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Nicotine Potentiation of Brain Stimulation Reward: An Analysis of Repeated Treatments

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Abstract

Nicotine Potentiation of Brain Stimulation Reward:
An Analysis of Repeated Treatments

Pasqualino Bauco

The "rate-frequency" variant of the "curve-shift" paradigm was used to address the question of whether nicotine potentiates the rewarding effects of midline mesencephalic brain stimulation and if so whether the magnitude of this potentiation changes with successive drug treatments. The effects of nicotine (0.05, 0.1, 0.2 or 0.4 mg/kg, s.c.) were assessed daily for 10 days in animals lever pressing under a FR-1 schedule for midline mesencephalic brain stimulation. The two lower doses caused parallel leftward shifts of the function relating response rate to stimulation frequency, suggesting synergism between nicotine and the rewarding impact of the stimulation. There was neither tolerance nor sensitization to the effects of repeated low doses. The two higher doses caused ataxia and depressed asymptotic responding on the first two days of testing; tolerance to these effects were seen and stable parallel leftward shifts in the rate frequency functions were observed from the third day of testing onward. The peak leftward shift was approximately 30-40% (approximately 0.2 log units). These results demonstrate that nicotine does not merely affect the capacity of animals to lever-press for brain-stimulation but also alters the rewarding

impact of the brain stimulation in a manner comparable to opiates and psychomotor stimulants.

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Dedication

This thesis is dedicated to my mother Teresa for her constant support, love, and understanding.

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Nicotine and the tobacco habit

Despite the current evidence linking chronic tobacco smoking to several diseases such as lung and pancreatic cancer and coronary disease many habitual smokers of tobacco who attempt to cease their habit are seemingly unable to do so. Of the many constituents of tobacco, nicotine has been the most extensively investigated for its possible contribution to the maintenance of the tobacco habit. Nicotine is an alkaloid that was first isolated from leaves of the tobacco plant by Posselt and Reiman in 1828. As early as the 1920s the view that nicotine is the substance that establishes and maintains the tobacco habit began to gain greater acceptance among scientists (Armstrong-Jones, 1929; Henningfield & Goldberg, 1988; Larson, Haag, & Silvette, 1961). There is now a general agreement among researchers that nicotine is the "habit-forming" substance present in tobacco (Gilbert, 1979; Henningfield, 1984a). Several lines of evidence support this view.

Physiological properties of nicotine

Nicotine has several physiological actions in the peripheral and in the central nervous system. In each system nicotine acts at nicotinic cholinergic receptors and mimics actions of the neurotransmitter acetylcholine (Aceto & Martin, 1982).

In the autonomic nervous system nicotine acts at the C6 type receptors found primarily at autonomic ganglia and at the C10 type receptors found at skeletal neuromuscular junctions (see, Taylor, 1990). Some effects of nicotine are vasoconstriction (associated with a decrease in skin temperature), abnormally fast heart beat (tachycardia), and an elevation in blood pressure (Henningfield, 1984b). When administered in relatively high intravenous doses, nicotine can produce an abnormally slow heart action (bradycardia) and an irregular heart beat (Henningfield, Miyasato, Johnson, & Jasinski, 1981).

Nicotine has many actions in the central nervous system. Injections of nicotine into different regions of the brain can cause such varied actions as changes in arterial blood pressure, decreased body temperature, increased respiration, increased salivation, antinociception, an increase in reflexes such as ear twitching (Hall, 1984), and increased locomotion (Museo & Wise, 1990a; Museo & Wise, 1990b); relatively large doses can produce ataxia, convulsions, and even catalepsy (Hall, 1984). The habit-forming actions of nicotine also appear to be centrally mediated and there is reason to believe that they involve the same central structures as are involved in the locomotor response (Clarke, 1987; Clarke, 1990; Clarke, Fu, Jakubovic, & Fibiger, 1988).

Evidence that the habit-forming effects of nicotine are centrally mediated comes from two paradigms: the intravenous self-administration paradigm and the conditioned place-preference paradigm. Intravenous self-administration is attenuated by centrally but not peripherally acting nicotinic antagonists in lower animals (Corrigall & Coen, 1989; Goldberg & Henningfield, 1988; Goldberg & Spealman, 1982; Goldberg, Spealman, & Goldberg, 1981; Risner & Goldberg, 1983) and in humans (Pomerleau, Pomerleau, & Majchrzak, 1987). Conditioned place preferences can be established by intraventricular or pedunculopontine nucleus injections of nicotine (Iwamoto, 1990). Microinjection of the nicotinic agonist cytisine into the ventral tegmental area is also effective (Museo and Wise, 1990c). While the minimally effective dose for the establishment of conditioned place preferences following intracranial administration is 2 to 3 µg (Iwamoto, 1990) a dose greater than 100 µg is required to establish conditioned preferences when nicotine is administered systemically (Fudala, Teoh, & Iwamoto, 1985). This evidence supports the view that the habit-forming effects of nicotine are centrally mediated.

The demonstration that a place preference can be established following injections of nicotine or an agonist into some but not all areas of the brain suggests that there exists some degree of localization of function within the central nervous system. Some areas in the central nervous

system that have been shown to contain high densities of nicotinic receptors are the interpeduncular nucleus, most of the thalamic nuclei, superior colliculus, medial habenula, ventral tegmental area, substantia nigra pars compacta, dentate gyrus, and layers III and IV of the cerebral cortex (Clarke, Pert, & Pert, 1984; Clarke, Schwartz, Paul, Pert, & Pert, 1985; London, Waller, & Wamsley, 1985; Rainbow, Schwartz, Parsons, & Kellar, 1984). Moderate nicotinic receptor densities have been found in the neostriatum, ventral striatum, dorsal tegmental nucleus, and cerebellum (Clarke, Pert, & Pert, 1984; Clarke, Schwartz, Paul, Pert, & Pert, 1985).

Interestingly, some areas in the brain that contain nicotinic receptors also possess dopamine-containing neurons. One hypothesis that has been under investigation is that the neurotransmitter dopamine is involved in the mediation of the habit-forming properties of nicotine as well as habit-forming drugs in general (Wise, 1978; Wise & Bozarth, 1987; Wise & Rompré 1989). The interaction of nicotine with the neurotransmitter dopamine is explored below.

Nicotine interacts with neurons that contain and release many neurotransmitters (e.g., serotonin, norepinephrine, and dopamine) and with neuroendocrinological substances (e.g., serum prolactin, adrenocorticotrophic hormone) (Aceto & Martin, 1982; Balfour, 1984). Yet, it is

the effects of nicotine on midbrain dopamine-containing neurons that have received the greatest degree of attention and appear to have the greatest relevance to the drug's rewarding properties. The hypothesized role of dopamine in mediating the rewarding effects of habit-forming substances (Wise, 1978; Wise & Bozarth, 1987; Wise & Rompré, 1989) and the high distribution of nicotinic receptors in regions of dopamine-containing neurons suggest that the midbrain dopamine system is implicated in the acquisition and maintenance of the nicotine habit.

The midbrain dopamine system comprises two populations of dopamine neurons: the ventral tegmental area, or A10 neurons, with axons projecting primarily to cortical and limbic structures such as the nucleus accumbens, olfactory tubercle, hippocampus, septum, and amygdala (Domesick, 1988; Fallon, 1988; Fallon & Moore, 1978); and the substantia nigra, or A9 neurons, that send fibres primarily to the caudate-putamen and to a lesser degree to some cortical and limbic structures (Fallon & Moore, 1978; Lindvall & Björklund, 1983; Lindvall & Björklund, 1984; Ungerstedt, 1971). The high density of nicotinic receptor binding sites at the level of the midbrain dopamine cell bodies, in addition to the more moderate densities at the level of the terminal regions, suggests that nicotine may influence the functioning of these neurons.

Nicotine's effects upon mesolimbic and nigrostriatal dopamine-containing neurons have been investigated using *in vitro* and *in vivo* preparations. In *in vitro* intracellular preparations, application of nicotine to ventral tegmental dopamine neurons potentiates dopamine impulse flow (Calabresi, Lacey, & North, 1989). In *in vivo* preparations, acute systemic (Clarke, Hommer, Pert, & Skirboll, 1985; Grenhoff, Aston-Jones, & Svensson, 1986; Lichtensteiger, Hefti, Felix, Huwyler, Melamed, & Schlumpf, 1982), intravenous (Clarke, Hommer, Pert, & Skirboll, 1985), or iontophoretic (Lichtensteiger, Hefti, Felix, Huwyler, Melamed, & Schlumpf, 1982) nicotine treatment potentiates substantia nigra dopamine cell firing as assessed by extracellular single unit recording in anaesthetized animals. Systemic and intravenous nicotine treatment have also been shown to increase firing of ventral tegmental area dopamine neurons (Grenhoff, Aston-Jones, & Svensson, 1986; Mereu, Yoon, Boi, Gessa, Naes, & Westfall, 1987). Furthermore, ventral tegmental dopamine neurons are more sensitive to nicotine's effect than are dopamine neurons in the substantia nigra (Mereu, Yoon, Boi, Gessa, Naes, & Westfall, 1987).

Dopamine release from the terminal areas has been investigated in preparations using the technique of *in vivo* microdialysis. Systemic injections of nicotine causes dopamine release in the striatum and nucleus accumbens;

this release of dopamine is greater in the nucleus accumbens than in the striatum (Di Chiara, & Imperato, 1988; Di Chiara, Imperato, & Mulas, 1987; Imperato, Mulas, & Di Chiara, 1986). Dopamine release is also caused or potentiated when nicotine is administered directly into nucleus accumbens (Mifsud, Hernandez, & Hoebel, 1989).

In in vitro slice or synaptosomal preparations, nicotine has been shown to increase dopamine release from striatal tissue (Giorguieff-Chesselet, Kemel, Wandscheer, & Glowinski, 1979; Sakurai, Takano, Kohjimoto, Honda, & Kamiya, 1982; Westfall, 1974; Westfall, Grant, & Perry, 1983). Dopamine release is also potentiated following the application of nicotine to nucleus accumbens tissue preparations (Rowell, Carr, & Garner, 1987). These data suggest that one of nicotine's actions is on the terminals of the dopamine fibers; nicotine can influence dopamine release from dopaminergic terminals that are no longer conducting impulses.

Behavioral properties of nicotine

Nicotine exerts several effects on the behavior of organisms. Some behavioral effects include changes in locomotor activity, operant responding, conditioned avoidance, aggression, and food and water intake (Clarke, 1987). Further, nicotine has been shown to improve subject performance on stimulus discrimination, learning, memory, as

well as other tasks (Pomerleau & Pomerleau, 1984). Nicotine can exert both depressant and stimulant behavioral actions in humans (Gilbert, 1979) and in lower animals (Clarke & Kumar 1983a; Clarke & Kumar, 1983b; Morrison, & Stephenson, 1972).

In acute preparations the depressant effects of nicotine typically dominate behavior. This behavioral depression is observed following a treatment that results in moderate to high circulating levels of nicotine in the brain. These high-dose effects have been demonstrated in studies of the effects of nicotine on locomotor activity (Clarke & Kumar, 1983a; Stolerman, Fink, & Jarvik, 1973), operant responding for brain stimulation, food or water reward, and shock avoidance (Domino, 1973; Pradhan, 1970; Pradhan & Bowling, 1971; Risner, Goldberg, Prada, & Cone, 1985; Spealman, Goldberg & Gardner, 1981). With repeated testing tolerance develops to the high-dose locomotor effect (Clarke & Kumar, 1983a; Clarke & Kumar, 1983b; Morrison & Stephenson, 1972) and only behavioral stimulation or activation is observed.

Immediately following treatment with a relatively low dose of nicotine and at longer latencies following treatment with a high dose, nicotine's stimulant action dominates behavior. Here, nicotine increases operant responding and conditioned avoidance behavior (Domino, 1973; Pradhan & Bowling, 1971; Risner, Goldberg, Prada & Cone, 1985;

Spealman, Goldberg, & Gardner, 1981). This low-dose effect is best characterized by nicotine's effect on locomotor activity. At relatively low doses nicotine acts predominately to stimulate locomotor activity in rats (Iwamoto, 1984; Morrison & Stephenson, 1973; Pradhan, 1970).

While tolerance develops to the high-dose effect of nicotine, with repeated testing it does not develop to the low-dose or potentiating effect. There is evidence to suggest that with repeated testing the low-dose locomotor-activating effects undergo sensitization (Hakan & Ksir, 1988; Ksir, Hakan, Hall, & Kellar, 1985), or to what some have interpreted as the development of tolerance to nicotine's sedative effects (Clarke & Kumar, 1983a; Clarke & Kumar, 1983b). This suggests that the depressant high-dose and the stimulant low-dose effects function under separate rather than a common mechanism of action.

Rewarding properties of nicotine

The habit-forming properties of drugs and other stimuli and events are discussed in psychological theory under the rubric of "reinforcement". It is widely held (e.g., Mowrer, 1947; Rescorla & Solomon, 1967; Schlossberg, 1937; Skinner, 1937) that there are two fundamentally different forms of reinforcement: "operant" reinforcement which involves strengthening of associations between responses and their consequences, and Pavlovian reinforcement which involves

the strengthening of associations between stimuli. Unlike the effects of drugs on behavior, drug reinforcement is an inferred rather than a directly observable phenomenon. Two paradigms, the drug self-administration and the conditioned place-preference paradigm, have been developed to assess the ability of habit-forming drugs to establish response habits and to establish conditioned stimulus preferences, respectively. Nicotine is reinforcing in each paradigm. In the operant tradition nicotine is said to be "reinforcing" because it maintains or strengthens a behavior upon which drug delivery is made contingent, as demonstrated in the drug self-administration paradigm (Weeks, 1962). Nicotine is seen to be reinforcing in the Pavlovian sense because by being "paired" or "associated" with certain environmental stimuli it establishes a preference for those stimuli, such that they come to elicit conditioned approach reactions (Beach, 1957a; Beach, 1957b; Rossi & Reid, 1976; Schwartz & Marchok, 1974; Spragg, 1940).

Drugs that are abused by humans are also self-administered by lower animals (Griffiths, Brady, & Bradford, 1979; Schuster & Johanson, 1974; Schuster & Thompson, 1969; Weeks, 1962; Woods, 1978). Given this parallel between human and animal drug self-administration, the self-administration paradigm has been proposed as a method to predict the "abuse liability" (Collins, Weeks, Cooper, Good, & Russell, 1984), or the habit forming potential of drugs.

The drug self-administration paradigm is an operant paradigm. The defining characteristic of operant reinforcement is that the reinforcer is administered or delivered to the animal in a response-contingent manner; the animal must earn the reinforcer. Cigarette smoking is the most common form of nicotine self-administration in humans. The self-administration of nicotine in this manner is under pharmacological control. Manipulations that alter the dosage of nicotine delivered per cigarette results in compensatory changes in smoking behavior (Benowitz, 1986; Henningfield, 1984b; Sepkovic, Parker, Axelrad, Haley, & Wynder, 1984). For example, increasing urinary pH (which increases the excretion of nicotine) results in compensatory increases in smoking (Benowitz & Jacob, 1985). Pretreatment with nicotine (by chewing nicotine gum) dose-dependently decreases subsequent cigarette smoking (Nemeth-Coslett, Henningfield, O'Keefe, & Griffiths, 1987). When given the opportunity to self-administer nicotine intravenously cigarette smoking decreases (Henningfield, Miyasato, & Jasinski, 1983). In contrast, treatment with centrally acting nicotinic antagonists increases tobacco smoking (Pomerleau, Pomerleau, & Majchrzak, 1987; Stolerman, Goldfarb, Fink, & Jarvik, 1973).

In the laboratory the self-administration of nicotine has been demonstrated across a range of species. Humans (Goldberg & Henningfield, 1988; Henningfield & Goldberg,

1983; Henningfield, Miyasato, & Jasinski, 1983) as well as rats (Corrigal & Coen 1989; Cox, Goldstein & Nelson, 1984; Goldberg & Henningfield, 1988; Griffiths & Henningfield, 1982), baboons (Ator & Griffiths, 1983), and squirrel monkeys (Goldberg, Spealman, & Goldberg, 1981; Goldberg, Spealman, Risner, & Henningfield, 1983) will self-administer nicotine intravenously.

Drugs known to serve as operant reinforcers also establish conditioned place preferences (Bozarth, 1987a; Carr, Fibiger, & Phillips, 1989; Wise, 1989; Wise & Bozarth, 1987). When drug injections are administered in a distinctive portion of the animal's environment, the animal will develop a learned preference for that portion of the environment that is revealed when it is tested in a drug-free state. These "conditioned place preferences" are established by Pavlovian pairing of drug injections with environmental stimuli; in the conditioned place-preference paradigm there is no contingency between the behaviour of the animal and the administration of drug. The Pavlovian conditioning involved in the conditioned place-preference paradigm is thus fundamentally different from the operant conditioning involved in the self-administration paradigm. The place-preference paradigm has been proposed as a reliable method to study this facet of drug reinforcement (van der Kooy, 1987; Wise, 1989).

Nicotine's ability to establish a conditioned place preference has been investigated under systemic and intracranial administration. Nicotine administered systemically has been reported by some investigators to establish conditioned place preferences (Fudala & Iwamoto, 1986; Fudala, Teoh, & Iwamoto, 1985). Pre-treatment with mecamylamine, a centrally acting nicotinic antagonist, blocks nicotine's effect in this paradigm while pre-treatment with hexamethonium, a nicotinic antagonist that does not readily enter the central nervous system, does not (Fudala, Teoh, & Iwamoto, 1985). Other investigators, however, have failed to demonstrate nicotine induced place preferences (Clarke & Fibiger, 1987; Jorenby, Steinpreis, Sherman, & Baker, 1990). Methodological differences across place-preference studies may account for this inconsistency. Intracerebroventricular or pedunculopontine microinjections of nicotine establish conditioned place preferences that are blocked by co-administration of mecamylamine (Iwamoto, 1990) (a nicotinic antagonist that readily enters the central nervous system). Microinjection of cytisine, a nicotinic agonist, into the ventral tegmental area also establishes conditioned place preferences (Museo & Wise 1990c). The ability of mecamylamine but not hexamethonium (a nicotinic antagonist that acts principally in the peripheral nervous system) to block systemic nicotine induced place preference suggests that these rewarding effects of nicotine are

centrally mediated. The demonstration that a place preference can be established following microinjections of nicotine or an agonist directly into the brain and that this effect also can be blocked by mecamylamine lends further support to this view.

Electrical stimulation of the medial forebrain bundle and the contiguous midline mesencephalon is powerfully rewarding (Olds & Milner, 1954; Miliaressis, Bouchard, & Jacobowitz, 1975; Rompré & Miliaressis, 1985). The stimulation serves as an operant reinforcer and is also reinforcing in the conditioned place-preference paradigm (Ettenberg & Duvauchelle, 1988); in addition to its response-contingent reinforcing effects, the stimulation has proactive "priming" effects that encourage responding in a manner that is thought to be independent of reinforcement per se (Gallistel, Stellar, & Bubis, 1974). The lay term "reward" is usually used to subsume these presumably independent effects of the stimulation.

Nicotine causes rats to increase the rate at which they self-administer rewarding brain stimulation (Newman, 1972; Olds & Domino, 1969a; Olds & Domino, 1969b; Pradhan & Bowling, 1971; Schaefer & Michael, 1986). It is not clear from this finding, however, whether nicotine increases the rewarding impact of the stimulation or rather increases the performance capacity of the animal. The hypothesis developed below is that nicotine, like other rewarding

drugs, potentiates the habit-forming properties of brain stimulation reward.

Interaction of rewarding drugs with rewarding brain stimulation

Drugs that are rewarding in their own right (as determined by the self-administration and conditioned place-preference paradigms) also appear to potentiate the rewarding action of brain stimulation reward. The evidence that amphetamine and morphine potentiate the rewarding effects of brain stimulation and not merely the response capacity of the animal has emerged from several recent refinements of the analysis of the brain stimulation reward paradigm.

Self-stimulation: Dissociating between performance and reward

A central issue in the self-stimulation literature is that of the "reward-performance" distinction. The question of interest is whether observed changes in an animal's behavioral output (typically lever pressing) following various manipulations reflect changes in the organism's capacity to respond or rather reflect changes in the rewarding impact of the brain stimulation.

The ability to distinguish between changes in performance and changes in reward are critical to the self-

stimulation and drug reward specialist. The choice of a dependent measure is therefore of utmost importance. Early self-stimulation work relied on an analysis of simple response rates as the dependent measure from which changes in the reward strength of the stimulation were inferred. The limitations of response rate measures are best characterized by data from "choice measure" experiments. Animals will often chose stimulation that supports low rates of self-stimulation (such as the septum) over sites that support high rates (Hodos & Valenstein, 1962; Ross, 1973). Animals responding for stimulation at a variety of frequencies or intensities that all produce asymptotic or maximal response rates will, when given the choice between low and high stimulation, consistently choose the high frequency or intensity over the low (Miliaressis & Malette, 1987; Waraczynski, Stellar, & Gallistel, 1987). A problem with simple response rate measures, therefore, is that they are insensitive to differences in reward strength that are clearly important to the animal when stimulation frequencies that produce maximal response rates are tested. In response to the major criticisms of the early self-stimulation paradigm several alternative dependent variables have been developed (Gallistel, 1983; Liebman, 1982; Stellar & Rice, 1989; Valenstein, 1964; Wise, 1989; Wise & Rompré, 1989). One of these involves threshold measures (Fenton & Liebman, 1982; Fouriezos & Wise, 1976; Franklin & McCoy, 1979;

Gallistel, Boytim, Gomita, & Klebanoff, 1982; Kornetsky & Esposito, 1981; Kornetsky, Esposito, McLean, & Jacobson, 1979; Kornetsky & Wheeling, 1982; Zarevics & Setler, 1981).

A paradigm that has emerged as the paradigm of choice when both the rewarding value of the stimulation and the performance capacity of the animal are to be measured is the "curve-shift" paradigm. The curve-shift paradigm was first extensively discussed by Edmonds and Gallistel (1974) and has since been used by many self-stimulation specialists (Fibiger & Phillips, 1981; Franklin, 1978; Gallistel & Freyd, 1987; Liebman, 1983; Miliaressis, Rompré, Laviolette, Philippe, & Coulombe, 1986; Shizgal & Murray, 1989; Stellar & Rice, 1989; Wise, 1989; Wise & Rompré, 1989; Yeomans, Kofman, & McFarlane, 1985). One variant of the curve-shift paradigm is the "rate-frequency" variant. In the rate-frequency variant, stimulation intensity, train of stimulation, and duration of the stimulation pulse are held constant and only stimulation frequency (pulses of stimulation per second) is varied from one trial to the next. The procedure involves recording the animal's performance at each frequency tested including frequencies that fail to sustain some level of responding, some that produce moderate responding, and some that produce maximal or asymptotic responding. When the rate of responding is plotted as a function of stimulation frequency, the

resulting rate-frequency curve approximates an ogival or sigmoidal form (Fig. 1).

Of interest is the displacement or shift of the rate-frequency curve following various manipulations. It is the displacement of the curve that allows one to infer changes in the rewarding impact of the stimulation. The rate-frequency curve can shift in two important ways. The first type of shift is a lateral (leftward or rightward) shift. Lateral shifts in the rate-frequency curve are thought to reflect changes in the rewarding impact of the stimulation. Parallel leftward shifts reflect an increase in the rewarding impact of the stimulation because the animal requires lower doses (frequency) of stimulation to produce responding at pre-treatment levels. Conversely, a parallel rightward shift reflects a decrease in the rewarding impact of the stimulation since higher stimulation frequencies are required to produce pre-treatment rates of responding.

A second type of shift that can occur in the rate-frequency curve is a vertical (upward or downward) shift. For example increasing the performance requirements on an animal results in a downward vertical shift. Marbles placed on the floor of a runway, making animals run on an incline (Edmonds & Gallistel, 1974), or increasing the force required to depress a lever (Miliaressis, Rompré, Laviolette, Phillippe, & Coulombe, 1986) all decrease

asymptotic performance but do not result in significant parallel lateral shifts of the rate-frequency curve.

Effects of rewarding drugs on brain stimulation

Drugs that are rewarding in their own right tend also to potentiate brain stimulation reward. The interaction of brain stimulation with habit-forming drugs from various drug classes is reviewed in the sections below.

Low and moderate systemic doses of amphetamine increase the rate of responding for brain stimulation (Domino & Olds, 1972; Robertson & Mogenson, 1979; Stein, 1964). Systemic treatment with amphetamine also lowers the threshold for brain stimulation (Esposito & Kornetsky, 1980; Greenshaw, Sanger, & Blackman, 1985; Hubner, Bain, & Kornetsky, 1987; Schaefer & Michael, 1988; Wauquier & Niemegeers, 1974). Systemic amphetamine produces a parallel leftward shift of the rate-frequency curve (Colle & Wise, 1988; Gallistel & Freyd, 1986; Gallistel & Karras, 1984). Amphetamine, therefore, potentiates the rewarding impact of brain stimulation.

Moderate and high systemic doses of morphine have biphasic effects on self-stimulation rate. Self-stimulation rate is depressed for one to three hours after initial injections of moderate systemic doses (Olds & Travis, 1960) and this period is followed by a period of one or two hours of response acceleration (Bush, Bush, Miller, & Reid, 197

Lorens, 1976; Lorens & Mitchell, 1973; Schaefer & Holtzman, 1979). Systemic morphine injections lower the threshold for self-stimulation even in the period when simple response rate is depressed (Esposito & Kornetsky, 1977; Esposito, McLean, & Kornetsky, 1979; Hubner, Bain, & Kornetsky, 1987; Marcus & Kornetsky, 1974; van Wolfswinkel & van Ree, 1985). When assessed using the curve-shift paradigm low systemic doses produce leftward shifts of the rate-intensity function (Glick, Weaver, & Meibach, 1982). The initial suppression in simple response rate following moderate and high systemic doses of morphine undergoes tolerance with repeated dosing (Bush, Bush, Miller, & Reid, 1976; Lorens, 1976). With repeated injections tolerance does not develop, however, to the reward potentiating (threshold lowering) effects of morphine (Kelley & Reid, 1977; van Wolfswinkel & van Ree, 1985).

The effects of ethanol have been inconsistent. Rate-dependent effects on self-stimulation have been reported. At equivalent doses systemic ethanol has, in a number of studies, been reported to increase rate of responding for self-stimulation (De Witte & Bada, 1983; Lewis, Andrade, & Reynolds, 1989; Lorens & Sainati, 1978) and, in other cases, to have no effect or to decrease response rates (Carlson & Lydic, 1976; Schaefer & Michael, 1987; Schaefer, Richardson, Bonsall, & Michael, 1988). In threshold studies ethanol has been reported to decrease self-stimulation thresholds in

some cases (Lewis & Phelps, 1987) and to have no effect on self-stimulation thresholds in others (Schaefer & Michael, 1987; Unterwald, Clark, Bain, & Kornetsky, 1984; Unterwald & Kornetsky, 1985). The effects of ethanol on self-stimulation using the curve-shift paradigm have only been investigated in a single experiment. Intravenous ethanol did not produce a clear parallel leftward shift of the rate-frequency curve (Trojniar & Wise, in preparation). Ethanol's intoxicating effects, rate-dependent effects, its relatively short duration of action, and the methodological differences across ethanol self-stimulation studies have made these data difficult to interpret.

Moderate and high systemic doses of delta^9-tetrahydrocannabinol (THC) (the psychoactive substance in marijuana) have biphasic effects on self-stimulation rate. Self-stimulation response rates are depressed in the first hour immediately following treatment and this period is followed by a one to two hour period of increased response rates (Bailey & Pradhan, 1972; Bhattacharyya, Aulakh, Pradhan, Ghosh, & Pradhan, 1980). With repeated injections, tolerance rapidly develops to the initial response suppressive effects (Becker & Reid, 1977). Systemic THC lowers the threshold for self-stimulation (Gardner, Paredes, Smith, Donner, Milling, Cohen, & Morrison, 1988; Gardner, Paredes, Smith, & Zukin, 1989). These data suggest that THC

shares with amphetamine and morphine the ability to potentiate the rewarding impact of brain stimulation.

Evidence of the ability of benzodiazepines to potentiate responding for brain stimulation is not as robust or as clear as it is for psychomotor stimulant drugs and opiates (Wise, 1980). Low to moderate systemic doses of benzodiazepines have been reported to increase self-stimulation rates in some animals and to decrease rates in other similarly treated animals (Olds, 1966; Panksepp, Gandelman, & Trowill, 1970). The effect of benzodiazepines on rate of responding for brain stimulation is also affected by the stimulation site chosen. Doses of diazepam that potentiate responding in animals with hippocampal electrodes reduce response rates in animals with hypothalamic stimulating electrodes (Caudarella, Campbell, & Milgram, 1982; Caudarella, Estrade, Cazala, & Gauthier, 1984). In the hands of some experimenters, however, increased rates of responding for brain stimulation have been obtained following treatment with low to moderate doses of chlordiazepoxide (Domino & Olds, 1972; Ichitani, Iwasaki, & Satoh, 1985; Lorens & Sainati, 1978; Olds, 1972; Wauquier, 1976) as well as for diazepam (Caudarella, Campbell, & Milgram, 1982; Olds, 1976; Wauquier, 1976). Systemic treatment with high doses of benzodiazepines have been shown to depress response rates (Domino & Olds, 1972; Olds, 1972; Olds, 1976). Low doses of chlordiazepoxide (Stark, Turk,

Redman, & Henderson, 1969) lower the threshold for self-stimulation thereby suggesting that under certain conditions benzodiazepines can potentiate brain stimulation reward.

Systemic injections of low to moderate doses of barbiturates such as pentobarbital increase the rate of responding for lateral hypothalamic brain stimulation while high doses depress response rates (Mogenson, 1964; Reid, Gibson, Gledhill, & Porter, 1964). No threshold or curve-shift studies have been undertaken to study the systemic effects of barbiturates on self-stimulation. As with benzodiazepines, the response potentiating effects of barbiturates are not as robust as those of opiates and stimulant drugs (Wise, 1980). The low dose response potentiating effects of barbiturates, however, do suggest that compounds from this drug class may also function in a synergistic manner with brain stimulation to potentiate reward.

Low systemic doses of caffeine increase the rate of responding for brain stimulation while high doses reduce response rates (Valdes, McGuire, & Annau, 1982). In one investigation using a threshold measure of self-stimulation, systemic low doses of caffeine had no effect on threshold while high doses increased the threshold for self-stimulation (Mumford, Neill, & Holtzman, 1988). In contrast equivalent low doses of caffeine reduced the "ON" latency (la ncy to trigger a photobeam that results in delivery of

continuous stimulation) which suggests that caffeine potentiated brain stimulation reward. The contradictory evidence from the threshold experiments is difficult to reconcile. The evidence that low doses increase response rates for brain stimulation, however, suggests that under certain conditions caffeine potentiates brain stimulation reward.

The mechanisms of drug reward seem homologous with those of facilitation of brain stimulation

The strongest empirical support for the notion that common brain mechanisms play a role in the rewarding and reward-facilitating effects of drugs (see below) comes from the fact that those brain sites in which central drug injections are rewarding in their own right are the same as those where central drug injections facilitate rewarding brain stimulation. To date amphetamine and morphine have been well characterized in each of the relevant paradigms.

The brain site identified with the rewarding and reward-facilitating effects of amphetamine is the nucleus accumbens. Rats lever press for microinjections of amphetamine directly into the nucleus accumbens (Hoebel, Monaco, Hernandez, Aulisi, Stanley, & Lenard, 1983; Lenard, Hernandez, & Hoebel, 1980; Monaco, Hernandez, & Hoebel, 1980) but not for amphetamine microinjections into the caudate, ventral accumbens (Hoebel, Monaco, Hernandez,

Aulisi, Stanley, & Lenard, 1983), or into the lateral ventricles (Monaco, Hernandez, & Hoebel, 1980). Selective neurotoxic lesions of the nucleus accumbens block the acquisition (Lyness, Friedle, & Moore, 1979) and maintenance of intravenous stimulant (cocaine or amphetamine) self-administration (Pettit, Ettenberg, Bloom, & Koob, 1984), as do selective neurotoxic lesions of ventral tegmental area dopamine neurons (Roberts & Koob, 1982); 6-hydroxydopamine (6-OHDA) lesions dorsal to the nucleus accumbens or lesions of the caudate do not disrupt stimulant self-administration (unpublished observation as reported in Roberts & Koob, 1982).

The same site that is implicated in amphetamine self-administration is involved in amphetamine-induced place preferences; amphetamine injections into the nucleus accumbens establish conditioned place preferences (Aulisi & Hoebel, 1983; Carr & White, 1983; Carr & White, 1986). Injections into the amygdala, medial prefrontal cortex, area postrema (Carr & White, 1986), and caudate (Carr & White, 1983; Carr & White, 1986) have been ineffective. Neurotoxin 6-OHDA lesions of the nucleus accumbens antagonize conditioned place preferences established with systemic amphetamine (Spyraki, Fibiger, & Phillips, 1982).

The only known site where amphetamine injections potentiate the rewarding effects of brain stimulation is also the nucleus accumbens. Amphetamine microinjected into

the nucleus accumbens has been shown to increase rates of medial forebrain bundle self-stimulation (Broekkamp, Pijnenburg, Cools, & Van Rossum, 1975), while injections into the anterior hypothalamus and ventricular system have little or no effect on rate of responding. Amphetamine injected into the nucleus accumbens produces a parallel leftward shift of the rate-frequency curve following drug treatment (Colle & Wise, 1988). When amphetamine is injected into the caudate, a dose four times that which produces a minimal effect in the nucleus accumbens is required to produce a leftward shift in the rate-frequency curve (Colle & Wise, 1988).

There are two sites where opiates have rewarding and reward-potentiating actions: the ventral tegmental area and the nucleus accumbens. Animals self-administer morphine directly into the ventral tegmental area (Bozarth & Wise, 1981; van Ree & de Wied, 1980; Welzl, Kuhn, & Huston, 1989) but not into the caudate, lateral hypothalamus or periventricular gray (Bozarth & Wise, 1980). Rats will also self-administer the selective mu and delta agonists DAGO and DPDPE into the ventral tegmental area (Devine & Wise, 1990). Morphine self-administration into the ventral tegmental area is blocked by systemic injections of the opiate antagonist naloxone (Bozarth & Wise, 1981) thereby confirming that the self-administration of morphine is an opiate receptor-mediated effect. Selective dopaminergic lesions of the

ventral tegmental area block the acquisition of intravenous opiate self-administration (Bozarth & Wise, 1986).

The nucleus accumbens is the second site where opiate injections are rewarding. Rats self-administer morphine or enkephalin directly into the nucleus accumbens (Goeders, Lane, & Smith, 1984; Olds, 1982). Co-treatment with naloxone results in compensatory increases in self-administration (Goeders, Lane, & Smith, 1984). Neurotoxin (6-OHDA) lesions of the nucleus accumbens attenuate responding for intravenous morphine such that a doubling of the dose is required (post lesion) to maintain self-administration (Smith, Guerin, Co, Barr, & Lane, 1985). The disruption of heroin self-administration correlates positively with the degree of nucleus accumbens destruction by kainic acid lesions (Zito, Vickers, & Roberts, 1985).

The brain sites implicated in the rewarding effects of self-administered opiates are also implicated in opiate-induced place-preferences. Morphine or the mixed opiate agonist [D-Ala^2]-Met^5-Enkephalinamide injections into the ventral tegmental area establish conditioned place preferences (Bozarth, 1987b; Phillips & LePiane, 1980; Phillips & Lepiane, 1982; Phillips, Lepiane, & Fibiger, 1983 as do morphine microinjections into the nucleus accumbens (van der Kooy, Mucha, O'Shaughnessy, & Bucenieks, 1982). Pretreatment with naloxone blocks the establishment of ventral tegmental morphine place preferences (Phillips &

LePiane, 1980). Electrolytic (Kelsey, Carlezon, & Falls, 1989) and 6-OHDA lesions (Schwartz & Marchok, 1974) of the nucleus accumbens block the establishment of conditioned preferences with systemic morphine. Opiate injections into other brain regions such as the amygdala, caudate, and nucleus ambiguous have failed to establish conditioned preferences (van der Kooy, Mucha, O'Shaughnessy, & Bucenieks, 1982).

The ventral tegmental area and the nucleus accumbens are also sites where opiate injections potentiate the rewarding impact of brain stimulation. Morphine injected into the ventral tegmental area and nucleus accumbens potentiate lever press rates for stimulation of the medial forebrain bundle (Broekkamp, Phillips, & Cools, 1979; Broekkamp, van den Boggard, Heijnen, Rops, Cools, & van Rossum, 1976). Using the curve-shift paradigm, Jenck, Gratton, and Wise (1987) have shown that injections of morphine or the delta opioid agonist DPDPE into the ventral tegmental area produce parallel leftward shifts of the rate-frequency curve in animals lever-pressing for hypothalamic brain stimulation. The reward potentiating effect of both morphine and DPDPE are antagonized by systemic pre-treatment with naloxone (Jenck, Gratton, & Wise, 1987). Ventral tegmental area morphine injections, but not injections dorsal to it, also produce parallel leftward shifts in the rate-frequency curve in animals lever-pressing for midline

mesencephalic brain stimulation (Rompré & Wise, 1989). Microinjections of morphine or the mu opioid agonist DAGO into the nucleus accumbens produce leftward shifts of the rate-frequency curve (West & Wise, 1988).

Brain stimulation reward as a paradigm with practical advantages

If it is true that the same brain mechanisms mediate the direct rewarding effects of drugs and also their ability to facilitate brain stimulation reward, the brain stimulation reward paradigm offers the student of drug reward several methodological advantages over the self-administration and the conditioned place-preference paradigms. The paradigmatic advantages of the brain stimulation paradigm as well as some limitations of the drug self-administration and conditioned place-preference paradigms are discussed in the sections below.

Limitations of self-administration

Despite important advances in our understanding of drug reward that continue to be made with the drug self-administration paradigm, there are some paradigmatic limitations that must be outlined. The first problem is the use of simple rate measures as the dependent variable. As with brain stimulation, dependent measures based on simple response rates can be affected by factors that alter the

capacity of the animal to make an appropriate response that leads to the delivery of the drug. Drugs that affect an animal's capacity to respond can alter self-administration response patterns without necessarily reflecting "true" changes in a drug's ability to serve as a reinforcer. Sedation seen following high-dose drug self-administration is one example of "non-reward" effects that may alter an animal's self-administration response profile. Conclusions from data derived from measures based on simple response rates should therefore be made with caution (see Wise, 1989). A second limitation of self-administration paradigms is that the animal and not the experimenter controls delivery of the drug. The volume of drug intake within subjects can be affected by factors that are not under the experimenter's control and that may not be exclusively related to a drug's rewarding properties. A third problem is that of scaling reward. Since the rate of lever-pressing is under control of the effective duration (Dougherty & Pickens, 1976; Yokel & Pickens, 1974) rather than the relative intensity of each rewarding injection, there is no established way to quantify reward strength from the performance of trained animals. Acquisition of the lever-pressing response offers a measure that varies with drug dose per reward, but acquisition is variable and rates of acquisition will also vary inversely with the duration of reward associated with earned injections. Thus this method

offers no obvious way to scale the degree of effectiveness of different drugs or even different doses of the same drug. If an animal self-administers a drug five times in one hour for dose one, ten times an hour for dose two, and twenty times an hour for dose three we can say that for this drug the animal's rate of self-administration doubled as we progressed from dose one to two and doubled again from dose two to three. There is no basis, however, to arrive at any conclusions regarding the magnitude of reward between the three doses of drug in this example. We cannot conclude that dose two is twice as rewarding as dose one or that dose two is only half as rewarding as dose three. Although we can say that this drug is rewarding we cannot arrive at any conclusions about how rewarding it is.

Limitations of conditioned place preference

The conditioned place-preference paradigm also has limitations. First, absolute preferences for the drug-paired compartment are rarely obtained. Thus it is difficult to know whether the drug establishes a true preference for the drug-associated cues or rather alleviates distress associated with the non-drugged (withdrawal) condition. Second, place preferences are frequently an all or none phenomenon; graded dose-response curves are rarely obtained. Essentially, the paradigm is susceptible to

ceiling or floor effects. A third problem is the inability to scale reward in this paradigm.

Advantages of brain stimulation reward

If the assumption is valid that a common mechanism mediates the direct rewarding and reward-facilitating effects of drugs of abuse, the brain stimulation reward paradigm offers the researcher a number of advantages over the self-administration and conditioned place-preference paradigms. First, the self-stimulation behavior is extremely robust. Animals lever press thousands of times per hour for rewarding brain stimulation. Starving animals will forgo eating if given free access to rewarding brain stimulation (Routtenberg, 1964) and will cross an electrified grid floor to obtain brain stimulation in the goal box (Olds, 1958). Second, the curve-shift paradigm enables us to dissociate reward-relevant from reward-irrelevant drug effects. Third, each rate-frequency or rate-intensity curve covers the full range of effective stimulation levels, rather than being based on arbitrary parameters that might be subject to floor or ceiling effects. Indeed, the curve-shift paradigm makes the experimenter aware of the floor and ceiling for the response rates of interest, thus insuring against misinterpretations that might arise from more arbitrary choices of experimental parameters. The fourth and perhaps most important advantage

of the curve-shift rate-frequency paradigm is that it allows us to assess reward value on a ratio scale, whereas the self-administration and place-preference paradigms do not. Equal changes in the log of the stimulation frequency following a drug manipulation reflect equal changes in the perceived impact of the stimulation (Gallistel & Freyd, 1987; Miliaressis, Rompré, Laviolette, Philippe, & Coulombe, 1986; Wise & Rompré, 1989), and equal changes in the stimulation frequency are directly related to the number of impulses evoked in the reward-related fibers at the electrode tip (Gallistel, Shizgal, & Yeomans, 1981).

Effects of nicotine on the rewarding effects of brain stimulation

Some of the first reports of the effects of nicotine on brain stimulation reward have come from studies in which the aim was to investigate the effects of different cholinergic agonists on self-stimulation (Olds & Domino, 1969a; Olds & Domino, 1969b). In the two decades following these first reports few experiments on the effects of nicotine on brain stimulation have been published.

The early studies involved the use of simple lever-pressing rates as the sole dependent measure. In acute systemic treatment, nicotine has been reported by some investigators to have a bi-phasic effect on self-stimulation rates. At moderate to high doses (Olds & Domino, 1969a;

Olds & Domino, 1969b) and when pre-drug response rates were high, (Pradhan & Bowling, 1971), nicotine was found by these workers to initially depress self-stimulation. This initial response suppression was followed minutes later by increased rates of responding. No initial suppression was observed when pre-drug response rates were low (Pradhan & Bowling, 1971). In contrast, nicotine has been reported by other workers to have no effect on rate of self-stimulation when tested on a continuous reinforcement schedule but to increase rates when tested at low doses on a partial reinforcement (FR-15) schedule (Schaefer & Michael, 1986). Using two variants of a shuttle paradigm, Clarke and Kumar (1983c, 1984) reported in one instance that nicotine affected the rate of responding but did not alter the efficacy of brain stimulation reward (Clarke & Kumar, 1983c) while in a second instance nicotine was argued to potentiate brain stimulation reward (Clarke & Kumar, 1984).

More recently two abstracts dealing with the effects of nicotine on brain stimulation reward have been published. In the first, nicotine was shown to lower self-stimulation thresholds (Lyons, Bain, & Kornetsky, 1988). In the second, nicotine increased response rates for brain stimulation in rats tested on a fixed-interval schedule where stimulation could be earned once every 15 sec (FI-15 schedule) or a fixed-ratio schedule where every 15th response was rewarded (FR-15 schedule: Schaefer & Michael, 1989).

Present investigation

The purpose of the present experiment was to more fully characterize the effects of systemic nicotine on brain stimulation reward. The curve-shift paradigm was used to characterize not only the effects of nicotine on the rewarding impact of the stimulation, but also the effects of nicotine on the response capability of the animal. Stimulation sites in the mesencephalic central gray were used because stimulation in this region activates the medial forebrain bundle reward system (Boye & Rompré, unpublished data) without directly activating the dopamine fibers that are activated by nicotine itself. Finally, the animals were tested ten times at one of four doses in order to assess the possibility that tolerance or sensitization might develop to any effects of the drug on the reward mechanism.

Methods

Subjects

Twenty-four male Long-Evans rats (Charles River, Boston, MA.) with pre-operative weights between 300 and 350 g were tested. The animals were housed individually in polyethylene cages with wood chip bedding. Lighting was maintained on a 12-h light 12-h dark cycle, and animals had free access to food and water. The animals were divided into four groups of six animals each.

Surgery

Each animal was implanted with a midline mesencephalic stimulating electrode under pentobarbital anesthesia (65 mg/kg, i.p.); atropine (0.6 mg/kg, i.p.) was administered 20 min prior to the anesthetic to minimize bronchial secretions. Each electrode (Miliaressis, 1981) consisted of a plastic guide and a moveable stainless-steel wire (0.25 mm in diameter). The wire was insulated with varnish, except for the rounded tip. Flat-skull coordinates for the intended midline mesencephalic electrode placements (n=24) were -7.6 mm posterior to bregma, 0.0 mm lateral to the midline, and 6.0 mm ventral to the skull surface. Four stainless-steel screws were used to anchor the electrode assembly; the screws were wrapped with uninsulated wire and

connected to an electrical contact to serve as anodes. The entire assembly was embedded in dental cement.

Materials and apparatus

Stimulation was controlled by a microprocessor-based system (Campbell, Evans, & Gallistel, 1985). A computer program controlled delivery of stimulation via a constant current generator (Campbell, Evans, & Gallistel, 1985). Stimulation was given in 0.5-sec trains of 0.1 ms rectangular cathodal pulses. Each animal was placed in a test cage and connected to the stimulator by a flexible wire lead (Miliaressis, 1981) and a mercury commutator (Mercotac Inc, San Diego CA).

The animals were tested in 26x26 cm cages with an operant lever protruding 2.5 cm from the rear wall at a height of 7.5 cm from the floor. The operant lever controlled a microswitch connected to the current generator. Each test cage was enclosed within a larger wooden box to attenuate external noise.

Procedure

The animals were screened for self-stimulation 7 days after surgery; stimulation frequency was set at 72 hz, and current intensity was set to a low value of 200 μa. The animal received several primes of stimulation, and if it began to explore the environment (e.g. sniffing, forward

locomotion) in response to the primes it was shaped by being rewarded for closer and closer approximations to the lever-press response. If an animal did not ultimately lever-press for stimulation at this intensity the current was increased in 50 μa increments and the shaping procedure repeated until the animal started lever-pressing or until the current intensity had been raised to 800 μa. Once a current level was reached that supported a minimum of 30 lever-presses per min the animal was allowed to lever press freely for this level of stimulation. The animal was screened for one hour on each of three consecutive days. If the animal did not learn to lever-press or if the current produced aversive side-effects (e.g., gross head or body movements to one side, spinning, retreating to a corner of the test cage, shrieking, or jumping) the electrode was lowered by 0.32 mm and the animal was retested 24 h later. This procedure was continued until the animal learned to lever-press or until the electrode had been lowered to its maximum.

Following the initial screening the animals were trained to lever-press for brain stimulation across a descending range of stimulation frequencies. Stimulation parameters were held constant for periods of 50-s; five 0.5-s "priming" stimulations were administered at the beginning of each 0.5-s trial. There was a half-second pause between trials. Each series of trials began with the highest frequency of stimulation for a given animal and stimulation

frequency was reduced by 0.05 log units (approximately 12%) for successive trials. The initial stimulation frequency was determined on an individual basis; it was set at one step higher than the average frequency that produced asymptotic (maximal) responding on the previous day. Stimulation frequency was stepped down in equal log units until three frequencies were tested with no responding. Rate of responding was measured at each stimulation frequency; the function relating response rate to stimulation frequency (rate-frequency function) was the basis for determinations of reward threshold and performance asymptote. Eight rate-frequency functions were determined daily, the end of one marking the start of the next. During the training period, the stimulation intensity (another contribution to the stimulation "dose") was adjusted to bring each animal's frequency threshold (the minimal stimulation necessary to maintain responding) within the range of 40-60Hz. When frequency thresholds varied by less than 10% over three consecutive days, an animal was deemed ready for drug testing.

Drug testing was conducted daily for 10 days with each group receiving one of the four doses of nicotine. The drug tests were preceded by a vehicle test (day 0). Each drug and vehicle test began with a baseline test in which each animal was tested such that a total of three rate-frequency functions were determined (10-12 min per function). In the

baseline condition the first rate-frequency function was considered unreliable and not used in the analysis. Following the baseline condition animals were removed from their test cages and injected with the drug or vehicle. Immediately following treatment the animals were returned to their test cages and tested such that five more rate-frequency functions could be determined (15 min per function).

Histology

At the end of the experiment the animals were anesthetized with an injection of chloral hydrate (400 mg/kg i.p.). Next, a 1.5 mA anodal current was passed through each animal's stimulating electrode. The animals were then perfused with physiological saline followed by a formalin-cyanide solution (10% formalin, 3% potassium ferrocyanide, 3% potassium ferricyanide, and 0.5% trichloroacetic acid). Each animal was then decorticated and the brain was stored in 10% formalin. The brains were placed in the formalin solution for a minimum of 7 days and then in a solution consisting of 10% formalin and 30% sucrose for 24-48 hours prior to histological sectioning. The brains were then frozen and sliced in 40 µm sections. Those sections containing the electrode track were mounted and stained with thionin for histological determination of electrode placements.

Estimate of self-stimulation threshold

The threshold frequency (Theta-0) was estimated from the rate-frequency functions as follows; the pulse-frequencies required to sustain responding at 20, 30, 40, 50, and 60% of asymptotic responding were estimated by graphic interpolation and the threshold for lever-pressing was defined as the point where a line of best fit through these points crossed the abscissa. This estimate of threshold represents one attempt to identify the lowest level of stimulation frequency that has a reinforcing impact for the animal (Coulombe & Miliaressis, 1987; Miliaressis, Rompré, Laviolette, Philippe, & Coulombe, 1986) and that does not rely on a single arbitrarily chosen point along the rate-frequency function as the threshold for self-stimulation.

Drug

Nicotine tartrate was administered in dosages of 0.05, 0.1, 0.2, or 0.4 mg/kg (dose was calculated as the free base); independent groups of animals (n=6 per group) each received one dose. The drug was dissolved in sterile physiological saline, prepared daily prior to testing.

Results

Nicotine caused parallel leftward shifts of the rate-frequency functions. Typical rate-frequency curves for baseline conditions and for each of the four nicotine doses are shown in Figure 1. Even at the 0.40 mg/kg dose, nicotine produced a parallel leftward shift without altering asymptotic response rates. Because nicotine caused parallel shifts in the functions, effects of nicotine on reward thresholds were the same regardless of whether the Theta-0 criterion or any of a number of alternative threshold criteria were used.

Nicotine was effective for approximately 45 minutes after these injections. Threshold and asymptote values are shown in Figure 2 for each of the five repeated rate-frequency functions averaged across days 3 to 10; values from the first two days were not included because the animals showed signs of ataxia and unstable thresholds on these but not subsequent days (see below). A repeated measures analysis of variance (ANOVA) revealed that thresholds varied significantly as a function of time after injection ($F[4,80]=32.47$, $p<0.01$). The threshold lowering effects of nicotine began to wane by the fourth rate frequency curve (60 min. post-injection). Nicotine had more complex effects on asymptotes, as revealed by Day X Time ($F[28,560]=2.03$, $p<0.01$) and Dose X Time ($F[12,80]=12.076$, $p<0.01$) interactions. The low doses of nicotine increased

Figure 1. Rate of bar-pressing as a function of stimulation frequency under baseline (open circles) and nicotine (filled squares) conditions. Data are from a single animal in each dose condition; data in the nicotine condition were taken in the second rate-frequency determination, approximately 30 min after injection.

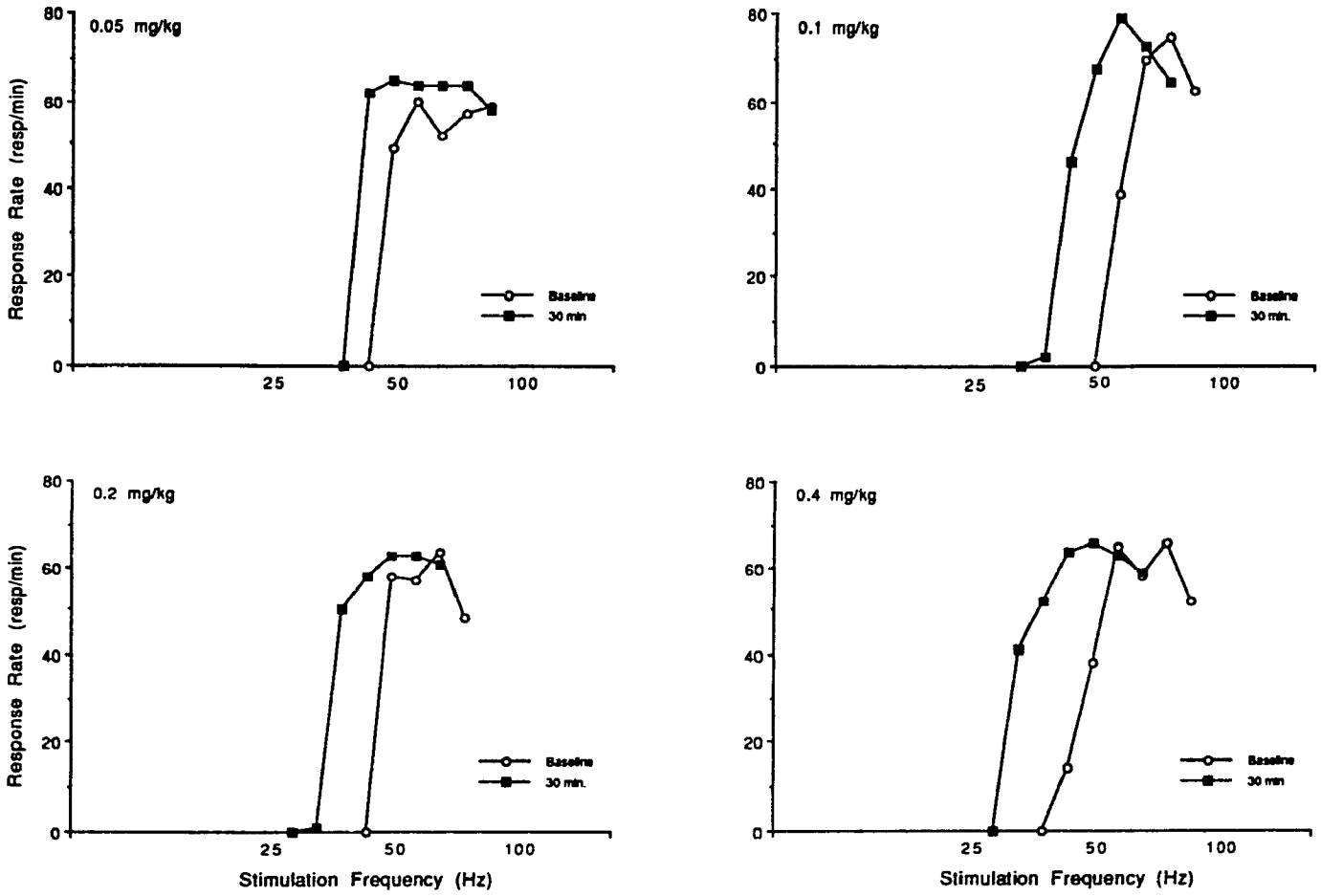
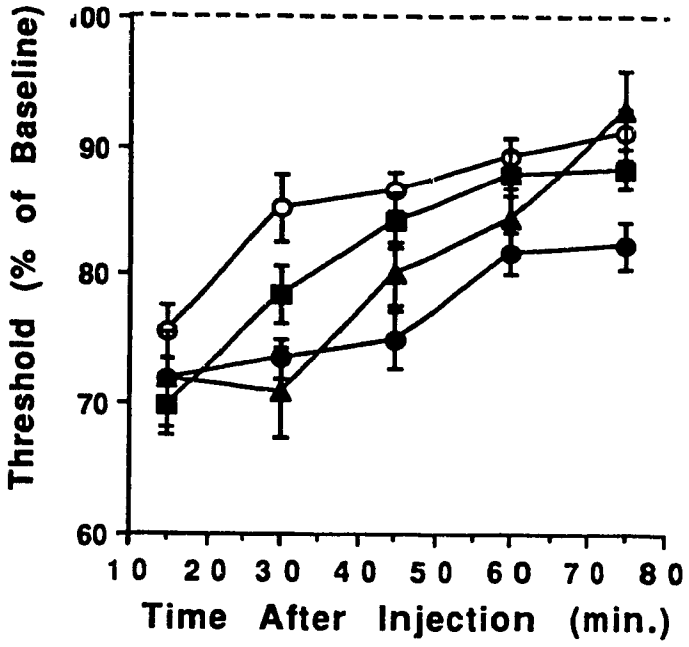
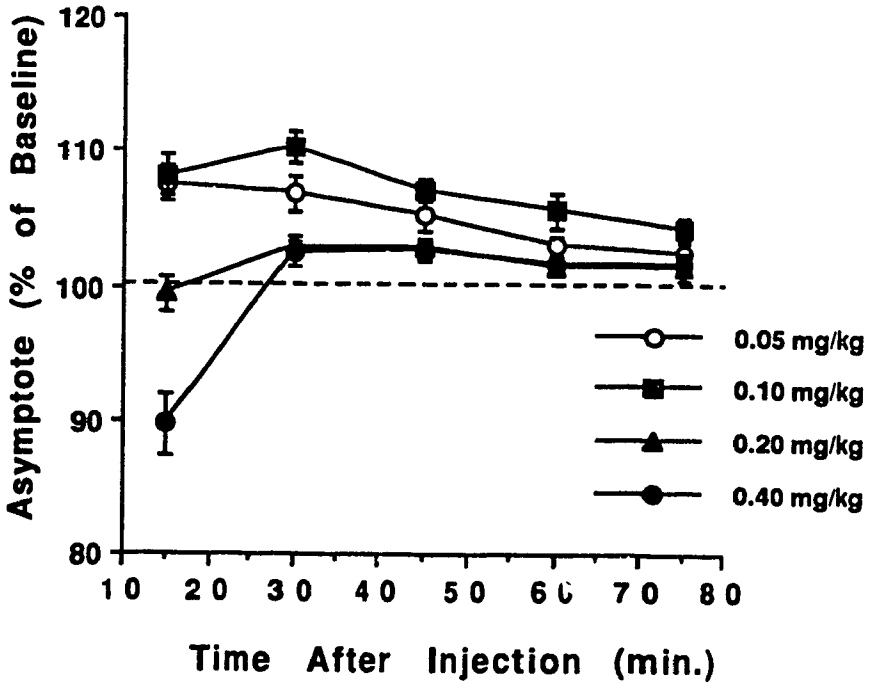

0.05 mg/kg
0.1 mg/kg
0.2 mg/kg
0.4 mg/kg
Response Rate (resp/min)
Stimulation Frequency (Hz)
Baseline
30 min
30 min.
0
20
40
60
80
25
50
100

Figure 2. Mean threshold and asymptote values (expressed as percentage of pre-injection baselines) as a function of dose and time after nicotine injection.


Threshold (% of Baseline)
100
90
80
70
60
10 20 30 40 50 60 70 80
Time After Injection (min.)


Asymptote (% of Baseline)
120
110
100
90
80
10 20 30 40 50 60 70 80
Time After Injection (min.)
0.05 mg/kg
0.10 mg/kg
0.20 mg/kg
0.40 mg/kg

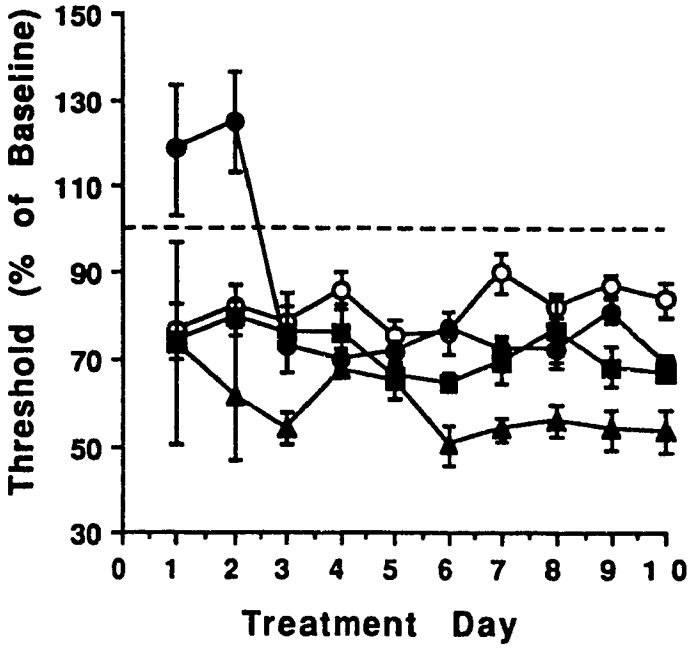
asymptotic responding; this effect was statistically significant in the first two rate-frequency determinations. The high dose decreased asymptotes during the first determination and had no further significant effect on asymptote. The high-dose suppression of asymptote was correlated with frank ataxia, which was particularly prominent the first two days of testing.

It was apparent from the time-course data that the effectiveness of nicotine was significantly reduced by the fourth threshold determination, so comparisons across days were made on the basis of the means of the first three determinations. This is reflected in the fact that while there were high-dose elevations of threshold and depressions of asymptote on the first two days of testing, both thresholds and the asymptotes were stable for the remaining 8 days of testing. While there were significant effects of days in both the threshold and the asymptote data when considered over the full 10 days of testing ($F[9,180]=3.83$, $p<0.01$ and $F[9,180]=7.37$, $p<0.01$, respectively), there were no significant effects of days when the data for the last 8 days were analyzed separately ($F[7,140]=1.13$, $p>0.05$ and $F[7,140]=1.96$, $p>0.05$, respectively). Both the elevations of threshold and the depressions of asymptote were associated with periods of obvious ataxia.

There were no significant differences between the effects of nicotine doses on either thresholds or asymptotes

as reflected in the ANOVAs for either days 1-10 or 3-10 (Fig. 3). While thresholds under nicotine were significantly different from thresholds under saline (the pre-nicotine saline data were compared to the effects of nicotine on day 3 and on day 10; $t=11.48$, $p<0.01$; $t=6.79$, $p<0.01$, respectively), thresholds under various doses of nicotine did not differ significantly as reflected in an ANOVA. While the differences between doses were not large and were not statistically significant as reflected in the ANOVAs, the effects of 0.2 mg/kg were consistently superior to the effects of the two lower doses and the one higher dose (binomial sign test, $p<0.01$; Fig. 4). All electrode tips were located in the caudal aspect of the mesencephalic central gray region within the area of the dorsal raphe nucleus (Fig. 5).

Figure 3. Mean threshold and asymptote values (expressed as a percentage of pre-injection baselines) across days of testing.


Threshold (% of Baseline)
150
130
110
90
70
50
30
0 1 2 3 4 5 6 7 8 9 10
Treatment Day

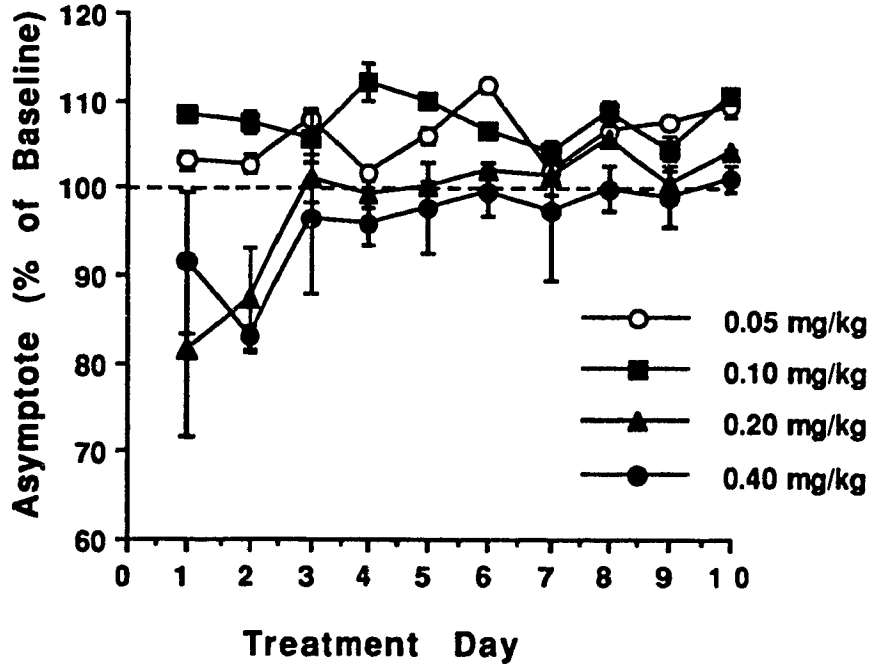
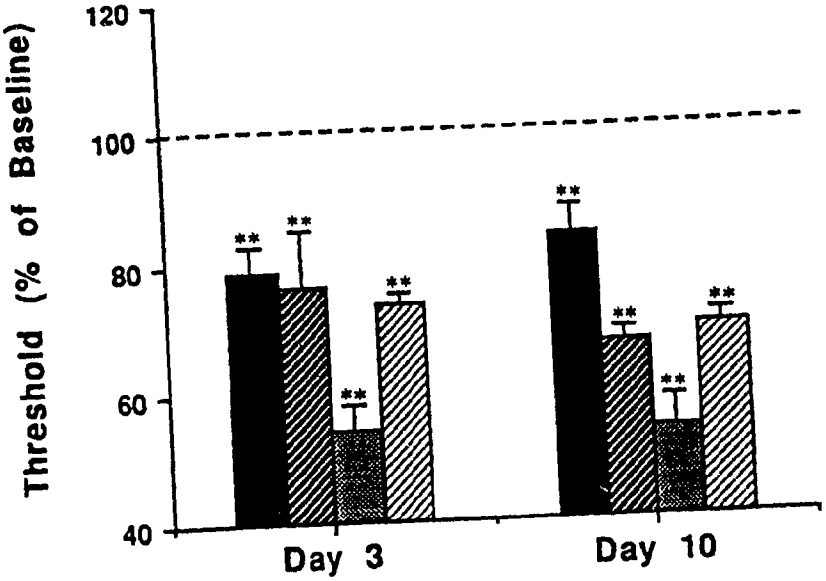

Asymptote (% of Baseline)
120
110
100
90
80
70
60
0 1 2 3 4 5 6 7 8 9 10
Treatment Day
0.05 mg/kg
0.10 mg/kg
0.20 mg/kg
0.40 mg/kg

Figure 4. Mean threshold and asymptote values across the first three rate-frequency curves for test days 3 and 10 (expressed as a percentage of pre-injection baselines). Asterisks indicate statistical significance of differences between mean values for drug and vehicle comparisons. (*$p<0.05$, **$p<0.01$).


Threshold (% of Baseline)
120
100
80
60
40
**
Day 3
Day 10

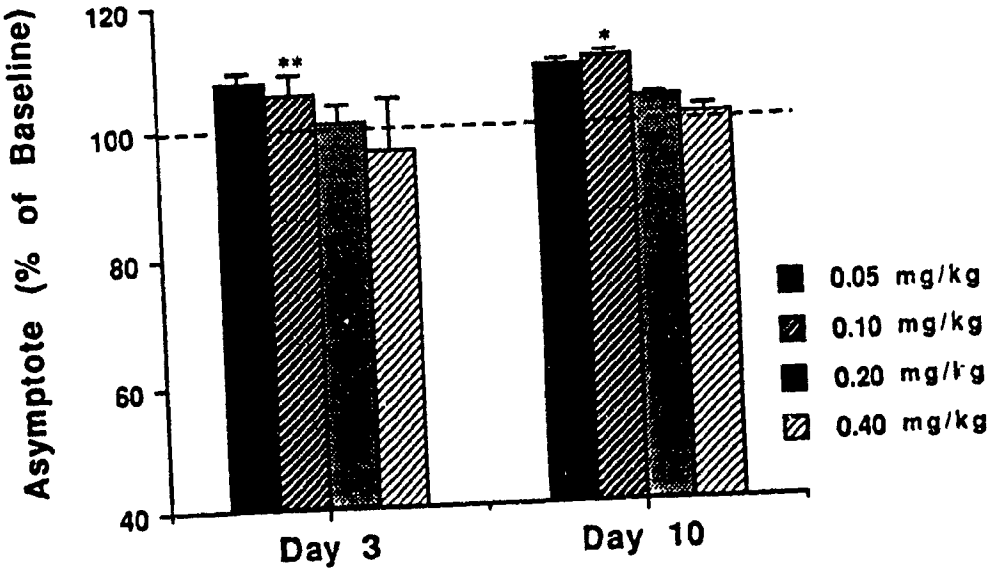
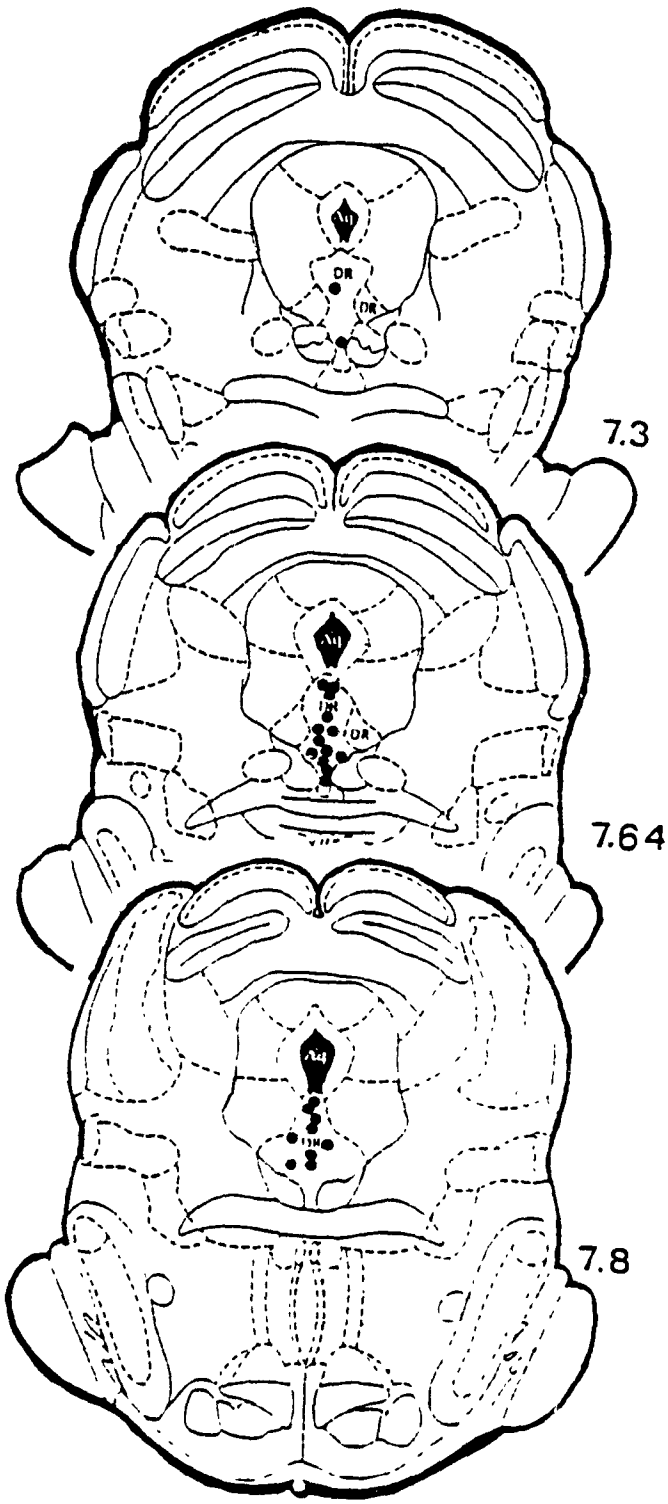

Asymptote (% of Baseline)
120
100
80
60
40
**
*
Day 3
Day 10
0.05 mg/kg
0.10 mg/kg
0.20 mg/kg
0.40 mg/kg

Figure 5. Histological localization of electrode tip. Reconstructions are based on the stereotaxic atlas of Paxinos and Watson (1986). The number beside each brain slice represents the distance posterior to bregma.


DR
DR
7.3
DR
7.64
7.8

Discussion

The present study confirms that nicotine shares with other habit-forming drugs the ability to potentiate the rewarding impact of midline mesencephalic brain stimulation. At each of the four doses tested nicotine produced a parallel leftward shift of the rate-frequency curve; that is, nicotine reduced the "dose" of stimulation needed to sustain responding at a given level. Thus the effects of nicotine summated with the rewarding effects of the brain stimulation.

Ataxia was evident in animals receiving the high dose of nicotine on the first two test days. This high dose effect was associated with increased self-stimulation thresholds and depressed asymptotic response rates. Tolerance developed to this high dose sedative effect of nicotine with subsequent treatments. From the third day nicotine decreased thresholds and the magnitude of the threshold lowering effect of nicotine did not change from one test to the next; there was neither tolerance nor sensitization to the reward potentiating effects of nicotine from the third day onward.

The failure to observe sensitization to the threshold-lowering effects of nicotine is at odds with a prediction of the psychomotor stimulant theory of Wise and Bozarth (1987). The psychomotor stimulant theory offers two relevant postulates. The first is that habit-forming drugs have both

locomotor-potentiating and reward-potentiating effects. The second is that common brain circuitry subserves both the locomotor activating and the reward potentiating effects of habit-forming drugs (Wise, 1988; Wise & Bozarth, 1987).

The theory thus predicts that treatments known to increase the locomotor-potentiating effects should also increase the reward-potentiating effects. However, while repeated injections of nicotine have been shown to sensitize animals to the locomotor-activating effects of the drug (Clarke & Kumar, 1983a; Clarke & Kumar, 1983b; Ksir, Hakan, Hall, & Kellar, 1985), repeated injections of nicotine caused no such sensitization to the reward-facilitating effects of nicotine. One possible interpretation is that the locomotor-activating and the reward-potentiating effects of habit-forming drugs are mediated by separate systems rather than by a homologous neural system. Separate branches of the dopamine system could, for example, mediate the two nicotine effects. While it is true that habit-forming drugs potentiate both locomotion and reward, the mechanism by which sensitization emerges may involve the neural circuitry mediating locomotion but not reward.

Part of the power of the rate-frequency variant of the curve-shift paradigm is the fact that it offers a ratio scale with which to quantify and compare the reward-potentiating, and, if the present analysis is correct, the rewarding effects of different drugs and different drug

doses. It is much more difficult to quantify and compare the rewarding effects of different drugs using either the self-administration or the place-preference paradigms. A comparison of the effects of nicotine obtained in the present experiment with those of systemic amphetamine obtained by other researchers illustrates the power of the curve-shift rate-frequency paradigm.

The maximum parallel leftward shift with nicotine in the present experiment was approximately 0.2 log units. The highest dose of nicotine caused less than this maximal shift. Systemic amphetamine treatment produces maximal parallel shifts of 0.3 log units at a dose of 1 mg/kg (while higher doses shift the curve even further, the shifts become non-parallel at this point: Colle & Wise, 1988; Gallistel & Karras, 1987). A 0.3 log unit leftward shift represents a doubling of the efficacy of the brain stimulation (see Gallistel & Freyd, 1987). It appears therefore that amphetamine can potentiate the rewarding effects of brain stimulation to a greater degree than can nicotine.

The maximum threshold lowering effect of nicotine was obtained with a 0.20 mg/kg s.c. dose. The threshold lowering effect of nicotine was weaker in animals treated with 0.40 mg/kg. Despite the weaker threshold lowering effect of the 0.40 mg/kg dose, the shifts of the rate-frequency curves in these animals were still parallel. In contrast to this, animals treated systemically with high

doses of amphetamine present a different type of curve-shift profile if tested immediately following the drug injection. Systemic amphetamine injections beyond a dose of 1 mg/kg result in reduced response rates for high stimulation frequencies and increased responding for low frequencies (see Colle & Wise, 1988 for illustration; Gallistel & Karras, 1984). The shift of the rate-frequency curves obtained following high dose amphetamine are no longer parallel. Under high dose amphetamine, animals fail to cease responding even when the stimulation generator is turned off such that continued responding goes unrewarded (Gallistel & Freyd, 1987; Gallistel & Karras, 1984).

The high dose effects of systemic nicotine and amphetamine on brain stimulation reward using the curve-shift paradigm suggest that there are very different limits to the reward potentiating effects of these drugs. This suggestion is consistent with known differences in the mechanisms by which nicotine and amphetamine influence the dopamine system. Nicotine potentiates ventral tegmental dopamine cell firing (Calabresi, Lacey, & North, 1989; Grenhoff, Aston-Jones, & Svensson, 1986; Mereu, Yoon, Boi, Gessa, Naes, & Westfall, 1987). In contrast, amphetamine causes dopamine release (Carlsson, 1970; Heikkila, Orlansky, & Cohen, 1975) and does so even if dopamine cell firing is blocked with gamma butyrolactone. Interestingly, the extent to which a cell can fire is limited by the intensity and

duration of the depolarizing intracellular current applied to the cell. While application of low constant depolarizing current increases cell firing, at higher depolarizing currents the same cell enters into a state of depolarization inactivation (Grace & Bunney, 1986). The ability of nicotine to cause dopamine release in the nucleus accumbens is limited at least in part by the capacity of the ventral tegmental area neurons to conduct neural impulses. This factor may explain why in the present experiment the 0.20 mg/kg dose was more effective in lowering self-stimulation thresholds than the 0.40 mg/kg dose. Data from measures of extracellular dopamine release into the nucleus accumbens using the technique of in vivo microdialysis demonstrate that amphetamine (1 mg/kg, s.c.) produces a 1000% increase in dopamine release while nicotine (0.6 mg/kg, s.c.) produces only a 220% increase. While amphetamine "floods" the dopamine synapse, nicotine's ability to do so appears limited by its mechanism of action. The degree to which nicotine and amphetamine potentiate dopamine release predicts the degree to which each drug can potentiate the rewarding impact of brain stimulation.

It has been demonstrated in the present experiment that nicotine like a variety of other habit-forming drugs, has the ability to potentiate the rewarding impact of brain stimulation. These data support the hypothesis that nicotine may be functionally involved in the maintenance of

the tobacco habit.

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