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Published Abstract

SELF-LIMITING ACTION OF NICOTINE ON BRAIN REWARD MECHANISMS. M.A. Bozarth,* C.M. Pudiak, & R. KuoLee. *Addiction Research Unit, Department of Psychology, University at Buffalo, Buffalo, NY 14260-4110.*

Previous work has shown that nicotine facilitates brain stimulation reward (BSR) but that the maximum effect obtainable with nicotine is similar to that seen with compounds having a low addiction liability (e.g., caffeine, diphenhydramine, pseudoephedrine). Two studies further explored nicotine's effects on BSR using a threshold-tracking procedure. Male, Long-Evans rats were implanted with stimulating electrodes at the lateral hypothalamic level of the medial forebrain bundle. Nicotine bitartrate (doses expressed as the freebase weight) was injected subcutaneously, and its effects on BSR were measured 15-30 min post injection.

The first study examined the effects of daily nicotine injections (0.5 mg/kg/day) across 21 consecutive days of testing. There were no changes in nicotine's facilitatory action across the 21-day test. The second study examined the effects of escalating nicotine doses: 0.5, 1, & 2 mg/kg/day were administered in sequential 5-day cycles. Nicotine lowered thresholds across the first two 5-day cycles (i.e., 0.5 & 1 mg/kg/day doses) but thresholds returned to baseline levels during the last 5-day cycle (i.e., 2 mg/kg/day). When the effect of the 2 mg/kg dose was examined in naïve rats, a time-course analysis revealed a biphasic action, with nicotine elevating thresholds 30-45 min post injection and lowering thresholds from 75-210 min post injection.

Nicotine activates the brain reward system also activated by addictive drugs, but it appears to have a self-limiting action on this system—some neurophysiological process limits the maximum activation produced by nicotine. Consideration of the BSR data suggests that nicotine's reward activation is limited by fractional activation of the reward substrate and by a high-dose self-inhibitory action at afferent neurons. These two mechanisms may explain why nicotine has a modest reward-modulating effect but fails to produce a potent rewarding action like addictive drugs.

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Background

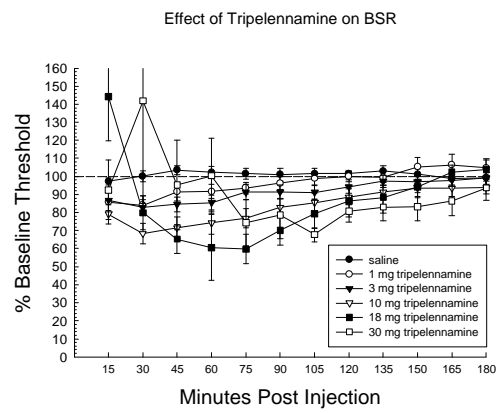
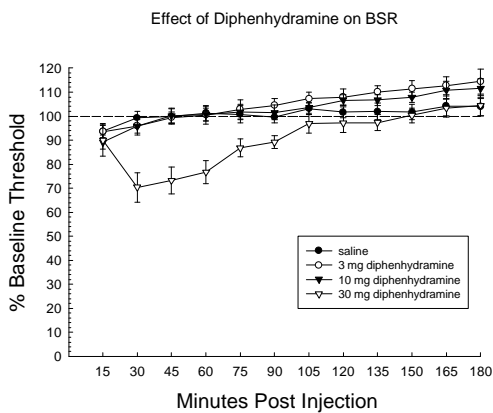
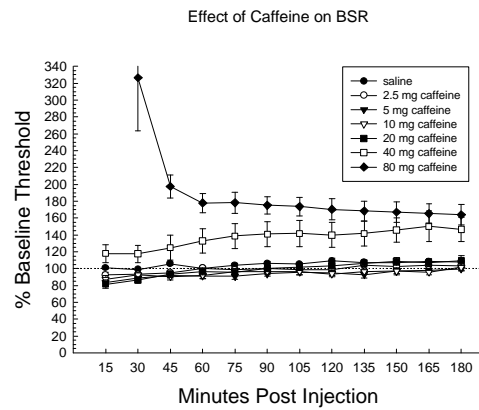
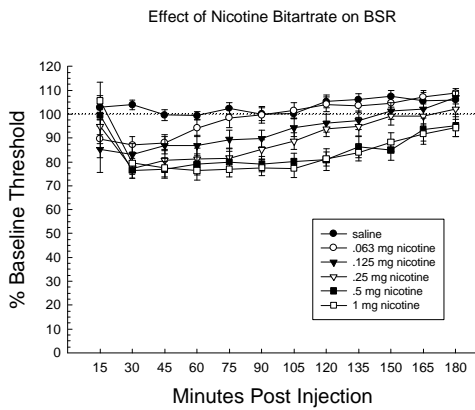
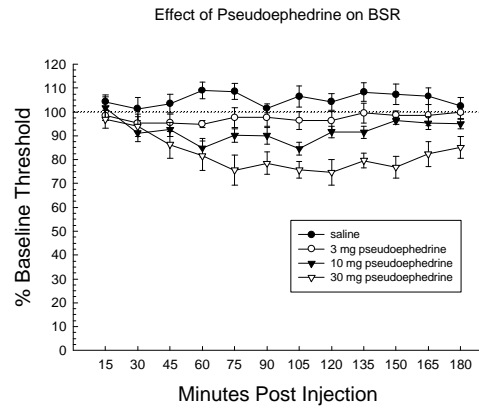
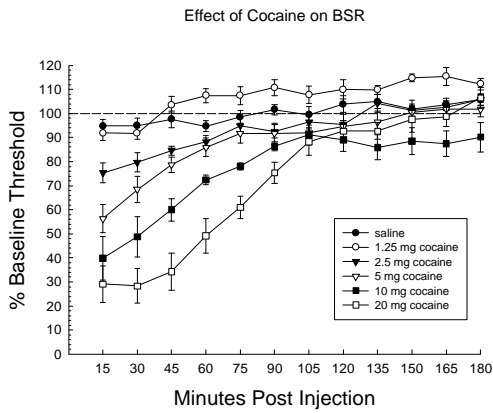
Nicotine has long been presumed to be the active ingredient in tobacco smoke and to produce the effects some people find desirable when using tobacco products. Since publication of the 1988 Surgeon General's Report on *The Health Consequences of Smoking: Nicotine Addiction*, nicotine has been viewed by many scientists and most public health workers as a highly addictive

substance comparable to cocaine in its addictiveness. This assertion is based in part on apparent similarities in nicotine's effects on brain reward mechanisms and in part on the widespread use of tobacco which continues despite public health warnings. The latter argument involves circular reasoning—persistent smoking behavior is argued to be motivated by nicotine addiction, while evidence for nicotine addiction comes from observed cases of persistent smoking behavior. Independent evidence for addiction must be obtained if addiction is to be used as an explanation of behavior. Furthermore, because human substance use is very complex—being influenced by many psychological and sociological factors as well as a substance's pharmacological effects—the addiction liability attributable directly to a substance is more accurately assessed using preclinical studies. These tests with laboratory animals can determine the addiction liability of a compound based solely on its pharmacological properties without the confounding influence of psychological and sociological variables present in human studies. Various studies have investigated the effects of nicotine on brain reward processes in an attempt to determine how nicotine influences behavior. Indeed, these studies have found evidence for some similarities between nicotine's effects and the effects of highly addictive drugs such as cocaine. But how similar are these substances?

Several animal models have been developed to study the rewarding properties of addictive drugs. One method involves voluntary intravenous self-administration. Laboratory animals quickly learn to self-administer highly addictive drugs such as cocaine and heroin. Tests with nicotine have been conflicting, with some investigators reporting intravenous nicotine self-administration when special testing conditions are used. However, interpretation of these findings is somewhat controversial, because no special testing conditions are necessary to demonstrate reward from highly addictive substances. Therefore, other tests of nicotine's effects on brain reward processes are especially important in determining its potential addiction liability.

Another method of assessing the potential rewarding impact of a compound is to examine its effect on electrically activated brain reward mechanisms. Animals implanted with electrodes lever press at high rates to obtain brief pulses of electrical stimulation in brain reward pathways. Addictive drugs dramatically enhance the effectiveness of the electrical stimulation. This facilitation effect can be easily demonstrated as a reduction in the minimum stimulation level necessary to produce a rewarding action (i.e., threshold lowering). The effect of a compound on brain stimulation reward (BSR) is viewed as an indicator of its ability to activate brain reward mechanisms and, hence, its potential addiction liability. Although BSR tests are indirect measures of potential drug reward, they have several advantages over other preclinical methods of assessing addiction liability.

A number of laboratories have studied the effects of addictive drugs on BSR, but most fail to make quantitative comparisons with nonaddictive substances that may have mild psychoactive effects. It is likely that some compounds have mildly rewarding effects that are not sufficient to motivate the strong drug-taking behavior associated with an addiction. We have examined the effects of a number of compounds, using reference compounds to determine the magnitude of BSR facilitation associated with high and low addiction liabilities (see Figures 1 & 2).



Figures 1a-1f: Time-course of BSR facilitation produced by various compounds (n=6-12/group). The figures show the mean (\pm SEM) percent of baseline thresholds. Injections were administered at the beginning of the test sessions, and thresholds were measured continuously for 3 hrs. All doses were administered in a counter-balanced order, with a minimum of 72 hrs between injections.

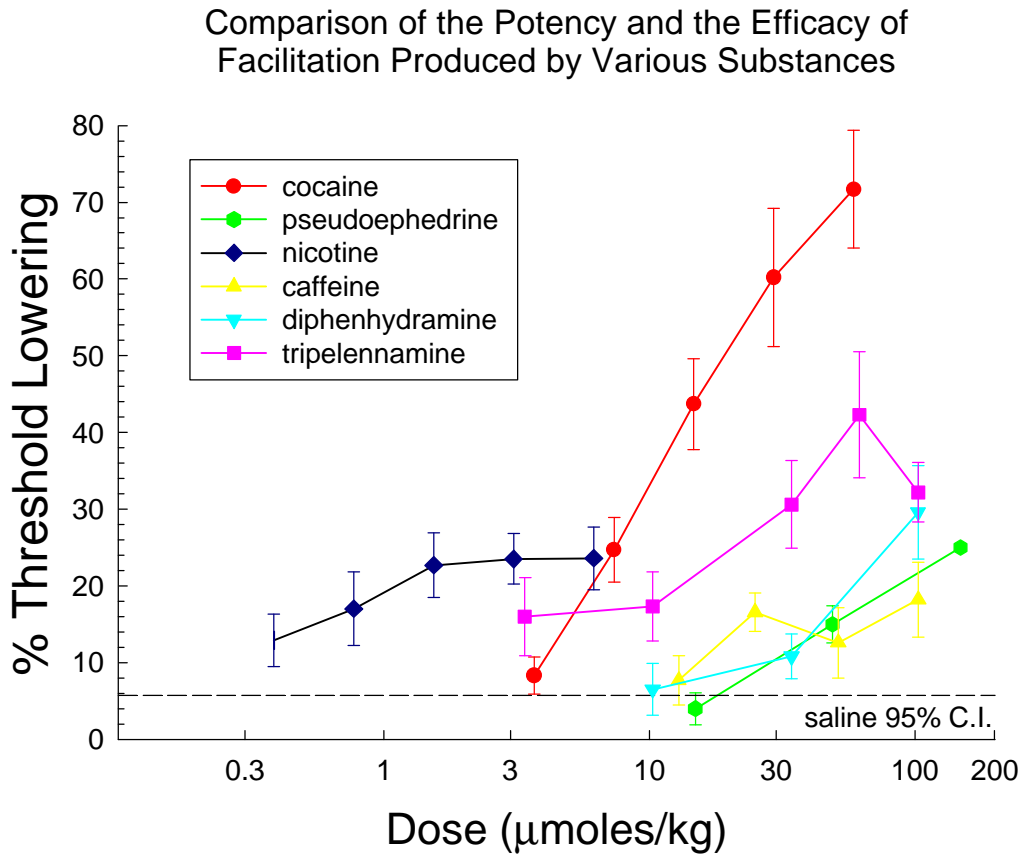


Figure 2: Comparison of the potency and the efficacy of various substances facilitating BSR. The maximum facilitation is shown for each compound at each dose level. The figure shows the mean (\pm SEM) percent of threshold lowering. Although nicotine is clearly the most potent substance facilitating BSR, its efficacy is far below that of cocaine. **Symbols:** cocaine, circles; pseudoephedrine, hexagons; nicotine, diamonds; caffeine, triangles; diphenhydramine, inverted triangles; tripeleennamine, squares.

Previous studies have shown that nicotine's effect on BSR is similar to the effects of caffeine and several over-the-counter medicines used as decongestants (i.e., pseudoephedrine), allergy treatments (i.e., diphenhydramine, tripeleennamine), and sleep aids (i.e., diphenhydramine). The effect of cocaine is distinctively different, producing an effect 2½ times greater than that seen with these compounds (see Figure 3). Studies reported here have attempted to enhance nicotine's BSR facilitation by giving nicotine repeatedly. This tests the hypothesis that chronic nicotine exposure can produce a potent rewarding action similar to that seen with prototypic addictive drugs such as cocaine.

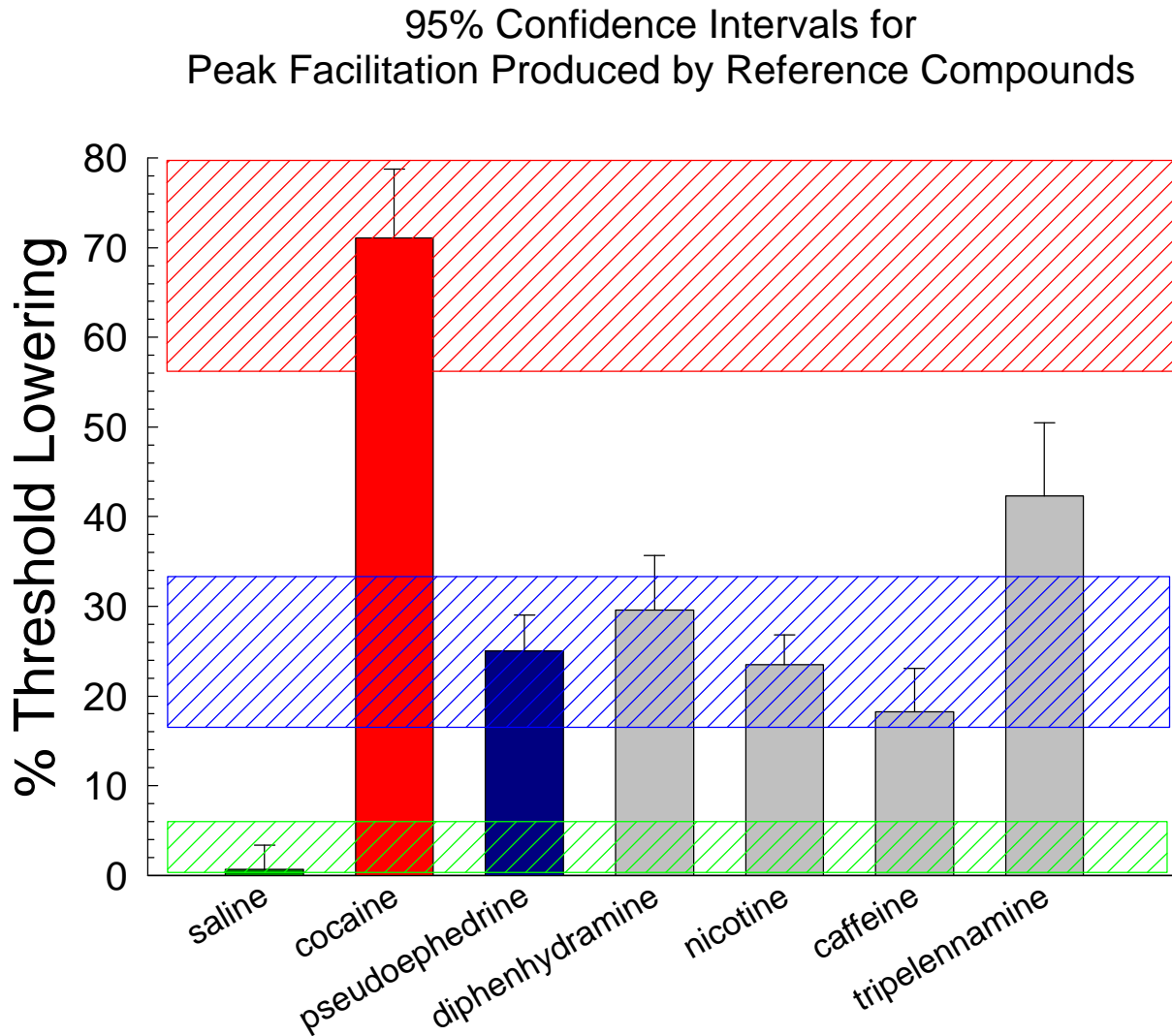


Figure 3: Comparison of peak facilitation produced by various substances. The figure shows the maximum facilitation produced by any dose of each compound at any time post injection. The lower 95% confidence limit for the maximum effect obtained with cocaine and the upper 95% confidence limit for the maximum effect obtained with pseudoephedrine define the expected boundaries for compounds with a high and low addiction liability, respectively. The upper 95% confidence limit for saline is also shown. These data illustrate the importance of using a quantitative measure for assessing a compound's reward-modulating effects.

Experiment I

Rats were injected with the same nicotine dose daily for 21 days. The selected dose has been previously shown to produce maximum facilitation of BSR when given acutely. No enhancement of nicotine's BSR facilitation was seen with repeated injections (see Figure 4). Therefore, nicotine does not appear to have a stronger effect on brain reward mechanisms with repeated exposure, despite the popular belief that nicotine's rewarding effect becomes stronger with repeated nicotine use.

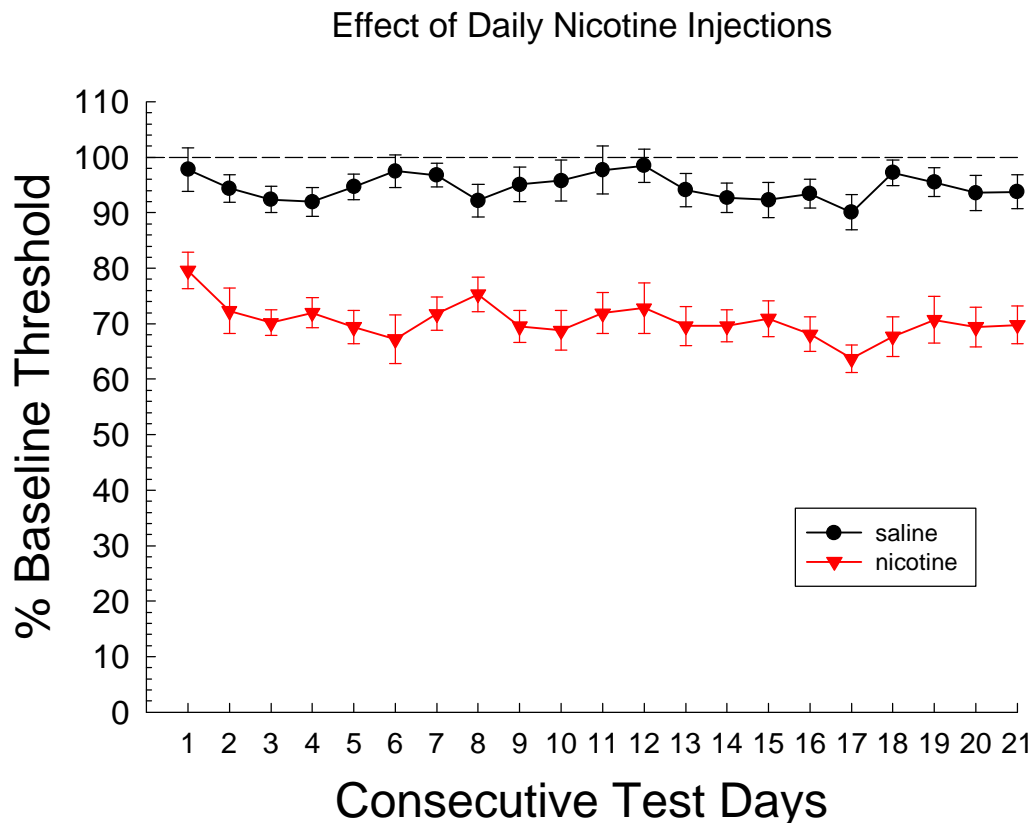


Figure 4: Effect of chronic nicotine on BSR. Data shown are the mean (\pm SEM) percent of baseline thresholds for the time period 16-30 min post injections. Subjects were injected daily with nicotine (0.5 mg/kg/day, s.c., dose expressed as freebase weight; $n=9$) or physiological saline (1 mg/kg/day, s.c.; $n=9$) at the beginning of each test session. Nicotine reliably facilitated BSR during chronic administration, with no significant changes in its threshold-lowering effect across the 21-day injection regimen. **Symbols:** *saline*, circles; *nicotine*, inverted triangles.

Experiment II

Rats were administered increasing doses of nicotine in an attempt to emulate the increasing nicotine exposure seen as humans develop smoking behavior (i.e., progress from smoking several to 20 or more cigarettes per day). Rats were initially given the nicotine dose previously found to produce maximum BSR facilitation for 5 days. The nicotine dose was then doubled for the next 5 days and was then doubled once again for the last 5 days. Nicotine initially facilitated BSR but doubling the dose produced no further enhancement of nicotine's effect (see Figure 5). Surprisingly, when the dose was doubled again during the last 5 days of testing, animals actually showed no facilitation of BSR during the 30-min test. This escalating dose study demonstrated that successively increasing nicotine exposure fails to increase nicotine's effect on brain reward mechanisms. In fact, the highest dose of nicotine did not appear to facilitate BSR.

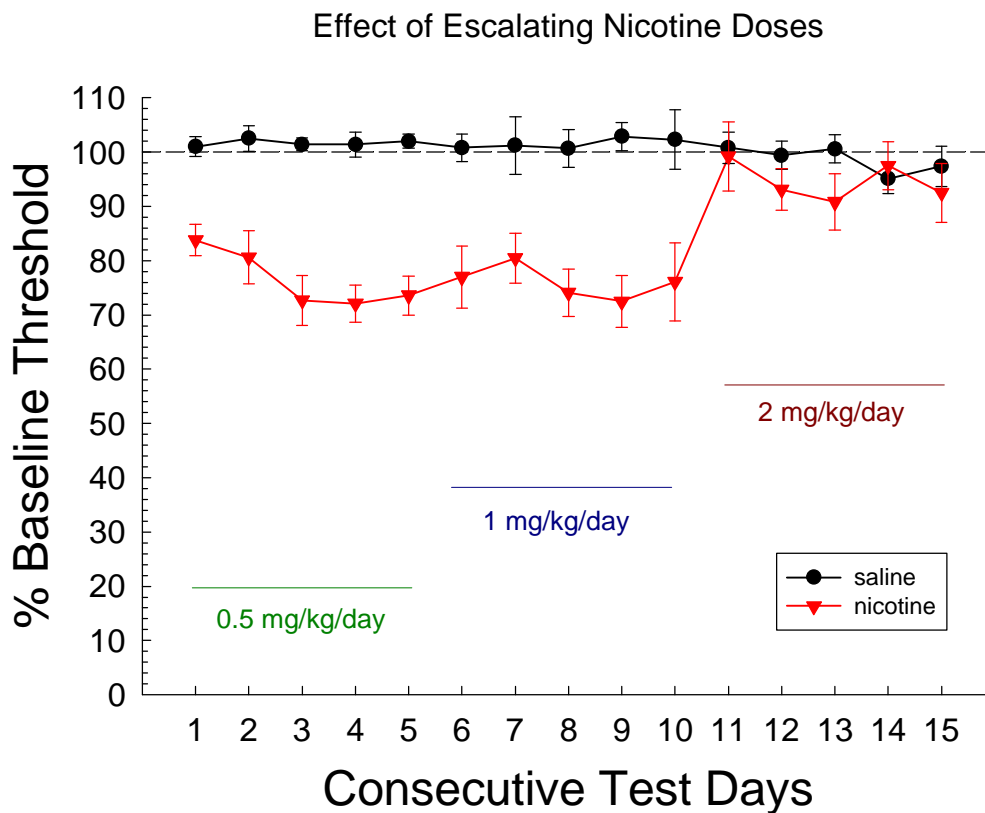


Figure 5: Effect of escalating nicotine doses on BSR. Data shown are the mean (\pm SEM) percent of baseline thresholds for the time period 16-30 min post injections. The nicotine dose was increased from 0.5 to 1 to 2 mg/kg/day (s.c., dose expressed as freebase weight; $n=10$) across 5-day cycles (indicated by the bars). Other animals were tested following daily injections of physiological saline (1 ml/kg/day, s.c.; $n=9$). Symbols: *saline*, circle; *nicotine*, inverted triangle.

Experiment III

To investigate the apparent ineffectiveness of high-dose nicotine, a single injection of the highest dose of nicotine tested was administered and BSR was continuously monitored for 3 hrs. This nicotine dose was well above the nicotine levels achieved by human tobacco use, as evidenced by the fact that animals experienced mild convulsions immediately following nicotine administration. Nicotine initially elevated BSR thresholds but showed a delayed facilitation of BSR beginning 75 min after injection (see Figure 6). This delayed facilitatory action was comparable to that seen sooner after the administration of smaller nicotine doses.

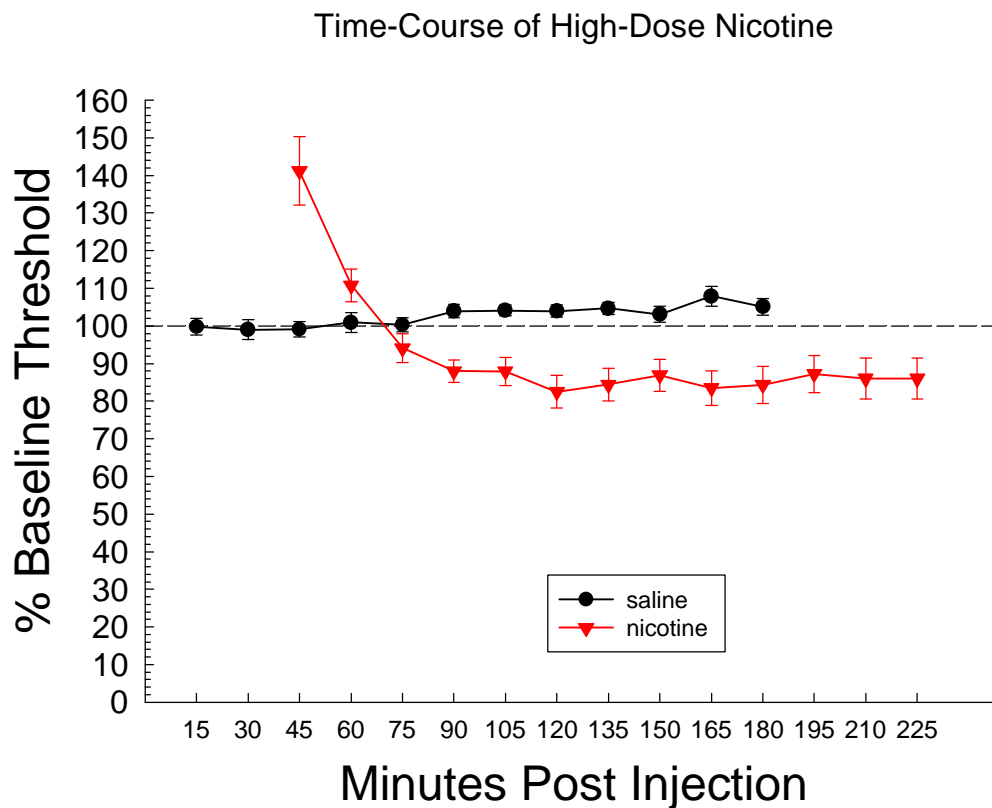


Figure 6: Time-course of high-dose nicotine's effect on BSR. The figure shows the mean (\pm SEM) percent of baseline thresholds across 15-min periods. Subjects were injected with nicotine (2 mg/kg, s.c., dose expressed as freebase weight; $n=6$) or with physiological saline (1 ml/kg, s.c.; $n=5$), and thresholds were determined continuously for 3 to 3.5 hrs post injection. High-dose nicotine produced a delayed facilitation beginning approximately 75 min after injection. This contrasts sharply with the peak nicotine facilitation usually seen 16-30 min post injection. Note that responding was inhibited by high-dose nicotine for the first 30 min post injections. **Symbols:** *saline*, circles; *nicotine*, inverted triangles.

Conclusion

These and previous studies suggest that nicotine's maximum effect on brain reward mechanisms is modest, comparable to caffeine and to several commonly used over-the-counter medicines. This action is distinctively different than the effect produced by highly addictive substances like cocaine. The similarities reported between nicotine and cocaine are superficial, not taking into consideration important differences in the magnitudes of their actions on brain reward mechanisms. Thus, nicotine may activate brain reward mechanisms but not with the efficacy of truly addictive drugs.

Nicotine appears to have a "self-limiting" effect on brain reward mechanisms. Unlike cocaine where increased doses produce increased effects, nicotine's ability to activate brain reward mechanisms seems to be limited by some neurophysiological process. This "self-limiting" action may actually prevent primary addiction to nicotine. Nicotine's modest effect on brain reward mechanisms could explain the failure of preclinical models to demonstrate a strong rewarding effect of nicotine comparable to that seen with highly addictive drugs and points to the importance of other factors in human tobacco use.