- **Results difficult to interpret**

CARDIOVASCULAR SYSTEM

1. Blood pressure

Caffeine and synephrine

- No studies designed to investigate the acute effects of synephrine beyond what could be expected from caffeine alone

- **Results** from intervention studies on synephrine alone and on caffeine + synephrine **difficult to interpret**

CARDIOVASCULAR SYSTEM

2. Myocardial blood flow

Hypothesis

- High density of A_{2A} receptors in the coronary arteries
- Physical exercise = increased production of adenosine by myocytes in response to hypoxia = **vasodilation**
- **Caffeine** = non-selective, competitive A_{2A} receptor antagonist = **may reduce myocardial blood flow during exercise**

CARDIOVASCULAR SYSTEM

2. Myocardial blood flow

Human intervention studies

- Few studies available in healthy subjects (2 used physical exercise and one regadenoson to induce cardiac hyperemia)
- Only 200 mg doses of caffeine tested
- Order of caffeine-placebo administration relative to exercise not randomised
- No clinically relevant changes in myocardial blood flow (MBF) at rest or under stress under normal environmental conditions
- Clinically significant reduction of MBF:
  - at low oxygen partial pressure (e.g. high altitude)
  - in subjects with MBF already compromised (CAD)

CARDIOVASCULAR SYSTEM

3. Cardiovascular disease risk

Hypothesis

- transient increase in BP induced by acute caffeine intake could increase the risk of cardiovascular events in the first hour after consumption

Human studies

- case-crossover study designs
- Risk of sudden cardiac death (SCD), myocardial infarction (MI), and ischemic stroke (one study per outcome)

CARDIOVASCULAR SYSTEM

3. Cardiovascular disease risk

Human studies (cont.)

- studies suggest an increased risk of acute cardiovascular events in the hour following consumption of caffeinated coffee, particularly in subjects with low habitual coffee intake

BUT

- conducted in subjects with an established (fatal or non fatal) cardiovascular event = do not provide information about the risk in the general population
- included few cases
- no information on the caffeine dose which could trigger the events

CARDIOVASCULAR SYSTEM

Conclusions

- A single dose of 200 mg of caffeine consumed 1-2 hours pre-exercise significantly increases BP and reduces MBF
- Whereas such changes could increase the risk of acute cardiovascular events in subjects with an increased risk for CVD, low clinical relevance for healthy individuals under normal conditions
- Consumption of alcohol in combination with caffeine does not appear to modify the CVD risk
- Insufficient information available on co-consumption of caffeine with other components of “energy drinks” or with synephrine

HYDRATION STATUS AND BODY TEMPERATURE

Caffeine

- Caffeine has a diuretic effect
- Chronic consumption unlikely to have adverse health consequences on hydration status in the general population
- Extreme case: acute consumption prior to intense exercise in hot environments
- Five intervention studies with doses of 3-9 mg/kg bw prior to endurance exercise under different conditions of temperature and humidity
- No increase in body temperature/hydration status beyond what could be expected by testing conditions = no health concern of fluid loses can be timely replaced

HYDRATION STATUS AND BODY TEMPERATURE

Caffeine + taurine

- One human intervention study (12 subjects)
- Four treatments: 80 mg caffeine, 1 g taurine, both, neither
- Caffeine significantly increased urinary output and natriuresis, whereas taurine had no effect on either outcome and did not appear to modify the diuretic effects of caffeine when administered simultaneously.

CENTRAL NERVOUS SYSTEM

1. Sleep, anxiety and behavioural changes

Adults

- Single doses of caffeine of about 100 mg (1.5 mg/kg bw per day) = increase sleep latency and reduce sleep duration when consumed close to bedtime. Lower doses = no effect

- Higher doses (≥ 400-500 mg) = increase anxiety mainly in non-habitual caffeine consumers = tolerance is induced with frequent consumption

CENTRAL NERVOUS SYSTEM

1. Sleep, anxiety and behavioural changes

Children and adolescents

- Two intervention studies available on single doses of caffeine (2.5-10 mg/kg bw)
- Higher doses (≥ 400-500 mg) = increase anxiety mainly in non-habitual caffeine consumers = tolerance is induced with frequent consumption
- No effect on most self-reported measures of anxiety in children
- No effect on nine investigator-rated items of behaviour
- A dose-response relationship (at 3 and 10 mg/kg bw) was observed only for one out of the 11 self-reported side effects tested (“feeling nervous/jittery”).

CENTRAL NERVOUS SYSTEM

2. Perceived exertion during exercise

As health claim

- Health claim evaluation = positive outcome for single caffeine doses of ≥ 4 mg/kg bw prior to exercise
- Considered beneficial as a mechanism to increase endurance capacity and performance for adults willing to obtain such effect
- Lower conditions of use were proposed for claims on endurance capacity and performance (3 mg/kg bw)
- No safety evaluation foreseen under the Claims Regulation

CENTRAL NERVOUS SYSTEM

2. Perceived exertion during exercise

As safety outcome

- A reduction in the perceived exertion/effort during exercise = considered a potential adverse health effect under the assumption that the perception of fatigue is a physiological mechanism leading to the spontaneous ending of physical activities that, due to their high intensity, extended duration, or both, may compromise the cardiovascular and/or the musculoskeletal systems.

CENTRAL NERVOUS SYSTEM

3. Subjective perception of alcohol intoxication

Hypothesis

- caffeinated beverages (including “energy drinks”) may ‘mask’ or alter the subjective perception of alcohol intoxication, which could increase the likelihood of engaging in potentially dangerous activities while intoxicated (i.e. risk- taking behaviour).

CENTRAL NERVOUS SYSTEM

3. Subjective perception of alcohol intoxication

Human intervention studies

- Many studies available, also providing caffeine as “energy drinks” = direct and indirect measures of subjective alcohol intoxication.
- Caffeine (0.6-7.0 mg/kg bw) + alcohol (0.29 to 1.068 g/kg bw; BAC 0.03 and 0.12 %).
- Most studies used 0.65 g/kg bw (BAC = 0.07-0.08%). Limit for driving a car = 0.05% or less in most EU countries.

CENTRAL NERVOUS SYSTEM

3. Subjective perception of alcohol intoxication

Conclusions

- Caffeine at doses up to 3 mg/kg bw (corresponding to 210 mg) from all sources, including “energy drinks”, is unlikely to mask the subjective perception of alcohol intoxication when alcohol is consumed at doses of about 0.65 g/kg bw.
- Higher doses of alcohol have not been systematically investigated.

CENTRAL NERVOUS SYSTEM

Conclusions

Adults

Single doses of caffeine up to about 200 mg per day (3 mg/kg/bw) do not appear to induce anxiety, reduce the perceived exertion/effort during exercise, or alter the subjective perception of alcohol intoxication

Children

Single doses of caffeine up to about 3 mg/kg/bw do not appear to induce anxiety or behavioural changes **BUT** inter-individual variability in relation to habitual caffeine intakes has not been studied

- *1.5 mg/kg bw close to bedtime may increase sleep latency and reduce sleep duration in some individuals (adults and children)*

ACUTE EFFECTS OF CAFFEINE

OPEN FOR DISCUSSION