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Reversal of Caffeine Withdrawal by Ingestion of a Soft Beverage

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WATSON, J.M., M.J. LUNT, S. MORRIS, M.J. WEISS, D. HUSSEY, AND D. KERR. *Reversal of caffeine withdrawal by ingestion of a soft beverage.* PHARMACOL BIOCHEM BEHAV **66**(1)15–18, 2000.—Following regular use, acute cessation of caffeine is associated with a characteristic withdrawal syndrome. Despite this, caffeine remains popular with its consumers. The aim of this study was to examine the physiologic and psychologic effects of small caffeine doses, administered in the form of a market-leading soft drink, on healthy women who were acutely withdrawn from caffeine. After 48-h abstinence and overnight fast, 11 healthy (22 to 40 years) female volunteers, all regular caffeine users (daily consumption 143 to 773mg) consumed using a double-blind, randomized, controlled cross-over design either 2 tins of regular or caffeine-free Diet Coke. On both visits a Mars bar was eaten to prevent hypoglycaemia. Thus, the caffeine load was 76 or 10 mg respectively. Following ingestion of regular Diet Coke, there was a 10% fall in middle cerebral artery velocity (95%CI [6%–14%], $p < 0.005$ versus caffeine free) and improvement in feelings of pleasure ($p < 0.046$) and energy ($p < 0.037$). Intellectual function (4-choice reaction time) was unaffected by caffeine status. On both visits, ingestion of Diet Coke induced a pressor response (maximum rise in systolic pressure $^{+}15 \pm 2$ mm Hg with caffeine and $^{+}12 \pm 2$ mm Hg with caffeine-free beverage, both $p < 0.001$ compared with baseline). In conclusion, in women acutely withdrawn from caffeine, ingestion of a popular soft beverage containing modest amounts of caffeine is associated with demonstrable physiologic and psychologic effects. © 2000 Elsevier Science Inc.

Caffeine Soft beverage Withdrawal Mood Cerebral blood flow Blood pressure

CAFFEINE, the most ubiquitous psychoactive substance in the world, continues to provoke controversy as to whether its use is associated with any adverse consequences for health (10). Whereas nicotine and alcohol are directly implicated in the deaths of more than 100,000 and 400,000 Americans each year (22), the direct risk of caffeine ingestion is likely to be negligible (6). However, potential problems associated with caffeine use maybe related to the issue of dependence and withdrawal.

Drug dependence is manifested by four criteria, namely withdrawal, tolerance, persistent desire, and unsuccessful attempts to reduce consumption (1). Unlike other major drugs of dependence, caffeine does not alter dopamine release or glucose utilization within the nucleus accumbens (21), nevertheless following regular caffeine ingestion acute cessation produces a specific symptom complex (23), which is widely experienced (25). Characteristic symptoms include headache, lethargy, fatigue and dysphoria (7), and physiologic changes, e.g., a fall in blood pressure and rise in cerebral blood flow have also been reported in caffeine-withdrawn subjects (3). Such evidence has lead to the inclusion of caffeine withdrawal as a specific syndrome within the *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association, albeit as a proposed category only (1).

Previous work examining the syndrome of caffeine withdrawal have used doses in excess of 100 mg usually given in the form of coffee or caffeine capsules (24). Depending on its duration of preparation, tea contains less caffeine than coffee (30 mg compared with 85 mg in a standard 150-ml cup), as do cola soft drinks (33 mg per can) (2). Although tea is the most widely consumed drink in the world, the rise in consumption of cola beverages is phenomenal. This third vehicle of caf-

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feine differs from coffee and tea in that approximately 95% of the caffeine is added during the manufacturing process (9).

The aim of this study was to determine the effects of a small dose of caffeine given in the form of a market leading soft beverage on the physiologic and psychologic effects of the caffeine withdrawal syndrome.

METHOD

Eleven nonsmoking nor drug-taking, healthy women (aged 24 to 40 years), who were regular caffeine users (average daily consumption 143 to 773 mg, as calculated using caffeine consumption diaries (11), were studied on 2 occasions during the follicular phase (days 1 to 14) of their menstrual cycle. All subjects gave written, informed consent for the study which was approved by the local hospital ethics committee, in compliance with the Declaration of Helsinki.

After abstaining from caffeine for 48 h and fasting for 8 h, subjects were admitted to the Research Unit in which a retrograde cannula was inserted into the back of the nondominant hand with the cannula kept patent by an infusion of 154 mmol/l sodium chloride. The hand was placed in a "hot-box" to arterialize venous blood. Potential distractions such as conversation and other background noise were minimized. After resting supine for 20 min, baseline measurements were taken of:

1. Heart rate and blood pressure using an automated device (Dinamap, Critikon, UK);
2. Brain blood flow using a transcranial Doppler technique (SciMed, Bristol, UK) to assess middle cerebral artery blood velocity (Vmca). The measured parameter was the mean value of the maximum velocity envelope. Although measurement of Vmca assumes that calibre changes in the vessel are small (13), alterations in Vmca reflect changes in cerebral blood flow during euglycaemia and hypoglycaemia (12);
3. Mood using the UWIST mood score (18) consisting of 24 adjectives divided into 3 groups describing hedonic (pleasurable), tense, and energetic mood: maximum score for each aspect is 32;
4. Cognitive function using 4-choice reaction time (26). Calculations were made of total and number of correct reactions over a timed 5-min period. Prior to the start of each study, all subjects familiarized themselves with the timer to minimize any practice effect; and
5. Plasma caffeine levels. Blood was taken from a vein draining the heated hand for subsequent measurement of caffeine by an enzyme immunoassay technique (EMIT®; Behring Diagnostics, Milton Keynes, UK) on an Olympus AU560 autoanalyser (Olympus Optical, Eastleigh, UK).

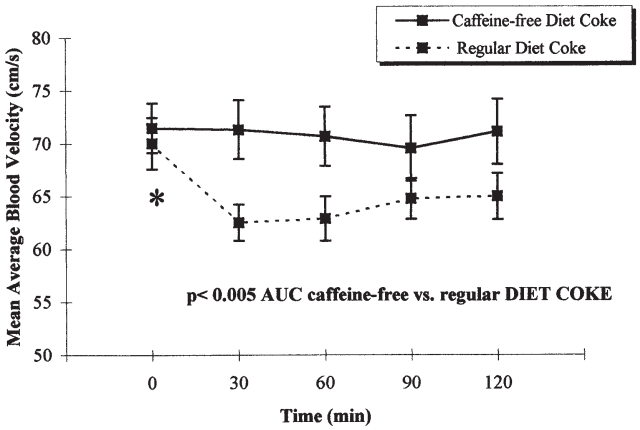

FIG. 1. Mean (SE) middle cerebral artery blood velocity for all subjects following ingestion of 2 tins of regular or caffeine-free Diet Coke . * = consumption of regular or caffeine-free Diet Coke and Mars Bar; AUC = area under the curve.

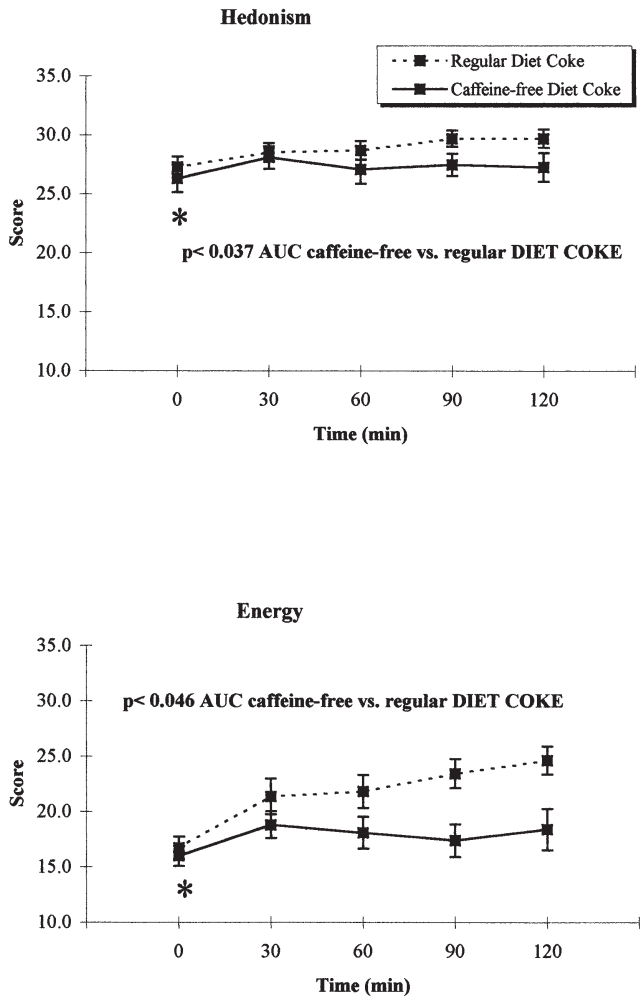

FIG. 2. Mean (SE) values for feelings of hedonism (upper panel) and energy (lower panel) (UWIST mood scores) for all subjects following ingestion of 2 tins of regular or caffeine-free Diet Coke.

Thereafter, subjects consumed, using a randomized and double-blind design, 660 ml (2 cans) of either regular (i.e., caffeinated) or caffeine-free Diet Coke (Coca-Cola Company, Atlanta, Georgia, USA). On both occasions subjects also ate a candy bar (Mars Bar, Mars Company, Slough, UK) containing 70 g of sucrose to prevent hypoglycaemia. Thus, the total caffeine load on each occasion was 76 or 10 mg (2) (assuming maximum caffeine content of Mars bar 10 mg, as per communication with Mars company). All measurements were repeated in the same position, at 30 min intervals for the next 2 h with blood glucose levels measured every 15 min (YSI 2300 Stat Plus glucose analyzer, Yellow Springs, Ohio, USA).

Statistical Analyses

Overall differences between serial measurements were examined by summary measures (19). Summary responses for each individual were calculated as area under the curve and contrasts in group means were compared by paired Student's *t*-test. Where data were not normally distributed comparisons were made after logarithmic transformation. Results are expressed as mean with 95% CI. Otherwise data are shown as mean ± SE.

RESULTS

Throughout both studies, there were no episodes of hypoglycemia and blood glucose profiles were identical (peak value 8.5 ± 0.6 mmol/l in both). Plasma caffeine levels were <0.1 mg/L at the start of both studies and remained so following ingestion of caffeine-free Diet Coke. In contrast, plasma caffeine levels increased to average 2.0 mg/L after drinking regular Diet Coke.

At the start of both studies, Vmca was similar (72 ± 2 and 70 ± 2 cm/s). Within 30 min of drinking regular Diet Coke, this fell by 10% (95% CI [6%–14%], $p < 0.005$) (Fig. 1) associated with improvement in feelings of energy and hedonic mood (both $p < 0.046$ and $p < 0.037$ vs. caffeine-free Diet Coke) (Fig. 2). Tense mood was unaffected.

At the start of both studies, total number of reactions (631 ± 25 for Diet Coke and 621 ± 23 for caffeine-free cola) and the number of correct reactions (620 ± 18 and 618 ± 19) performed over 5 min were similar. Both were unaffected by consumption of either cola drink (maximum total 654 ± 22 and correct 648 ± 21 for regular Diet Coke and 633 ± 22 and 630 ± 23 for caffeine-free cola, $p = 0.144$ and $p = 0.194$ respectively). On both occasions systolic blood pressure increased 30 min after ingesting the drinks (maximum increase $^{+}15 \pm 2$ and $^{+}12 \pm 2$ mm Hg after regular and caffeine-free Diet Coke respectively, both $p < 0.001$) and remained above baseline values for the duration of the studies (Fig. 3). Diastolic pressure increased to a lesser extent ($^{+}9 \pm 1$ and $^{+}6 \pm 2$ mm Hg, both $p < 0.021$).

DISCUSSION

In everyday life, the amount of caffeine consumed produces effects that are difficult to detect or so subtle as to go unnoticed. Caffeine is frequently added to nonalcoholic proprietary drinks as part of the manufacturing process although caffeine per se has no intrinsic nutritional value. The health consequences of this (if any) are unknown.

In the present study, subjects acutely withdrawn from caffeine ingestion of modest amounts of caffeine (76 mg) caused an almost immediate fall in middle cerebral artery blood velocity (an index of brain blood flow), together with marked improvement in subjects' mood without any change in cognitive function. Surprisingly, both systolic and diastolic blood pressure increased above baseline values after drinking both types of cola, irrespective of caffeine load.

Abstinence from caffeine leads to the symptoms of caffeine withdrawal. Consuming as little as 100mg each day is required before a person is at risk (7). This state can be associated with marked functional impairment (22) although this has not been consistently demonstrated (14). Here we did not show any change in intellectual function as assessed by visual reaction time, with the reinstatement of caffeine consumption. This was unexpected as others have reported shown that as little as 32 mg caffeine (less than in a single can Diet Coke) can increase 4-choice reaction time (15) after 12 h of caffeine abstinence. Durlach has also demonstrated significant speeding of the reaction time with 60 mg of caffeine consumed as a cup of tea (5). Although it is possible that tea contains other psychoactive substances that may alter reaction time, other possible explanations for our results include differing plasma caffeine levels following administration (not measured in the 2 studies referenced). Alternatively differences could relate to fluctuation in blood glucose levels as hypoglycaemia negatively affects cognition. Interestingly 4-choice reaction time is particularly sensitive to mild hypoglycaemia (20) (16). Blood glucose levels were not reported in the earlier caffeine studies. Under normal circumstances, glucose is the sole metabolic fuel for normal brain function. In healthy people, prior ingestion of caffeine can be associated with the development of classical autonomic symptoms if peripheral blood glucose levels fall into the low normal range as may occur after a large carbohydrate load (12). Here, subjects ate a candy bar in order to prevent neuroglycopenia. Subsequently, peripheral blood glucose levels remained well above the glycaemic thresholds release for activation of the sympathetic nervous system, release of adrenaline, alterations in cerebral blood flow and cognitive performance (20).

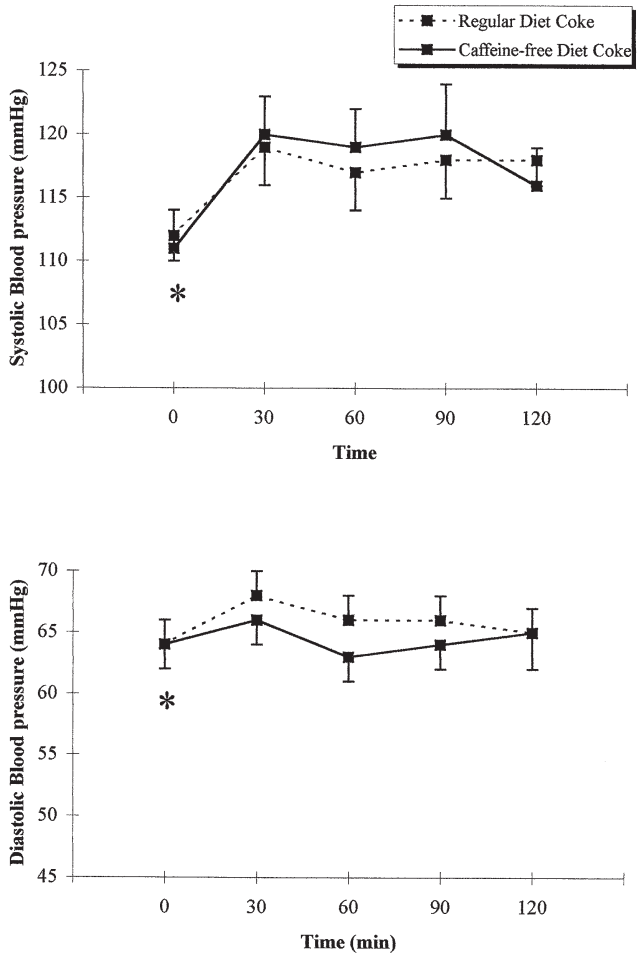

FIG. 3. Mean (SE) values for systolic (upper panel) and diastolic (lower panel) blood pressure following ingestion of 2 tins of regular or caffeine-free Diet Coke.

This study demonstrates a positive effect of a small amount of caffeine on its own withdrawal syndrome. Although in popular culture caffeine is thought to produce relief of fatigue and be mildly stimulating, it is possible that use continues in order to prevent the development of an unpleasant and perplexing withdrawal syndrome. Earlier work showed that when caffeine tolerant 92% of subjects would chose to drink caffeine compared to 52% of them when caffeine-naïve (8)

Caffeine has a vasoconstricting effect on the brain (17). In caffeine naive individuals, ingestion of 250 mg reduces brain blood flow by approximately 20% associated with a rise in blood pressure and plasma epinephrine levels. In the present study, the pressor response to both types of Diet Coke was unexpected. Although it is well known that caffeine has a pressor response, the mechanism involved in the rise in blood pressure seen with caffeine-free cola is unknown but unlikely to relate to acute volume loading (4). Unfortunately, we were unable to obtain information concerning other substances present in Diet Coke that might induce a pressor response.

Tea, coffee and in a lesser amount cola beverages all contain caffeine as it is present in the raw materials from which the beverage is made. Consumers can choose not to drink these beverages or select decaffeinated versions. For those who decide to continue with regular caffeine use, this maybe in order to prevent or ameliorate the syndrome of acute caffeine withdrawal.

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