Anxiety and Muscle Tension as Consequences of Caffeine Withdrawal

Abstract. *Regular consumers of caffeine had higher muscle tension after three or more hours of abstinence than low caffeine consumers. This difference was absent after double-blind administration of caffeine citrate or placebo. In a discriminative reaction time test, caffeine treatment improved performance. Among subjects receiving placebo, anxiety was highly correlated with prior caffeine use, suggesting that even a brief abstinence may produce anxiety in the regular user.*

Caffeine is probably the most extensively used substance taken for its psychoactive effects. Several recent clinical reports (*1-4*) have suggested a link between caffeine consumption and anxiety in psychiatric patients. Greden *et al.* (*1*) found that psychiatric inpatients' estimates of prehospitalization caffeine consumption were correlated with anxiety, depression, and the use of sedative hypnotics and minor tranquilizers. In another report (*2*) Greden concluded that for three patients, excessive caffeine consumption produced anxiety symptoms indistinguishable from anxiety neurosis. Paradoxically, a group of housewives from a student housing facility were more likely to report relaxation and reduced irritability from morning coffee, if their daily consumption of coffee equaled five cups or more (*5*). This latter study suggests that anxiety may be a consequence of abstinence from caffeine in the regular user, and that caffeine can relieve this abstinence anxiety.

To determine whether caffeine consumption is related to anxiety and muscle tension in nonclinical subjects, college student volunteers (*6*) with a wide range of caffeine experience (0 to 1140 mg/day) abstained from caffeine for at least 3 hours before being tested for muscle tension, reaction time, and anxiety. Muscle tension was assessed before and after treatment with grapefruit juice (*7*) containing 300 mg of caffeine citrate ($N = 19$) or citric acid (placebo, $N = 17$). Although the subjects were informed of the possibility of receiving caffeine, the actual administration was double-blind. Anxiety and reaction time were measured only after juice treatment in order to avoid test-retest contamination. Most subjects were tested between 8:00 and 11:00 a.m., which allowed them to obtain their first caffeine for the day in the experiment. This meant that for most subjects abstinence was longer than the minimum of 3 hours—30 of the 36 subjects exceeded 7 hours.

Initial assessment of caffeine consumption history determined a crude classification of the subjects into high or low caffeine consumers allowing caffeine and placebo groups to be balanced according to caffeine history. Caffeine intake was estimated for the previous 24 hours and for usual daily consumption (*8*). At the completion of the study, high and low consumers (mean, 376 and 87 mg of caffeine during the previous 24 hours) were designated to be those above and below the median (190 mg) for the previous 24 hours intake. Estimates of usual daily intake and previous 24-hour consumption were highly correlated ($r = .88$).

Electromyographic (EMG) activity was measured before and approximately 30 minutes after grapefruit juice consumption. Recording was done with the aid of an EMG biofeedback apparatus (Cyborg model J33), an integrator (Cyborg model Q700), and 25-mm disposable electrodes (Jet). The integrator was set to average the EMG over consecutive 1-minute intervals. The subject was seated comfortably in a dental chair, and electrodes were attached 2 cm apart to the volar portion of the right forearm. The electrodes formed a straight line along the brachioradialis, beginning 3 cm from the elbow. The EMG score was defined as the mean of the last two of six 1-minute recordings.

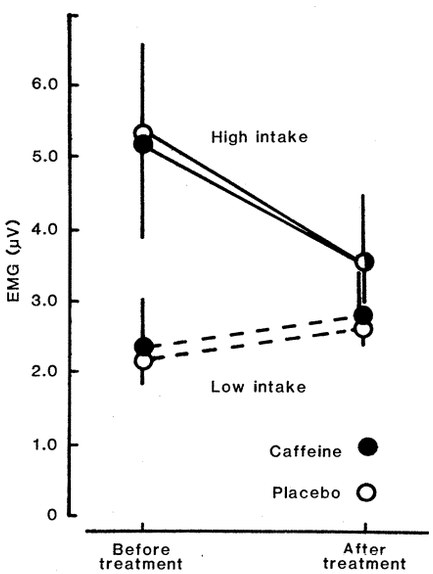

Fig. 1. Mean ± S.E.M. for EMG scores taken before and after treatment with caffeine or placebo. High and low intake designations refer to previous 24-hour consumption of caffeine. Measures before treatment followed previous caffeine intake by a minimum of 3 hours.

High caffeine consumers had significantly higher EMG scores before treatment than did low consumers [F (1, 32) = 8.44, $P < .01$] (Fig. 1). This result suggests that an increase in muscle tension may be a consequence of abstinence from caffeine in the high consumer. The absence of a significant difference between high and low consumers after caffeine treatment is consistent with this conclusion [F (1, 32) = 1.25; $P > .25$] (Fig. 1). The apparent reduction in muscle tension in high consumers after treatment regardless of whether they received caffeine or placebo was not statistically significant.

Positive effects of caffeine were obtained with a discriminative reaction time test, given about 15 minutes after the grapefruit juice was drunk. In this task the subject was instructed to depress one of two telegraph keys to indicate when a red or a blue light appeared in a 1-cm (diameter) hole about 40 cm from the subject's head (Lafayette reaction time apparatus, model 302B). The caffeine group [mean ± standard error of the mean (S.E.M.) = 0.508 ± 0.011 second, $N = 11$] had significantly shorter reaction times than did the placebo group (0.547 ± 0.018 second, $N = 10$) ($t = 2.42$, $P < .05$, two-tailed). Because of mechanical failure, reaction time scores were obtained on only the first 21 subjects (8 high and 13 low consumers balanced across caffeine and placebo groups), precluding analysis of the role of past consumption on performance. However, these results indicate that the caffeine treatment had a measurable effect on the subjects.

The final measure after treatment was the state-trait anxiety index, designed to measure state (or present) anxiety and trait (or general) anxiety (*9*). The subjects completed the state index and then the trait scale. Neither scale revealed significant differences between the caffeine and placebo groups or between high and low consumers (F's < 1). However, within the placebo group (which approximates a pretreatment condition), state anxiety scores were correlated significantly with previous caffeine consumption ($r = .52$, $P < .05$, two-tailed). Computing the same correlation with only the high consumers from the placebo group shows that they account for the relationship between past consumption and state anxiety ($r = .94$, $P < .01$). This relationship did not hold for the low consumers from the placebo group

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($r = -.09$) nor for the caffeine group ($r = -.09$), regardless of consumption experience (high intake: $r = .14$; low intake: $r = -.07$). Trait anxiety did not show significant relationships with consumption levels in either group (range of r's = $-.37$ to .20).

These findings demonstrate that caffeine consumption has consequences for anxiety, muscle tension, and reaction time in nonclinical subjects. The relations among these variables are not simple. Recent abstinence from caffeine may cause increased anxiety and muscle tension reactivity in the regular user. Caffeine administration appears to relieve the anxiety and decrease reaction time. Since these effects are apparent after a relatively short abstinence, they may contribute to the maintenance of regular caffeine use. This hypothesis is supported by Mikkelsen's report that excessive caffeine consumption occurred with psychiatric patients at a time when they experienced anxiety from sources unrelated to caffeine use (*4*).

Although the physiological correlates of caffeine tolerance and withdrawal have not been identified, several caffeine-related changes may underlie the anxiety and muscular effects reported here. Caffeine produces contraction of human striated muscle by facilitating calcium transport, alters release and metabolism of monoamines, and inhibits phosphodiesterase, which is involved in the metabolism of cyclic nucleotides (*10*).

Progress has been made in the characterization of a caffeine withdrawal syndrome (*11*). We suggest that anxiety and muscle tension be added to the list of caffeine withdrawal symptoms, which already includes headache, irritability, drowsiness, and lethargy. Perhaps caffeine withdrawal deserves diagnostic status similar to that of caffeine toxicity—caffeinism (*12*).

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6. In addition to informed consent, subjects were screened for circulatory, thyroid, gastric, or other problems that might be affected by caffeine or citric acid. Information about recent medication and tobacco use were solicited in the initial questionnaire. These factors were comparable for the caffeine and noncaffeine groups. Only four subjects in each group smoked more than two cigarettes per day, precluding evaluation of smoking habits as a correlate of caffeine use, anxiety, or muscle tension. One smoker was in the high-intake caffeine group and three were in the low-intake group. The noncaffeine group had three smokers in the high intake subgroup and one in the low. Although no subjects withdrew from the study, their right to withdraw was stated when they initially volunteered and restated when they came to the laboratory. At the completion of the experiment, all subjects were informed of their actual treatment and of the major results of the study.
7. Grapefruit juice was selected as the vehicle because of its acidic and slightly bitter taste, which, to our perception, completely masked the taste of the caffeine citrate and citric acid. At the end of testing, each subject was asked whether his or her grapefruit juice had caffeine in it. Only 4 of the 19 caffeine subjects and 8 of the 17 placebo subjects correctly identified their conditions.
8. Caffeine concentrations reported in *The Medical Letter* [**19**, 65 (1977)] were used to estimate caffeine consumption in brewed coffee (125 mg per cup), instant coffee (70 mg per cup), tea (70 mg per cup), and soft drinks containing caffeine (25 mg per cup). These values are somewhat arbitrary in that other sources (*4*) report higher concentrations of caffeine per cup of coffee. Our estimates are conservative and may underestimate actual consumption. However, we believe that the relative differences between individual subjects are accurate, because students at Centre College are required to participate in the food services, and therefore have a common source of coffee, tea, and cola beverages. For this reason we have considerable confidence in our correlational analyses.
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Juvenile Hormone Induction of Biting Behavior in *Culex* Mosquitoes

Abstract. *Juvenile hormone deprivation caused by surgical removal of corpora allata shortly after adult emergence blocked the initiation of biting behavior in* Culex pipiens *and* Culex quinquefasciatus. *Reimplantation of corpora allata or injection of a synthetic juvenile hormone (JH-I) corrected the juvenile hormone deficiency and restored biting behavior. Ovariectomy experiments demonstrated that this behavioral effect of juvenile hormone was independent of ovarian involvement.*

In terms of disease transmission, mosquitoes are among the world's most important blood-feeding insects. Pathogens and parasites transmitted by the bites of mosquitoes cause encephalitis, dengue, filariasis, malaria, yellow fever, and a number of other well-known diseases. Yet, despite the epidemiological significance of blood feeding, little information is available on the events that initiate mosquito biting behavior.

Adult mosquitoes feed readily on sugar soon after they emerge from the aquatic pupal stage. There is usually a 2- to 3-day interval, however, before the female initiates biting behavior. During this interval, mosquitoes initiate sexual behavior and begin to develop ovarian follicles. Since these last events are induced by juvenile hormone (JH) (*1*), several investigators have speculated that biting behavior is also hormonally induced (*2, 3*). To test this hypothesis, we investigated the effect of JH on the biting behavior of the mosquitoes *Culex pipiens* and *Culex quinquefasciatus*. Our results provide experimental evidence for the hormonal induction of biting behavior in a blood-feeding insect.

Mosquitoes were reared and maintained in a daily photoperiod of 14 hours of light and 10 hours of darkness at 26°C (*4*). Larvae were fed a diet described previously (*5*). The procedures we used for surgical removal of the corpora allata (allatectomy), the ovaries (ovariectomy), and hormone injection have also been described (*6, 7*).

Earlier studies on *C. pipiens* (*8*) established that allatectomy of 1-hour-old adults created a JH deficiency that prevented the development of resting-stage ovarian follicles, an event that precedes egg maturation in mosquitoes (*9*). We therefore subjected *C. pipiens* and *C. quinquefasciatus* to allatectomy 1 hour after they emerged to determine whether JH deprivation would prevent the initiation of biting behavior. Mosquitoes subjected to sham operations or no operations were used as controls. Sham operations involved opening and then resealing the neck membrane without removing the corpora allata.

The mosquitoes were placed in Formica and Plexiglas cages (26 by 18 by 18

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