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Reinforcing Properties of Caffeine: Studies in Humans and Laboratory Animals

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GRIFFITHS, R. R. AND P. P. WOODSON. *Reinforcing properties of caffeine: Studies in humans and laboratory animals.* PHARMACOL BIOCHEM BEHAV **29**(2) 419–427, 1988.—Three types of experimental studies are reviewed: (1) intravenous and oral caffeine self-administration by laboratory animals, (2) oral caffeine self-administration by humans, and (3) human subjective effects of caffeine relevant to reinforcing effects. These studies show that, under appropriate conditions, caffeine can serve as a reinforcer and can produce elevations in subjective drug liking and/or euphoria. In this regard, caffeine can be distinguished from a wide range of behaviorally active compounds, such as the amphetamine analog fenfluramine and the major tranquilizer chlorpromazine, which do not produce such effects. Caffeine can also be distinguished from classic drugs of abuse such as cocaine, *d*-amphetamine or pentobarbital which generally maintain high levels of self-administration (or liking) in contrast to caffeine which tends to maintain lower levels of self-administration (or liking) or maintain self-administration under a more narrow range of parametric conditions. Several human studies and one animal experiment suggest that physical dependence substantially potentiates the reinforcing effects of caffeine. Other human and animal studies indicate that there may be substantial differences between individual subjects in the reinforcing effects of caffeine. An important challenge for future human and animal drug self-administration research will be to delineate more precisely the conditions under which caffeine does and does not serve reliably as a reinforcer.

Caffeine Coffee Reinforcer Drug self-administration Subjective effects Drug dependence Drug abuse Withdrawal Humans Animals

CAFFEINE is the most widely used behaviorally active drug in the world, with one or more caffeine-containing beverages and food consumed regularly by most adults and children [14]. Caffeine was, of course, first used by societies which had ready access to naturally occurring caffeine-containing plants. Records of use of tea, a caffeine-containing beverage, date back at least 1,600 years, and possibly 4,700 years in China [19], while records of coffee use in Ethiopia date back at least 1,000 years, with evidence for use 1,300 years ago [2]. Use of these caffeine-containing foods spread systematically from these countries, despite recurring efforts, motivated on moral, economic, medical, or political grounds, to restrict or eliminate their use [2, 19, 21].

Given the high prevalence and remarkable persistence of caffeine use, it perhaps is not surprising that caffeine has been intermittently identified as a drug of abuse [2, 13, 21]. A defining characteristic of an abused drug is that it has reinforcing properties [29]. Although the effects of caffeine have been and are continuing to be extensively studied [11, 13, 48, 51], the reinforcing properties of caffeine remain poorly characterized. For example, although it is widely believed that caffeine is the primary pharmacological constituent responsible for maintaining chronic consumption of beverages such as tea and coffee, an unequivocal experimental demonstration of this effect was only recently published [24]. The relative lack of understanding of the reinforcing properties of caffeine is all the more surprising because methodologies for conducting drug self-administration studies in humans and laboratory animals have been well established [23].

The purpose of this paper is to evaluate the current understanding of the reinforcing properties of caffeine by reviewing three types of experimental studies: (1) Reinforcing properties of caffeine in laboratory animals; (2) Subjective effects of caffeine in humans; and (3) Reinforcing properties of caffeine in humans.

REINFORCING PROPERTIES OF CAFFEINE IN LABORATORY ANIMALS

Reinforcing efficacy of a drug refers to the relative effectiveness in maintaining behavior on which the delivery of drug is dependent [28]. Over the last 20 years, reliable experimental models of drug taking behavior in laboratory animals have been developed which provide valid information about the relative reinforcing properties of psychoactive drugs [23].

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Intravenous drug self-injection procedures in nonhuman primates, which have reliably shown drugs such as cocaine and *d*-amphetamine to be reinforcers have not consistently shown caffeine to be self-administered. Of the six studies of caffeine self-injection in nonhuman primates reported to date, two showed that caffeine maintained erratic self-injection [10,28], one reported inconsistent results across animals [46], while three failed to demonstrate caffeine self-injection [34, 52, 53].

The results of five oral and intravenous caffeine self-administration studies in rats provided results consistent with the findings in nonhuman primates. Two self-injection studies in rats gave only equivocal evidence for the reinforcing effects of caffeine, along with suggestive evidence that there may be individual differences among animals [1,9]. In oral drinking studies in naive rats, preference for caffeine solution over water control was demonstrated only at extremely low caffeine concentrations which resulted in low (probably trivial) caffeine intake [33]. Preference for caffeine concentrations resulting in intake relevant to behaviorally active effects of caffeine was demonstrated only after a 14-day period of forced exposure to relatively high caffeine concentrations [49]. Studies in rats also suggest that levels of oral caffeine self-administration may be increased by food deprivation or a period of chronic nicotine exposure [33,44].

One study using a taste-aversion paradigm in rats provided evidence for both the aversive properties of caffeine in naive rats and the aversive properties of absence of caffeine in rats repeatedly exposed to caffeine [50]. In this study, injections of caffeine to naive rats produced a dose-related avoidance of a novel flavor associated with caffeine. However, rats which had previously received injections of caffeine on each of twelve days showed a dose-related avoidance of a novel flavor associated with the absence of caffeine. These interesting findings, which are consistent with several human studies (described below) suggesting that the reinforcing effects of caffeine may be potentiated by physical dependence or a recent history of caffeine exposure, should be systematically extended by using conventional drug self-administration methods in laboratory animals.

The results of an intravenous self-injection experiment in baboons [28] illustrate the reinforcing effects of caffeine and their differentiation from cocaine. Injections of drug were dependent upon completion of 160 lever-presses (a 160-response fixed-ratio schedule). A 3-hour time-out period followed each injection, permitting a maximum of eight injections per day. Before testing each dose of drug, self-injection performance was established with a standard dose of cocaine (0.4 mg/kg/injection). Subsequently, a range of doses of cocaine hydrochloride (0.01 to 3.2 mg/kg/injection) and caffeine citrate (0.1 to 10.0 mg/kg/injection) were substituted for the standard dose of cocaine for a period of 12 or more days. Drug doses are expressed as the salt.

Figure 1 shows mean number of self-injections on days 8 through 12 after substitution, expressed as a function of dose. As can be seen, at appropriate doses, cocaine maintained near-maximal self-injection performance. These results with cocaine are similar to those obtained using this same paradigm with other commonly abused psychomotor stimulant drugs such as *d*-amphetamine and phenmetrazine [30]. In contrast, the mean data with caffeine show that caffeine only occasionally maintained performance above the range of vehicle control. Examination of daily caffeine data, however, revealed that at some doses caffeine maintained

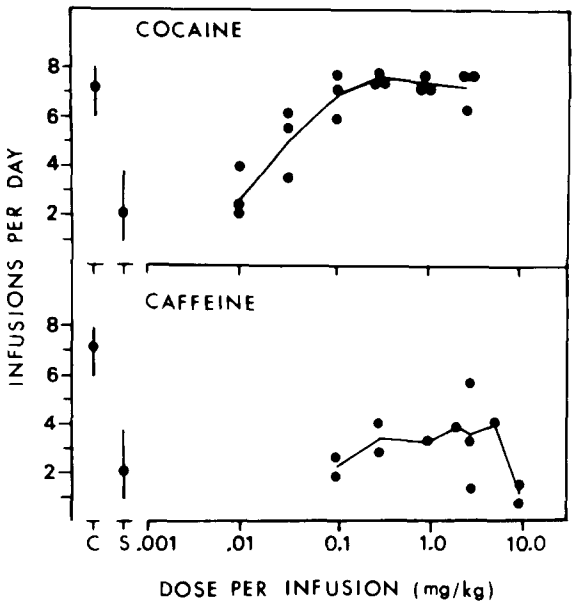

FIG. 1. Mean number of cocaine and caffeine self-infusions per day in baboons. Intravenous infusions were delivered upon completion of 160 lever presses; a 3-hour timeout followed each infusion, permitting a maximum of eight infusions per day. C indicates mean of all the 3-day periods with cocaine (0.4 mg/kg/infusion) which immediately preceded every substitution of a test dose of cocaine or caffeine. S indicates mean of days 8 to 12 after substitution of saline. Brackets indicate ranges of individual baboons' means. Drug data points indicate mean of days 8 to 12 after substitution of a test dose in individual baboons. Lines connect means at indicated doses of drug. (Data are from [28].)

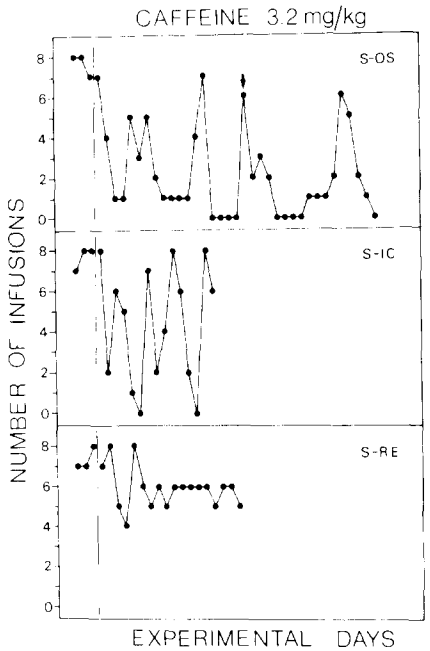

FIG. 2. Daily pattern of self-infusion maintained by 3.2 mg/kg/infusion caffeine in three baboons. The initial 3-day period in each panel shows the number of infusions maintained by cocaine (0.4 mg/kg/infusion) before substitution of caffeine. The arrow on day 22 for Baboon S-OS indicates a day on which the animal received one forced infusion of caffeine. (Figure is reprinted from [28].)

steady or erratic daily patterns of self-injection in all three baboons tested. Figure 2 presents such daily data for the three baboons tested at 3.2 mg/kg/injection.

As a whole, the drug self-administration research in laboratory animals indicates that caffeine does not maintain self-administration behavior as reliably as classic drugs of abuse such as cocaine, *d*-amphetamine or pentobarbital. The fact that caffeine does maintain self-administration behavior under some conditions differentiates caffeine from a wide range of behaviorally active drugs (including the amphetamine analog fenfluramine and chlorpromazine) which do not maintain self-administration under a variety of conditions [23,28].

SUBJECTIVE EFFECTS OF CAFFEINE IN HUMANS

An indirect approach to assessing reinforcing properties of caffeine in humans is to undertake placebo controlled, double-blind studies using scale- or item-based questionnaires to characterize caffeine-induced mood changes. With this approach, the reinforcing properites are assumed to be a function of the degree to which a drug produces pleasant subjective effects (sometimes called euphoria or liking). Although it is sometimes explicitly or implicitly assumed that reinforcing effects of drugs are causally dependent upon the pleasant subjective effects they produce [35], such assumptions can be reasonably questioned [45]. Furthermore, although there appears to be a generally good correspondence between pleasant subjective effects and reinforcing effects, there have been reports of dissociations between these effects [26,36]. Thus, at best, the assessment of such subjective effects provides an indirect and possibly spurious approach to predicting future drug-taking behavior.

With these caveats aside, there is a sizable research literature evaluating various subjective effects of caffeine that might plausibly be related to reinforcing properties. This literature shows that, in contrast to amphetamine which generally produced prominent elevations in ratings indicating "euphoria" and "well-being," caffeine generally failed to produce such effects (cf., [3, 6, 51]). In fact, a number of studies showed that caffeine produced prominent "dysphoric" changes in mood such as increases in anxiety and nervousness (e.g., [6, 7, 16, 20, 43]).

These general conclusions are nicely illustrated in a study which evaluated such subjective effects of caffeine and *d*-amphetamine [6]. The subjects were healthy volunteers who were light to moderate users of caffeinated beverages (e.g., one to four cups of coffee per day) and who agreed to abstain from caffeinated beverages for at least three hours before coming to the laboratory. The study used a within-subject, repeated-measure design in which each subject received orally administered placebo, caffeine base (50 to 800 mg), or *d*-amphetamine sulfate (25 mg) under blind conditions. The subjective effects of the drugs were evaluated on various questionnaires 2.5 and 3.5 hours after receiving caffeine and *d*-amphetamine, respectively. The questionnaires included the short form of the Addiction Research Center Inventory (ARCI) and the Profile of Mood States (POMS). The ARCI is a true-false questionnaire with empirically derived scales that are sensitive to various classes of abused drugs [32]. The MBG scale of the ARCI is generally considered to provide a measure of drug-induced euphoria, while the LSD scale provides a measure of dysphoric and somatic symptoms. The POMS is an empirically derived mood adjective checklist which contains scales that are sensitive to changes in mood and affect [40]. The study showed that caffeine and *d*-amphetamine produced markedly different subjective and behavioral effects. Of relevance to the present discussion, *d*-amphetamine produced prominent increases in the MBG (euphoria) scale of the ARCI in contrast to caffeine which produced only very modest, but significant, dose-related increases in euphoria (Fig. 3). In terms of adverse subjective effects, Fig. 3 also shows that caffeine produced significant dose-related increases on the LSD (dysphoria) scale of the ARCI and the Tension-Anxiety scale of the POMS. *d*-Amphetamine, in contrast, produced only nonsignificant decreases on these scales.

Some of the best initial evidence for positive caffeine-induced mood changes came from a survey and a clinical pharmacology study conducted by Goldstein and colleagues which showed that after overnight caffeine abstinence, heavy coffee users (5 or more cups per day) reported pleasant and desirable effects of coffee drinking and caffeine administration in contrast to coffee abstainers who reported unpleasant and undesirable effects [15,17]. Whether the difference between users and abstainers was related to differences in tolerance/dependence or, alternatively, reflected some other pre-existing difference between the self-selected subject populations was unclear. Recent experiments described in more detail below [24], extended these findings by showing substantial differences in liking of caffeinated vs. decaffeinated coffee under conditions in which subjects were given recent histories of heavy caffeine intake (i.e., were caffeine tolerant/dependent) (Figs. 6 and 8). These latter results emphasize the importance of tolerance/dependence as determinants of subjective liking of caffeine independent of other possible sensitivity differences between coffee users and abstainers.

Overall, these experiments show that caffeine produced modest, condition-dependent increases in subjective liking and/or euphoria which were of lower magnitude than those produced by classic drugs of abuse such as *d*-amphetamine or cocaine [6,12]. That caffeine produced some liking and/or euphoria distinguishes caffeine from a variety of psychoactive compounds, such as fenfluramine and chlorpromazine, which do not produce such effects as reliably [22,31].

REINFORCING PROPERTIES OF CAFFEINE IN HUMANS

The reinforcing properties of drugs in humans can be investigated by adapting procedures developed in the animal drug self-administration laboratory [23]. To date, only four reports have been published which provide information about the behavioral reinforcing effects of caffeine in humans. All four of these self-administration reports investigated the effects on coffee consumption of manipulating caffeine concentration under blind conditions [24, 27, 37, 41]. In addition to these published reports, this section will summarize some results from a previously unpublished study by Griffiths and Woodson which examined the reinforcing effects of caffeine in capsules.

In an abstract, Podboy and Mallory [41] reported that substitution of decaffeinated for caffeinated coffee in a group of fifteen severely retarded patients resulted in a decrease in coffee consumption from about seven to two cups per day. Absence of a control group and/or the failure to attempt to re-establish self-administration of caffeinated coffee renders the significance of these results uncertain.

In a series of experiments, Kozlowski [37] manipulated the caffeine concentration of coffee (25, 50, or 100 mg per

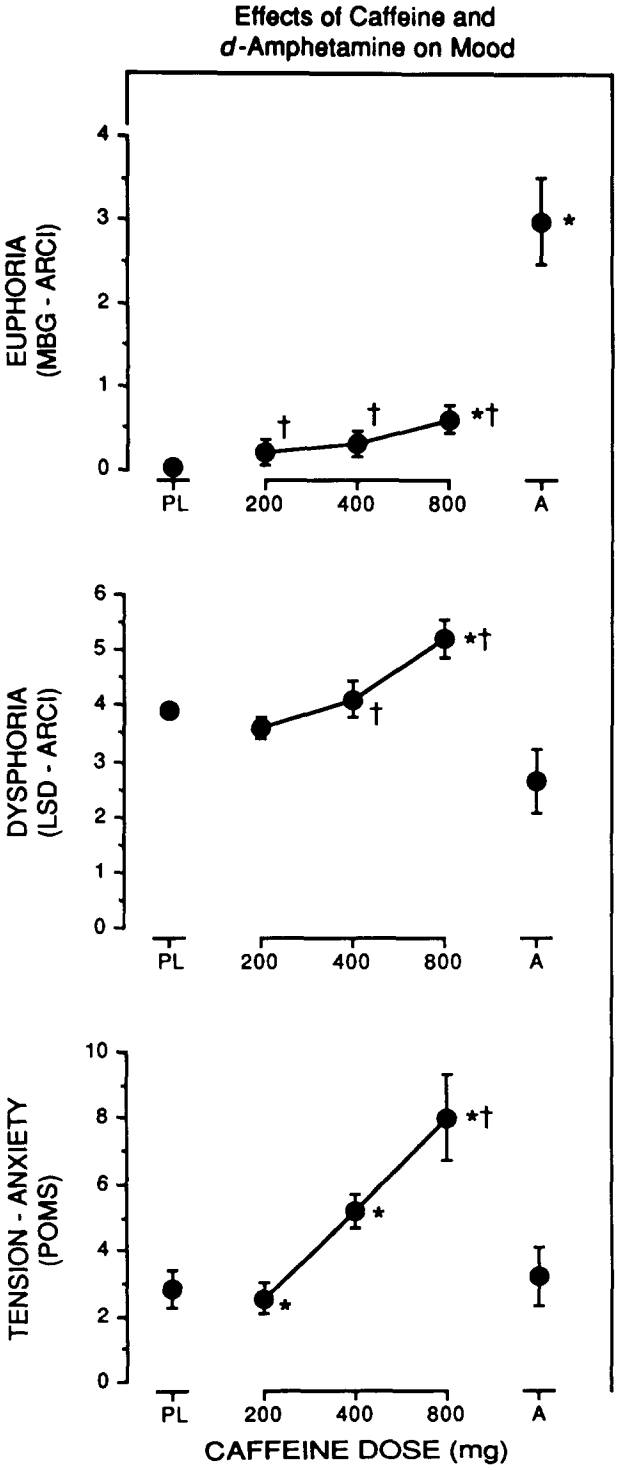

FIG. 3. Effects of placebo, caffeine base (200, 400, and 800 mg), and *d*-amphetamine sulfate (25 mg) on mood in five healthy subjects with histories of light to moderate caffeine use. y-Axes: euphoria as measured by the MBG scale of the ARCI; dysphoria as measured by the LSD scale of the ARCI; and tension-anxiety as measured by the POMS. x-Axes: caffeine dose, log scale; "PL" indicates placebo; "A" indicates *d*-amphetamine. Each data point and bracket indicates mean ± 1 standard error for 5 subjects (N=5). Absence of a bracket indicates that the radius of the data point is greater than 1 standard error. Asterisk and dagger indicate data point was significantly different ($p<0.05$) from placebo and *d*-amphetamine, respectively. (Data are from an experiment described in [6].)

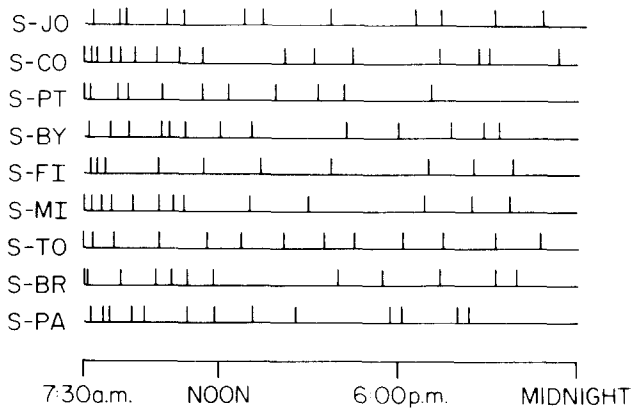

FIG. 4. Representative distributions of caffeinated coffee drinking for each of 9 subjects with histories of heavy coffee drinking. Data are from a baseline coffee drinking phase in which coffee (100 mg caffeine per cup) was available ad lib from 7:30 a.m. to midnight daily and until stable patterns of drinking emerged (5 to 17 days). Times at which individual cups of coffee were dispensed are represented by vertical hatch marks. (Data are from an experiment described in [24].)

cup) and showed that the highest dose was associated with less coffee consumed than the lower doses. Although Kozlowski interpreted these results as indicating caffeine "regulation" and, by implication, caffeine reinforcement, a more parsimonious interpretation of these data is that the highest dose of caffeine suppressed coffee consumption. Indeed, a more recent study showed that when caffeine was manipulated over a wide dose range, (50, 100, 200, and 400 mg per cup), caffeine produced a monotonic dose-related suppression of number of cups consumed and subject rated coffee "liking" [27].

In a series of experiments published in two reports, Griffiths and colleagues investigated the self-administration and reinforcing effects of caffeine in coffee in subjects who resided in a research ward [24,27]. All subjects reported histories of heavy coffee drinking (mean: 14 cups of coffee per day) and most reported histories suggesting problems with alcohol drinking and/or drug abuse. When cups of coffee were freely available, stable day-to-day patterns of coffee consumption emerged, with coffee drinking tending to be rather regularly spaced during the day and with intercup intervals becoming progressively longer throughout the day (Fig. 4). Experimental manipulation of coffee concentration, caffeine concentration, and caffeine preload showed that this lengthening of intercup interval was not due to accumulating caffeine levels. These manipulations also provided evidence for the suppressive effects of caffeine on coffee drinking. Examination of total daily coffee and caffeine intake across manipulations, however, provided no evidence for precise regulation (i.e., titration) of coffee or caffeine intake.

Three separate experiments in these residential subjects with histories of heavy coffee drinking provided information about the reinforcing effects of caffeine in coffee. In these experiments, caffeine was manipulated under double-blind conditions by adding various amounts of caffeine to decaffeinated coffee. One experiment involved manipulation of the caffeine dose per cup, with different doses block randomized across days [27]. Figure 5 shows the number of cups of coffee consumed. For all 3 subjects, cups consumed

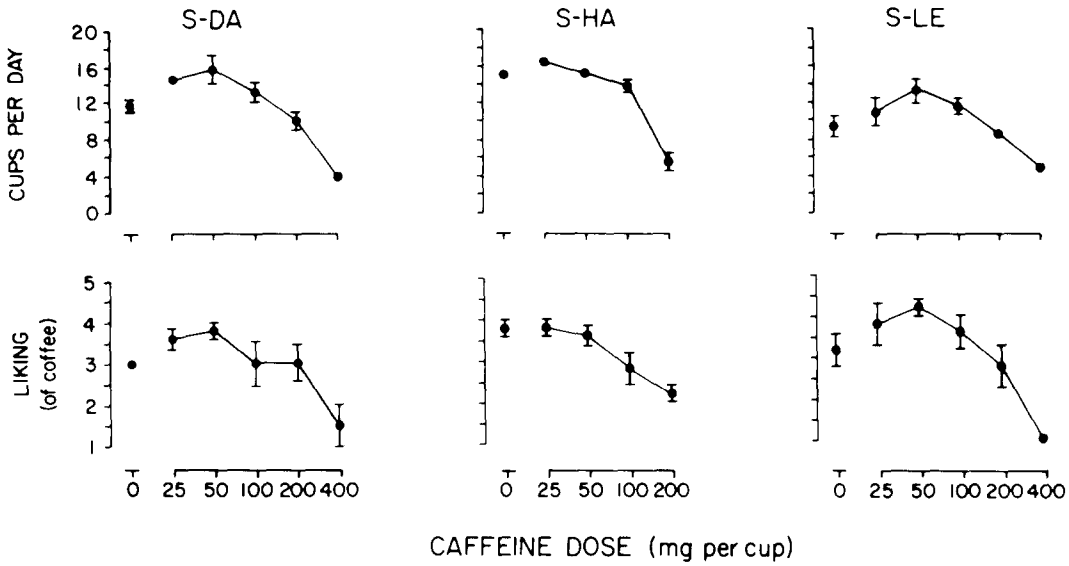

FIG. 5. Effects of caffeine dose on coffee drinking and subject rated liking for each of 3 subjects with histories of heavy coffee drinking. Caffeine dose was manipulated across days. Each day subjects were required to drink one cup of coffee at 7:30 a.m. From 8:45 unitl 12:00 midnight subjects had ad lib access to coffee. y-Axes: number of cups per day and 5:00 p.m. ratings of liking. x-Axes: caffeine dose in milligrams of caffeine added to each cup of decaffeinated coffee, log scale. Each data point shows mean and each bracket shows ± 1 standard error for 5 days (N=5) except for S-LE at 400 mg, at which N=1. Absence of a bracket indicates that the radius of the data point is greater than 1 standard error. (Data are from [27].)

increased slightly from 0 to 25 or 50 mg caffeine (maximum effect for decaffeinated vs. caffeinated conditions, respectively: 11.8±0.8 vs. 15.8±1.6 cups in S-DA; 15.2±0.3 vs. 16.6±0.2 cups in S-HA; and 9.6±1.1 vs. 13.4±1.3 cups in S-LE). This small increase in number of cups of caffeinated coffee consumed over the decaffeinated condition provides some limited evidence for the reinforcing effects of low doses of caffeine under these conditions. Ratings of coffee liking showed corresponding increases in two of the three subjects. The figure also shows that for all three subjects, higher doses of caffeine (50 to 400 mg) produced orderly dose-related decreases in cups consumed and ratings of liking, as previously mentioned in regard to interpretation of the study by Kozlowski [37].

Since the first experiment involving daily manipulation of caffeine dose provided only limited information about the reinforcing effects of caffeine, a second experiment was undertaken to examine longer periods of exposure to decaffeinated coffee [24]. If coffee drinking were maintained predominately by caffeine, it was reasoned that coffee drinking might progressively decrease (due to behavioral extinction) with prolonged exposure to decaffeinated coffee. Three subjects were exposed to phases involving the sequential availability of caffeinated, decaffeinated, caffeinated, decaffeinated, and caffeinated coffee, with decaffeinated phases being up to 13 to 17 days in each subject. An additional four subjects were exposed to phases of 10 or more days of decaffeinated coffee after a period of continuous exposure to caffeinated coffee. These double-blind manipulations provided no evidence for the behavioral extinction of coffee drinking in the decaffeinated coffee phases. Figure 6 shows group data for number of cups consumed and subject rated coffee liking for the last 5 days of caffeinated coffee and the first 10 days of decaffeinated coffee availability. On the first few days after substitution of decaffeinated coffee, coffee drinking decreased slightly but nonsignificantly while coffee liking decreased significantly on the first two days after substitution and subsequently progressively increased to pre-substitution levels. This transient decrease in liking was probably due to caffeine withdrawal which was measured concurrently on other subjective and objective scales and showed a similar time-course [24]. Decreased liking of decaffeinated coffee was probably not observed in the preceding study (Fig. 5) because subjects did not have continuous prior exposure to caffeine and they did not show signs of withdrawal. As a whole, the experiment exemplified in Fig. 6 provided no evidence for progressive deterioration of coffee drinking or liking as would be predicted on the basis of behavioral extinction. To the extent that liking might predict reinforcing effects, the experiment did provide suggestive evidence that, relative to caffeinated coffee, decaffeinated coffee may be aversive in subjects physically dependent on caffeine.

Since the results of the preceding experiment showed that a free self-administration approach was insensitive to possible differences in the reinforcing properties of caffeine in coffee, a third experiment in this same subject population was undertaken which utilized a choice procedure to explore the relative reinforcing effects of caffeinated (100 mg per cup) vs. decaffeinated coffee [24]. On some days ("no choice" days) the available coffee was indentified to subjects and staff by a letter code. On "choice" days, two letter-coded coffees (to which the subject had previously been exposed) were available for consumption and subjects made a mutually exclusive choice as to which lettered coffee would be consumed that day. Subjects were exposed to these choice tests under two different "background" conditions (i.e., double-blind caffeinated or decaffeinated background

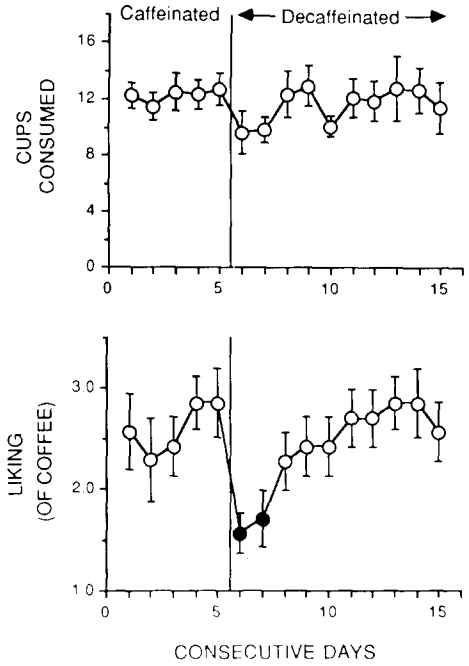

FIG. 6. Effects of substituting decaffeinated coffee for caffeinated coffee on coffee drinking and subject rated liking in 7 subjects with histories of heavy coffee drinking. The decaffeinated phase was preceded by a mean of 10 successive days of drinking only caffeinated coffee (100 mg caffeine per cup). y-Axes: number of cups per day and 8:30 p.m. ratings of liking. x-Axes: consecutive days. Each data point with brackets indicates mean ± 1 standard error for seven subjects (N=7). Filled data points indicate which decaffeinated coffee days are significantly different ($p<0.05$) from the five day period preceding substitution of decaffeinated coffee. (Data are from [24].)

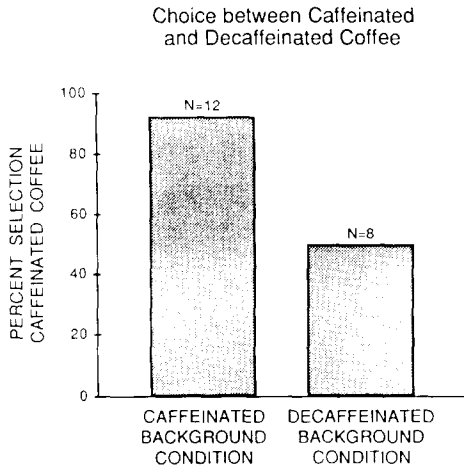

FIG. 7. Percent selection of caffeinated coffee in choice tests between caffeinated and decaffeinated coffee in subjects with histories of heavy coffee drinking. The two background conditions involved consumption of either caffeinated or decaffeinated coffee for a week or more before choice tests. Twelve and eight tests were conducted under the caffeinated and decaffeinated background conditions, respectively. (Data are from [24].)

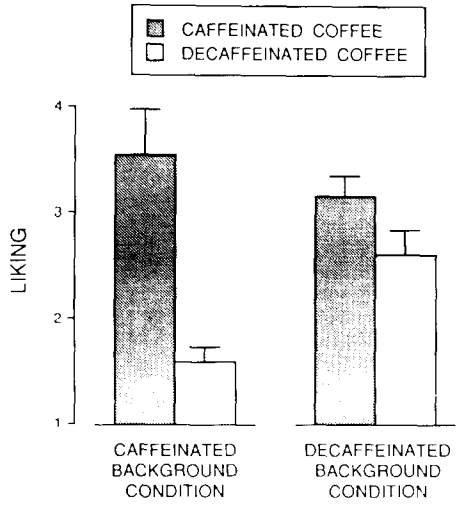

FIG. 8. Subject rated liking of caffeinated coffee (filled bars) and decaffeinated coffee (open bars) on no choice days that preceded choice opportunities in the choice sequences. y-Axes: 8:30 p.m. ratings of liking. Each bar shows mean and each bracket shows one standard error for N=6 subjects under the caffeinated background condition and N=4 under the decaffeinated background condition. For purposes of data presentation, when a subject received more than one exposure to a choice sequence, mean subject data were used. All subjects had histories of heavy coffee drinking. (Data are from [24].)

condition in which subjects consumed only caffeinated or decaffeinated coffee for a week or more before the first choice test). The purpose of the background conditions was to determine whether a history of continuous caffeine exposure (i.e., induction of caffeine physical dependence) might increase the relative reinforcing effects of caffeinated vs. decaffeinated coffee as suggested by the liking data in Fig. 6. One to three double-blind and independent choice tests were conducted in each of six subjects in the caffeinated background condition and in each of four subjects in the decaffeinated background condition.

Figure 7 shows the results of these choice tests. Of the twelve choice tests conducted under the caffeinated background condition, caffeinated coffee was overwhelmingly preferred (92%) to decaffeinated coffee. Although one subject chose decaffeinated coffee on one occasion, this same subject chose caffeinated coffee in two additional tests. The figure also shows that caffeinated coffee was not reliably chosen under the decaffeinated background condition. Of the eight choice tests conducted under the decaffeinated background condition, caffeinated and decaffeinated coffee were chosen equally often (50%). Of the four subjects examined, one chose only caffeinated coffee, two chose only decaffeinated coffee, and one chose both caffeinated and decaffeinated coffee on different occasions. Figure 8 shows that the liking ratings from the no choice days were consistent with the choice results. Under the caffeinated background condition, caffeinated coffee was rated as better liked than the decaffeinated coffee, which was rated very unfavorably. Under the decaffeinated background condition, however, there was no such pronounced difference in liking between caffeinated and decaffeinated coffee. Comparing across the two background conditions, it appeared that the difference in liking under the caffeinated background condition was due primarily to a decreased liking for the decaffeinated coffee

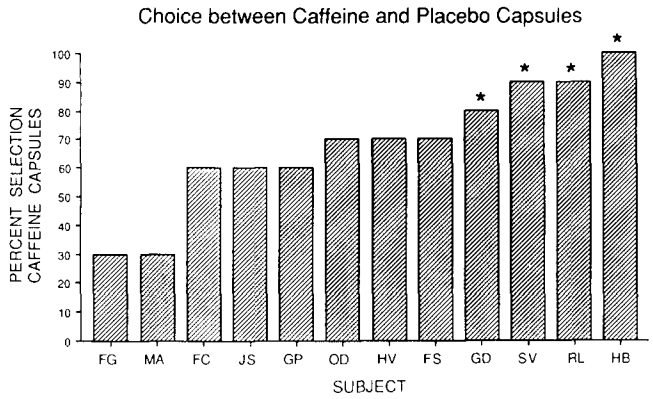

FIG. 9. Percent selection of caffeinated capsules in blind choice tests between caffeine and placebo capsules in twelve normal subjects with varying histories of caffeine intake. After two forced exposure days on which subjects received color-coded capsules containing either 200 mg caffeine or placebo, subjects had a choice day on which they decided which one of the two types of color-coded capsules would be ingested. Using different color-coded capsules, each subject was exposed to ten independent sequences of two forced exposure days followed by a choice day. Each bar shows the percentage of the ten choice tests on which caffeine capsules were selected. Asterisks indicate a statistically significant preference for caffeine capsules ($p<0.05$).

rather than a change in liking for the caffeinated coffee. This result is consistent with the liking result shown in Fig. 6 and is probably attributable to caffeine withdrawal.

The latter choice experiment provided the first unequivocal demonstration in humans of the behavioral reinforcing properties of caffeine in coffee. The study showed that, under conditions in which subjects with histories of heavy coffee drinking were presumably caffeine tolerant/dependent (caffeinated background condition), subjects reliably preferred caffeinated to decaffeinated coffee in choice tests. Under conditions in which subjects were nontolerant/nondependent, however, the reinforcing effects of caffeine were equivocal, with evidence for between-subject differences in caffeine preference.

In previously unpublished research Griffiths and Woodson have recently replicated and extended these observations of individual differences in the reinforcing effects of caffeine to a group of "normal" subjects who were selected without regard to histories of caffeine use. Twelve normal healthy subjects who were employees of Francis Scott Key Medical Center and whose mean daily caffeine intake was 361 mg (ranging between 3 and 1032 mg) participated in an experiment in which they were given opportunities to choose between caffeine or placebo capsules under blind conditions. They were told that the experiment involved taking various compounds (e.g., chlorogenic acids, kahweol, caffeine, tannin, sugar, theophylline, theobromine) found in the coffee, tea, chocolate and soft drinks which they normally ingest as a part of their daily diet. They were told that because the test compounds might interact with drugs and with chemical constituents in some foods, they were required to eliminate prescription and over-the-counter drugs and certain foods from their diets on experimental days until approximately eight hours after receiving capsules. The list of restricted foods involved all caffeine-containing substances. Five days each week, subjects reported to the laboratory in the morning, usually before going to work, at which time they orally ingested two identical color-coded capsules under blind conditions. After two "no choice" forced exposure days on which subjects received two different types of color-coded capsules on different days (e.g., 2 red capsules on one day and 2 green capsules on the next day), subjects were exposed to a "choice" day on which they chose which one of the two types of color-coded capsules would be administered. Using this procedure, each of twelve subjects had ten choice tests between color-coded capsules containing 200 mg of caffeine base and placebo. Each choice test for each subject was independent (i.e., involved exposure and choice between novel color-coded capsule conditions). Figure 9 shows the percent selection of caffeine on the ten independent choice tests for each of the twelve subjects. The figure shows that there were substantial differences across subjects with respect to the frequency of caffeine choice and that statistically significant preference for caffeine was demonstrated in four of the twelve subjects ($p<0.05$, binomial probability). Interestingly, level of caffeine consumption prior to the study did not appear to be a determinant of caffeine choice: estimated daily caffeine intake did not significantly correlate with percent selection of caffeine ($r=0.26$) and the four subjects who demonstrated caffeine reinforcement (subjects GD, SV, RL and HB) had widely variable estimated caffeine intakes (3, 350, 421, and 741 mg/day, respectively).

This study significantly extends the findings of Griffiths, Bigelow and Liebson [24] by demonstrating clear individual differences in the reinforcing properties of caffeine in a "normal" unselected subject group. The study also provides the first demonstration that caffeine alone, independent of coffee, can function as a reinforcer in some subjects.

Overall, the experiments reviewed in this section provide clear evidence for the behavioral reinforcing effects of caffeine in humans. The equivocal or inconsistent reinforcing effects of caffeine in nontolerant/nondependent subjects with histories of heavy caffeine use [24] is in marked contrast to the reliable reinforcing effects that have been demonstrated when the self-administration of classic drugs of abuse such as cocaine or pentobarbital have been investigated in drug abuser subjects (e.g., [12,39]). The fact that caffeine does serve as a reinforcer in some subjects both with and without histories of heavy use, however, distinguishes caffeine from behaviorally active drugs such as fenfluramine and chlorpromazine which do not maintain human drug self-administration behavior [4,25].

DISCUSSION

Although many questions remain, there are remarkable consistencies across the results of these studies of animal and human drug self-administration and human subjective effects. These studies clearly show that under appropriate conditions, caffeine can serve as a reinforcer and can produce elevations in subjective drug liking and/or euphoria. In this regard, caffeine can be distinguished from a wide range of behaviorally active compounds, such as the amphetamine analog fenfluramine and the major tranquilizer chlorpromazine, which do not produce such effects. These studies also show that these effects of caffeine can be distinguished from classic drugs of abuse such as cocaine, *d*-amphetamine or pentobarbital which generally maintain high levels of self-administration (or liking) in contrast to caffeine which tends to maintain lower levels of self-administration (or liking) or maintains self-administration under a more narrow range of parametric conditions.

Several human studies [15, 17, 24] and one animal experiment [50] suggest that physical dependence (or at least a recent history of substantial caffeine intake) may substantially potentiate the reinforcing effects of caffeine in coffee. Further studies are needed to determine the extent to which physical dependence may be a necessary condition for caffeine to function as a reinforcer in some subjects. Also, the studies suggesting the importance of physical dependence have been conducted in subjects with histories of very heavy caffeine use. It will be of importance to determine the extent to which low dose physical dependence may be significant in helping to establish and maintain the chronic, societally-sanctioned patterns and amounts of caffeine use.

It is interesting that some of the reviewed research shows that ad lib consumption of decaffeinated coffee occurs at about the same rate as consumption of usual-strength caffeinated coffee (cf., Fig. 6) [24,27]. It is possible that the many sensory, motor, and social events that comprise habitual coffee drinking function as discriminative stimuli and/or conditioned reinforcers to maintain drinking of decaffeinated coffee. It is also possible that drinking of decaffeinated coffee is maintained, in part, by pharmacologically active substances in coffee other than caffeine [5, 8, 47]. Further research will be needed to clarify and differentiate these possibilities.

Animal and human studies have clearly documented substantial differences between individual subjects in the behavioral effects of caffeine (e.g., [18,38]). Caffeine self-administration studies also provide evidence for such individual differences in the reinforcing properties of caffeine ([1, 9, 24, 46], Fig. 9). For example, in one of the experiments by Griffiths and colleagues [24] some nontolerant/nondependent subjects consistently preferred decaffeinated coffee to caffeinated coffee, citing adverse symptoms suggesting caffeine toxicity after consuming caffeinated coffee. One of nontolerant/nondependent subjects, however, reliably chose caffeinated coffee over decaffeinated coffee and, in written comments, expressed an exceptionally strong liking for the caffeinated coffee, making a favorable comparison of the coffee to "speed" (i.e., amphetamines). This observation of individual differences in caffeine reinforcement was subsequently replicated in a "normal" subject group who were selected without regard to history of caffeine use (Fig. 9). The suggestion that there may be meaningful individual differences in the reinforcing effects of caffeine is also consistent with the observation that levels of self-selected dietary intake of caffeine may predict the behavioral response to caffeine challenge [42]. Further research will be necessary to establish the reliability and mechanism(s) for such individual differences in caffeine reinforcement.

The present review documents the sometimes subtle, condition-dependent reinforcing properties of caffeine. The challenge for future animal and human research will be to delineate the precise conditions under which caffeine does and does not serve reliably as a reinforcer, thereby elucidating the behavioral and pharmacological mechanisms by which caffeine comes to capture and control human behavior. Such a careful analysis of the reinforcing properties of the most widely used behaviorally active drug in the world should provide valuable insights into the general nature of the drug dependence process.

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