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Conditioned opponent responses in human tolerance to caffeine

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Regular coffee drinkers show tolerance to the salivation-inducing effects of caffeine. We present evidence indicating that this tolerance results from a conditioned inhibition of salivation, with coffee as the conditioned stimulus. The tolerance disappears when caffeine is presented in an unfamiliar vehicle, and inhibition of salivation occurs when coffee drinkers drink decaffeinated coffee. These two findings are predictions of a conditioned opponent view, which holds that stimuli associated with the administration of caffeine induce physiological conditioned responses that oppose the basic effects of the drug. In contrast with salivation, the alerting effects of caffeine show little tolerance, and no evidence for conditioned opponent processes. Thus, different effects of the same drug can perhaps display totally different conditioning properties.

Drug tolerance is the decrease in responsiveness to a drug with repeated use. Traditional accounts of this phenomenon refer to physiological mechanisms such as changes in drug absorption or excretion, and changes in receptor sensitivity or availability. Although such factors surely are involved, tolerance may also result from adaptive, neurally organized, compensatory responses that function to oppose the effects of the drug. With repeated exposure to the drug, these reponses are postulated to increase in strength, either through associative learning (Schull, 1979; Siegel, 1978, 1980) or according to nonassociative laws that govern opponent processes (Solomon, 1980; Solomon & Corbit, 1974).

The associative or conditioned opponent view has its origins in the work of Pavlov (1927) and Bykov (1927/1960) and has assumed its modern form in the experimental studies and theorizing of Siegel (e.g., 1978, 1979) and Schull (1979). According to this view, contextual stimuli that have been associated with specific drug effects come to elicit, by Pavlovian conditioning, internal conditioned responses that oppose the primary effects of the drug. For example, with repeated injections of morphine in a particular environment, rats show tolerance to the hypothermic and analgesic effects of the drug. If, following the achievement of tolerance in a well-defined injection situation, the rat is given a morphine injection in a totally new situation, the tolerance disappears (context-specific tolerance) (Adams, Yeh, Woods, & Mitchell, 1969; Kayan, Woods, & Mitchell, 1969; Siegel, 1975). If a tolerant rat is given a saline injection under the usual conditions of morphine administration, it shows a response opposite to the normal drug effects (hyperalgesia instead of analgesia, hyperthermia instead of hypothermia). This response, which we will call the "drug-negative conditioned response," is explained as an opponent response stimulated by the drug-administration context, in the absence of the direct drug effect that it would normally oppose. Context-specific tolerance, drug-negative conditioned responses, and other empirically demonstrated characteristics of morphine tolerance (Siegel, 1978, 1980, 1981) are predicted from Pavlovian principles, but do not follow from traditional views of tolerance.

It is not clear when stimuli paired with a drug state should be expected to generate "drug-negative" responses that oppose the original drug effect or "drug-positive" ("placebo") responses that mimic it. The latter is the type of conditioning that would be expected by traditional Pavlovian theory and that has been incorporated into Solomon's (1980; Solomon & Corbit, 1974) original opponent process theory.

In human subjects, there have been no clear-cut demonstrations of compensatory conditioning (context-specific tolerance and/or the conditioned drug-negative responses). One substance that offers particular advantages for investigation of conditioning and drug effects in humans is caffeine, since most people take it regularly and reliably in association with a convenient conditioned stimulus, the cup of coffee. Of the many effects of

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caffeine, we elected to examine increased salivation and subjective reports of increasing alertness. There is clear experimental evidence for tolerance to the salivation-inducing effects of caffeine (Winsor & Strongin, 1933). In contrast, the experimental literature suggests that there is at most a weak, low-grade tolerance to the alerting effects (Colton, Gasselin, & Smith, 1968; Gilbert, 1976; Goldstein & Kaizer, 1969; Goldstein, Kaizer, & Whitby, 1969). This is what one would expect, since most regular coffee drinkers still find that caffeinated coffee disturbs sleep if taken at bedtime, and few coffee drinkers have to increase continually the amount that they drink in the morning to produce an appropriate wakening effect.

In this study, we offered habitual coffee drinkers coffee and hot apple juice, both with and without caffeine. In accordance with the conditioned opponent view, we predicted, for salivation, greater tolerance (less salivation) when the caffeine was presented in the familiar context (coffee), since this would set in motion the conditioned opponent process (context-specific tolerance). Similarly, we predicted that coffee without caffeine would produce an inhibition of salivation below baseline (the drug-negative conditioned response), but that such a response would not be elicited by the apple-juice context, which would not have been associated with caffeine. We did not make similar predictions for alertness, since the existence of tolerance for this effect is questionable.

METHOD

The subjects were 24 university students, ranging in age from 19 to 35 years, who had been drinking at least 2 cups of caffeinated coffee per day (range 2-11 cups per day) for at least 1 year. The study was described to the subjects as an experiment about the effect of different beverages on salivation and performance. No mention was made of the presence or absence of caffeine. The subjects were told not to eat or drink for at least 2 h prior to the experimental sessions; they were run at the same time each day.

Salivation was measured with a Lashley cup (Lashley, 1916), which was placed over one parotid duct. The experimenter counted the drops of saliva (approximately .03 ml per drop) dripping from the end of a tube connected to the cup. In order to be assured that the cup had been properly placed, each subject ingested a few milliliters of a sour solution (.03 M HCl) and swirled it around in his or her mouth. If salivary flow through the tube did not increase, the cup was relocated. When the salivary stimulation from the sour stimulus had abated (defined as three consecutive 1-min periods in which the number of drops varied by no more than 2 drops), baseline salivation was recorded for 10 min.

Wakefulness was assessed with a questionnaire. In response to the question "How do you feel right now?", subjects rated 18 adjectives on a 5-point scale (0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, and 4 = extremely). To compute a single wakefulness score for each administration of the checklist, we added together the ratings for 10 positive caffeine effects (tense, lively, shaky, on edge, efficient, alert, restless, full of pep, agitated, and irritable). For 8 negative caffeine effects (worn out, unable to concentrate, listless, fatigued, exhausted, sluggish, weary, and bushed), we inverted the scores (subtracted them from 4) before adding them to the previous total. The maximum caffeine effect would thus be a score of 72 (18 x 4); the minimal effect would be 0.

The beverages employed were instant or brewed Sanka (decaffeinated) coffee and Tropicana apple juice, heated in the same manner as the coffee and served at the same temperature. The coffee was prepared for each subject in the manner to which he or she was accustomed: brewed or instant, with or without cream and/or sugar. After the beverage was heated, caffeine or lactose (preweighed 100-mg amounts) was added to each of two 5-oz (150-ml) cups (double blind).

Experimental sessions were preceded by an orientation session in which the cup was attached and the subject was introduced to the experimental situation and stimuli. The experiment involved four sessions, each of about 1 h in duration, scheduled over a 2-week period; all sessions were identical in format. At each session, we installed the Lashley cup, obtained a 10-min salivary baseline, and administered a wakefulness adjective checklist during the baseline determination. During the next 5 min, the subject drank two 5-oz cups of coffee or apple juice. Salivation was measured for another 40 min, with a second administration of the adjective checklist at 30 min postdrinking. To occupy the subject, and incidentally to provide data for another study, the subjects engaged in a memory search task presented by a microcomputer located in front of them. Equivalent tasks were presented in all four sessions. The task took approximately 30 min, and commenced after the subjects had finished drinking.

The four experimental sessions were always run in the order: coffee-apple-coffee-apple. However, the presence of caffeine or lactose in the beverage for any day was randomized and counterbalanced: 6 of the 24 subjects were exposed to each of the four possible orders, for example, coffee-caffeine (CC), apple-no caffeine (AN), coffee-no caffeine (CN), and apple-caffeine (AC). Thus, on caffeine days, the subjects consumed two cups of beverage with a total of 200 mg of caffeine, the equivalent of two strong cups of brewed coffee. Neither the subject nor the experimenter knew whether the beverage in question was caffeinated.

RESULTS

The basic unit of salivation was the change in the number of drops of salivation from baseline, per 5-min period. Since, within subjects, baseline varied to some extent from one session to the next, we computed a hybrid baseline that was the average of the mean number of drops per 5 min during the 10-min baseline period for all four sessions and the mean number of drops per 5 min for the baseline period on the particular day in question. All data are presented in terms of departure from this hybrid baseline. The course of salivation from 5 to 45 min postdrinking is displayed in Figure 1.

For purposes of deriving a single representative number for each condition, we also calculated the average change from baseline over the period from 20 to 45 min postdrinking (Table 1). Figure 1 and Table 1 both indicate a number of significant effects. A two-way repeated measures ANOVA (vehicle x drug) based on the composite (20-to-45-min) scores indicates a strong effect of caffeine on salivation [$F(1,23) = 30.89$, $p < .001$] in the expected direction, and a surprisingly strong effect of beverage [$F(1,23) = 18.35$, $p < .001$]. Hot apple juice was a much stronger and more long-lasting salivary stimulant than coffee (Figure 1).

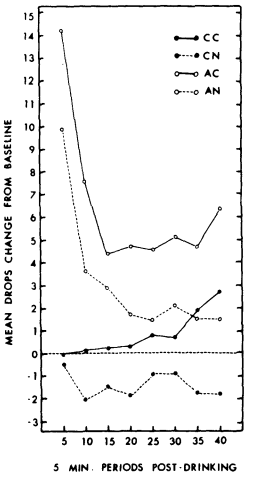

Figure 1. Mean change in salivation rate from baseline, in number of drops per 5-min period, for four conditions. CC = coffee with caffeine, CN = coffee without caffeine, AC = apple juice with caffeine, and AN = apple juice without caffeine. The first 5-min period, which includes the actual ingestion of the two cups of beverage, is not included. Salivation rate was very high in this period.

We tested for the drug-negative conditioned response to decaffeinated coffee by comparing each subject's salivation after he or she had drunk CN with his or her baseline salivation. As predicted, salivation rates went significantly below baseline [mean change of 1.43 drops per 5 min; $t = 2.75$, $p < .01$; see Table 1] and remained inhibited for the entire testing period (Figure 1). Salivation was significantly decreased in five of the eight 5-min intervals from 5 to 45 min ($p < .01$, one-tailed t tests in each of the five cases).

The other phenomenon predicted by the conditioned opponent view is context-specific tolerance: Caffeine in apple juice should have a greater effect on salivation than would caffeine in coffee. Our test of this prediction was complicated by the fact that, for most subjects, salivation following apple juice never returned to its baseline level. We have corrected for this in two ways.

Table 1
Effect of Vehicle and Caffeine Presence on Salivation and Mood Change

	Session Condition			
	Coffee		Apple Juice	
	Caffeine	No Caffeine	Caffeine	No Caffeine
	Salivation			
Mean Drops*	1.30	−1.43	5.11	1.69
SD	3.38	2.54	4.16	2.39
	Mood Change			
Mean Change**	6.62	−0.17	2.29	−0.58
SD	11.34	5.87	7.81	4.27

**Mean drops from baseline per 5 min. **After − before.*

First, we compare CC with the quantity (AC−AN), which gives the net effect of caffeine in apple juice, with the salivary contribution of apple juice per se factored out (the abbreviations CC, CN, AC, and AN refer to rates of salivation relative to baseline under the indicated conditions). If context-specific tolerance holds, the quantity [(AC−AN)−CC] should be greater than zero. Caffeine produced about 2 more drops of saliva per 5-min period in apple juice than in coffee {mean of [(AC−AN)−CC] = 2.12; $t = 2.74$, $p < .01$; see Table 1}. Computing this same measure of tolerance separately for each 5-min interval shows that there is a significant difference in six of the eight intervals ($p < .05$ or better, one-tailed t test in each case; see Figure 1).

Our second correction for the apple-juice problem is to reanalyze the data for just those subjects whose salivation after apple juice (AN) did return close to baseline (scoring less than 1 drop above baseline for the 20-to-45-min period). The 11 subjects who met this criterion showed the same pattern of results that was shown by the total sample (CC = .68; CN = −.98; AC = 1.90; AN = −.03). In this much smaller sample, the drug-negative conditioned-response effect remains significant ($t = 1.89$, $p < .05$, one-tailed), whereas the context-specific tolerance finding remains in the right direction but is not significant ($t = 1.61$).

The salivation data thus provide evidence for both context-specific tolerance and the drug negative response. Since the conditioned opponent view claims that both phenomena are manifestations of the same conditioned opponent response, the strength of the two effects in each subject should be correlated. Computation of the Pearson r correlation for each of the eight 5-min intervals yielded significant correlations ranging from .382 to .465 during the three 5-min periods from 15 to 30 min ($p < .05$, one-tailed or better in each case).

The data on wakefulness effects of caffeine present a different picture. To examine wakefulness effects, we subtracted the subject's wakefulness score prior to drinking from that obtained 30 min after drinking, for each session. Caffeine increased wakefulness significantly [$F(1,23) = 6.41$, $p < .05$], as did coffee in comparison with apple juice [$F(1,23) = 7.52$, $p < .05$]. The coffee vehicle was a more effective stimulant than was the apple-juice vehicle, whether one compares CC with AC or CN with AN (Table 1). This nonsignificant trend is opposite to the pattern for salivation and is suggestive of conventional drug-positive conditioning (the placebo effect), in which the coffee beverage itself acquires some caffeine-like properties. [These results are tentative, however, because the prebeverage wakefulness scores on CC days (the days showing the greater "positive" mood change) were significantly lower than on any other day, and the postbeverage scores alone do not show significant differences. Equalization of predrinking scores across conditions through elimination of nine subjects with particularly low CC predrinking wakefulness scores leads to a similar pattern of results, but with

the reduced number of subjects, the effect is not significant.]

Our data suggest that conditioning in different caffeine-sensitive response systems can proceed according to opposite principles. Furthermore, the drug-positive (wakefulness) and drug-negative (salivation) systems seem to operate independently, even in the same individual. The correlation of the conditioned opponent effects for salivation {context-specific tolerance and reverse placebo [(AC–AN–CC)–CN]} with the placebo conditioning of wakefulness [(CC–AC) + (CN–AN)] is small and negative ($r = -.247$, n.s.). The simultaneous presence of opposite conditioning principles is paralleled by laboratory observations of addicts who have reported subjective drug-positive "highs" from the heroin-injection ritual while showing physiological responses suggestive of withdrawal (J. W. Ternes, personal communication, October 6, 1983).

DISCUSSION

These data thus provide several kinds of evidence for the existence of conditioned opponent responses to pharmacological stimuli in humans. Before discussing the implications of these findings, several alternative interpretations of the data should be considered.

First, it is conceivable that the reduction in salivation below baseline is due to progressive caffeine withdrawal with time, rather than to drug-negative conditioning. We consider this to be unlikely: The reduction appears within 10 min and remains steady rather than getting stronger, as would be expected from a gradual "drying-out" process. In addition, we have subsequently run coffee drinkers under the same procedure used here but without administering caffeine or any beverage. There was no general decline in salivation.

Second, one might be concerned that the apple-juice/coffee differences are due to faster absorption of caffeine from apple juice than from coffee, rather than to context-specific tolerance. However, the literature indicates that, if anything, the opposite should be the case (Marks & Kelly, 1973). Furthermore, the data on wakefulness are suggestive of greater, not lesser, effects of caffeine in coffee.

Our findings of drug-negative conditioned responses, of context-specific tolerance, and of the within-subject correlation between these two findings, are all suggestive of the existence of a conditioned opponent process operating in the salivary response systems. As such, they represent the first controlled demonstration of conditioned opponent responses to pharmacological stimuli in humans. In contrast, our data provide markedly little support for the existence of such a process operating in the systems responsible for the alerting effects of caffeine. Thus, although these results do not resolve the problem of defining the conditions under which drug-positive or drug-negative conditioning occurs, they do suggest that a primary determinant is the relation between the drug and the particular response system.

Our data do not indicate the extent of "pharmacological" tolerance in our subjects. Since, for ethical reasons, we did not give caffeine to non-coffee drinkers, we cannot say whether our conditioning effects were superimposed upon a substantial amount of pharmacological tolerance. It is quite possible that salivation in the AC condition was lower in our coffee drinkers than it would have been in nondrinkers.

In conclusion, we recommend the use of the coffee-caffeine preparation for investigating conditioned drug effects. Coffee is a substance of low toxicity, with convenient and reliable subjective and physiological response measures. And because there are hundreds of millions of coffee drinkers in the world who regularly pair the stimulus of coffee with the pharmacological effects of caffeine, there should be no shortage of subjects.

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