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Journal of Substance Abuse & Alcoholism

Research Article

Predicting Addiction Liability from Brain Stimulation Reward Data: A Comparison of the Acute Effects of Cocaine, Pseudoephedrine, Nicotine, and Caffeine

Michael A Bozarth[1]* and Cindy M Pudiak[2]

Addiction Research Unit, Department of Psychology, State University of New York at Buffalo, Buffalo, New York 14260-4110

***Corresponding author**

Dr. Michael A Bozarth, Department of Psychology, State University of New York at Buffalo, Buffalo, New York 14260-4110, phone: 716-645-3650 ext. 687, fax: 716-645-3801; Email: bozarth@acsu.buffalo.edu

Submitted: 26 June 2021

Accepted: 28 July 2021

Published: 30 July 2021

ISSN: 2373-9363

Keywords

- Addiction liability; Brain stimulation reward; Caffeine, cocaine; Drug abuse; Intracranial self-stimulation; Nicotine; Pseudoephedrine; Psychomotor stimulants; Reward

Abstract

Male, Long-Evans rats with lateral hypothalamic stimulating electrodes were tested using a threshold-tracking procedure. This procedure determined the minimum stimulation frequency (i.e., stimulation threshold) necessary to maintain ≥30 presses/min during daily 30-min test sessions. Rats were injected with cocaine hydrochloride (2.5 to 20 mg/kg, i.p.), pseudoephedrine hydrochloride (3 to 100 mg/kg, i.p.), nicotine bitartrate (0.063 to 1 mg/kg, s.c.), or caffeine (5 to 80 mg/kg, i.p.) immediately before testing. Peak threshold-lowering effects were determined during 180-min test sessions. Another series of tests compared the facilitatory effects produced by (i) different nicotine bitartrate administration conditions (i.e., pH-adjusted vs. pH-unadjusted solutions and s.c. vs. i.p. injection routes), (ii) nicotine freebase in pH-adjusted and pH-unadjusted solutions, and (iii) repeated nicotine bitartrate injections. These comparisons ensured that the most effective nicotine administration parameters were used.

All compounds facilitated BSR. The prototypic addictive drug cocaine lowered thresholds over twice as much as the nonaddictive compound pseudoephedrine. This shows that BSR facilitation can be used to predict reinforcing drug action, but quantitative measures of facilitation must be used to distinguish drugs with high and low addiction liabilities. Nicotine's facilitation of BSR was quantitatively similar to that seen with pseudoephedrine and markedly different from cocaine's effect. Caffeine produced BSR facilitation comparable to that seen with nicotine and with pseudoephedrine. Similar peak-facilitation effects were seen with all nicotine administration conditions. This suggests that even under optimal administration conditions, nicotine's profile in this animal model is that of a substance with a low addiction liability.

ABBREVIATIONS

BSR-brain stimulation reward, **CNS**-central nervous system, **IP-intraperitoneal, MIN-minute/minutes; SEM**-standard error of the mean, **SC**-subcutaneous

INTRODUCTION

Considerable evidence suggests that a compound's effect on brain stimulation reward (BSR) provides a useful assessment of its potential addiction liability (for reviews, see Esposito and Kornetsky, 1978; Kornetsky et al., 1979; Reid, 1987; Wise, 1996). Drugs that enhance the rewarding effects of electrical brain stimulation are generally highly addictive, and drugs that are not addictive usually fail to enhance (or even inhibit) BSR. The interaction of a compound with BSR does not, of course, directly assess the compound's addiction liability. Rather, the enhancement of BSR is though to reflect the drug's rewarding properties, and this rewarding action is thought to underlie the drug's ability to reinforce behavior and thus to produce an addiction (see Bozarth, 1987a).

Most investigators studying the facilitation of BSR by various drugs consider this a qualitative measure: drugs that facilitate BSR are likely to possess potent reinforcing and hence addictive properties. Earlier work comparing the effects of various opioids on BSR suggested that quantitative aspects of a compound's facilitatory action may be important in determining its addiction liability. The prototypic addictive drug morphine produced robust facilitation of BSR, while codeine and nalorphine, compounds with a low addiction liability, produced only a modest facilitation effect (Bozarth, 1978; Bozarth and Reid, 1978; Reid and Bozarth, 1978). Furthermore, pentazocine, an opioid with mixed agonist-antagonist properties that reportedly has significant abuse liability only in exaddicts, produced robust facilitation of BSR only after rats had prior exposure to morphine (Bozarth, 1978; Bozarth and Reid, 1978; Reid and Bozarth, 1978). These data suggest that BSR may indeed provide a useful assessment of a compound's addiction potential, but **quantitative** aspects of the facilitation

effect must be considered to distinguish compounds with a high addiction liability from substances with a low addiction liability (Bozarth, 1978; Bozarth and Reid, 1978). Unfortunately, most investigators fail to compare the effects of various compounds with those of prototypic addictive drugs (e.g., cocaine, heroin). Most BSR studies simply compare the effect of the test compound with that obtained with drug vehicle (e.g., physiological saline). Any enhancement of BSR is usually interpreted as indicating the compound has potent rewarding effects and hence a significant addiction liability.

The present study compares the effects of four psychoactive substances on BSR. The facilitation produced by a prototypic addictive drug (i.e., cocaine) is compared with the facilitatory action of a compound generally considered to have a low addiction liability (i.e., pseudoephedrine). The effects of two other commonly used substances with controversial addictive properties (e.g., caffeine, nicotine) are evaluated by considering the range of facilitation produced by addictive and nonaddictive 1 drug actions.

Pseudoephedrine was selected as the nonaddictive comparison compound because (i) it is widely prescribed by physicians and is available over-the-counter in the United States and Canada, and (ii) it has mild stimulatory properties similar to psychomotor stimulants. Although pseudoephedrine is restricted by prescription in some European countries (e.g., Germany and Sweden but not Great Britain), its widespread use without reported addiction 2 in North America suggests that this compound has a very low addiction liability. In the United States cases of pseudoephedrine abuse appear restricted to excessive use of weight loss preparations and to high-dose use of preparations marketed as a safe, "natural high." The sale of over-the-counter medicines containing pseudoephedrine remain very popular for use as a nonsedating nasal decongestant, but some restrictions in terms of the quantity that may be purchased within a given time-period have been enacted because of its diversion as a precursor chemical for the illicit manufacture of methamphetamine. Previously the very limited abuse of pseudoephedrine appears to have been driven by sociological rather than pharmacological factors (i.e., there is no indication of potent anorexic or mood-elevating effects even from excessively high doses). Restrictions on sales and distribution are designed to prevent the high-dose intake that can produce toxic reactions and the diversion to clandestine laboratories that may convert pseudoephedrine to methamphetamine. There are no documented cases of pseudoephedrine addiction nor any indication of euphoria or substantial mood-elevating effects from this compound.

GENERAL METHOD

Subjects

Male, Long-Evans rats (Harlan Sprague-Dawley, Altamont, NY), weighting 225 to 300 g at the time of surgery, were implanted with monopolar stimulating electrodes aimed at the lateral hypothalamic level of the medial forebrain bundle. With the upper incisor bar 3.3 mm below the interaural plane, the coordinates were posterior 3.3 from bregma, lateral ± 1.8 from the midline mm, and 8.4 mm below dura. Electrodes were fabricated from 0.25 mm stainless steel wire insulated with Formvar except at the cross section of the tip. The stimulation ground was formed by wrapping 0.25 mm annealed stainless steel wire around two stainless steel screws (#80) anchored into the rostral aspect of the skull. Both the stimulating electrode and the ground terminated in gold-plated Amphenol pins that were connect to the stimulation lead during testing by mating Amphenol sockets.

Electrodes were implanted under sodium pentobarbital (65 mg/kg, i.p.) anesthetic, with atropine sulfate (0.4 mg/kg, i.p.) given to decrease mucosal secretions. Electrodes were anchored to the skull using three stainless steel screws embedded in dental acrylic. A single dose of penicillin-G (60,000 units, i.m.) was administered prophylactically following the completion of surgery. Animals were allowed a minimum of 5 days recovery from surgery before screening for BSR.

Rats were individually housed in stainless steel cages contained in a temperature and humidity controlled environment (22 ± 1 °C, 40 to 60 %-RH). A 14-hour light/10-hour dark cycle of illumination was used, with all behavioral testing occurring during the light phase of this cycle. Subjects were given *ad libitum* access to food and water, except during behavioral testing. At the end of the experiment, animals were sacrificed with an overdose of sodium pentobarbital (c. 80 mg/kg, i.p.) and were transcardially perfused with normal saline followed by phosphate-buffered formalin. The brains were removed and stored in formalin before sectioning into 40 m sections using a cryostat-microtome. The brain sections were stained using crystal violet, and electrode placements were verified at 10x magnification.

Apparatus

Stimulation pulses consisted of 300 msec trains of 300sec cathodal pulses, with the electrode shunted to ground during the interpulse interval to prevent electrical charge build-up in the stimulated tissue. Various current intensities (100 to 500A) and frequencies (32 to 126 Hz) were used. Stimulation pulses were controlled by a computer program, which determined all stimulation parameters except current intensity which was controlled by a constant-current stimulator (Mundl, 1980). Current intensity was monitored by the voltage drop across a 1 kohm resistor in series with the stimulating electrode. Pulse form and current intensity were monitored throughout the test sessions using Textronic oscilloscopes.

Rats were tested in 26 x 47 x 38 cm operant chambers containing a lever located 8 cm above the floor. Each lever press produced a single train of stimulation. Subjects were connected to the stimulator with a flexible lead attached to an electrical commutator. Unrestricted movement of the subjects was maintained throughout the experimental sessions.

Compounds

Cocaine hydrochloride (National Institute on Drug Abuse Drug Procurement Program, Research Triangle Park, NC), pseudoephedrine hydrochloride (Sigma Chemical, St. Louis), and anhydrous caffeine (Sigma Chemical, St. Louis) were dissolved in physiological saline and were injected intraperitoneally. Both cocaine and pseudoephedrine doses refer to the salt form of these

compounds. Nicotine bitartrate and nicotine freebase (Sigma Chemical, St. Louis) were dissolved in physiological saline. Some tests involved nicotine solutions that were pH-adjusted to 7 0.2, while other tests used unadjusted nicotine solutions (bitartrate pH 3.4; freebase pH 11.4). Nicotine was injected in some tests subcutaneously and in other tests intraperitoneally. All nicotine doses refer to the freebase weight of this compound. Injections were given in a 1 ml/kg volume, except for the two highest caffeine doses (i.e., 40 and 80 mg/kg) which were injected in 2 and 4 ml/kg volumes because of the limited solubility of anhydrous caffeine.

Procedure

Rats were screened for BSR at 79 to 126 Hz using various current intensities (100 to 500 A). Subjects showing vigorous lever-pressing were tested for several 30-min sessions at fixed stimulation parameters. After stable responding developed, testing with the threshold-tracking procedure was begun using daily 30-min sessions. Stimulation frequencies decreased 0.1 log unit per minute until responding fell below criterion (i.e. 30 presses/min). Stimulation frequencies then increased 0.1 log unit per minute until responding met criterion (i.e., 30 presses/min). Alternating descending and ascending thresholds were continuously determined throughout the test session. Threshold was defined as the average stimulation frequency that maintained criterion responding. Ascending and descending threshold were generally the same, producing response patterns that alternated vigorous pressing (at threshold) and nonresponding across successive 1-min periods.

Rats were tested daily with 30-min sessions. Mean frequency thresholds were calculated daily for each rat. Responding was considered stable when thresholds were within 10% of the previous 5-day mean. After frequency thresholds had stabilized (range 2 to 3 weeks), drug testing began. Subjects were injected immediately before BSR testing and were tested continuously for 3 hours following injections. The longer session duration was used to document the entire time-course of drug action, with specific attention to detecting any delayed facilitatory effect on BSR. Data were analyzed by comparing the effects of various drug doses (including the drug vehicle, physiological saline) with mean 5-day pretreatment baseline thresholds. Each 180-min test session was divided into successive 15-min periods, and the average threshold was computed for each test at each time interval. Data are expressed as the percentage of baseline thresholds. A minimum of 72 hours separated each drug test.

EXPERIMENT I: A COMPARISON OF THE EFFECTS OF COCAINE AND PSEUDOEPHEDRINE ON BSR

The first experiment compared the effects of two drugs with well-documented addiction liabilities-cocaine and pseudoephedrine. Cocaine is a prototypic addictive drug, with a very high addiction liability, while pseudoephedrine addiction has not been reported. These two compounds serve to define the magnitude of facilitation produced by addictive and nonaddictive compounds, respectively. Cocaine defines the lower limit of facilitation expected from a compound with a high addiction liability (i.e., potentially addictive compounds ≥ cocaine's facilitatory effect), while pseudoephedrine defines the upper limit of facilitation expected from a compound with a low addiction liability (i.e., low addiction liability compounds ≤ pseudoephedrine's facilitatory effect). In determining the lower and upper limits of both profiles, it is necessary to consider the maximum facilitation produced by each compound. This is because both humans and laboratory animals can control how much drug they self-administer and it is presumed that both increase their dosage levels to produce the desired (i.e., rewarding) effect. Increases in drug dosage to potentially reinforcing levels is limited only by toxic and neurological side-effects of drug treatment. To ensure that the maximum facilitatory effect was obtained with each compound, full dose-response and time-course analyses were performed for each substance.

Procedure

Rats were assigned to one of two groups to receive either cocaine hydrochloride (1.25, 2.5, 5, 10, & 20 mg/kg, i.p., n = 10) or pseudoephedrine hydrochloride (3, 30, 56, & 100 mg/kg, i.p., n = 6) injections. All rats received all doses of a given compound administered in a counterbalanced order. At least 72 hours separated each injection, and injections were postponed if the subject was not within 10% of its pretreatment baseline mean on the day prior to a scheduled injection. Animals were tested continuously for 180 min immediately after injections and for 30 min on days between drug tests.

Results

Figures 1 and 2 illustrate the percent of baseline thresholds for cocaine and for pseudoephedrine across the entire 180-min test session. Cocaine produced a strong, dose-dependent lowering of thresholds [$F(5, 35) = 73.874$, $p < .001$]. Pseudoephedrine also produced a dose-dependent threshold lowering [$F(3, 15) = 11.514$, $p < .001$], but the effect was weaker. A higher dose of cocaine (i.e., 30 mg/kg, i.p.) produced stereotypy which disrupted responding for BSR. The higher doses of pseudoephedrine (i.e., 56 & 100 mg/kg, i.p.) also produced stereotypy accompanied by an apparent increase in thresholds for some animals. The increases in stimulation thresholds seen with stereotypic drug doses are considered artifactual and are probably not representative of changes in the rewarding impact of the electrical stimulation. Data obtained with these doses are not shown in the figures. Both cocaine [$F(11, 77) = 53.768$, $p < .001$] and pseudoephedrine [$F(11,55) = 3.671$, $p < .005$] effects changed across the 180-min test sessions. There was also a significant Dose x Minutes post injection interaction for cocaine [$F(55,385) = 4.207$, $p < .001$] and for pseudoephedrine [$F(55,165) = 2.535$, $p < .01$]. [Figure 1, 2]

Discussion

Cocaine produced a strong facilitation of BSR as shown by its dramatic threshold-lowering effect. This is consistent with numerous other reports showing a potent facilitatory action of cocaine, but the threshold-tracking method permitted a detailed time-course analysis not offered by other measures. Cocaine's BSR facilitation peaked within the first time bin (i.e., 1-15 min post injection) and declined rapidly thereafter.

Pseudoephedrine produced a significant facilitation of BSR, but unlike cocaine, pseudoephedrine's facilitatory action was

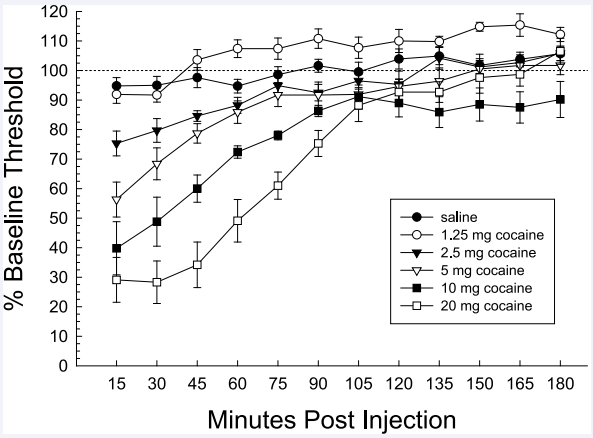

Figure 1 Time course of cocaine's facilitation of BSR. Animals were injected with cocaine hydrochloride (i.p.) at the beginning of the test session. The figure shows the mean (SEM) percent of baseline thresholds for each 15-min time period following injections. Cocaine produced a strong, dose-dependent threshold lowering. The facilitation effect was apparent during the first 15-min interval and terminated by 90 min post injection. Symbols: saline, open circles; 1.25 mg/kg

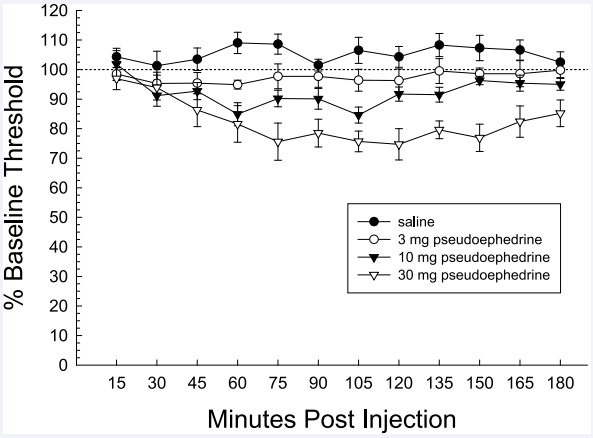

Figure 2 Time course of pseudoephedrine's facilitation of BSR. Animals were injected with pseudoephedrine hydrochloride (i.p.) at the beginning of the test session. The figure shows the mean (± SEM) percent of baseline thresholds for each 15-min time period following injections. Pseudoephedrine produced a delayed, dose-dependent threshold lowering. Symbols: saline, filled circles; 3 mg/kg pseudoephedrine, open circles; 10 mg/kg pseudoephedrine, filled triangles; 30 mg/kg pseudoephedrine, open triangles. cocaine, filled circles; 2.5 mg/kg cocaine, open squares; 5 mg/kg cocaine, filled squares; 10 mg/kg cocaine, open triangles; 20 mg/kg cocaine, filled triangles.

markedly delayed peaking about 60 min post injection. There was also an important quantitative difference in the magnitude of facilitation produced by cocaine and by pseudoephedrine: the maximum facilitation produced by cocaine was approximately 2 ½ times greater than the maximum facilitation produced by pseudoephedrine.

Despite the pronounced difference in peak effects, there is partial overlap in the dose-response curves for these two

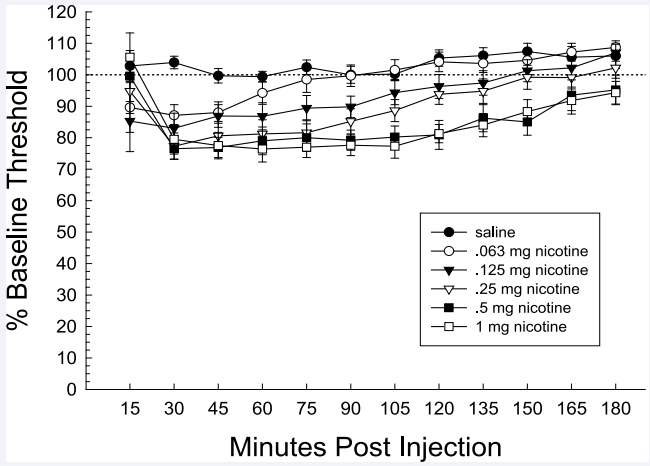

Figure 3 Time course of nicotine's facilitation of BSR. Animals were injected with nicotine bitartrate (s.c., pH = 7 0.2) at the beginning of the test session. The figure shows the mean (SEM) percent of baseline thresholds for each 15-min time period following injections. Nicotine doses are expressed as the freebase weight. Note that peak facilitation changes little as a function of nicotine dose, while duration of facilitation increases in a dose-dependent manner. Symbols: saline, filled circles; 0.063 mg/kg nicotine, open circles; 0.125 mg/kg nicotine, filled triangles; 0.250 mg/kg nicotine, open triangles; 0.50 mg/kg nicotine, filled squares; 1.0 mg/kg nicotine, open squares.

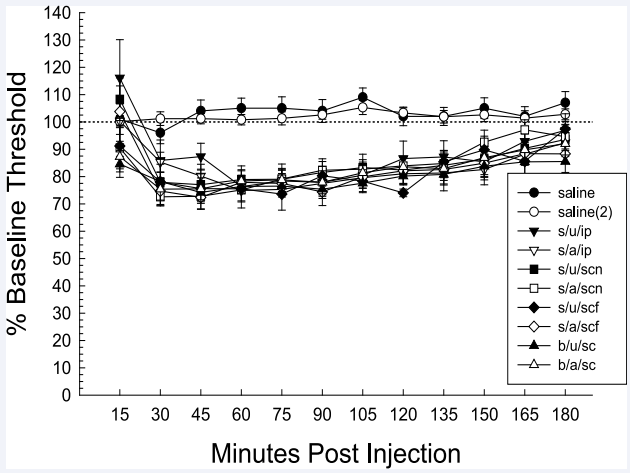

Figure 4 Effect of nicotine administration parameters on nicotine's facilitation of BSR. Animals were injected with 0.5 mg/kg nicotine (dose expressed as free-base weight) at the beginning of the test session. The figure shows the mean (± SEM) percent of baseline thresholds for each 15-min time period following injections. Various nicotine formulations and two routes of administration (s.c. & i.p.) were compared, using nicotine bitartrate with pH-adjusted (pH = 7 ± 0.2) and pH-unadjusted (pH ± 3.4) solutions and using nicotine freebase with pH-adjusted (pH = 7 ± 0.2 and pH-unadjusted (pH ± 11.4) solutions. Similar levels of BSR facilitation were seen with the various nicotine administration parameters, but the s.c. pH-adjusted nicotine bitartrate condition was somewhat less variable than the other treatment conditions. Symbols: saline, open circles; s.c. nicotine bitartrate pH-adjusted, open squares; i.p. nicotine bitartrate pH-adjusted, filled squares; s.c. nicotine bitartrate pH-unadjusted, open triangles; i.p. nicotine bitartrate pH-unadjusted, filled triangles; s.c. nicotine freebase pH-adjusted, open diamonds; s.c. nicotine freebase pH-unadjusted, filled triangles.

compounds: the 30 mg pseudoephedrine dose produced facilitation similar to that seen with 2.5 mg cocaine. This suggests that the maximum effect produced by pseudoephedrine is comparable to a low dose of cocaine. Cocaine doses in this range (i.e., 2.5 to 5 mg/kg) can produce a conditioned place preference (Brown et al. 1991; Nomikos and Spyraki, 1988; Spyraki et al. 1982; see also Bardo et al. 1995), and these conditioning studies provide independent evidence that these low cocaine doses are rewarding. It is likely that the mildly rewarding effects of low-dose cocaine and of pseudoephedrine are reflected by the modest facilitation seen with these conditions. However, the modest rewarding effect of pseudoephedrine is insufficient to produce compulsive drug-taking behavior and addiction as evidenced by the widespread use of this compound without reported addiction liability.

Pseudoephedrine and related compounds (e.g., ephedrine) have mild psychoactive properties. This mild psychoactive effect is probably reflected by pseudoephedrine's modest facilitation of BSR. The Chinese herb Ma Huang contains pseudoephedrine and ephedrine, and Ma Huang has been marketed in the United States both as a diet aid and as a stimulant. Despite its aggressive promotion, there have been few reports of widespread abuse of Ma Huang or related substances. Indeed, restrictions on the sale and distribution of preparations containing these compounds in some countries are probably related to their misuse as a diet aids (i.e., escalating dosage to produce stronger appetite suppression) and not because of their 'recreational' use. Furthermore, tests with humans investigating the reinforcing and subjective effects of the more potent isomer ephedrine reveal a low abuse liability of this compound compound (Chait, 1994). 3

There are important pharmacokinetic differences between these two compounds. Cocaine's effect is immediate and begins to decline by the end of the first hour of testing (see Figure 1). Pseudoephedrine's effect is delayed and lasts for much of the 3-hr test session (see Figure 2). The delayed onset and the long duration of action seen with pseudoephedrine make it a poor candidate for reliable intravenous self-administration in laboratory animals. Compounds with a rapid onset and a short duration of action produce the most robust intravenous self-administration (e.g., cocaine, heroin). Nonetheless, this compound may be interesting to examine for intravenous self-administration. Alternatively, it is likely that pseudoephedrine would produce a conditioned place preference. This latter method may be particularly well-suited to detecting marginal rewarding drug effects and appears less sensitive to latency to onset than the intravenous self-administration method. Conditioned place preference offers a viable method of independently verifying the mildly rewarding effect produced by pseudoephedrine.

EXPERIMENT II: THE EFFECT OF NICOTINE ON BSR

Nicotine has equivocal reinforcing properties, with some investigators reporting potent rewarding effects (Corrigall and Coen, 1989; Donny et al., 1995; Fudala and Iwamoto, 1986) and others finding difficulty establishing even weak reinforcement (e.g., Clarke and Fibiger, 1987; Dworkin et al., 1993; Jorenby et al., 1990). Studies directly assessing nicotine reinforcement using the intravenous self-administration method are conflicting, with previous lever training, food deprivation, and other factors confounding the interpretation of reported self-administration. BSR tests have the advantage of minimizing the influence of these factors, providing an unbiased assessment of reward potential from a compound. Nicotine has been reported to facilitate BSR (Huston-Lyons and Kornetsky, 1992; Newman, 1972; Olds and Domino, 1969; Pradhan and Bowling, 1971), but quantitative comparisons with prototypic addictive drugs have not been made. This experiment compared the effects of nicotine to those obtained with the two reference compounds-a prototypic addictive drug and a nonaddictive substance.

Procedure

Rats (n = 12) were injected with nicotine bitartrate (0.063, 0.125, 0.250, 0.500, & 1.000 mg/kg, s.c.) immediately before testing. Thresholds were continuously measured during 180-min test sessions. Injection doses were given in a counterbalanced order, with a minimum of 72 hrs between injections. If the subject was not within 10% of its baseline threshold on the day prior to the scheduled nicotine injection, the injection was postponed.

Results

Nicotine produced a significant lowering of BSR thresholds. A 6 x 12 within subjects ANOVA revealed significant effects for nicotine Dose [$F(5,55) = 12.233$, $p < .001$] and for Minutes post injection [$F(11,121) = 11.818$, $p < .001$]. The Dose x Minutes post injection interaction was also significant [$F(55,605) = 2.267$, $p < .01$]. Nicotine's effect peaked during the second time interval (16-30 min post injection), and the two highest doses produced significant facilitation for over 2 hrs after injections (see Figure 3). The peak effect was somewhat dose dependent, but the time-course analysis revealed stronger dose dependency. The 0.5 and 1.0 mg/kg nicotine doses produced almost identical effects on BSR. [Figure 3]

Discussion

Nicotine produced reliable facilitation of BSR. The optimal nicotine dose for producing facilitation appeared to be 0.5 mg/kg, with the maximum threshold-lowering effect beginning at 16-30 min post injection and lasting for about an hour. The effect of nicotine on BSR was more like pseudoephedrine than like cocaine. Both compounds produced a delayed facilitation lasting most of the 3-hr test period, although nicotine's effect peaked considerably sooner. Both compounds also produced quantitatively similar peak threshold-lowering. These results suggest that the rewarding action of nicotine closely resembles that of pseudoephedrine and is markedly different than that of cocaine. Thus, this preclinical measure indicates that nicotine has a relatively low addiction liability 4 comparable to pseudoephedrine.

1 Addiction liability is a complex concept beyond the scope of this discussion. In the present context, addiction liability of a compound is viewed as emanating from the compound's pharmacological action and relatively independent of subject variables (e.g., personality traits). Preclinical tests reflecting a substance's rewarding action are the strongest indicators of the substance's **inherent** addiction liability, but they ignore important subject variables that may produce compulsive substance use in some individuals (e.g., use of an anxiolytic compound by highly anxious individuals). Throughout this paper, addiction liability is used in reference to the general population and not in regards to special populations that may display markedly different responses dependent upon specific subject

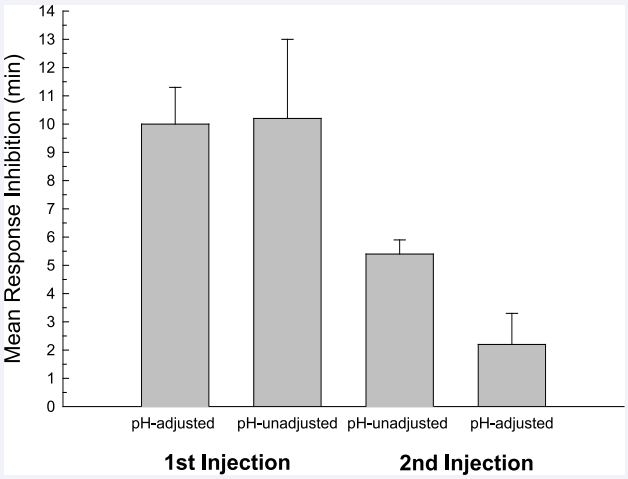

Figure 5 Response inhibition produced by freebase nicotine. The figure shows the mean (± SEM) duration responding was inhibited following the first and the second nicotine injections. Similar effects were seen with the nicotine bitartrate routes and formulations.

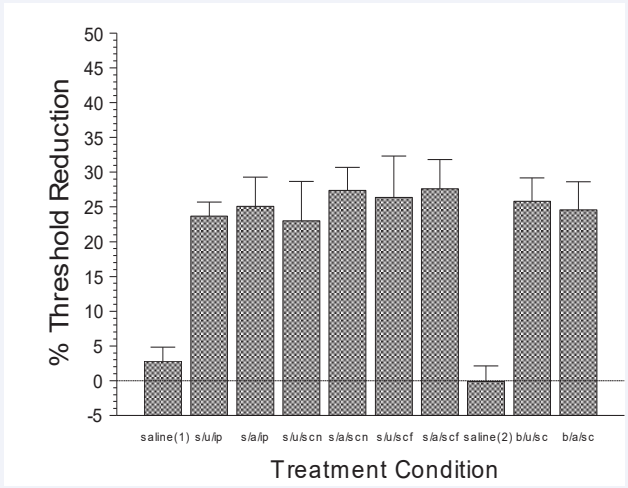

Figure 6 Comparison of peak facilitation produced by each nicotine treatment condition. The figure shows the mean (± SEM) percent threshold lowering from each treatment condition. There were no significant differences among the various nicotine treatment conditions. **Abbreviations**: see Table I for description; *saline(1)*, saline test with subjects used in first sequence; *saline(2*), saline test with subjects used in freebase tests.

The results from the quantitative analysis of BSR correspond well with studies of intravenous nicotine self-administration in laboratory animals. Some investigators report reliable intravenous self-administration (Corrigall and Coen, 1989; Donny et al., 1995), but reliable nicotine self-administration has generally been elusive (Bozarth and Pudiak, 1996a; Dworkin et al., 1993). Reliable self-administration of nicotine appears to depend on the use of special testing parameters (e.g., rapid infusions) and is not readily established without them (see Bozarth and Pudiak, 1996b; Henningfield et al., 1996). Even reviewers who argue that intravenous nicotine self-administration is reliable (e.g., Goldberg and Henningfield, 1988; Henningfield and Goldberg, 1983) acknowledge that it is not as robust as intravenous cocaine self-administration. Indeed, the few studies that have directly compared the reinforcing efficacy of nicotine with cocaine show that cocaine is a much more powerful reinforcer (Ator and Griffiths, 1980; Goldberg and Spealman, 1982; Griffiths et al., 1979; Risner and Goldberg, 1983), and this finding corroborates the quantitative differences seen in the present BSR study. These and other differences between self-administration established with prototypic addictive drugs (e.g., cocaine, heroin) and nicotine self-administration suggest that nicotine has only a mildly rewarding action. This would explain why nicotine self-administration is so sensitive to testing parameters, why the results with conditioned place preference have been conflicting, and why large quantitative differences exist in BSR facilitation from nicotine and cocaine.

EXPERIMENT III: THE EFFECTS OF FORM, SOLUTION PH, AND ROUTE OF ADMINISTRATION ON NICOTINE'S FACILITATION OF BSR

The modest but reliable facilitation of BSR by nicotine suggests that nicotine has the profile of a non-addictive compound. However, several additional tests were conducted to determine if the effect of nicotine was limited by the nicotine formulation or route of administration. These tests were essential to ensure that the maximum obtainable effect was seen with nicotine and that nicotine's maximum effect was used in the quantitative comparison with the two reference substances.

Nicotine bitartrate was selected for most tests because

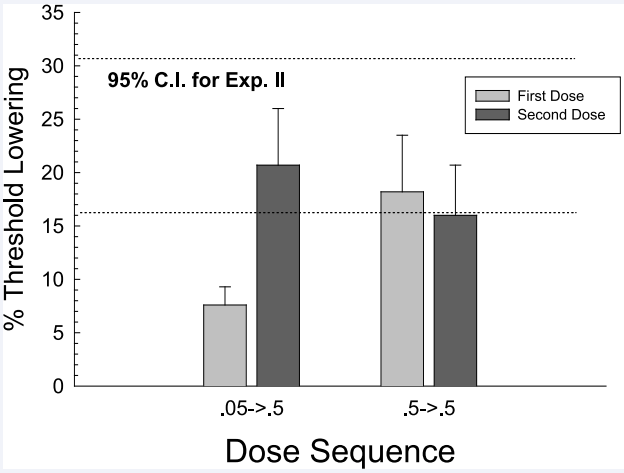

Figure 7 The effect of prior nicotine exposure on facilitation of BSR. Animals were injected with nicotine bitartrate (0.05 or 0.5 mg/kg, s.c., pH-adjusted; dose expressed as freebase weight) immediately before testing. Seventy-two hours later, the same subjects were injected with nicotine again (0.5 mg/kg, s.c., pH-adjusted) and thresholds measured. The figure shows the mean (± SEM) percent of baseline thresholds following injections. Prior exposure to low (0.05 mg/kg) or high (0.5 mg/kg) nicotine doses did not significantly modify the facilitation produced by the second nicotine injection administered 72 hours later. The upper and lower limits of the 95% confidence interval (95% C.I.) for the data from Experiment II are also shown. Symbols: first injection, shaded bar; second injection, solid bar.

characteristics (e.g., psychological depression).

it has been used more extensively than nicotine freebase in similar studies and because some investigators argue that the bitartrate salt form is necessary to demonstrate reliable rewarding effects of nicotine. The initial dose-response analysis used nicotine bitartrate (0.063 to 1 mg/kg) subcutaneously administered without pH adjustment. This is the most commonly studied form of this compound and the most often used route of administration. Further tests were conducted to ensure that the most effective nicotine solution and route of administration were used. These tests compared the effects obtained with a fixed dose of nicotine bitartrate (0.5 mg/kg), using pH-adjusted subcutaneous and intraperitoneal injections compared with pH-unadjusted subcutaneous and intraperitoneal injections. The pH of the nicotine bitartrate solution was adjusted in some tests (pH = 7 0.2) with sodium hydroxide because some investigators assert that pH adjustment affects the rewarding properties of this compound. Additional tests were conducted comparing the effects of nicotine freebase in pH-adjusted and unadjusted solutions following subcutaneous injections in another group of subjects.

Procedure

Separate groups of subjects were used for the nicotine bitartrate and the nicotine freebase studies. Animals in the nicotine bitartrate study (n = 6) were administered 0.5 mg/kg nicotine bitartrate (dose expressed as freebase weight) in pH-adjusted (pH = 7 ± 0.2) and pH-unadjusted pH ≈ 3.4 solutions by subcutaneous and intraperitoneal injections in a quasiradom order. At least 72 hrs separated each injection, and injections were postponed if the subject was not within 10% of its baseline threshold on the day prior to the scheduled nicotine injection. Not all subjects were tested under each condition. Subjects in the nicotine freebase study (n = 10) were injected with 0.5 mg/kg nicotine freebase in pH-adjusted (pH = 7 ± 0.2) and pH-unadjusted pH ≈ 11.4 solutions by subcutaneous injection. Treatments were administered in a counterbalanced order, and 72 hrs separated each treatment condition. All subjects were tested in both treatment conditions. BSR tests were conducted for 30 min on most days, with 180-min sessions during nicotine tests. Animals in both groups received a saline injection during a single 180-min test. [Table 1]

Results

Figure 4 shows the time-course of threshold lowering for each treatment condition. All nicotine treatment conditions produced similar facilitation of BSR, although the subcutaneous route of administration was somewhat less variable than intraperitoneal injections. Because the design of Experiment III included subjects tested at several but not all treatments, direct statistical comparisons were not made across these treatment conditions. However, the same subjects were tested in both freebase conditions (i.e., pH-unadjusted vs. pH-adjusted) permitting direct statistical comparison. A 2 x 12 within subjects ANOVA conducted on the two nicotine treatment conditions revealed that there were no appreciable differences between the pH-unadjusted and pH-adjusted nicotine freebase treatments [F (1,9) = 0.865 p > .25], although the effect of minutes post injections was significant [F(11,99) = 8.565, p < .001]; the Treatment x Minutes post injection interaction was not significant [F(11,99)= 0.272, p > .25]. [Figure 4]

Figure 5 shows the mean response inhibition produced by the first and the second nicotine freebase injections. The effects of the four treatment conditions are plotted separately (n = 5/condition). The first nicotine injection produced considerably more response suppression than the second injection for both the pH-adjusted [t (4) = 4.894, p = .004]5 and the pH-unadjusted [t (4) = 2.505, p = .033]6 solutions administered first. Interestingly during the second injection, the pH-adjusted nicotine solution appeared to produce less response suppression than did the pH-unadjusted solution [t (9) = 2.613, p = .031]. [3] Apparent differences seen during the second injection between the pH-adjusted and pH-unadjusted nicotine freebase solutions should be interpreted cautiously, because they were not predicted *a priori* and because these effects just achieved statistical significance. Nonetheless, it seems plausible that the pH-unadjusted solution might cause more irritation because of its basic nature or that the degree of ionization might produce more rapid nicotine delivery and hence more malaise. [Figure 5]

Similar response inhibitions were produced by the initial nicotine bitartrate injections in Experiment II, but counterbalancing treatment conditions prohibited direct comparison of this effect (i.e., the number of subjects tested under each condition in sequence [e.g., 0.125 . 0.5 mg/kg, 0.5 . 0.250 mg/kg] was too small for meaningful comparison). Response inhibition and ataxia from initial nicotine injections have been noted by other investigators studying BSR (e.g., Bauco and Wise, 1994). Two other studies conducted in this laboratory using 0.5 mg/kg, s.c., pH-adjusted nicotine bitartrate solutions have also reported response inhibition (Bozarth et al., 1998a, 1998b), but the inhibition seen during the first (≈ 6.5 min) and the second (≈ 2.5 min) nicotine injections was somewhat less than that seen in the present study from freebase nicotine injections. It is possible that initial nicotine freebase injections are more behaviorally disruptive than nicotine bitartrate injections and that this disruptive effect remains slightly stronger during the second injection with pH-unadjusted freebase solutions.

Figure 6 compares the peak facilitation seen with each nicotine treatment. All 8 nicotine treatment conditions produced similar peak facilitation. This analysis shows there are no important differences in BSR peak-facilitation between the bitartrate salt and freebase forms nor any significant effect of adjusting the pH from acidic (i.e., bitartrate salt) or basic (i.e., freebase) to neutral. Based on this comparison, there is no rationale for deviating from use of the natural freebase form of nicotine in pH-unadjusted solutions. Finally, the nicotine administration parameters used in the full-dose response analysis (i.e., Experiment II) should have accurately identified the maximum obtainable facilitation of BSR from acute nicotine treatment. [Figure 6]

Discussion

There were no appreciable differences in BSR facilitation seen from the various nicotine formulations and routes of administration. Similar peak-facilitation, latency to onset, and duration of action were produced by all preparations. This finding questions the common practice of using the salt form

for behavioral research. Generally, the salt form of a compound is used when the freebase form has limited solubility. Nicotine freebase, however, is readily soluble in aqueous solutions. Similarly, solutions not adjusted to pH 7 produced the same facilitation effect as pH-adjusted solutions. Therefore, there is no apparent rationale for adjusting the pH of the injected nicotine solutions nor for using the salt form instead of the freebase form of nicotine.

EXPERIMENT IV: EFFECT OF PRIOR NICOTINE EXPOSURE ON NICOTINE'S FACILITATION OF BSR

Animals in Experiment II received various doses of nicotine in a counterbalanced order, but the possibility remains that prior nicotine exposure may alter the subsequent effect of nicotine on BSR. Although counterbalancing minimizes the influence of prior nicotine exposure on any single treatment condition by distributing the associated variance across all treatment conditions (i.e., nicotine doses), the maximum facilitation might be over- or under-estimated by this repeated testing design. Therefore, a separate experiment was conducted to determine if prior nicotine exposure altered the effect of nicotine on BSR.

Procedure

After thresholds for BSR had stabilized, animals were divided into two groups (n = 7/group). One group was injected with 0.05 mg/kg nicotine bitartrate and the second group was injected with 0.5 mg/kg nicotine bitartrate (doses refer to freebase weight). Nicotine bitartrate solutions were pH-adjusted to 7 ± 0.2, and all injections were given subcutaneously. Animals were tested for 30 min immediately following injections. Seventy-two hours later, both groups received 0.5 mg/kg nicotine bitartrate (s.c.) and were again tested for 30 min using the threshold-tracking procedure. Data are expressed as the percent reduction in threshold based on each animal's baseline threshold, and the time period when nicotine produces its peak effect (i.e., 16-30 min post injection) was used in the analysis.

Results

Figure 7 shows the threshold lowering 16-30 min post nicotine injections. Each treatment condition was compared with the facilitation produced by the 0.5 mg/kg nicotine dose from Experiment II. There was a significant difference in threshold-lowering produced by the 0.5 mg/kg nicotine dose tested earlier and the 0.05 mg/kg dose tested in the current study [$t(17) = 3.526$, $p = .003$]. However, all three tests with 0.5 mg/kg nicotine yielded similar threshold reductions [t's (17) = 0.474 to 1.342, p's = .197 to .641]. [Figure 7]

The response inhibition produced by the nicotine injections is shown in Figure 8. The lowest nicotine dose produced no significant behavioral disruption, while the 0.5 mg/kg dose inhibited responding. There was a significant reduction in response inhibition following the second 0.5 mg/kg nicotine injection for the group initially receiving 0.5 mg/kg nicotine [$t(6) = 4.684$, $p = .003$]. Animals receiving the 0.5 mg/kg dose after the 0.05 mg/kg dose showed a significant increase in response inhibition [$t(6) = 2.540$, $p = .04$]. There was evidence of partial tolerance to the response suppressing effect of the 0.5 mg/kg nicotine dose for animals initially receiving 0.05 mg/kg nicotine, but this effect was not statistically significant [$t(12) = 1.506$, $p = .158$]. The low power of the statistical test (The power of the t-test with $\alpha = .05$ was .170.) may have permitted a Type II statistical error [Figure 8].

Discussion

Prior nicotine exposure had no significant effect on the threshold-lowering produced by the 0.5 mg/kg nicotine dose. Therefore, the influence of using a fully counterbalanced design in Experiment II appears negligible with respect to nicotine's effect on thresholds. However, significant changes in response inhibition were seen with repeated nicotine administration. Tolerance rapidly developed to the disruptive effect of nicotine on BSR, with animals showing only about a 4 min response inhibition by the second nicotine administration. It is likely that at least partial tolerance to the disruptive effect of nicotine on operant responding was maintained during the dose-response analysis conducted in Experiment II, despite the fact that a minimum of 72 hrs separated each nicotine test. The response inhibition initially seen with 0.5 mg/kg nicotine bitartrate was comparable to that seen with the same dose of nicotine freebase.

Experiment V: The Effect of Caffeine on BSR

Experiment I established the reference points for facilitation produced by addictive and nonaddictive substances. Experiment II revealed that nicotine, which has controversial addictive properties, has a profile like a nonaddictive substance, while Experiments III and IV further examined the ability of nicotine to facilitate BSR by determining the effects of various nicotine administration parameters and of repeated nicotine injections, respectively. This experiment examined the effect of another commonly used substance, caffeine, on BSR.

Caffeine-containing beverages are used widely throughout the world (Gilbert, 1984), and this substance is presumed to have a mild reinforcing action. The effects of caffeine on BSR are equivocal. Early work using a rate measure reported a facilitation of BSR (Valdes et al. 1988), but later work using a threshold measure reported threshold elevations (Mumford and Holtzman 1990, 1991; Mumford et al. 1988). There are no apparent differences in caffeine administration parameters among the conflicting reports, so the obtained differences in BSR effects are presumed to be related to BSR methodology. The present study examined the effects of caffeine on BSR using the threshold-tracking method which is very sensitive to a compound's facilitatory action (Bozarth et al., 1990). The effect of a wide range of caffeine doses was examined across 180-min sessions beginning immediately after caffeine administration.

Procedure

Rats (n = 10) were injected with anhydrous caffeine (2.5, 5, 10, 20, 40, or 80 mg/kg, i.p.) immediately before testing. All rats received all doses of caffeine administered in a counterbalanced order. At least 72 hours separated each injection, and injections were postponed if the subject was not within 10% of its pretreatment baseline mean on the day prior to a scheduled injection. Animals were tested continuously for 180 min immediately after injections.

Table 1: Nicotine Formulations & Routes of Administration Tested in Experiment.

NICOTINE FORMULATION				
Nicotine Bitartrate			Nicotine Freebase	
IINJECTION ROUTE	pH-unadjusted [1]	pH-adjusted [2]	pH-unadjusted [3]	pH-adjusted [4]
ip [5]	s/u/ip	s/a/ip	_	_
sc-neck [6]	s/u/scn	s/a/scn	b/u/scn	b/a/scn
sc-flank [7]	s/u/scf	s/a/scf	_	_

Notes:
1: pH ≈ 3.4 (*u*: pH-**u**nadjusted)
2: pH adjusted to 7 ± 0.2 with sodium hydroxide (*a*: pH-**a**djusted)
3: pH ≈ 11.4 (*u*: pH-**u**nadjusted)
4: pH adjusted to 7 ± 0.2 with acetic acid (*a*: pH-**a**djusted)
5: intraperitoneal injection (*ip*)
6: subcutaneous (*sc*) injection administered along dorsal neck region (*scn*)
7: subcutaneous (*sc*) injection administered along lower flank region (*scf*)
s: **s**alt (nicotine bitartrate)
b: **b**ase (nicotine freebase)

Results

Figure 9 shows the effect of caffeine on BSR thresholds. Caffeine appeared to have two distinctively different effects on BSR: low caffeine doses facilitated BSR, while high caffeine doses inhibited BSR. To simply the analysis, separate two-way within subjects ANOVAs were computed for each effect (i.e., low-dose facilitation and high-dose inhibition). The ANOVA conducted on saline and the four lowest caffeine doses (i.e., 2.5, 5, 10, & 20 mg/kg) revealed a significant effect of caffeine Dose [F (4, 36) = 5.957, p < .01], of Minutes post injection [F (11,99) = 14.417, p < .01], and a significant Dose x Minutes interaction [F(44,396) = 1.780, p < .01]. Because of missing data for the 80 mg/kg caffeine dose (see below), the second analysis was performed comparing only the 40 mg/kg caffeine dose with saline. The ANOVA conducted on saline and the 40 mg/kg caffeine dose showed a significant effect of caffeine Treatment [F (1, 9) = 5.641, p < .01] and of Minutes post injection [F(11,99) = 9.497, p < .01]; the Treatment x Minutes interaction was also significant [F(11,99) = 1.981, p < .05]. [Figure 9]

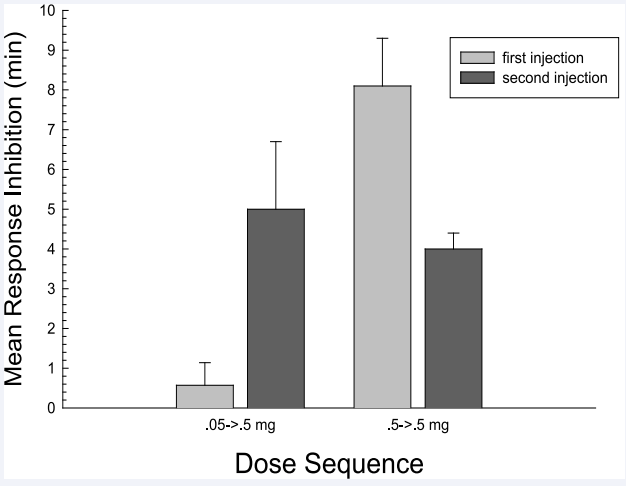

Figure 8 Response inhibition produced by nicotine bitartrate. The figure shows the mean (± SEM) duration responding was inhibited following the first and the second nicotine injections. One group received 0.05 mg/kg nicotine followed 72 hrs later by 0.5 mg/kg nicotine (0.05->0.5 mg), while the other group received 0.5 mg/kg nicotine followed 72 hrs later by another 0.5 mg/kg nicotine injection (0.5->0.5 mg). Partial tolerance to the behavioral suppressant effect of nicotine developed after one injection and was demonstrable 72 hrs later.

The 80 mg/kg caffeine dose disrupted responding for BSR in 60% of the subjects during the first 15-min interval and in 20% of the subjects during the second 15-min interval. One of the subjects failed to reliably respond for BSR during the entire 180-min test (i.e., apparent response extinction). For this reason, these data were not included in the statistical analysis. However, large and sustained threshold elevations were seen following the 80 mg/kg caffeine dose, and these threshold elevations showed little evidence of diminishing by the end of the 3-hr test. The 40 and 80 mg/kg caffeine doses also produced a significant dose-dependent weight-loss 24 hr after injections [mean ± SEM: 40 mg/kg dose = -6.2 g ± 1.5, t (9) = 2.516, p = .033; 80 mg/kg dose = -15.1 g ± 2.9, t (9) = 4.250, p = .002]. Weight changes after saline and the other caffeine doses were not significant (mean changes = -0.9 to + 2 g).

Discussion

The lower caffeine doses facilitated BSR, while higher caffeine doses elevated BSR thresholds. The threshold-lowering effect had a rapid onset and a very short duration of action. The maximum threshold elevation seen with the 40 mg/kg dose was somewhat delayed, but this inhibitory effect lasted throughout the 180-min test session. The 80 mg/kg dose initially disrupted responding in some animals but produced sustained threshold elevations when animals resumed responding during the second and third 15-min periods.

Two of the three studies failing to detect facilitation from low-dose caffeine began testing their subjects 15 to 30 min after injections. The modest threshold-lowering produced by caffeine has largely dissipated by this time. Other differences include the method of measuring thresholds (i.e., threshold-tracking vs. autotitration), the stimulation parameter manipulated (i.e., stimulation frequency vs. current intensity), and the form of caffeine used (i.e., anhydrous freebase vs. sodium-benzoate salt). Of these differences, the method of measuring thresholds

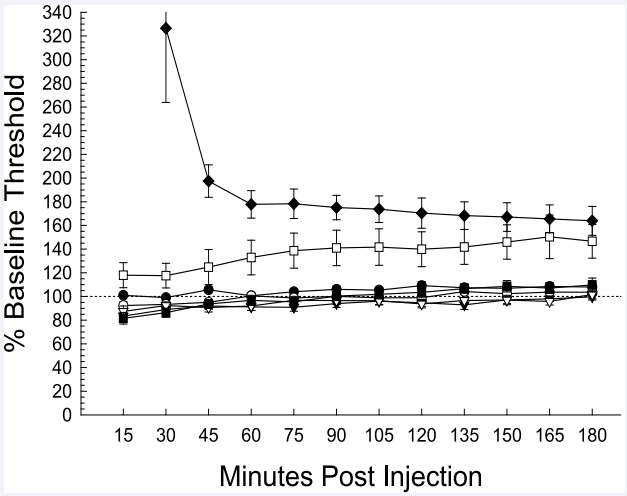

Figure 9 Time course of caffeine's effect on BSR. Animals were injected with caffeine (i.p.) at the beginning of the test session. The figure shows the mean (± SEM) percent of baseline thresholds for each 15-min time period following injections. Caffeine produced dose-dependent effects on BSR thresholds—lower doses produced BSR facilitation, while higher doses produced threshold elevations. Note the change in scale (i.e., Mean Threshold) used in this figure which includes threshold elevations. Symbols: saline, filled circles; 2.5 mg caffeine, open circles; 5 mg caffeine, filled triangles; 10 mg caffeine, open triangles; 20 mg caffeine, filled squares; 40 mg caffeine, open squares; 80 mg caffeine, filled diamonds.

is likely to be the most significant. The autotitration method used in the earlier studies may have problems detecting some facilitatory drug actions 7 (Fouriezos and Nawiesniak, 1987; see also Esposito et al., 1987), although it detects the facilitatory action of amphetamine (Schaefer and Holtzman, 1979; Stein, 1962; Zarevics and Setler, 1979) and heroin (Bozarth et al., 1980). In contrast to the differences seen with low-dose caffeine, threshold-elevations are produced by the higher caffeine doses in both the threshold-tracking and autotitration methods. Both techniques reveal a significant threshold elevation with 40 and 30 mg/kg caffeine (freebase equivalent), respectively. The threshold-tracking method yielded maximum threshold elevations around 45% following the 40 mg/kg caffeine dose, while the autotitration method showed elevations around 10 to 20% with a 30 mg/kg dose and around 35 to 40% with a 56 mg/kg dose. The 80 mg/kg caffeine dose, tested in the present study, disrupted responding for 60% of the rats during the first 15 min but produced a peak threshold elevation of over 200% and a sustained threshold elevation of 70 to 75%.[8] Thus, threshold-tracking appears more sensitive to both the facilitatory and the inhibitory effects of caffeine.

Caffeine appears to have two distinct effects of brain reward mechanisms—low caffeine doses enhance while higher doses inhibit reward processes. Corroborative evidence of caffeine's dual action on reward processes comes from studies assessing potential rewarding effects using the conditioned place preference method. Low-dose caffeine has been reported to produce a conditioned place preference, while a conditioned place aversion is produced from higher doses (Brockwell et al., 1991). Some investigators have had difficulty demonstrating a conditioned place preference from caffeine (Steigerwald et al., 1989), but this is probably related to the modest effect of low-dose caffeine on brain reward mechanisms and to the different experimental procedures used in the conditioning studies. In contrast, conditioned place and taste aversions from higher caffeine doses are robust (Brockwell et al., 1991; Steigerwald et al., 1989). This parallels the findings with BSR, indicating that caffeine's reward-enhancing effect is more difficult to demonstrate than its reward-inhibiting action. The biological mechanism mediating the reward-enhancing effect of caffeine is not known, but there is some evidence that suggests caffeine's antagonism at adenosine A1 receptors increases dopamine release (Okada et al., 1996). Higher caffeine doses may also inhibit adenosine A2 receptors, and this action may produce decreases in dopamine release (see Okada et al., 1996) and may mediate BSR threshold elevations (Mumford and Holtzman, 1990; cf. Mumford and Holtzman, 1991).

The BSR facilitation effect is consistent with reports of the subjective effects of caffeine in humans and with studies of intravenous caffeine self-administration in laboratory animals. Caffeine-containing beverages are widely self-administered by humans and some clinical studies have reported mild mood-enhancing effects from caffeine (e.g., Griffiths et al., 1986; Rush et al., 1995). In contrast, other studies have failed to detect significant elevations in mood or reliable caffeine self-administration in laboratory settings (e.g., Lieberman et al., 1987; Stern et al., 1989). Similarly, caffeine self-administration in laboratory animals is equivocal. A few studies have reported sporadic intravenous caffeine self-administration in laboratory animals (e.g., Atkinson and Enslen, 1976; Deneau et al., 1969; Dworkin et al., 1993; Griffiths et al., 1979), but investigators have been unable to obtain reliable caffeine self-administration (for reviews, see Griffiths and Mumford, 1995, 1996; Heishman and Henningfield, 1992). This situation closely parallels that seen with intravenous nicotine self-administration. Early studies were generally unsuccessful in establishing nicotine self-administration, while several later studies using special testing parameters have reported reliable self-administration (see Goldberg and Henningfield, 1988; Henningfield and Goldberg, 1983). It is likely that special testing parameters will be identified that produce reliable caffeine self-administration. But the fact that the self-administration may be only obtainable under a narrow set of conditions, like intravenous nicotine self-administration, strongly suggests that caffeine has, at best, a mildly rewarding action and consequently a low addiction liability.[9] Even though caffeine use can show the characteristics of addiction in some individuals (e.g., Strain et al., 1994), this probably occurs infrequently despite the widespread use of caffeine (Hughes et al., 1993; see also Mumford and Griffiths, 1995). Thus, the animal and clinical studies are concordant in suggesting that caffeine has a relatively low addiction liability.

GENERAL DISCUSSION

These data suggest an important consideration for interpreting the results of BSR studies-simple facilitation of brain stimulation is insufficient to suggest that a substance is addictive. Nonaddictive substances can also facilitate BSR, thus reflecting their potential reinforcing effects. BSR tests are

still useful for assessing a compound's addiction liability, but quantitative aspects of the facilitation effect must be considered when evaluating a compound's effect on BSR.[10] A. A range of maximum facilitation effects must be obtained with addictive and nonaddictive drugs (see Figure 10). Substances with a high addiction liability would be expected to produce facilitation quantitatively similar to that seen with prototypic addictive drugs. Mildly rewarding effects may be detectable with BSR which are insufficient to produce the potently rewarding effects characteristic of addictive drugs. This attests to the methods high sensitivity in detecting a compound's effect on brain reward processes but cautions against an overly simplistic interpretation of these data and their relevance to addiction liability. [Figure 10]

Although the simple comparison of peak-facilitation might be sufficient to estimate each compound's potential reinforcing action, a more detailed analysis using time-course data may provide a more accurate assessment. Figure 11 shows the time-course of the optimal dose (i.e., dose producing maximum BSR facilitation) tested for each substance. This analysis takes into consideration not only the magnitude of facilitation but also the time-course of the facilitatory effect. Pharmacokinetic parameters related to onset of drug action are important for producing potent reinforcing effects (e.g., short delay of reinforcement following drug administration) and should be considered when evaluating a substance's potential addiction liability. For example, cocaine (i.e., the high addiction liability reference compound) produces facilitation with (i) a very rapid onset, (ii) a relatively short duration of action, and (iii) a large magnitude of effect. These characteristics make it a potent reinforcing compound and are probably the reason it is so readily self-administered. In comparison, pseudoephedrine (i.e., the low addiction liability reference compound) produces a delayed facilitation with a long duration of action and a modest level of BSR facilitation. The simple quantitative comparison of peak facilitation groups these substances into two categories—cocaine and other compounds-but consideration of the pharmacokinetic profiles permits a more specific rank ordering. The relative reinforcing efficacy predicted from this analysis is cocaine >> caffeine > nicotine > pseudoephedrine. This conclusion is based on the following considerations. Cocaine has a rapid onset and large facilitatory action. Caffeine has a rapid onset (equal to cocaine) but a much lower magnitude of effect. Nicotine has a maximum facilitatory effect similar to caffeine but the onset of action is somewhat delayed. And pseudoephedrine has a maximum facilitation comparable to caffeine and to nicotine but with a much delayed onset of action. The rapid onset of action is probably related to reinforcing efficacy by (i) enhancing learning (i.e., minimizing the delay of reinforcement effect) and (ii) by producing stronger subject effects.[11] [Figure 11]

The maximum facilitation produced by nicotine in the present study is similar to that reported by other investigators using lateral hypothalamic stimulation (e.g., Bauco and Wise, 1994). The strength of facilitation seen with cocaine is also similar to that reported previously, but other investigators have ignored the quantitative differences between facilitation produced by nicotine and prototypic addictive drugs. The effects of cocaine and of nicotine on BSR correspond well with their respective effects of mesolimbic dopamine release. Cocaine produces a

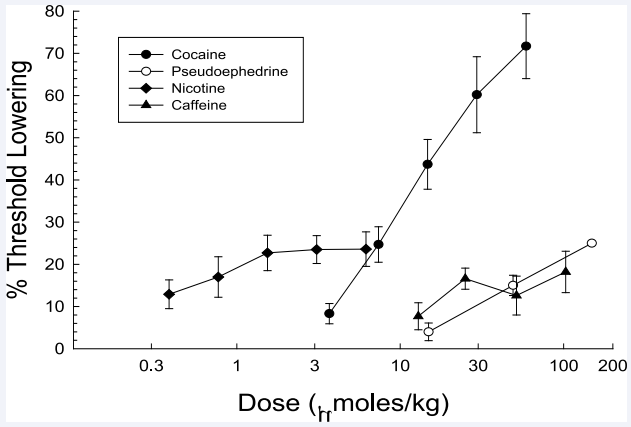

Figure 10 Dose-response comparison of peak-facilitation produced by addictive and nonaddictive substances. The maximum facilitation is shown for each compound at each dose level. The figure shows the mean (± SEM) percent of threshold lowering. Symbols: cocaine, filled circles; pseudoephedrine, open circles; nicotine, filled diamonds; caffeine, filled triangles.

dramatic increase in nucleus accumbens dopamine overflow (e.g., 300 to 1000%; e.g., Brown and Fibiger, 1992; Maisonneuve et al., 1994; Parsons et al., 1995; Wise et al., 1995), while nicotine produces only a modest increase in dopamine overflow (e.g., 50 to 100%; e.g., Brazell et al., 1990; Damsma et al., 1989; Imperato et al., 1986; Nisell et al., 1994), sometimes even requiring repeated administration to significantly increase extracellular dopamine levels (e.g., Benwell et al., 1994, 1995). The 3 to 20-fold[12] greater efficacy of cocaine in stimulating dopamine release probably underlies cocaine's more potent rewarding action. This potent rewarding action, in turn, produces robust cocaine self-administration in laboratory animals and is an important component in cocaine's inherently high addiction liability in humans.

Nicotine appears to have a "self-limiting" action on brain reward mechanisms. This is apparent from examination of the dose-response curve and from consideration of the behavioral effects of this compound. Several nicotine doses produce maximum facilitation of BSR. Increasing the nicotine dose 4-times the lowest dose producing maximum facilitation fails to increase nicotine's maximum effect (see Figure 10), although it does increase the duration of the peak effect slightly. Furthermore, the fact that these nicotine doses were not behaviorally disruptive at the time of peak facilitation indicates that neither behaviorally disruptive nor toxic effects limit the maximum facilitatory action produced by nicotine. Thus, some neurophysiological processes appears to limit nicotine's action on brain reward mechanisms.

One viable explanation of nicotine's ceiling on threshold lowering is based on a two-stage trans-synaptic activation model. This model proposes that a descending fiber system is directly activated by electrical stimulation and trans-synaptically activates the ascending mesolimbic dopamine system (see Bozarth, 1987b; Wise and Bozarth, 1984; see also Yeomans et al., 1993). A subpopulation of the descending component (i.e., first-stage neurons; see Shizgal, 1989) may be cholinergic (or synapse on cholinergic interneurons; see Yeomans et al., 1993), and

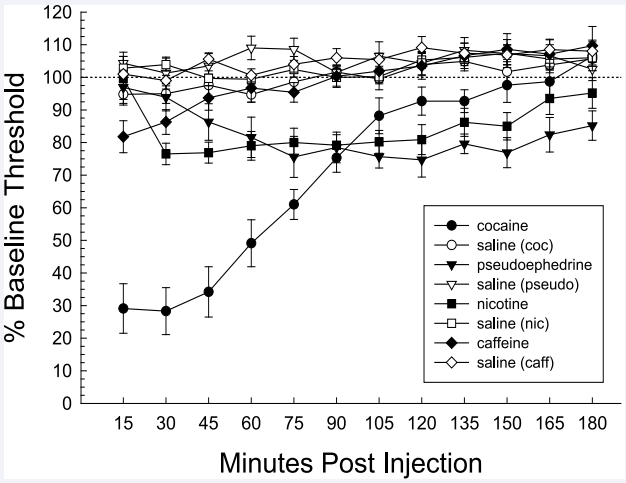

Figure 11 Time-course analysis of the maximum facilitation produced by cocaine, pseudoephedrine, nicotine, and caffeine. Doses producing maximum facilitation were selected for each compound. Note that facilitation from the prototypic addictive drug cocaine has the (i) shortest latency to onset, (ii) strongest peak effect, and (iii) shortest duration of action. Symbols: cocaine, filled circles; pseudoephedrine, filled triangles; nicotine, filled squares; caffeine, filled diamonds; saline response levels for the cocaine, pseudoephedrine, nicotine, and caffeine groups are shown by the open circles, open triangles, open squares, and open diamonds, respectively.

nicotine's ability to stimulate the mesolimbic dopamine system may be limited to activation of this cholinergic input which is only a portion of the total afferent neural population activated by lateral hypothalamic stimulation. Evidence that a cholinergic mechanism modulates mesolimbic dopamine activity at the level of the ventral tegmental area comes from several findings. First, nicotinic receptors are located on dopamine neurons in the ventral tegmentum (Clarke and Pert, 1985). Second, nicotine increases cell firing in the ventral tegmental dopamine cells (Calabresi et al., 1989; Gernhoff et al., 1986; Mereu et al., 1987; Nisell et al., 1996), and this activation produces an increased release of dopamine in the nucleus accumbens terminal field (e.g., Brazell et al., 1990; Damsma et al., 1989; Imperato et al., 1986; Nisell et al., 1994). Furthermore, the activation of this system by systemic nicotine is blocked by ventral tegmental nicotinic antagonist infusions (Nisell et al., 1994). And third, cholinergic antagonists microinjected directly into the ventral tegmentum elevate BSR thresholds (Kofman and Yeomans, 1989). Evidence that a subpopulation of the first-stage neurons is cholinergic comes from a study showing that only a fraction of the rewarding effects of lateral hypothalamic BSR is attenuated by systemic cholinergic antagonist treatment (Gratton and Wise, 1985). Alternatively, receptor desensitization or depolarization block may produce a "self-limiting" effect of nicotine on BSR.

Nicotine administration parameters appear to have little effect on nicotine's facilitation of BSR and, presumably, on its ability to activate brain reward mechanisms. For example, there appears to be no empirical evidence to support the popular notion that freebase nicotine is less effective (i.e., rewarding) than the bitartrate salt form of nicotine. Experiment III specifically compared the effectiveness of various nicotine formulations, solution pH's, and routes of administration on the BSR facilitation produced by nicotine. Nicotine bitartrate and nicotine freebase produced similar BSR facilitation. Similarly, pH-adjustment had no effect on the facilitation effect. There was some indication that initial nicotine freebase solutions may cause more behavioral disruption than initial nicotine bitartrate injections. Nonetheless, the various nicotine administration parameters produced equivalent peak-facilitation of BSR. Also, Experiment IV showed that the prior administration of a low or moderate dose of nicotine had no significant effect on the facilitation produced by a moderate nicotine dose. Similarly, daily fixed-dose nicotine injections have been shown to produce the same level of BSR facilitation across daily tests with no apparent tolerance or enhanced facilitation from chronic nicotine administration (Bauco and Wise, 1994; Bozarth et al., 1998a). These data strongly suggest that the maximum BSR facilitation obtainable with nicotine was accurately determined by the nicotine dose-response analysis and that changes in testing conditions are unlikely to reveal a much stronger effect.

Nicotine from smoked tobacco is often argued to have a faster onset of psychoactive affects that nicotine delivered by other routes of administration. However, the results from the BSR studies argue strongly against major differences in the onset of nicotine's CNS effects from various routes of administration. Specifically, the highly lipophilic nature of nicotine permits its rapid penetration into CNS regardless of administration route. Subjects receiving nicotine show an initial disruption of responding for BSR that occurs within seconds of the injection. However, nicotine's BSR facilitatory action is delayed by 15 min or more. The significance of rapid delivery has been argued to explain why it is difficult to demonstrate strong rewarding effects of nicotine in laboratory animals (i.e., they don't smoke) and why special testing parameters are necessary to demonstrate intravenous nicotine self-administration (e.g., very rapid infusions). The BSR data suggest that some process limits the onset of nicotine's rewarding effect despite its rapid entry into the CNS. Slight changes in nicotine CNS delivery are unlikely to significantly affect this process. In contrast, the rewarding effect of cocaine has a very rapid onset, peaking within the first 15 min of testing. Hence, relatively small differences in CNS delivery might be expected to increase the subjective impact of this compound.

This series of studies illustrates important guidelines that should be considered when using BSR studies to assess the potential addiction liability of a compound. First, full dose-response and time-course analyses are critically important for quantitative comparisons of each compound's effect on BSR, [13] and this can only be achieved by administering drug doses which approach behaviorally disruptive (even toxic) levels. Also, most investigators make tenuous assumptions regarding a compound's time course, and this can lead to underestimating the maximum effect produced on BSR. The present study examined a wide range of doses and measured BSR thresholds a full 3 hours after drug administration. The threshold-tracking procedure is particularly effective for determining time course, because thresholds are stable over long session durations and because thresholds remain stable when animals are tested for only 30 min per day during intervening test sessions. Second, another critically

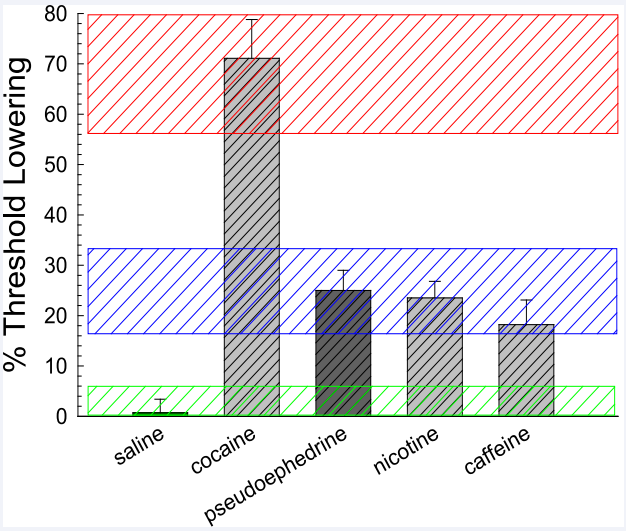

Figure 12 Comparison of peak facilitation produced by cocaine, pseudoephedrine, nicotine, and caffeine. The figure shows the maximum facilitation produced by any dose of each compound at any time post injection. The lower 95% confidence limit for the maximum effect obtained with cocaine and the upper 95% confidence limit for the maximum effect obtained with pseudoephedrine define the expected boundaries for compounds with a high and low addiction liability, respectively. Note: The lower limit of the 95% confidence interval for saline and the upper limit for cocaine are truncated in the figure.

important feature of this work is using a method for quantifying the effects of a compound on BSR that is a sensitive measure-one that has a low minimum detection level and is not restricted by ceiling effects. Using the threshold-tracking method, the present study was able to demonstrate a moderate BSR facilitation from low-dose caffeine and a pronounced threshold elevation from higher caffeine doses. Third, quantitative comparisons must be made. This avoids the hasty conclusion that all substances which facilitate BSR (but may have only mild rewarding effects) have a high addiction liability. Specifically, the range of facilitation effects must be established using compounds with high and low addiction liabilities. And the effect of the test compound must be interpreted within the framework that distinguishes high from low addiction liability compounds (see Figure 12).[14]

If a behavioral objective were to obtain a mild mood-elevating effect, the optimal substance, from the list of compounds tested in this series, would probably be nicotine. Nicotine produces its mild subjective effect with only a moderate delay and has a wide range of doses that can be self-administered without apparent toxic effects. In comparison, caffeine's reward-enhancing effect has a very short duration of action and a relatively narrow window where its rewarding effects emerge before the development of aversive effects. Once aversive effects develop from caffeine, they have a very long duration of action. Pseudoephedrine has a markedly delayed onset and produces behaviorally disruptive effects with only slightly increasing doses. Its long duration of action might be desirable, but miscalculating the dose makes the behaviorally disruptive (and presumably aversive) effects last for a similarly long period of time. Thus, nicotine is clearly the substance of choice for obtaining a mildly rewarding action (viz., socially acceptable). This probably contributes significantly to the popularity of tobacco use.

One important aspect of nicotine's potential impact on brain reward processes not investigated in the studies reported here is the effect of chronic nicotine administration. However, the possibility of a facilitation-enhancing effect from chronic nicotine administration was previously examined using the optimal nicotine administration parameters identified in this series of experiments. There was no evidence of tolerance or enhanced responsiveness to chronic nicotine administration across 30-days of repeated administration (Bozarth & Pudiak, 1998a) or to repeated, escalating-dose nicotine administration designed to mimic the commonly observed behavior of increased levels of tobacco use (Bozarth & Pudiak, 1998b). Nicotine's effect on BSR is simply dose-dependent and is generally independent of other parameters such as acute vs. chronic, freebase- vs. salt-forms, and route of administartion.

In conclusion, this series of experiments implications for the "nicotine addiction" hypothesis and for the current trend to blur the distinction among reinforcement, addiction, and the casual use of mildly psychoactive substances. This BSR study complements work with the intravenous self-administration method suggesting that nicotine is at best a very weak reinforcer. (e.g., Bozarth & Pudiak, 1996a, 1996b; Pudiak & Bozarth, 1996). The present study suggests that the rewarding impact of nicotine is quantitatively similar to that obtained from compounds with a low addiction liability such as Caffeine and pseudoephedrine. Caffeine has been the subject of intense study and this substance appears to be only a marginally effective reinforcer despite its widespread use throughout the world. The results of the BSR tests are consistent with this interpretation. On the other hand, nicotine's facilitation of BSR has been presented as evidence that nicotine is highly addictive. Unfortunately, few compounds have been examined that have mild psychoactive effects and no systematic comparisons have been previously reported between these compounds and prototypic addictive drugs.

ACKNOWLEDGMENTS

Bemina Anatanico, Ronda KuLee, Rafia Mirza, and Matt Morris are thanked for assistance in behavioral testing. All animals were treated following the guidelines of NIH publication no. 94-3207, and the research protocol was reviewed by University at Buffalo's Institution Animal Use Review Committee. This research report is from the *Nicotine Evaluation Program* supported by a grant from the Philip Morris Research Center (Richmond, VA). The views expressed herein are those of the authors and do not necessarily reflect the views of the sponsoring agency. The sponsor exerted no influence on the design, implementation, or reporting of the work presented in this series of experiments.

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Cite this article

Bozarth MA, Pudiak CM (2021) Predicting Addiction Liability from Brain Stimulation Reward Data: A Comparison of the Acute Effects of Cocaine, Pseudoephedrine, Nicotine, and Caffeine. J Subst Abuse Alcohol 8(2): 1092.