INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

UMI

A Bell & Howell Information Company
300 North Zeeb Road, Ann Arbor MI 48106-1346 USA
313/761-4700 800/521-0600

Nicotine Withdrawal Causes Transient Elevations in Brain Stimulation Reward Thresholds

Mark A. Legault

A Thesis

in

The Department

of

Psychology

Presented in Partial Fulfillment of the requirements

for the degree of Master of Arts at

Concordia University

Montreal, Quebec, Canada

June 1995

ABSTRACT

Nicotine Withdrawal Causes Transient Elevations in Brain Stimulation Reward Thresholds

Mark A. Legault

Nicotine withdrawal is associated with dysphoria and depression in humans. In rats, withdrawal from amphetamine, cocaine, or morphine attenuates the motivation to respond for rewarding electrical brain stimulation. It has been proposed that such attenuation of brain stimulation reward reflects opponent-process depression of brain reward circuitry and underlies the dysphoric symptoms of drug withdrawal in humans. In the present study the rate-frequency variant of the curve-shift paradigm was used to examine the effects of nicotine withdrawal on brain stimulation reward. Animals were injected with either saline, 0.5 or 1.5 mg/kg of nicotine once on the first day of treatment then twice daily for the next 13 days (equaling a dose of 1.0 or 3.0 mg/kg/day) and on the morning of the final day (day 15). Brain stimulation reward thresholds were then determined periodically for 24 hours. Withdrawal from 3.0 mg/kg/day of nicotine increased the frequency required to sustain responding to approximately 132% of baseline. This increase was evident 8 hours after the last nicotine injection and remained so for 24 hours. Nicotine withdrawal did not effect maximal response rates. There was no effect of withdrawal from 1.0 mg/kg/day of nicotine or from daily saline. The present study provides evidence that nicotine withdrawal attenuates brain stimulation reward in a manner similar to amphetamine and morphine withdrawal. This evidence supports the view that depression of the reward system is a withdrawal symptom common to several classes of drugs.

Acknowledgments

The people who have contributed to this thesis are almost too numerous to mention. I have profited in one way or another from almost everyone I have worked with at the CSBN.

First let me thank my supervisor, Roy Wise, for guidance, patience, and support throughout the course of this thesis. What I have learned from his anecdotes and experiences is too vast to put into words. Thanks for giving me the freedom to succeed or fail on my own. I hope, of course, that I have succeeded so far.

Thanks to those in the Wise lab. Those who are still here, Kath, Liz, and Pat are still going to have to put up with for a while longer. Those who are gone, Bill (and Fay), Dany, Kira, and Darragh are certainly not forgotten. Zvani Rossetti deserves a special thank you for his insightful conversations and especially for being patient enough to tolerate my bad temper and still remain my friend. And thanks to Adriana for friendship and wonderful Italian cuisine.

Thanks also to those who have been my office mates and friends. Kim, Marylin, Francis, Sylvie (where ever she is). I guess we'll still be together a bit longer.

A special thanks to Mom and Gord for getting me through the undergrad years and then leaving the province. I miss you guys.

Finally, thanks to Martina for coming along at just the right time and giving me the incentive (a swift kick in the butt) to get this wrapped up. Stick around Sunshine, I'm not finished yet.

Table of Contents

List of Figures

Nicotine is the primary pharmacologically active constituent of the tobacco plant (Clarke, 1987; Henningfield, 1984; Hennigfield & Goldberg, 1988). Like the psychomotor stimulants cocaine and amphetamine and the opiates morphine and heroin, nicotine establishes and maintains self-administration habits in humans. The establishment of self-administration habits in drug-naive humans and animals is thought to involve the activation of brain circuitry that subserves natural rewards (Stein & Wise, 1973; Wise, 1989; Wise & Rompre, 1988). It remains unclear to what extent the habit-forming properties of these drugs are affected by prolonged drug self-administration. Prolonged or repeated drug administration causes physiological adaptations resulting in a drug-dependent state in which an organism no longer functions normally without the drug (Collier, 1968; Himmelsbach, 1943; Limdsmith, 1947). Drug-dependence is, therefore, identified by the emergence of a withdrawal syndrome when drug administration is discontinued. Alleviation or avoidance of the withdrawal syndrome may augment the inherently rewarding properties of these drugs and contribute to their habit-forming potential (Himmelsbach, 1943; Solomon & Corbit, 1974). Although drug-reward and drug-dependence have been thought to be function of anatomically distinct brain systems (Bozarth & Wise, 1984; Deneau, Yanagita, Seevers, 1969) recent attention has focused on the idea that a common brain system may be involved in some of the dependence producing and rewarding properties of habit-forming drugs (Dackis & Gold, 1985; Gawin & Ellinwood, 1989; Koob, Stinus, Le Moal, & Bloom, 1989; Rossetti, Hmaidan, & Gessa, 1992).

I. Drug Reward

A. Reward & Positive Reinforcement

It is thought that the brain circuitry activated by rewarding drugs is the same circuitry as mediates the incentive properties of such biologically significant behaviors as exploratory locomotion, eating, and copulation (Wise, 1989; Wise & Rompre, 1989).

Rewarding drugs activate this circuitry directly rather than through the stimulation of peripheral sensory neurons; it is this property that is thought to underlie the establishment of self-administration habits. The direct activation of brain reward circuitry produces complex motivational and behavioral effects; rewarding drugs reinforce behaviors through both operant and Pavlovian mechanisms and also proactively energize, or prime, behaviors (Wise, 1989). The reward relevant properties of drugs are assessed in several distinct behavioral paradigms (Wise, 1989).

Two paradigms that are used to assess drug reinforcement are the self-administration paradigm and the conditioned place preference paradigm. The drug self-administration paradigm is used to assess a drug's ability to serve as an operant reinforcer. Operant reinforcement concerns the learning of associations between a behavior and its consequences. In this paradigm drug injections are made contingent on the performance of some arbitrary behavior (usually the depression of a lever); if a drug increases the occurrence of that behavior it is a reinforcer. The conditioned place preference paradigm is used to evaluate a drug's effectiveness in reinforcing associations between stimuli and is not contingent on behavior; in this case the drug injection is given in a response-independent manner in association with a distinct portion of the animal's environment. The animal is then tested in a drug free state. If the time spent in the drug-associated environment increases then reinforcement of drug-place associations is inferred.

In addition to establishing self-administration and conditioned place preferences rewarding drugs also have incentive properties that are not adequately defined by either operant or Pavlovian paradigms. These properties are reflected in the ability of rewarding drugs to energize or "prime" behaviors. Two paradigms that are used to asses this energizing property are the reinstatement paradigm and the brain stimulation reward paradigm. In the reinstatement paradigm (Gerber & Stretch, 1975; Stewart & de Wit, 1987) animals are trained to lever-press for intravenous drug injections. The drug is then withheld and lever-pressing is extinguished. Test drugs are then administered

noncontingently and nonreinforced lever-pressing is observed. If the test drug reinstates lever-pressing, then drug reward is inferred. In this paradigm the term reinforcement inadequately describes the reinstatement of lever-pressing; whereas lever-pressing is initially established by operant reinforcement, the test drug is administered in the Pavlovian (response-independent) manner and the subsequent lever-pressing occurs independent of further operant reinforcement.

Rewarding drugs also potentiate electrical brain stimulation reward (Wise & Rompre, 1989). Electrical stimulation of the medial forebrain bundle (MFB) can be powerfully rewarding; it is readily self-administered (Rompre & Miliaressis 1985; Olds & Milner, 1954) and establishes conditioned place preferences (Ettenberg & Duvauchell, 1988). Stimulation of the MFB also produces a proactive priming effect that influences the effort with which an animal will work to gain the opportunity to lever-press for further stimulation (Gallistel, Stellar & Bubis, 1974). The priming effect of MFB stimulation is unconditioned and is not contingent on responding (Gallistel et al.,, 1974). The general term reward is used to describe the confounded reinforcing and priming effects of electrical brain stimulation.

Most habit-forming drugs increase lever-pressing rates for brain stimulation reward (Bush, Bush, Miller, & Reid, 1976; Crow, 1970; Gallistel & Karras, 1984; Pradhan & Bowling, 1971). However, the measure of simple response rate is of limited value in that it does not permit the distinction between drug-induced changes in performance capability, arousal, or reward (Valenstein, 1964). In response to this limitation researchers have adopted a variety of reward threshold measures (Edmonds & Gallistel, 1974; Kornetsky & Esposito, 1981; Miliaresis, Rompre, Laviolette, Philippe, & Coulombe, 1986). The best indication that a drug potentiates brain stimulation reward is that it lowers reward threshold. The ability of drugs to potentiate brain stimulation reward does not qualify as reinforcement in either the operant or Pavlovian sense. In the brain stimulation reward paradigm, lever-pressing is maintained by operant reinforcement

but the drug is delivered in the Pavlovian manner and the drug effect on brain stimulation reward is unconditioned.

B. Brain Reward Circuitry

Recently, the study of brain reward circuitry has focused predominantly on the dopamine neurons of the ventral mesencephalon and their ascending projections to limbic and cortical structures. Of central interest are the dopaminergic projections from the ventral tegmental area to the nucleus accumbens (NAS) of the ventral striatum. The VTA is located in the ventromedial mesencephalon. Extending laterally from the VTA in a contiguous band of dopamine cells is the substantia nigra pars compacta and pars lateralis (SN) (Dahlstrom & Fuxe, 1964; Fallon & Moore, 1978;). Projections from the VTA and SN to forebrain regions are topographically organized (Fallon & Moore, 1978; Fallon, 1988). Axons of the medial VTA ascend the medial forebrain bundle and terminate in limbic and cortical structures including the olfactory tubercle, lateral septum, nucleus accumbens and prefrontal cortex; the lateral neurons of the SN project primarily to the caudate nucleus and putamen (Dahlstrom & Fuxe, 1964; Fallon & Moore, 1978; Fallon, 1988).

Both rewarding drugs and brain stimulation have been important tools in characterizing the pharmacology and anatomy of brain reward circuitry. A common property of these rewards is the ability to increase extracellular dopamine in the NAS. Cocaine and amphetamine increase extracellular dopamine by blocking reuptake of released dopamine (Heikkila, Orlansky, & Cohen, 1975). In addition, amphetamine causes dopamine to be released directly from nerve terminals (Axelrod, 1970; Carlsson, 1970). Opiates elevate extracellular dopamine by increasing the firing of dopamine neurons through suppression of inhibitory GABAerigc neurons (North, 1992). Electrical stimulation of the MFB or VTA also elevates NAS dopamine (Fiorino, Coury, Fibiger, & Phillips, 1993; Nakahara, Fuchikami, Ozaki, Iwasaki, & Nagatsu, 1992). Self-

administration of psychomotor stimulants (Pettit and Justice, 1989; Pettit and Justice, 1991; Wise & Leeb, 1994; Wise, Newton, Leeb, Burnette, Pocock, & Justice, 1994), heroin (Rivest, Leeb, Leone, & Wise, 1993; Pocock, Leeb, & Wise, 1994), and electrical brain stimulation (Bauco, Rivest, Wang, & Wise, 1993; Fiorino, Coury, Fibiger, & Phillips, 1993; Nakahara, Fuchikami, Ozaki, Iwasaki, & Nagatsu, 1992; Phillips, Coury, Fiorino, LePiane, Brown, & Fibiger, 1992; Rivest, Bauco, Wang, Wise, 1993) are all correlated with elevations in NAS dopamine.

Brain Stimulation Reward

The importance of dopaminergic neurotransmission in brain stimulation reward is evident from the effects of dopamine antagonists (neuroleptics) on self-administration of electrical brain stimulation. Following neuroleptic treatment lever-pressing rates (Fenton, & Liebman, 1982; Franklin & McCoy, 1979; Fouriezos, & Wise, 1976; Fouriezos, Hansson, & Wise, 1978) or alleyway running speed (Gallistel. Boytim, Gomita, & Klebanoff, 1982; Fouriezos, Hansson, & Wise, 1978; Franklin, 1978) are normal early in test sessions but decrease and eventually cease as testing continues. Neuroleptics also increase brain stimulation reward thresholds (Franklin, 1978; Gallistel, & Freyd, 1987; Gallistel, & Karras, 1984; Huston-Lyons, Sarkar, & Kornetsky, 1993; Miliaressis et al., 1986). Neuroleptic-induced changes in response rates, running speed, and reward threshold mirror the effect of decreasing stimulation intensity suggesting that blockade of dopaminergic transmission reduces the rewarding impact of the stimulation (Fouriezos et al., 1978; Gallistel et al., 1982; Miliaressis et al., 1986).

Dopamine-specific lesions or central injections of neuroleptics provide further evidence that dopaminergic neurotransmission is important for brain stimulation reward. Destruction of midbrain dopamine neurons by injection of 6-OHDA into the lateral hypothalamus attenuates electrical self-stimulation of the VTA (Phillips & Fibiger, 1978; Fibiger, LePiane, Jakubovic, & Phillips, 1987). Lateral hypothalamic self-stimulation is

reduced by 6-OHDA lesions of the VTA (Koob, Fray, & Iversen, 1978). However, because these lesions deplete DA in the NAS, olfactory tubercle, and striatum it can not be determined which specific DA terminal regions are important for brain stimulation reward. Attempts to localize DA terminal regions involved in brain stimulation reward have employed intracranial microinjections of neuroleptics. Neuroleptic injections into the NAS but not into the striatum, medial prefrontal cortex, or amygdala, reduce self-stimulation rates (Mogenson, Takigawa, Robertson, & Wu, 1979) and elevate reward thresholds (Stellar and Corbett, 1989).

Psychomotor Stimulant Reward

The role of dopamine in drug reward was initially inferred from the observation that neuroleptics altered self-administration of cocaine or amphetamine. Low doses of neuroleptics increase self-administration of cocaine (de Wit & Wise, 1977; Ettenberg, Pettit, Bloom & Koob, 1982; Herling & Woods, 1980; Wilson & Schuster, 1972) and amphetamine (Risner & Jones, 1976; Wilson & Schuster, 1972; Yokel & Wise, 1975, 1976), whereas high doses cause a brief increase followed by cessation of self-administration (de Wit & Wise, 1977; Wilson & Schuster, 1972; Yokel & Wise 1975, 1976). Low doses of neuroleptics are thought to increase drug self-administration by attenuating reward such that the animal is required to self-administer more drug in order to achieve satiety (Yokel & Wise, 1975; Wise 1987). Cessation of self-administration is thought to reflect the complete blockade of drug reward (Yokel & Wise, 1975).

Dopaminergic neurotransmission in the NAS appears to be critical for cocaine and amphetamine reward. Intravenous self-administration of cocaine and amphetamine is attenuated by disruption of dopaminergic neurotransmission in the NAS. Cocaine self-administration is blocked by microinjections of spiroperidol into the NAS (Phillips, Broekkamp, & Fibiger, 1983) and self-administration of cocaine and amphetamine is disrupted by 6-OHDA lesions of the NAS (Lyness, Friedel, & Moore, 1979; Roberts,

Corcoran, & Fibiger, 1977; Roberts, Koob, Klonoff, & Fibiger, 1980). Cocaine self-administration is also blocked by 6-OHDA lesions of the dopamine cell bodies in the VTA (Roberts & Koob, 1982). Infusion of 6-OHDA into other dopamine terminal fields fails to reduce psychomotor stimulant self-administration. Lesions of the medial prefrontal cortex either not affect (Martin-Iverson, Szostak, Fibiger, 1986) or increase (Schenk, Horger, Perltier, Shelton, 1991) cocaine self-administration. Destruction of the dopamine terminals in the amygdala may increase cocaine (McGregor, Baker & Roberts, 1994) and amphetamine (Deminiere, Taghzouti, Tassin, Le Moal & Simon, 1988) self-administration. Moreover, kainic acid lesions of the NAS, which destroy perikarya while leaving fibers of passage intact, reduce cocaine self-administration (Zito, Vickers, & Roberts, 1985). Finally, amphetamine is self-administered directly into the NAS (Hoebel, Monaco, Hernandez, Ausili, Stanley, & Lenard, 1983).

Conditioned place preferences established by cocaine and amphetamine also depend on NAS dopamine. Intra-accumbens microinjections of amphetamine (Carr & White, 1983, 1986) or cocaine (Aulisi & Hoebel, 1983) establish conditioned place preferences whereas injections of amphetamine into the dopamine terminal fields of the caudate nucleus, amygdala or frontal cortex do not (Carr & White, 1983, 1986). Dopamine antagonists block both cocaine (Mackey & van der Kooy, 1985; Morency & Beninger, 1986) and amphetamine (Mackey & van der Kooy, 1985; Spyraki, Fibiger & Phillips, 1982) conditioned place preferences. The establishment of amphetamine conditioned place preferences can also be prevented by 6-OHDA lesions of the NAS (Spyraki, Fibiger & Phillips, 1982).

In addition to establishing self-administration and conditioned place preferences both cocaine (Frank, Martz, & Pommering, 1988; Kornetsky, & Esposito, 1981; Wise et al., 1992) and amphetamine (Esposito, Perry, & Kornetsky, 1980; Gallistel, & Freyd, 1987; Gallistel, & Karras; Schaefer, & Michael, 1988) lower brain stimulation reward thresholds. Injections of amphetamine into the NAS potentiates brain stimulation reward

(Colle & Wise, 1988). The effect of intra-accumbens amphetamine is consistent with the notion that the rewarding actions of amphetamine and brain stimulation occur through increasing NAS dopamine.

Opiate Reward

Dopaminergic neurotransmission is also important for opiate reward. The acquisition of heroin self-administration is prevented by 6-OHDA lesions of the VTA (Bozarth & Wise, 1985) and established heroin self-administration is reduced by high doses of neuroleptics (Gerber & Wise, 1989; Ettenberg, Petit, Bloom, & Koob, 1982; Nakajima & Wise, 1987). High doses of neuroleptics (Bozarth & Wise, 1981; Spyraki, Fibiger & Philips, 1983) or 6-OHDA lesions of the NAS (Spyraki, Fibiger, & Philips, 1983) also prevent the establishment of conditioned place preferences with heroin.

The VTA is a site of opiate reward. Microinjections of morphine (Bozarth & Wise, 1981; Welzl, Kuhn, & Huston, 1989), the selective u receptor agonist [d-Ala2, N-Me-Phe4-Gly5-ol]-enkephalin (DAMGO), or the d agonist [d-Pen2, d-Pen5]-enkephalin (DPDPE) (Devine, & Wise, 1994) are self-administered directly into the VTA. Microinjections of morphine (Bozarth, 1987; Phillips, & LePiane, 1980) or [D-ala2]-met5 -enkephalinamide (D-Ala) (Phillips, LePiane, & Fibiger, 1983) into the VTA also establish conditioned place preferences. Morphine, however, does not establish place preferences when injected into areas just beyond the dorsal (Phillips, & LePiane, 1980), rostral, or caudal (Bozarth, 1987) boundaries of the VTA. The demonstration that morphine injections around the VTA do not establish place preferences helps to establish the VTA as a discrete site of opiate reward. Finally, microinjections of morphine or DPDPE directly into the VTA potentiate brain stimulation reward (Bauco, Wang, & Wise, 1993; Jenck, Gratton, & Wise, 1987; Rompre & Wise, 1989).

In addition to having rewarding actions in the VTA, opiates are also rewarding in the NAS. Both morphine (Olds, 1982) and methionine enkephalin (Geoders, Lane, &

Smith, 1984) are self-administered into the NAS. Morphine also establishes conditioned place preferences when injected into the NAS (van der Kooy, Mucha, O'Shaugnessy, & Bucenieks, 1982) although effective doses are ten-fold greater than those required to establish CPP in the VTA (Phillips & LePiane, 1980). Morphine, DAMGO, or DPDPE also lower brain stimulation reward thresholds when injected into the NAS (West & Wise, 1988); again, the effective doses are much higher than the doses required for VTA injections. Thus, opiates are rewarding at both the dopamine cell body region of the VTA and the terminal region in the NAS.

In summary, it appears that the dopaminergic projections from the VTA to NAS and the synaptic targets of these projections are important links in the brain circuitry subsuming psychomotor stimulant, opiate, and brain stimulation reward. The disruption of dopaminergic transmission, specifically in the NAS, blocks drug and brain stimulation reward. Central injections of amphetamine and opiates establish self-administration, conditioned place preferences, and potentiate brain stimulation reward at sites where they increase NAS dopamine.

II. DRUG DEPENDENCE

The origin of dependence theories can be traced back to the study of opiate self-administration (Collier, 1968; Himmelsbach, 1943; Lindsmith, 1947). Abstinence from opiates is associated with an aversive withdrawal syndrome characterized by physical disturbances; avoidance or alleviation of physical distress formed the basis of early dependence theories. In opiate dependent humans and rats, drug withdrawal gives rise to tremors and muscle spasms (wet-dog shakes), diarrhea, intestinal cramps, restlessness and hyperexcitability (Jaffe, 1990; Wei, Loh, & Way, 1973). The opiate withdrawal syndrome is described by humans as aversive and is clearly so in rats; rats avoid or escape from environments that are associated with opiate withdrawal (Bechara & van der Kooy, 1992; Bozarth & Wise, 1984; Stinus, LeMoal, & Koob, 1990).

A. Physical Dependence

Although opiate withdrawal results in profound physical disturbances, the importance of physical dependence in drug self-administration remains equivocal. Physical dependence is neither necessary nor sufficient for the establishment or maintenance of drug self-administration habits. Some drugs, including tricyclic antidepressants and b-adrenergic antagonists, cause physical dependence but are not habit-forming (Jaffe, 1990). Psychomotor stimulants and nicotine establish and maintain self-administration habits but are not associated with severe physical disturbances following withdrawal (Gawin & Ellinwood, 1989; Jaffe, 1990; Kalant, LeBlanc & Gibbins, 1971; Shiffman, 1979). Moreover, morphine self-administration into the VTA is not associated with physical dependence (Bozarth & Wise, 1981). Even following 72-hour continuous infusions of morphine into the VTA naloxone fails to precipitate any classical physical withdrawal signs (Bozarth & Wise, 1984; but see Baumeister, Anticich, Hebert, Hawkings, & Nagy, 1989). The demonstration that physical dependence is not necessary for the establishment of self-administration habits has led to the suggestion that the brain mechanisms involved in drug reward may be distinct from those involved in dependence (Wise, 1988).

The central mechanisms of opiate dependence have been widely studied. Of the many brain sites that have been examined, the periaqueductal gray (PAG) is strongly implicated in opiate dependence. Injections of opiate antagonists into the PAG precipitate physical withdrawal signs in rats that have been infused with morphine for 72 hours (Wei, Loh, & Way, 1973). Physical withdrawal signs can also be precipitated by systemic injections of naloxone in rats that have received 72-hour infusions of morphine into the PAG (Bozarth & Wise, 1984; Wei & Loh, 1976). However, there is scant evidence that the PAG is involved in opiate reward. Drug naive rats do not learn to self-administer opiates directly into this region (Bozarth & Wise, 1982) and doses of

morphine that are sufficient to establish conditioned place preferences in the VTA do not establish conditioned place preferences in the PAG (Phillips & LePiane, 1980).

B. Opponent-Process Depression of Brain Reward Circuitry

A recent variant of dependence theory is the opponent-process theory of Solomon and Corbit (1974). The opponent-process theory is based on the postulate that within the central nervous system there are many systems which "suppress or reduce all excursions from hedonic neutrality" (Solomon & Corbit, 1973). These proposed systems are thought to decrease the intensity of all affective experiences, minimizing both the positive and negative properties of stimuli. According to this view, habit-forming drugs activate brain reward processes, and, in so doing, invoke an opponent-process. In this theory, the opponent-process is initially slow in onset and weak in magnitude. However, it is thought that with repeated activation of the same circuitry the opponent-process decreases in latency of onset and increases in magnitude and duration. During drug abstinence the exaggerated opponent-process is thought to be left unopposed resulting in dysphoria and depression. According to this theory, it is the alleviation of opponent-process depression that is thought to underlie drug craving and perpetuate drug self-administration (Solomon & Corbit, 1974).

Whereas physical dependence is not essential to establishment drug self-administration, the alleviation of opponent-process depression may be important in maintaining drug self-administration habits. Withdrawal from psychomotor stimulants (Dackis & Gold, 1985; Gawin & Ellinwood, 1989), opiates (Jaffe, 199o), and nicotine (Hatsukami, Hughes, Pickens, & Svikis, 1984; Hughes, Gust, Skoog, Keenan, & Fenwick, 1991; Shiffman, 1979) is associated with depression, anhedonia, and dysphoria. Unlike the traditional physical dependence signs associated with opiate withdrawal, these withdrawal symptoms are common across a range of drug classes. The observation that these drugs share common withdrawal symptoms has led some investigators to suggest

that opponent-process depression of brain reward circuitry underlies at least some of the aversive sequelae of drug withdrawal (Dackis & Gold, 1985; Di Chiara, Acquas, Carboni, 1992; Koob & Bloom, 1988; Koob, Stinus, Le Moal, & Bloom, 1989; Rossetti, Hmaidan, & Gessa, 1992) and may contribute to the habit-forming properties of these drugs. The view that opponent-process depression of brain reward circuitry underlies some features of drug dependence has prompted a great deal of interest in the effects of drug withdrawal on NAS dopamine. Determination of extracellular dopamine using microdialysis has revealed that basal dopamine in the NAS is lower in animals withdrawn from morphine (Acquas, Carboni, & Di Chiara, 1991; Crippens & Robinson, 1994; Pothos, Rada, Mark, & Hoebel, 1991; Rossetti, Hmaidan, & Gessa, 1992), amphetamine (Rossetti et al., 1992; but see Crippens & Robinson, 1994) or cocaine (Imperato, Mele, Scrocco, & Puglisi-Allegra, 1992; Maisonneuve, Ho, & Kreek, 1995; Parsons, Smith, & Justice, 1991; Robertson, Leslie, & Bennett, 1991; Weiss, Markou, Lorang, & Koob, 1992; Weiss, Hurd, Ungerstedt, Markou, Plotsky, & Koob, 1992). Dopamine depletion has recently been proposed as a cause of depression and craving associated with cocaine withdrawal (Dackis and Gold, 1985; Markou and Koob, 1991).

Whereas increases in dopaminergic neurotransmission are associated with drug and brain stimulation reward, reduced dopaminergic neurotransmission is associated with psychological depression (Fibiger, 1984; Kokkinidis & McCarter 1990; Kokkinidis, Zacharko, Predy, 1980), anhedonia (Markou & Koob, 1992; Wise, 1982) and dysphoria (Frank, Manderscheid, Panicker, Williams, & Kokoris, 1992). If NAS dopamine is a common link in the brain circuitry activated by drug and brain stimulation reward then an attenuation of brain stimulation reward should be a correlate of opponent-process depression of dopaminergic neurotransmission following withdrawal from amphetamine (Barret, & White, 1980; Cassens, Actor, Kling, & Schildkraut, 1981; Kokkinidis, & McCarter, 1990; Kokkinidis et al., 1980; Wise & Munn, 1995), cocaine (Frank, et al., 1992; Markou & Koob, 1991; Markou & Koob, 1992) and morphine (Schaefer &

Michael, 1986). The idea that the reduction of brain stimulation reward caused by drug withdrawal is a function of decreased dopaminergic neurotransmission is advanced by the finding that the D2 agonist bromocriptine reverses threshold changes following cocaine withdrawal (Markou & Koob, 1992).

III. NICOTINE

The physiological processes underlying habitual nicotine self-administration are not well understood. The evidence reviewed above suggests that the factors contributing to the establishment and maintenance of nicotine self-administration may be two-fold. If nicotine is rewarding it should establish self-administration habits. Moreover, with repeated activation of brain reward circuitry abstinence may result in opponent-process depression of reward circuitry and an aversive withdrawal syndrome. The alleviation of withdrawal symptoms may then become an additional incentive to maintain self-administration habits.

A. Nicotine Reward

Nicotine is self-administered by both humans and animals. In humans cigarette smoking is the most popular form of nicotine self-administration but nicotine is also self-administered via pipe and cigar smoke, smokeless tobacco, and polacrilex gum. Humans will also learn to lever-press for intravenous injections of nicotine (Henningfield & Goldberg, 1983, 1988; Henningfield, Miyasato, & Jasinski, 1983). Intravenous injections of nicotine are also self-administered by a variety of animal species' including squirrel monkeys (Goldberg, Spealman, & Goldberg, 1981; Goldberg, Spealman, Risner, & Henningfield, 1983), rhesus monkeys (Slifer & Balster 1985), baboons (Ator & Griffiths, 1983), beagle dogs (Goldberg, Spealman, Risner, & Henningfield, 1983), and rats (Corrigall & Coen, 1989; Cox, Goldstein, & Nelson 1984; Hanson, Ivester, & Morton, 1979).

Some investigators have reported that systemically administered nicotine establishes conditioned place preferences (Fudala & Iwamoto, 1986; Fudala, Teoh, & Iwamoto, 1985). Other investigators have, however, either failed to confirm that nicotine is an effective reinforcer in this paradigm (Clarke & Fibiger, 1987), or reported conditioned place aversions with nicotine (Jorenby, Steinpreis, Sherman & Baker, 1990). One reason for these inconsistent findings may be that systemically administered nicotine acts throughout the periphery and central nervous system. The actions of nicotine at one site might produce a rewarding effect while the drug's concurrent actions at another site might have aversive consequences that interfere with the establishment of conditioned place preferences. Determining specific brain sites where nicotine is rewarding may be accomplished by injecting the drug directly into the brain. Indeed, nicotine conditioned place preferences may be more readily demonstrated after central than systemic injections (Iwamoto, 1990). Administration of nicotine into the cerebral ventricles or into the area in and around the pedunculopontine nucleus establishes place preferences (Iwamoto, 1990). Microinjections of nicotine (Brace, Calder, Cooke, Inglis, Parker, Robertson, & Winn, 1993) or the nicotinic agonist cytisine (Museo & Wise, 1994) into the VTA also establish conditioned place preferences.

In addition to establishing intravenous self-administration and conditioned place preferences, nicotine also potentiates brain stimulation reward. Systemic injections of nicotine increase self-stimulation rates (Clarke & Kumar, 1983; Pradhan & Bowling, 1971) and lower brain stimulation reward thresholds (Bauco & Wise, 1994; Huston-Lyons & Kornetsky 1992; Huston-Lyons, Sarkar & Kornetsky 1993).

Nicotine reward is centrally mediated. Nicotine self-administration by humans and rats is blocked by the nicotine antagonist mecamylamine (a drug that blocks the effects of nicotine in the brain) whereas antagonists that do not enter the brain are without effect (Corrigall and Coen, 1989; Stolerman et al., 1973; Tennant, Tarver & Rawson, 1984). Intraventricular injection of the nicotine antagonist chlorisondamine, a drug that

does not easily cross the blood-brain barrier, also abolishes intravenous self-administration of nicotine (Corrigall, Franklin, Coen & Clarke, 1992). Mecamylamine prevents the establishment conditioned place preferences (Fudala et al., 1985) and blocks the ability of nicotine to potentiate brain stimulation reward (Huston-Lyons & Kornetsky 1992).

Dopamine & Nicotine

As with amphetamine, cocaine, and opiate reward the dopaminergic projections from the VTA to NAS appear to be an essential component of brain circuitry involved in nicotine reward (Clarke, 1990; Grenhoff, & Svensson, 1989; Stolerman & Shoaib, 1991). Nicotine increases dopaminergic neurotransmission by activating a subset of acetylcholine receptors (Taylor, 1992). Nicotinic acetylcholine receptors labeled with tritiated nicotine, cytisine, or acetylcholine are found in high densities in both the ventral tegmental area and substantia nigra (Clarke, Pert, & Pert, 1984; Clarke, Schwartz, Paul, Pert, & Pert, 1985; Happe, Peters, Bergman, & Murrin, 1994; Martino-Barrows & Kellar, 1986) and in moderate densities in the striatum and NAS (Clarke et al., 1984; Clarke et al., 1985; Happe et al., 1994). At least a portion of nicotinic receptors in these regions are located on dopamine neurons. Clarke and Pert (1985) destroyed the midbrain dopamine systems by injecting 6-OHDA into the MFB. The resulting lesions caused a near total loss of striatal dopamine and retrograde degeneration of dopamine cell bodies. There was a coincidental reduction in tritiated nicotine binding in the dopamine terminal areas of the NAS, OT and striatum, as well as in the cell body regions of the VTA and SN. In the striatum the reduction in nicotine binding was correlated with the degree of dopamine depletion. The distribution of nicotinic receptor-like immunoreactivity in the rat brain (Deutch, Holliday, Roth, Chun, & Hawrot, 1987; Swanson, Simmons, Whiting, & Lindstrom, 1987), and the distribution of nicotinic receptor mRNA (Wada, Wada,

Boulter, Deneris, Heinemann, Patrick, & Swanson, 1989) is similar to the distribution of nicotine binding sites labeled by radioactive tracers.

Single unit recordings in the SN or VTA have revealed that nicotine excites identified dopamine neurons; systemic (Clarke, Hommer, Pert, & Skirboll, 1985; Grenhoff, Aston-Jones, Svensson, 1986), intravenous (Clarke, Hommer, Pert, & Skirboll, 1985; Mereu, Yoon, Boi, Gessa, Naes, & Westfall, 1987) or iontophoretically applied (Lichtensteiger, Hefti, Felix, Melamed, & Schlumpf, 1982) nicotine increases the firing of dopamine neurons. Intracellular recordings from VTA dopamine neurons in vitro indicate that nicotine-induced depolarizations are blocked by the nicotine antagonist hexamethonium but not tetrodotoxin (TTX), a drug that blocks sodium channels and prevents the propagation of action potentials (Calabresi, Lacey, & North, 1989).

Nicotine increases dopamine release in the NAS. Extracellular dopamine is elevated in the nucleus accumbens following subcutaneous (Damsma, Day, & Fibiger, 1989; Imperato, Mulas, & Di Chiara, 1986; Nisell, Nomikos, & Svensson, 1994) or intravenous injections (Brazell, Mitchell, Joseph, & Gray, 1990) of nicotine. Systemic nicotine can increase NAS dopamine through actions at the level of the VTA and at the level of the NAS. Direct infusion of nicotine into the VTA increases dopamine in the NAS, presumably by increasing cell firing. Infusion of mecamylamine into the VTA blocks the ability of systemic nicotine to increase NAS dopamine (Nisell, et al., 1994). Infusion of nicotine into the NAS also increases dopamine levels in this region (Mifsud, Hernandez, & Hoebel, 1989; Nisell et al., 1994) however infusion of mecamylamine into the NAS does not block the ability of systemic nicotine to stimulate dopamine release (Nisell et al., 1994). Thus, it appears to be the VTA that is more sensitive to nicotine.

Nicotine Reward & Dopamine

Dopaminergic neurotransmission in the NAS appears to be an important mechanism of nicotine reward (Clarke, 1990; Stolerman & Shoaib, 1991). Nicotine

establishes conditioned place preferences (Fudala & Iwamoto, 1986; Fudala, Teoh & Iwamoto, 1985) and potentiates brain stimulation reward (Bauco & Wise, 1994; Huston-Lyons & Kornetsky, 1992; Huston-Lyons et al., 1993) at doses that increase NAS dopamine. Blockade of dopaminergic neurotransmission attenuates nicotine self-administration (Corrigall & Coen, 1991) and nicotine's ability to potentiate brain stimulation reward (Huston-Lyons et al., 1993). Nicotine self-administration is also reduced by 6-OHDA lesions of the NAS (Corrigall, Franklin, Coen, & Clarke, 1992). It appears to be the VTA that is the critical site of action for nicotine. Blockade of nicotinic receptors in the VTA abolishes nicotine induced elevations NAS dopamine (Nisell et al., 1994) and reduces nicotine self-administration (Corrigall, Coen, & Adamson, 1994) whereas blockade of nicotinic receptors in the NAS fails to reduce nicotine induced increases Nas dopamine (Nisell et al., 1994) or nicotine self-administration (Corrigall, Coen, & Adamson, 1994).

B. Nicotine Dependence

Only recently has dependence on tobacco products been extensively characterized. Traditionally, tobacco products have not been regarded as dependence producing, due primarily to the absence of severe physical withdrawal signs in abstinent smokers. Indeed, signs of dependence are quite variable and abstinent smokers suffer only from mild physical disturbances (Shiffman, 1979). The physical consequences of tobacco withdrawal include decreased heart rate (Hatsukami, Hughes, Pickens and Svikis, 1984; West and Schneider, 1988), increased skin temperature (Gilbert and Pope, 1982), weight gain and increased caloric intake (Gilbert & Pope, 1982; Hatsukami, Dahlgren, Zimmerman, & Hughes, 1998). Other subjectively reported physical disturbances include headache, constipation, and diarrhea (Shiffman, 1979). Decreased arousal (Ulett & Itil, 1969) and difficulty concentrating (Hatsukami, et al., 1984) are also characteristic of abstinent smokers and may be related to alterations in EEG activity (Herning, Jones, &

Bachman, 1983; Knott & Venables, 1977; Ulett & Itil, 1969). Changes in mood predominate the withdrawal syndrome. Irritability, anxiety, and depression are characteristic symptoms of nicotine withdrawal (Hatsukami et al., 1984, 1988; Hughes et al., 1991; Shiffman, 1979; West et al., 1984). The alleviation or avoidance of this dysphoric withdrawal state has been proposed to maintain smoking behavior (Schachter, 1978; Solomon & Corbit, 1973).

It is widely accepted that nicotine is the dependence producing constituent of tobacco products. The primary evidence is that nicotine replacement in the form of transdermal patch or polacrilex gum is effective in alleviating many tobacco withdrawal symptoms (Fagerstrom, Schneider, & Lunell, 1993; Hughes, Hatsukami, Pickens, Krahn, Malin, & Luknic, 1984; West, Jarvis, Russell, Carruthers, & Feyerabend, 1984). It has recently been demonstrated that nicotine is capable of producing dependence in rats. As with human smokers, physical dependence signs are not severe in rats and are observed only following continuous infusion of high doses of nicotine. Nicotine dependence signs resemble mild opiate dependence signs and include writhing, shaking, and teeth chattering. The occurrence of physical dependence signs peaks within 40 hours following withdrawal (Malin, Lake, Newlin-Maultsby, Roberts, Lanier, Carter, Cunningham, & Wilson, 1992). Nicotine withdrawal also results in behavioral alterations. Locomotor depression follows withdrawal from continuous infusion of nicotine (Malin et al., 1992). Nicotine withdrawal also results in decreased operant responding for food (Corrigall, Herling, & Coen, 1989) or sucrose (Carroll, Lac, Asencio, & Keenan, 1989). Lever-pressing to avoid unsignalled electric shock is also impaired following nicotine withdrawal (Balfour, 1990; Morrison, 1974).

Although the nicotine withdrawal syndrome is characterized primarily by aversive subjective symptoms in humans there have been few attempts to examine these symptoms in animal models. Recently, the anxiogenic effects of nicotine withdrawal have been modeled in a drug-discrimination paradigm (see Emmet-Oglesby, Mathis,

Moon, & Lal, 1990, for review). In this paradigm rats are trained to operantly respond for food in a two-lever chamber. Following drug treatment with the anxiogenic (and epileptogenic) drug pentylenetetrazol (PTZ), responding on one lever is reinforced whereas responding on the alternate lever is reinforced following saline. Withdrawal from repeated injections of nicotine produces a mild PTZ-like stimulus; 48 hours following withdrawal 50% of rats responded preferentially on the PTZ-trained lever and this effect was blocked by pretreatement with the anxiolytic (and anticonvulsant) diazepam (Harris, Emmett-Oglesby, Robinson, & Lal, 1986).

I V. The Present Study

The brain stimulation reward paradigm has recently been suggested to offer an animal model of psychomotor stimulant withdrawal depression (Markou & Koob, 1991). Elevated brain stimulation reward thresholds following cocaine withdrawal are thought to reflect depression of brain reward circuitry (Markou & Koob, 1991; Markou & Koob, 1992) which has been proposed to underlie the depressive symptoms of cocaine withdrawal in humans (Dackis & Gold, 1985; Gawin & Ellinwood, 1989). There is little known of the brain mechanisms involved in nicotine dependence. There is, however, evidence that nicotine is rewarding through the same brain circuitry as is involved in psychomotor stimulant, opiate, and brain stimulation reward. Moreover, there is increasingly compelling evidence that opponent-process depression of this reward circuitry is a correlate of the depressive symptoms of psychomotor stimulant and opiate withdrawal. The present study was designed to examine the effects of nicotine withdrawal on lateral hypothalamic brain stimulation reward.

The curve-shift paradigm (Edmonds, & Gallistel, 1974) was used to determine brain stimulation reward threshold. Analogous to the dose-response curve of pharmacology (Leibman, 1983), the curve-shift paradigm involves the delivery of brain stimulation across a range of stimulation doses, including some that maintain high and

moderate levels of operant responding and some that produce no responding. The dose of stimulation can be varied by changing either the intensity, frequency or duration of the stimulation while all other parameters are held constant. The magnitude of operant responding is then analyzed as a function of stimulation dose. When operant response rate is the dependent variable and is sampled across a range of pulse frequencies the function relating response-rate to stimulation frequency is sigmoidal in shape when plotted and is commonly referred to as the rate-frequency curve.

The rate-frequency curve is characterized by two important ranges of stimulation frequencies: a range over which increases in pulse frequency produce a rapid rise in response rate and a higher range in which further increases in pulse frequency fail to further increase responding. Reward threshold is determined from the rate-frequency function by choosing an arbitrary response requirement associated with the rising portion of the curve and interpolating the pulse frequency required to maintain that response rate. Two commonly used threshold measures are the pulse frequency that is associated with half of the maximal response rate (M50) or the highest pulse frequency that is associated with no responding within the time limit of a given frequency trial (theoretical or "theta" zero, T0).

Experimental manipulations can shift the curve of the curve-shift paradigm both laterally and horizontally. Horizontal, downward shifts in the curve are produced by making the operant task more difficult or by impairing the animals performance capacity. Placing hurdles on the floor of a runway or forcing animals to run uphill by increasing the grade of the runway decreases the magnitude of operant responding and shifts the curve downward (Edmonds, & Gallistel, 1974). Another way to shift the curve downward is by increasing the weight of a lever that animals must press for stimulation (Miliaresis, Rompre, Laviolette, Philippe, & Coulombe, 1986). The curve can also be shifted downwards by treating animals with methocarbamol, a drug that causes flaccid paralysis and impairs the animal's performance capacity (Edmonds, & Gallistel, 1974; Miliaresis et

al., 1986). Manipulations that produce moderately decrease maximal response rate do not affect reward threshold (Miliaresis et al., 1986). The stability of threshold measures across a variety of conditions that alter performance capacity makes the curve-shift paradigm a valuable tool for dissociating manipulations that affect the reward and those that affect performance.

The curve can also be shifted laterally, either to the left or right, by manipulations that do not effect the maximal response rate. So long as lateral displacements of the curve are parallel the choice of threshold measure is arbitrary since each point on the curve will be shifted by the same value. Rewarding drugs shift rate-frequency curves to the left (Wise et al., 1992; Wise & Rompre, 1989). Rate-frequency curves are shifted leftwards because pulse frequencies that had failed to maintain responding in non-drug conditions become sufficient to maintain responding under drug treatment. In other words, animals will work to obtain doses of stimulation that were not rewarding when the animal was tested in a drug-free state. The decrease in the pulse frequency required to maintain a given level of responding is seen as a decrease in the brain stimulation threshold, and is generally interpreted as indicating an increase in the rewarding impact of the stimulation.

In the present study the rate-frequency variant of the curve-shift paradigm was used to determine whether withdrawal from repeated injections of nicotine is associated with a rightward shift in the rate-frequency curves. Rightward shifts are seen when higher pulse frequencies are required in order to maintain responding. Withdrawal from amphetamine (Wise, & Munn, 1995), cocaine (Kokkinidis & McCarter, 1990), or morphine (Wise, Bauco & Carlezon, unpublished observations) shifts the curve to the right. The rightward shift caused by withdrawal from rewarding drugs is consistent with the hypothesis that withdrawal is associated with a state of anhedonia.

METHOD

Subjects Subjects were 45 male Long-Evans rats (Charles River, Quebec) weighing between 325 and 450 grams at the time of surgery. Each animal was individually housed in a hanging stainless steel cage. The colony room was maintained at 70o F on a 12- hour light-dark cycle. Food and water were freely available at all times.

Surgery Each animal was anaesthetized with 60 mg/kg of sodium pentobarbital (Somnitol) and pretreated with atropine sulphate to minimize respiratory distress. Each animal was then stereotaxically implanted with a flat tipped, 254-um stainless steel, monopolar electrode (Plastics One) that was insulated with Formvar varnish except at the cross section of the tip. The electrode was implanted into the medial forebrain bundle at the level of the lateral hypothalamus. The electrode coordinates, with the incisor bar raised 5.0 mm above the intra-aural line, were 1.8 mm lateral from the midline, 0.8 mm caudal from bregma and 8.0 mm below the dural surface. Stainless steel jeweler's screws were implanted into the skull and an uninsulated stainless steel wire serving as the current return was wrapped around one of the screws. The screws served as an anchor for dental cement which was used to hold the electrode in place.

As a precaution against post-surgical infection each animal was given intra-muscular penicillin (2 mg/kg, Ayercillin) prior to surgery. At the end of the surgical procedure the wound was treated with an antibacterial agent (Neosporin) and animals were placed under a heating lamp until post-surgical locomotion was observed. Each animal recovered for one week prior to screening for electrical self-stimulation.

Apparatus Animals were trained to lever press for electrical brain stimulation in 27 x 27 cm chambers. A lever extended 2.5 cm from the back wall of each chamber. Stimulation was triggered by depression of the lever. The stimulation amplitude was controlled by a constant current generator (Mundl, 1980). A flexible lead connected the animal's

electrode assembly to a mercury commutator (Mercotac inc., San Diego), which was in turn connected to the stimulator. A micro-processor based system was used to control the stimulation parameters and to record response rates.

Procedure

Training. Each animal was placed in an operant chamber and allowed to lever-press for electrical stimulation. Each lever press resulted in the delivery of a 0.5 sec train of 0.1 msec square wave cathodal pulses, unless the lever was pressed during the delivery of a pulse train. Lever presses that occurred during a pulse train were recorded but did not result in the delivery of stimulation. During the initial screening sessions the stimulation pulse frequency was fixed at 96 Hz with the initial current intensity set at 200 uamps. Each animal received 5 trains of stimulation and behavior was observed. If an animal jumped, vocalized, or backed into a corner stimulation was determined to be aversive and the animal was not used in the study. If an animal engaged in forward locomotion and exploratory behavior then the current intensity was held at 200 uamps. If an animal did not engage in exploratory behavior and stimulation at 200 uamps was not aversive then the current intensity was increased by 50 uamp increments until noncontingent stimulation elicited exploratory behavior, aversive behavior or until the intensity reached 900 uamps. Each animal was then allowed to lever-press freely for stimulation for 120 minutes each day. Following the first 60 minutes of training the lever-pressing rate of each animal was determined. If an animal did not press at least 30 times per minute the stimulation intensity was adjusted to increase response rate.

Each animal that lever-pressed reliably during screening was trained to respond during daily sessions of several series of stimulation. Each series of stimulation consisted of ten 50 second trials. The stimulation frequency for the first trial was set at 110 Hz and was decreased by 0.05 log units on each subsequent trial. The beginning of each trial was signaled by the delivery of 5 "priming" trains of stimulation, delivered at 1 second

intervals, at the same pulse frequency as was to be presented during the trial. Noncontingent stimulation was followed by a 5 second adaptation period during which lever-presses resulted in the delivery of stimulation but responses were not recorded. Each trial began immediately following the adaptation period. Data were recorded for analysis during this period only. Following each trial came another five second period during which lever-presses did not result in the delivery of stimulation. After the lowest frequency (36 Hz) was tested the stimulation frequency was reset at 110 Hz and the series was repeated. The series was repeated ten times over a total time of approximately 100 minutes.

During the training period the stimulation intensity of each animal was individually adjusted so that the animal would lever-press for the highest 5 frequencies and not for lower frequencies. Once this criterion was established the stimulation intensity was fixed and each animals was trained until frequency thresholds did not differ by more than 10 percent over three consecutive days.

Experimental Procedure. Once an animal had stable frequency threshold the experimental treatment began. Baseline frequency thresholds were determined for each animal on the morning of the first treatment day . At approximately 6 PM the same day each animal was removed from its home cage and injected subcutaneously, behind the nape of the neck, with either nicotine (1.5 or 0.5 mg/kg) or saline and returned to its cage. For the following 13 days each animal was removed from its cage and injected with the appropriate solution twice a day: first at approximately 9 am and again at approximately 6 PM. A minimum of 8 hours separated each injection. Thus, the total dose for nicotine treated animals was either 3.0 or 1.0 mg/kg/day. During the second week of treatment six frequency threshold determinations were made for each animal prior to the morning injection. Three more frequency threshold determinations were made after the injection following which each animal was returned to its home cage until it was time for the

evening injection. On day 14 each animal received its last injection in the morning and frequency thresholds were determined intermittently during the following 28 hours.

Nicotine bitartrate (ICN Pharmaceuticals) was dissolved in bacteriostatic saline and the pH was adjusted to 7.0 + 0.2 with NaOH. All doses are reported as free base.

Histology. At the end of the experiment each animal was anaesthetized with chloral hydrate (400 mg/kg i.p.). A 1.0 mA cathodal current was passed through each animal's electrode for 10 seconds. Each animal was then transcardially perfused with 0.9% saline followed by a formalin cyanide solution (10% formalin, 3% potassium ferrocyanide, 3% potassium ferricyanide, 0.5% trichloracetic acid). The brain was then removed from each animal and stored in 10% formalin until sectioning. Each brain was frozen sliced into 40 um sections. The sections that contained the electrode track were mounted on slides for verification of the electrode placement.

RESULTS

Nicotine caused dose-dependent leftward shifts in rate-frequency curves. Representative rate-frequency curves for baseline and for each dose of nicotine are shown in Figure 1. Initially 0.5 and 1.5 mg/kg of nicotine each caused prostration and ataxia. The duration of this effect varied with dose; typically, 0.5 mg/kg of nicotine decreased lever-pressing during the first rate-frequency determination whereas several animals treated with 1.5 mg/kg remained ataxic through the first and into the second rate-frequency determination. For this reason, only the third rate-frequency function, determined 30 minutes after the nicotine injection, was used as a measure of reward threshold.

Thirty minutes after 0.5 mg/kg of nicotine rate-frequency curves were shifted to the left. Because leftward shifts in the rate-frequency curves were parallel, only the theta-zero measure of threshold is reported. Threshold values following daily nicotine treatments are represented in Figure 2. Nicotine decreased reward threshold to 79% percent of normal. Decreases in threshold were evident on the first day of testing and remained stable through the 7 days of testing. The effects of 1.5 mg/kg of nicotine on rate-frequency curves was variable between animals. As a group, animals treated with this high dose of nicotine had only marginal decreases in reward thresholds. The mean threshold was 87% of baseline. Nicotine did not cause horizontal shifts in the rate-frequency curves determined 30 minutes after the injection. The maximal response rate, defined as the highest rate of lever-pressing that occurred during any frequency trial within each rate-frequency determination, was not affected by either dose of nicotine.

Nicotine withdrawal caused dose-dependent rightward shifts in rate-frequency curves. Typical rate-frequency curves determined at 12 and 24 hours following the last nicotine injection are shown in Figure 3. Withdrawal from 3.0 mg/kg/day of nicotine shifted rate-frequency curves to the right. Nicotine withdrawal affected the threshold measures of theta-zero and M50 differently, reflecting the fact that the rightward shifts in

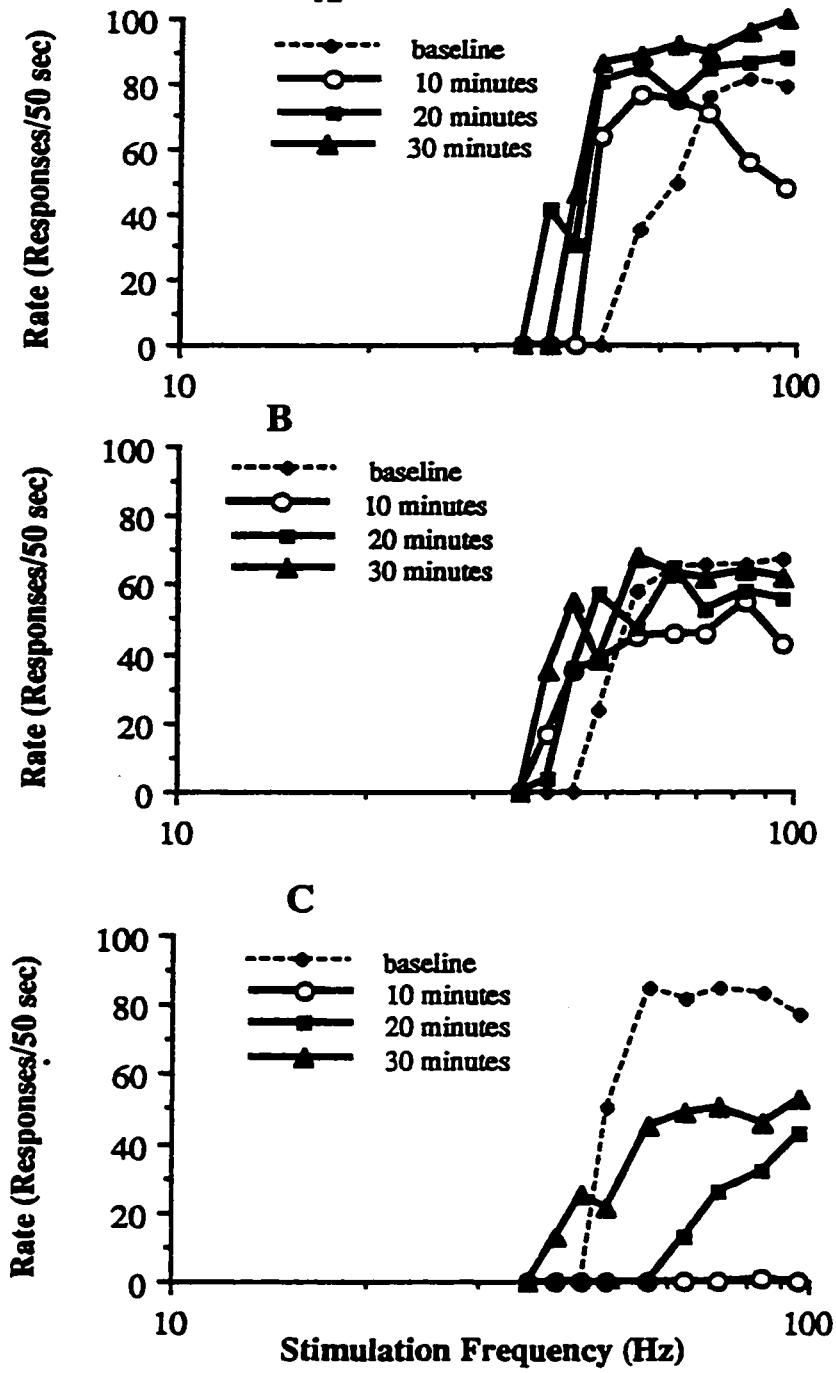


Figure 1. Rate of lever-pressing as a function of stimulation frequency. Each plot represents data from a single animal under pretreatment baseline and one test day following injection of (A) 0.5 mg/kg of nicotine or (B & C) 1.5 mg/kg of nicotine. Rate-frequency curves in the nicotine condition were determined 30 minutes after injections.

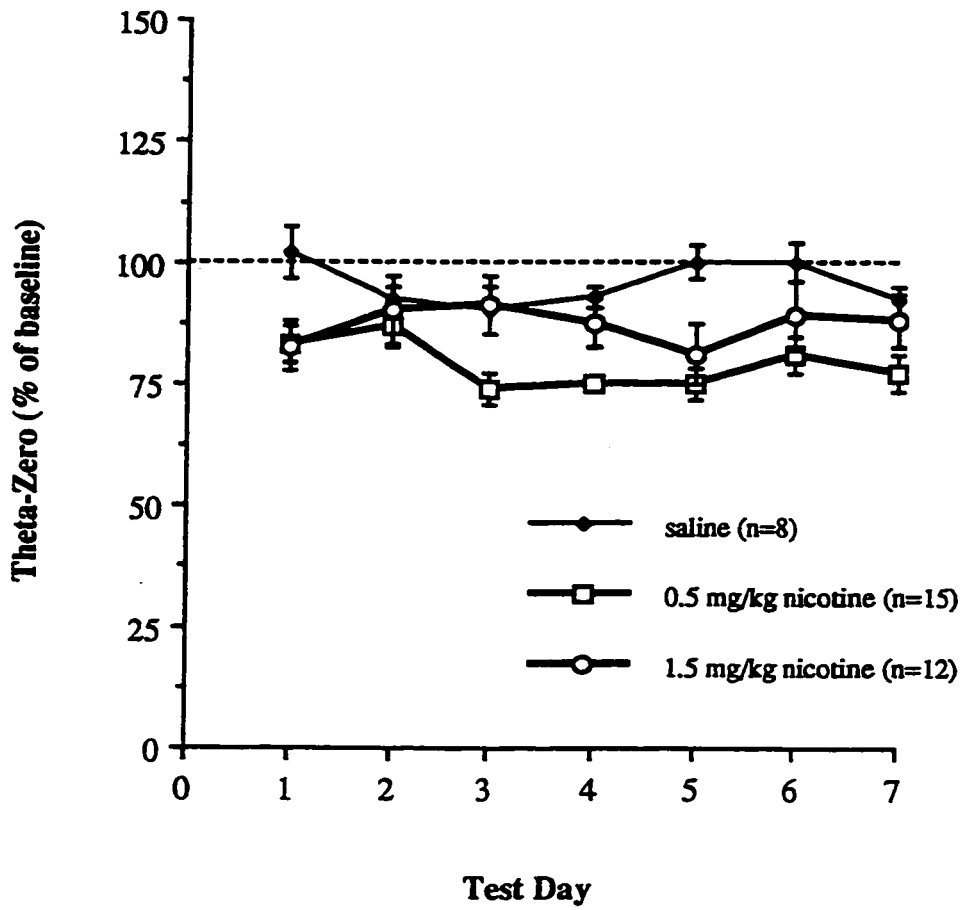


Figure 2. Mean threshold (T0) values across successive daily nicotine treatments. Nicotine decreased threshold in a dose dependent manner ($F[2,192] = 4.151$, $p<0.05$); Post Hoc comparisons (Scheffe) revealed that 0.5 mg/kg of nicotine lowered thresholds beyond saline (p,0.02).

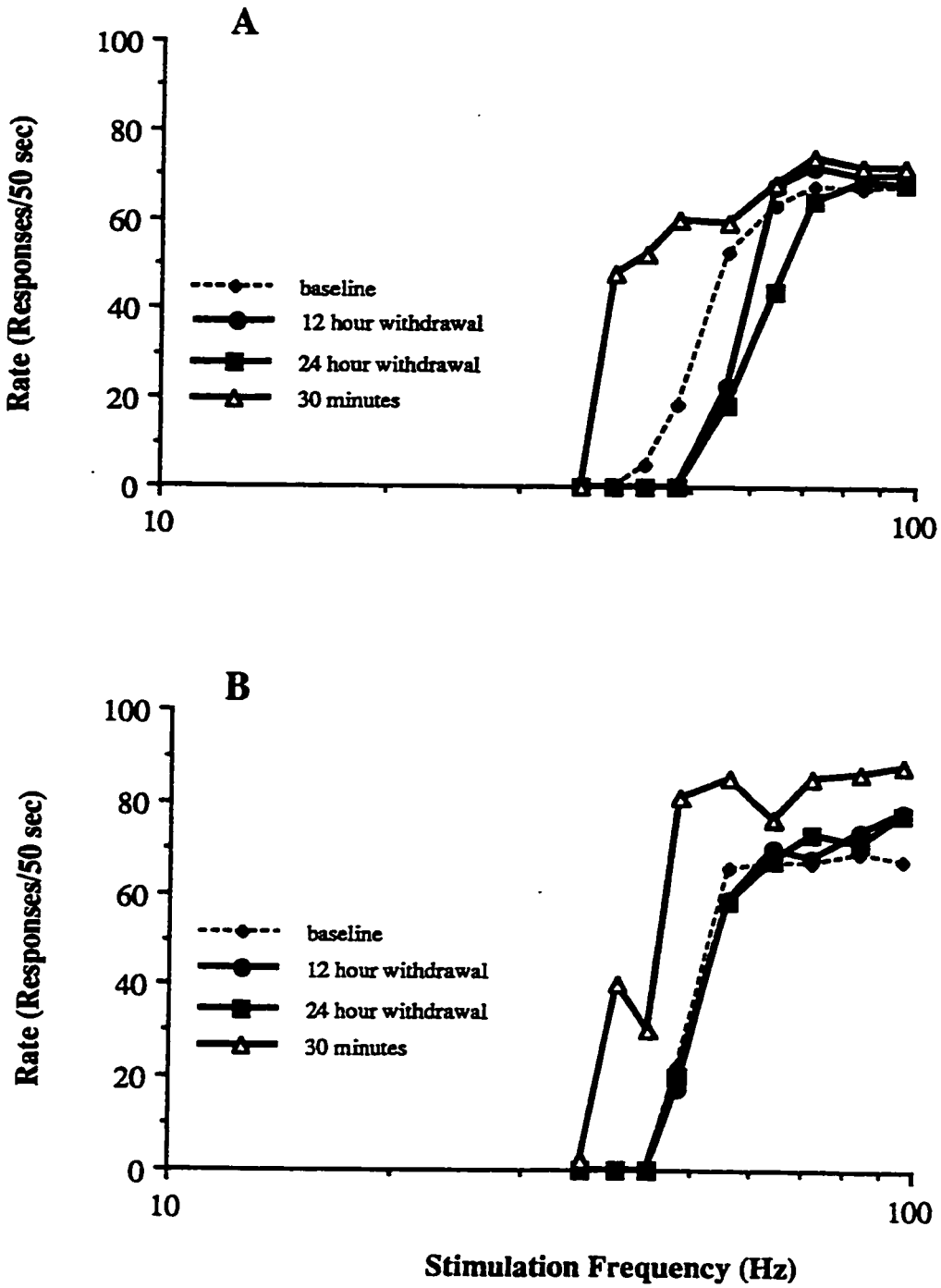


Figure 3. Rate of lever-pressing as a function of stimulation frequency. Each plot represents data from a single animal following withdrawal from (A) 3.0 or (B) 1.0 mg/kg/day of nicotine.

rate-frequency curves were not parallel. The effect of nicotine withdrawal on theta-zero is shown in Figure 4. Theta-zero was elevated to 126% of baseline 8 hours following the last injection of nicotine and increased to 135% of baseline 24 hours after withdrawal. The mean value for theta-zero over the 24 hour test period was 132% of baseline. The increase in T0 was not permanent, thresholds determined one week after withdrawal were not different from pre-nicotine baseline (data not shown). The effect of nicotine withdrawal on the threshold measure of M50 is shown in Figure 5. During the 24 hour test period M50 was elevated to 112% of baseline. Withdrawal from 1.0 mg/kg/day of nicotine did not shift rate-frequency curves (Figure 3). The mean values for theta-zero and M50 over the 24 hour test period were 107% and 103% of baseline respectively. There was no change in maximal response rate associated with withdrawal from either dose of nicotine (Figure 6).

All electrodes were located in the medial forebrain bundle at the level of the lateral hypothalamus.

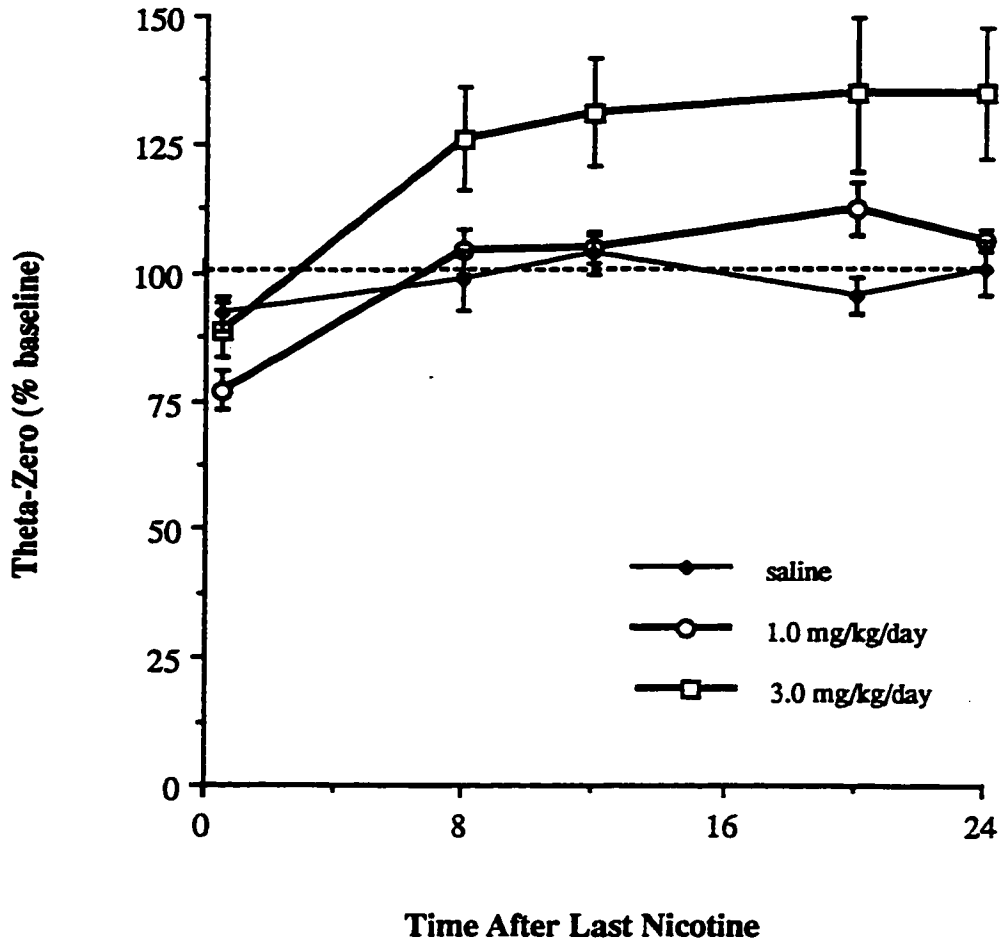


Figure 4. Mean threshold (T0) values determined following withdrawal from saline, 1.0, or 3.0 mg/kg/day of nicotine. Increases in threshold following nicotine withdrawal were dose dependent ($F[2,99] = 4.434$, $p<0.05$); Post Hoc comparisons (Scheffe) revealed that withdrawal from 3.0 mg/kg of nicotine increased thresholds above withdrawal from saline and 1.0 mg/kg of nicotine (p,0.04).

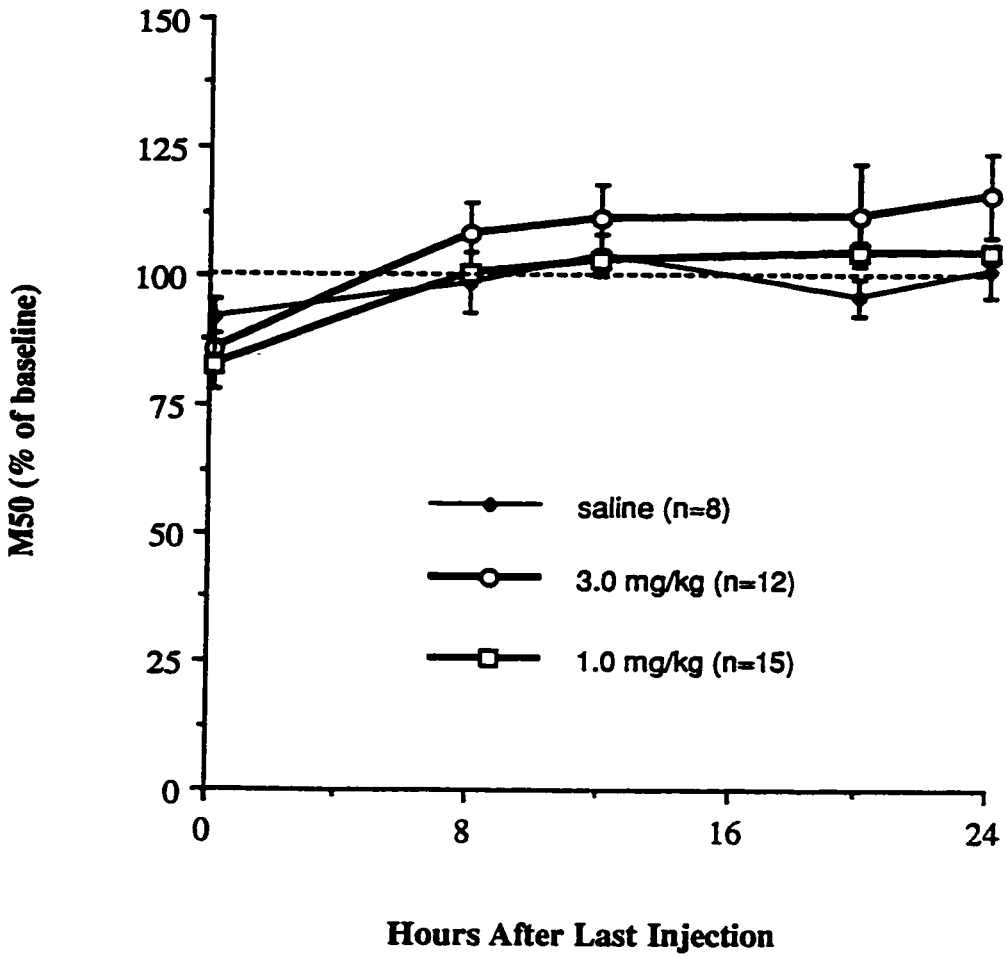


Figure 5. Mean threshold (M50) values determined following withdrawal from saline, 1.0 or 3.0 mg/kg/day of nicotine, M50 was not affected by withdrawal from nicotine ($F[2,99] = 1.12$, $p>0.05$).

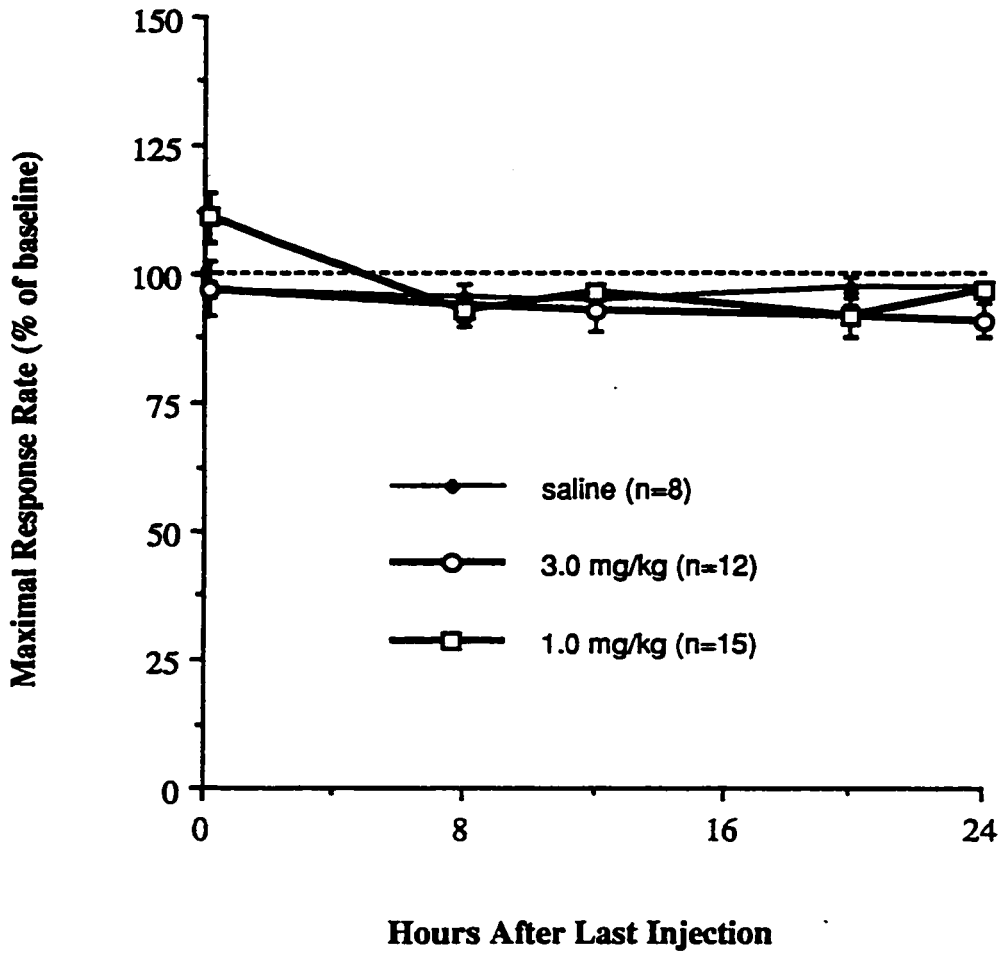


Figure 6. Maximal repsonse rates following withdrawal from saline, 1.0 or 3.0 mg/kg/day of nicotine.

DISCUSSION

Withdrawal from repeated injections of a high dose of nicotine caused transient rightward shifts in the rate-frequency curves and elevated the reward threshold measure of theta-zero. These results confirm that nicotine shares with amphetamine (Barret & White, 1980; Cassens, Actor, Kling, & Schildkraut, 1981; Kokkinidis et al., 1980; Wise & Munn, 1995), cocaine (Frank, et al., 1992; Kokkinidis & McCarter, 1990; Markou & Koob, 1991; Markou & Koob, 1992), and morphine (Schaefer & Michael, 1986; Wise and Carlezon - unpublished) the ability to cause a dependence syndrome that is characterized by attenuation of brain stimulation reward following withdrawal. Withdrawal from 2 weeks of repeated injections of amphetamine (Wise & Munn, 1995) or morphine (Wise & Carlezon - unpublished observations) is associated with rightward shifts in the rate-frequency curve. Reward thresholds (T0) were elevated to approximately 130% of baseline (corresponding to about a 0.2 log unit shift in the rate-frequency curve) following amphetamine or morphine withdrawal. In the present study, withdrawal from repeated injections of nicotine also elevated T0 to approximately 130% of baseline.

Alleviation of opponent-process depression of brain reward circuitry has been suggested to motivate self-administration of psychomotor stimulants (Dackis & Gold, 1985; Koob & Bloom, 1988), opiates (Koob, Stinus, Le Moal, & Bloom, 1989), and nicotine (Solomon & Corbit, 1973). Depression of brain reward circuitry is a withdrawal symptom common to both psychomotor stimulants (Dackis & Gold, 1985; Markou & Koob, 1991; Weiss, Hurd, Ungerstedt, Markou, Plotsky, & Koob. 1992), opiates (Koob, Stinus, Le Moal, & Bloom, 1989), and the present study now extends this generalization to nicotine. Inasmuch as depression of brain reward circuitry contributes to the habit-forming properties of these drugs the present study suggests that a common brain

mechanism is involved in the habit-forming properties of nicotine as both psychomotor stimulants and opiates.

The effects of nicotine withdrawal on T0 were dose dependent. Withdrawal effects were observed in animals that had been treated with 3.0 mg/kg/day of nicotine but not in animals treated with 1.0 mg/kg/day. Following withdrawal from the high dose of nicotine elevations in T0 were evident 8 hours after withdrawal and throughout the 24 hour testing period. There was a tendency for T0 to increase between 8 and 20 hours following the last nicotine injection. The increase in T0 from 8 to 20 hours after withdrawal from the high dose of nicotine reflects a progressive exacerbation of the withdrawal syndrome. The time of onset of this effect is consistent with physical, behavioral, and subjective effects of nicotine withdrawal reported by other authors. Physical withdrawal signs and decreased locomotor activity are observed 16 hours following the termination of continuous nicotine infusion but are not evident after 40 hours (Malin et al., 1992). Deficits in operant responding are evident within 24 hours of nicotine withdrawal (Carroll et al., 1989; Corrigall et al., 1989; Morrison, 1974). A PTZ-like discriminative cue is evident 24 hours and peaks at 48 hours after nicotine withdrawal (Harris et al., 1986).

The best evidence that elevations in T0 reflect attenuation of brain stimulation reward would be parallel rightward shifts in the rate-frequency curves. Inasmuch as the rate-frequency curve is analogous to the dose-response curve of pharmacology, rightward shifts of the rate-frequency curve indicate a decrease in the potency of the stimulation; that is, higher stimulation frequencies (doses) are required to attain a given response. Nicotine withdrawal did not cause parallel rightward shifts in the rate-frequency curves; whereas withdrawal from the high dose of nicotine increased the threshold measure of T0 the tendency for M50 to increase was not statistically reliable. It is not clear why these two threshold measures were differentially affected by nicotine withdrawal. In addition to manipulations that alter reward, shifts in rate-frequency curves may result from

alterations in performance capacity (Miliaresis et al., 1986). However, it is unlikely that performance factors are responsible for the shift in T0 in the present study. In the curve-shift paradigm the simplest indication of performance capacity is the maximal response rate that occurred for a frequency trial during a rate-frequency determination. Nicotine withdrawal did not affect the maximal response rates and did not cause downward shifts in the rate-frequency curves. Moreover, when performance capacity is impaired the slope of the rate-frequency curve decreases (Miliaresis et al., 1986). Decreases in the slope of the rate-frequency curve are associated with relatively greater increases in M50 than T0, the opposite effect of that obtained in the present study. Thus, there is no evidence that performance deficits were responsible for shifts in the rate-frequency curves. The fact that T0 was increased more than M50 indicates that nicotine withdrawal attenuated the rewarding effects of low stimulation frequencies without affecting the rewarding impact of higher frequencies.

Whereas the high dose of nicotine was associated with elevations in reward threshold following withdrawal only the low dose was associated with an immediate decrease in reward threshold. Thirty minutes after injections of the low dose of nicotine (0.5 mg/kg/injection) rate-frequency curves were shifted to the left and corresponding reward threshold values were decreased. This effect is in agreement with previous studies of the effects of nicotine in the curve-shift paradigm (Bauco & Wise, 1994) as well as other brain stimulation reward threshold measures (Huston-Lyons & Kornetsky, 1992). The high dose of nicotine (1.5 mg/kg/injection) did not reliably shift rate-frequency curves or reduce reward thresholds determined 30 minutes after injection; although the mean value for T0 across 7 days of testing was 87% of baseline this decrease was not statistically significant.

The absence of a threshold lowering effect in response to high doses of nicotine is not inconsistent with the dose-response effects of nicotine in the curve-shift paradigm; the function relating nicotine dosage to shifts in rate-frequency curves appeared to be u-

shaped (Bauco & Wise, 1994). Increasing nicotine dosage from 0.05 mg/kg to 0.4 mg/kg causes dose-dependent decreases reward threshold. Increasing dosage to 0.8 mg/kg is less effective than 0.4 mg/kg. The present results are consistent with this biphasic dose-response curve for nicotine; a higher dose of nicotine, 1.5 mg/kg, was less effective than 0.8 mg/kg at shifting rate-frequency curves. In fact, nicotine is only self-administered by rats within a narrow range of doses and the 1.5 mg/kg dose is approximately 3 times the dose of nicotine that rats will self-administer in a 1-hour daily session (Corrigall & Coen, 1989) or 1.5 times higher than rats will self-administer in a 12-hour daily session (Cox et al., 1984). The most parsimonious explanation for the biphasic dose-response curve is that high doses of nicotine impair the ability of animals to work for brain stimulation. Indeed, in the present study 1.5 mg/kg of nicotine produced ataxia and prostration which interfered with lever-pressing for up to 15 minutes. However, there is no indication that responding was impaired during the last rate-frequency trial which was used to determine reward threshold; during this time maximal response rates averaged 95% of baseline and rate-frequency curves were parallel. A second possibility is that high doses of nicotine produce aversive effects that mask or block the rewarding effects. Nicotine has been shown to establish conditioned place aversions (Jorenby et al., 1990). Finally, it is possible that high doses of nicotine cause either desensitization or inactivation of the nicotinic acetylcholine receptor which may limit the rewarding effects of nicotine during the test period. Desensitization of the nicotinic acetylcholine receptor occurs in response to acute exposure to nicotine and is associated with a transient shift in the conformation of the receptor to an inactive state which may last for seconds to minutes (Katz & Thesleff, 1957; Lena & Changeux, 1993). Functional inactivation of the nicotinic receptor occurs following long-term exposure to nicotine and may last hours to days (Lukas, 1991; Simasko, Soares, & Weiland, 1986; Lapchak, Araujo, Quiron, & Collier, 1989). It remains to be determined whether the nicotine treatment used in the present study results in long term inactivation of nicotinic receptors. It is possible that with

longer test periods after the injection the rewarding effects of nicotine would become evident.

Although no neurobiological mechanism has been directly implicated in the reward-attenuating effects of drug withdrawal there is increasing evidence that withdrawal from opiates (Acquas et al., 1991; Pothos et al., 1991; Rossetti et al., 1991) and psychomotor stimulants (Imperato et al., 1992; Maisonneuve et al., 1995; Parsons et al., 1991; Robertson, et al., 1991; Weiss et al., 1992) causes depletion of extracellular dopamine in the NAS. Moreover, both the magnitude of elevations in brain stimulation reward threshold and degree of dopamine depletion are both correlates of the amount of cocaine consumed during a self-administration session (Markou & Koob, 1991; Weiss et al., 1992). Thus, withdrawal from higher doses of cocaine is associated with greater dopamine depletion and greater elevations in brain stimulation reward thresholds. Inasmuch as brain stimulation reward is mediated by dopaminergic neurotransmission in the NAS, dopamine depletion in this region may underlie depression of the reward system associated with drug withdrawal.

Currently, little is known of the effects of long-term nicotine administration on the functioning of dopamine neurons. Studies of dopamine turnover and receptor binding following chronic nicotine treatments have yielded contradictory results which may be related, in part, to differences in treatment regimens, nicotine dose, and receptor ligand. Repeated intermittent injections of nicotine are reported to increase the ratio of DA/DOPAC in the Nas 24 hours after withdrawal, suggesting a decrease in dopamine turnover in this region (Lapin, Maker, Sershen, & Lajtha, 1989). However, continuous infusions of nicotine fail to alter dopamine turnover, TH accumulation, or total dopamine level in the Nas (Carr, Rowell, & Pierce, 1989; Fung & Lau, 1992) although dopamine turnover in striatal tissue may be reduced (Fung & Lau, 1989). Alterations in dopamine receptor binding remain equally equivocal. Repeated injections of nicotine increase the number of binding sites for tritiated domperidone in Nas when assayed 24 hrs after the

last injection (Reilly, Lapin, Maker, & Lajtha, 1987). In contrast, continuous infusion of nicotine is reported to decrease binding of the D2 agonist N-propylnorapomorphine (Janson, Hedlund, Hillefors, & von Euler, 1992). Whereas continuous infusions of nicotine do not affect spiperone binding in the Nas (Fung & Lau, 1992) spiperone binding is reported to increase in striatal tissue (Carr, Rowell, & Pierce, 1989; Fung & Lau, 1988; Fung & Lau, 1989). Treatment with higher doses of nicotine for a longer period caused no changes in the binding of tritiated ligands for either the D1 receptor (SCH23390) or the D2 receptor (spiperone) in striatal tissue either immediately after 21 days or following a withdrawal period of 7 days (Kirch, Taylor, Creese, Xu, & Wyatt, 1992). Thus, there is only minimal evidence that long-term nicotine treatment alters midbrain dopamine neurons. The fact that investigations have yielded such disparate results suggests that the effect of long-term nicotine on the functioning of the midbrain dopamine systems is not a robust phenomenon. Experiments designed to examine in vivo changes in dopamine functioning both during and following long-term nicotine treatments may be more conclusive.

The present study provides evidence for suppression of the brain reward system following nicotine withdrawal and indicates that nicotine, like psychomotor stimulants and opiates, is capable of causing dependence syndrome which may contribute to its habit-forming potential. Suppression of the reward system following drug withdrawal may prove to be more fundamental to dependence theories than the classical physical withdrawal signs associated with opiate dependence. Opiate self-adminstration can be dissociated from physical withdrawal disturbances (Wise & Bozarth, 1984); and physical withdrawal signs are not a predominant feature of psychomotor stimulant or nicotine dependence (Gawin & Ellinwood, 1989; Shiffman, 1979). Suppression of brain reward circuitry, as indicated by the attenuation of brain stimulation reward, offers a withdrawal symptom that is common to several classes of habit-forming drugs and suggests the involvement of a common brain system in both drug reward and dependence. It remains

unclear to what extent suppression of the reward system serves as an impetus to maintain drug self-administration. Effective stimuli for reinstating drug self-administration include the training drug or related drugs (de Wit & Stewart, 1983; Stewart & de Wit, 1987; Stewart & Wise, 1992). In contrast, chlorpromazine and naltrexone both attenuate brain stimulation reward (West & Wise, 1988) but fail to reinstate psychomotor stimulant self-administration (Gerber & Stretch, 1975; Stewart & Wise, 1992).

References

Acquas, E., Carboni, E., & Di Chiara, G. (1991). Profound depression of mesolimbic dopamine release after morphine withdrawal in dependent rats. European Journal of Pharmacology, 193, 133-134.

Ator, N. A., & Griffiths, R. R. (1983). Nicotine self-administration in baboons. Pharmacology Biochemistry and Behavior, 19, 993-1009.

Ausili, E. F., & Hoebel, B. G. (1983). Rewarding effects of amphetamine and cocaine in the nucleus accumbens and block by alpha-flupenthixol. Society for Neuroscience Abstracts, 9, 121.

Axelrod, J. (1970). Amphetamine: Metabolism, physiological disposition, and its effects on catecholamine storage. In E. Costa & S. Garatini (Eds.), Amphetamines and related compounds, (207-216). New York: Raven Press.

Barret, R. J., & White, D. K. (1980). Reward system depression following chronic amphetamine: Antagonism by haloperidol. Pharmacology Biochemistry and Behavior, 13, 555-559.

Bauco, P., Rivest, R., Wang, Y., & Wise, R. A. (1993). In vivo microdialysis monitoring of extracellular dopamine and metabolite levels in the nucleus accumbens during mesencephalic brain stimulation reward. International Symposium on Microdialysis and Allied Analytical Techniques.

Bauco, P., Wang., & Wise, R. A. (1993). Lack of sensitization or tolerance to the facilitating effect of ventral tegmental area morphine on lateral hypothalamic brain stimualtion reward. Brain Research, 617, 303-308.

Baumeister, A. A., Anticich, T. G., Hebert, G., Hawkings, M. F., & Nagy, M. (1989). Evidence that physical dependence on morphine is mediated by the ventral midbrain. Neuropharmacology, 28(11), 1151-1157.

Bechara, A., & van der Kooy, D. (1992). A single brain stem substrate mediates the motivational effects of both opiates and food in nondeprived rats but not in deprived rats. Behavioral Neuroscience, 106(2), 351-363.

Bozarth, M. A. (1987). Neuroanatomical boundaries of the reward-relevant opiate-receptor field in the ventral tegmental area as mapped by the conditioned place preference method in rats. Brain Research, 414, 77-84.

Bozarth, M. A., & Wise, R. A. (1981a). Intracranial self-administration of morphine into the ventral tegmental area of rats. Life Science, 28, 551-555.

Bozarth, M. A., & Wise, R. A. (1981b). Heroin reward is dependent on a dopaminergic substrate. Life Sciences, 29, 1881-1886.

Bozarth, M. A., & Wise, R. A. (1982). Dissociation of the rewarding and physical dependence-producing properties of morphine. In L. S. Harris (Ed.), Problems of Drug Dependence, National Institute on Drug Abuse, 158-164. Washington DC: U.S. Government Printing Office.

Bozarth, M. A., & Wise, R. A. (1984). Anatomically distinct opiate receptor fields mediate reward and physical dependence. Science, 224, 516-517.

Bozarth, M. A., & Wise, R. A. (1985). Involvement of the ventral tegmental dopamine system in opioid and psychomotor stimulant reinforcement. In L.S. Harris (Ed.), Problems of Drug Dependence, National Institute on Drug Abuse Research Monograph 67, 190-196. Washington DC: U.S. Government Printing Office.

Brace, H. M., Calder, F., Cooke, P., Inglis, W. L., Parker, G. C., Robertson, A., & Winn, P. (1993). Cholinergic stimulation of rat substantia nigra and ventral tegmental area: Responding for conditioned reinforcement and formation of place preferences. Society for Neuroscience Abstract, 19, 1832.

Brazell, M. P., Mitchell, S. N., Joseph, M. H., & Gray, J. A. (1990). Acute administration of nicotine increases the in vivo extracellular levels of dopamine, 3,4-dihydroxyphenylacetic acid and ascorbic acid preferentially in the nucleus

accumbens of the rat: Comparison with the caudate-putamen. Neuropsychopharmacology, 29(12), 1177-1185.

Bush, H. D., Bush, M. A., Miller, M. A., & Reid, L. D. (1976). Addictive agents and intracranial self-stimulation: Daily morphine and lateral hypothalamic self-stimulation. Physiological Psychology, 4, 79-85.

Carlsson, A. (1970). Amphetamine and brain catecholamines. In E. Costa & S. Garattini (Eds.), Amphetamines and related compounds, (289-300). New York: Raven Press.

Carr, G. D., & White, N. M. (1983). Conditioned place preference from intra-accumbens but not intra-caudate amphetamine injections. Life Sciences, 33, 2551-2557.

Carr, G. D., & White, N. M. (1986). Anatomical dissociation of amphetamine's rewarding and aversive effects: An intracranial microinjection study. Psychopharmacology, 89, 340-346.

Carr, L. A., Rowell, P. P., & Pierce, W. M. (1989). Effects of subchronic nicotine administration on central dopaminergic mechanisms in the rat. Neurochemical Research, 14(6), 511-515.

Carroll, M. E., Lac, S. T., Asencio, M., & Keenan, R. M. (1989). Nicotine dependence in rats. Life Sciences, 45, 1381-1388.

Cassens, G., Actor, C., Kling, M., & Schildkraut, J. J. (1981). Amphetamine withdrawal: Effects on threshold of intracranial reinforcement. Psychopharmacology, 73, 318-322.

Clarke, P. B. S. (1987). Nicotine and smoking: A perspective from animal studies. Psychopharmacology, 92, 135-143.

Clarke, P. B. S. (1990). Mesolimbic dopamine activation-the key to nicotine reinforcement? The Biology of Nicotine Dependence. Ciba foundation symposium.(153-168). Wiley, Chichester. .

Clarke, P. B. S., & Fibiger, H. C. (1987). Apparent absence of nicotine-induced conditioned place preference in rats. Psychopharmacology, 84-88.

Clarke. P. B. S., Hommer, D. W., Pert, A., & Skirboll, L. R. (1985). Electrophysiological actions of nicotine on substantia nigra single units. British Journal of Pharmacology, 85, 827-835.

Clarke, P. B. S., & Kumar, R. (1983). Nicotine does not improve discrimination of brain stimulation reward by rats. Psychopharmacology, 79, 271-277.

Clarke, P. B. S., & Pert, A. (1985). Autoradiographic evidence for nicotine receptors on nigrostriatal and mesolimbic dopaminergic neurons. Brain Research, 348, 355-358.

Clarke, P. B. S., Pert, C. B., &†Pert, A. (1984). Autoradiographic distribution of nicotine receptors in rat brain. Brain Research, 323, 390-395.

Clarke, P. B. S., Schwartz, R. D., Paul, S. M., Pert, C. B., & Pert, A. (1985). Nicotinic binding in rat brain: Autoradiographic comparison of [^{3}H]acetylcholine, [^{3}H]nicotine and [125I]-a-bungarotoxin. Journal of Neuroscience, 5(5), 1307-1315.

Colle, L. M., & Wise R. A. (1988). Effects of nucleus accumbens amphetamine on lateral hypothalamic brain stimulation reward. Brain Research, 459, 361-368.

Collier, H. O. J. (1968). Supersensitivity and dependence. Nature, 220, 228, 231.

Corrigall, W. A., & Coen, K. M. (1989). Nicotine maintains robust self-administration in rats on a limited-access schedule. Psychopharmacology, 99, 471-478.

Corrigall, W. A., & Coen, K. M. (1991). Selective dopamine antagonists reduce nicotine self-administration. Psychopharmacology, 104 171-176.

Corrigall, W. A., Coen, K. M., & Adamson, K. L. (1994). Self-administered nicotine activates the mesolimbic dopamine system through the ventral tegmental area. Brain Research, 653, 278-284.

Corrigall, W. A, Franklin, K. B. J., Coen K. M., & Clarke, P. B. S. (1992). The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. Psychopharmacology, 107, 285-289.

Corrigall, W. A., Herling, S., & Coen, K. M. (1989). Evidence for a behavioral deficit during withdrawal from chronic nicotine treatment. Pharmacology Biochemistry and Behavior, 33, 559-562.

Cox, B. M., Goldstein, A., & Nelson, W. T. (1984). Nicotine self-administration in rats. British Journal of Pharmacology, 83, 49-55.

Crippens, D., & Robinson, T. E. (1994). Withdrawal form morphine or amphetamine: Different effects on ventral striatal dopamine studied with microdialysis. Brain Research, 650, 56-60.

Crow, T. J. (1970). Enhancement by cocaine of intra-cranial self-stimulation in the rat. Life Sciences, 9, 375-381.

Dackis, C. A., & Gold, M. S. (1985). New concepts in cocaine addiction: The dopamine depletion hypothesis. Neuroscience and Biobehavioral Reviews, 9, 469-477.

Dahlstrom, A., & Fuxe, K. (1964). Evidence for the existence of monoamine-containing neurons in the central nervous system . I. Demonstration of monoamines in the cell bodies of brain stem neurons. Acta Physiologica Scandinavica, 62, 1-55.

Damsma, D., Day, J., & Fibiger, H. C. (1989). Lack of tolerance to nicotine-induced dopamine release in the nucleus accumbens. European Journal of Pharmacology, 168, 363-368.

Deminiere, J. M., Taghzouti, K., Tassin, J. P., Le Moal, M., & Simon, H., (1988). Increased sensistivity to amphetamine and facilitation of amphetamine self-administration after 6-hydroxydopamine lesions of the amygdala. Psychopharmacology, 94, 232-236.

Deneau, G., Yanagita, T., & Seevers, M. H. (1969). Self-administration of psychoactive substances by the monkey: A measure of psychological dependence. Psychopharmacologia, 16, 30-48.

Deutch, A. Y., Holliday, J., Roth, R. H., Chun, L. L. Y., & Hawrot, E. (1987). Immunohistochemical localization of a neuronal nicotinic acetylcholine receptor in mammalian brain. Proceedings of the New York Academy of Sciences USA, 84, 8697-8701.

de Wit, H., & Stewart, J. (1983). Drug reinstatement of heroin-reinforced responding in the rat. Psychopharmacology, 79, 29-31.

de Wit, H., & Wise, R. A. (1977). Blockade of cocaine reinforcement in rats with the dopamine receptor blocker pimozide but not the noradrenergic blockers phentolamine or phenoxybenzamine. Canadian Journal of Psychology, 31, 195-203.

Devine, D., & Wise R. A. (1994). Self-administration of morphine, DAMGO, and DPDPE into the ventral tegmental area of rats. Journal of Neuroscience, 14(4), 1978-1984.

Di Chiara, G., Acquas, E., Carboni, E. (1992). Drug motivation and abuse: A neurobiological perspective. Annals of the New York Academy of Sciences, 654, 207-219.

Edmonds, D. E., & Gallistel, C. R. (1974). Parametric analysis of brain stimulation reward in the rat: III. Effect of performance variables on the reward summation function. Journal of Comparative and Physiological Psychology, 87, 876-883.

Emmett-Oglesby, M. W., Mathis, D. A., Moon, R, T, Y., & Lal, H. (1990). Animal models of drug withdrawal. Psychopharmacology, 101, 292-309.

Esposito, R. U., Perry, W., & Kornetsky, C. (1980). Effects of d-amphetamine and naloxone on brain stimulation reward. Psychopharmacology, 69, 187-191.

Esposito, R. U., Motola, A. H. D., & Kornetsky, C. (1977). Cocaine: Acute effects on reinforcement thresholds for self-stimulation behavior to the medial forebrain bundle. Pharmacology Biochemistry and Behavior, 8, 437-439.

Ettentberg, A., & Duvauchell, C. L. (1988). Haloperidol blocks the conditioned place preferences induced by rewarding brain stimulation. Behavioral Neuroscience, 102, 687-691.

Ettenberg, A., Pettit, H. O., Bloom, F. E., & Koob, G. F. (1982). Heroin and cocaine intravenous self-administration in rats: Mediation by separate neural systems. Psychopharmacology, 78, 204-209.

Fagerstrom, K. O., Schneider, N. G., & Lunell, E. (1993). Effectiveness of nicotine patch and nicotine gum as individual versus combined treatments for tobacco withdrawal symptoms. Psychopharmacology, 111, 271-277.

Fallon, J. H. (1988). Topographic organization of ascending dopaminergic projections. Annals of the New York Academy of Sciences, 537, 1-9.

Fallon, J. H., & Moore, R. Y. (1978). Catecholamine innervation of the basal forebrain. IV. Topography of the dopamine projection to the basal forebrain and neostriatum. Journal of Comparative Neurology, 180, 545-580.

Fenton, H. M., & Liebman, J. M. (1982). Self-stimulation response decrement patterns differentiate clonidine, baclofen and dopamine antagonists from drugs causing performance deficit. Pharmacology Biochemistry and Behavior, 17, 1207-1212.

Fibiger, H. C. (1984). The neurobiological substrates fo depression in Parkinson's disease: A hypothesis. Canadian Journal of Neurological Sciences, 11, 105-107.

Fibiger, H. C., Le Piane, F. G., Jakubovic, A., & Phillips, A. G. (1987). The role of dopamine in intracranial self-stimulation of the ventral tegmental area. Journal of Neuroscience, 7, 3888-3896.

Fiorino, D. F., Coury, A., Fibiger, H. C., & Phillips, A. G. (1993). Electrical stimulation of reward sites in the ventral tegmental area increases dopamine transmission in the nucleus accumbens of the rat. Behavioural Brain Research, 55, 131-141.

Fouriezos, G., & Wise, R. A. (1976). Pimozide-induced extinction of intracranial self-stimulation: Response patterns rule out motor or performance deficits. Brain Research, 103, 377-380.

Fouriezos, G., Hansson, P., & Wise, R. A. (1978). Neuroleptic-induced attenuation of brain stimulation reward in rats. Journal of Comparative and Physiological Psychology, 92(4), 661-671.

Frank, R. A., Martz, S., & Pommering, T. (1988). The effect of chronic cocaine on self-stimulation train-duration thresholds. Pharmacology Biochemistry and Behavior, 29(4), 755-758.

Frank, R. A., Manderscheid, P. Z., Panicker, S., Williams, H. P., & Kokoris, D. (1992). Cocaine euphoria, dysphoria and tolerance assessed using drug-induced changes in brain-stimulation reward. Pharmacology Biochemistry and Behaivor, 42(4), 771-779.

Franklin, K. B. J. (1978). Catecholamines and self-stimulation: Reward and performance effects dissociated. Pharmacology Biochemistry and Behavior, 9(6), 813-820.

Franklin, K. B. J., & McCoy, S. N. (1979). Pimozide-induced extinction in rats: Stimulus control of responding rules out motor deficit. Pharmacology Biochemistry and Behavior, 11(1), 71-75.

Fudala, P. J., & Iwamoto, E. T. (1986). Further studies on nicotine-induced conditioned place preference in the rat. Pharmacology Biochemistry and Behavior, 25, 1041-1049.

Fudala, P. J., Teoh, K. W., & Iwamoto, E. T. (1985). Pharmacologic characterization of nicotine-induced conditioned place preference. Pharmacology Biochemistry and Behavior, 22, 237-241.

Fung, Y. K., & Lau, Y.-S. (1989). Effect of nicotine pretreatment on striatal dopaminergic system in rats. Pharmacology Biochemistry and Behavior, 32, 221-226.

Fung, Y. K., & Lau, Y.-S. (1992). Chronic effects of nicotine on mesolimbic dopaminergic system in rats. Pharmacology Biochemistry and Behavior, 41, 57-63.

Gallistel, C. R., Boytim, M., Gomita, Y., & Klebanoff, L. (1982). Does pimozide block the reinforcing effect of brain stimulation? Pharamacology biochemistry and Behavior, 17(4), 769-781.

Gallistel, C. R., & Freyd, G. (1987). Quantitative determination of the effects of catecholaminergic agonists and antagonists on the rewarding efficacy of brain stimulation. Pharmacology Biochemistry and Behavior, 26(4), 731-741.

Gallistel, C. R., & Karras, D. (1984). Pimozide and amphetamine have opposing effects on the reward summation function. Pharmacology Biochemistry and Behavior, 20(1), 73-77.

Gallistel, C. R., Stellar, J. R., & Bubis, E. (1974). Parametric analysis of brain stimulation reward in the rat: I. The transient process and the memory-containing process. Journal of Comparative and Physiological Psychology, 87, 848-859.

Gawin F. H., & Ellinwood, E. H. (1989). Cocaine dependence. Annual review of Medicine, 40, 149-161.

Gerber, G. J., & Stretch, R. (1975). Drug-induced reinstatement of extinguished self-administration behavior in monkeys. Pharmacology Biochemistry and Behavior, 3, 1055-1061.

Gerber, G. J., & Wise R. A. (1989). Pharmacological regulation of intravenous cocaine and heroin self-administration in rats: A variable dose paradigm. Pharmacology Biochemistry and Behavior, 32, 527-531.

Gilbert R. M., & Pope, M. A. (1982). Early effects of quitting smoking. Psychopharmacology, 78, 121-127.

Goeders, N. E., Lane, J. D., & Smith, J. E. (1984). Self-administration of methionine enkephalin into the nucleus accumbens. Pharmacology Biochemistry and Behavior, 20, 451-455.

Goldberg, S. R., Spealman, R. D., & Goldberg, D. M. (1981). Persistent behavior at high rates maintained by intravenous self-administration of nicotine. Science, 214, 573-575.

Goldberg, S. R., Spealman, R. D., Risner, M. S., & Henningfield, J. E. (1983). Control of behavior by intravenous nicotine injections in laboratory animals. Pharmacology Biochemistry and Behavior, 19, 1011-1020.

Grenhoff, J., Aston-Jones, G., & Svensson, T. H. (1986). Nicotinic effects of the firing pattern of midbrain dopamine neurons. Acta Physiologica Scandinavica, 128, 351-358.

Grenhoff, J., & Svensson, T. H. (1989). Pharmacology of nicotine. British Journal of Addiction, 84, 477-492.

Hanson, H. M., Ivester, C. A., & Morton, B. R. (1979). Nicotine self-administration in rats. In N. A. Krasnegor (Ed.), Cigarette Smoking as a Dependence Process, National Institute on Drug Abuse Research Monograph, (158-184). Washington, DC: U.S. Government Printing Office.

Happe, H. K., Peters, J. L., Bergman, D. A., & Murrin, L. C. (1994). Localization of nicotinic cholinergic receptors in rat brain: Autoradiographic studies with [3H]cytisine. Neuroscience, 62(3), 929-944.

Harris, C. M., Emmett-Oglesby, M. W., Robinson, N. G., & Lal, H. (1986). Withdrawal from chronic nicotine substitutes partially for the interoceptive stimulus produced by pentylenetetrazol (PTZ). Psychopharmacology, 90, 85-89.

Hatsukami, D. K., Hughes, J. R., Pickens, R. W., & Svikis , D. (1984). Tobacco withdrawal symptoms: An experimental analysis. Psychopharmacology, 84, 231-236.

Hatsukami, D., Dahlgren, L., Zimmerman, R., Hughes, J. R. (1988). Symptoms of tobacco withdrawal from total cigarette cessation versus partial reduction. Psychopharmacology, 94, 242-247.

Heikkila, R. E., Orlansky, H., & Cohen, G. (1975). Studies on the distinction between uptake inhibition and release of (3H) dopamine in rat brain tissue slices. Biochemical Pharmacology, 24, 847-852.

Henningfield, J. E., (1984). Pharmacological basis and treatment of cigarette smoking. Journal of Clinical Psychiatry, 45, 24-34.

Henningfield, J. E., & Goldberg, S. R. (1983). Control of behavior by intravenous nicotine injections in human subjects. Pharmacology Biochemistry and Behavior, 19, 1021-1026.

Henningfield, J. E., & Goldberg, S. R. (1988). Pharmacologic determinants of tobacco self-administration by humans. Pharmacology, Biochemistry and Behavior, 30, 221-226.

Henningfield, J. E., Miyasato, K., & Jasinski, D. R. (1983). Cigarette smokers self-administer intravenous nicotine. Pharmacology Biochemistry and Behavior, 19, 887-890.

Henningfield, J. E., & Goldberg, S. R. (1988). Pharmacologic determinants of tobacco self-administration by humans. Pharmacology Biochemistry and Behavior, 30, 221-226.

Herning, R. I., Reese, T. J., & Bachman, J. (1983). EEG changes during tobacco withdrawal. Psychophysiology, 20(5), 507-512.

Himmelsbach, C. K. (1943). Morphine, with reference to physical dependence. Federation Proceedings, 2, 201-203.

Hoebel, B. G., Monaco, A. P., Hernandez, L., Ausili, E. F., Stanley, B. G., & Lenard, L. (1983). Self-injection of amphetamine directly into the brain. Psychopharmacology, 81, 158-163.

Hughes, J. R., Gust, S. W., Skoog, K., Keenan, R. M., & Fenwick, J. W. (1991). Symptoms of tobacco withdrawal. Archives of General Psychiatry, 48, 52-59.

Hughes, J. R., Hatsukami, D. K., Pickens, R. W., Hrahn, D., Malin, S, & Luknic, A. (1984). Effect of nicotine on the tobacco withdrawal syndrome. Psychopharmacology, 83, 82-87.

Huston-Lyons, D., & Kornetsky, C. (1992). Effects of nicotine on the threshold for rewarding brain stimulation in rats. Pharmacology Biochemistry and Behavior, 41, 755-759.

Huston-Lyons, D., Sarkar, M., & Kornetsky, C. (1993). Nicotine and brain-stimulation reward: Interactions with morphine, amphetamine and pimozide. Pharmacology Biochemistry and Behavior, 46, 453-457

Imperato, A., Mele, A., Scrocco, M. G., Puglisi-Allegra, S. (1992). Chronic cocaine alters limbic extracellular dopamine: Neurochemical basis for addiction. European Journal of Pharmacology, 212, 299-300.

Imperato, A., Mulas, A., & Di Chiara, G. (1986). Nicotine preferentially stimulates dopamine release in the limbic system of freely moving rats. European Journal of Pharmacology, 132, 337-338.

Iwamoto, E. T. (1990). Nicotine conditions place preferences after intracerebral administration in rats. Psychopharmacology, 100, 251-257.

Jaffe, J. H. (1990). Drug addiction and drug abuse. In L. S. Goodman & A. Gilman (Eds.), The Pharmacological Basis of Therapeutics, Vol 8, 522-573. New York: Macmillan.

Janson, A. M., Hedlund, P. B., Hillefors, M., & von Euler, G. (1992). Chronic nicotine treatment decreases dopamine D2 agonist binding in the rat basal ganglia. Neuroreport, 3(12), 1117-1120.

Jenk, F., Gratton, A., & Wise, R. A. (1987). Opioid receptor subtypes associated with ventral tegmental facilitation of lateral hypothalamic brain stimulation reward. Brain Research, 423, 34-38.

Jorenby, D. E., Steinpreis, R. E., Sherman, J. E. A., & Baker, T. B. (1990). Aversion instead of preference learning indicated by nicotine place conditioning in rats. Psychopharmacology, 101, 533-538.

Kalant, H., LeBlanc, A. E., & Gibbins, R. J. (1971). Tolerance to and dependence on some non-opiate psychotropic drugs. Pharmacological Reviews, 23(3), 135-191.

Katz, B., & Thesleff, S. (1957). A study of the "desenstization" produced by acetylcholine at the motor end plate. Journal of Physiology, 138, 63-80.

Kirch, D. G., Taylor, T. R, Creese, I., Xu, S.-X., & Wyatt, R. J. (1992). Effect of chronic nicotine treatment and withdrawal on rat striatal D1 and D2 dopamine receptors. Journal of Pharmacy and Pharmacology, 44(2), 89-92.

Knott, V., & Venables, P. (1977). EEG alpha correlates of non-smokers, smokers, smoking and smoking deprivation. Psychophysiology, 14, 150-156.

Kokkinidis, L., & McCarter, B. D. (1990). Postcocaine depression and sensitization of brain-stimulation reward: Analysis of reinforcement and performance effects. Pharmacology Biochemistry and Behavior, 36, 463-471.

Kokkinidis, L., Zacharko, R. M., & Predy, P. A. (1980). Post-amphetamine depression of self-stimulation responding from the substantia nigra: Reversal by tricyclic antidepressants. Pharmacology Biochemistry and Behavior, 13, 379-383.

Koob, G. F., & Bloom, F. E. (1988). Cellular and molecular mechanisms of drug dependence. Science, 242, 715-2723.

Koob, G. F., Fray, P. J., & Iversen, S. D. (1978). Self-stimulation at the lateral hypothalamus and locus coeruleus after specific unilateral lesions of the dopamine system. Brain Research, 146, 123-140.

Koob, G. F., Stinus, L., Le Moal, M., & Bloom, F. E. (1989). Opponent-process theory of motivation: Neurobiological evidence from studies of opiate dependence. Neuroscience and Biobehavioral Reviews, 13, 135-140.

Kornetsky, C., & Esposito R. U. (1981). Reward and detection thresholds for brain stimulation: Dissociative effects of cocaine. Brain Research, 209, 496-500.

Lapchak, P. A., Araujo, D. M., Quiron, R., & Collier, B. (1989). Effect of chronic nicotine treatment on nicotinic autoreceptor function and N-[3H]methylcarbamylcholine binding sites in the rat brain. Journal of Neurochemistry, 52(2), 483-491.

Lapin, E. P., Maker, H. S., Sershen, H., & Lajtha, A. (1989). Action of nicotine on accumbens dopamine and attenuation with repeated administration. European Journal of Pharmacology, 160, 53-59.

Leeb, K., & Wise, R. A. (1994). Effect of intravenous self-administration of d- and l-amphetamine on nucleus accumbens (NAc) dopamine levels. Society for Neuroscience Abstract, 20, 1622.

Lena, C., & Changeux, J. -P. (1993). Allosteric modulations of the nicotinic acetylcholine receptor. Trends in Neuroscience, 16(5), 181-186.

Lichtensteiger, W., Hefti, F., Felix, D., Huwyler, T., Melamed, E., & Schlumpf. (1982). Stimulation of nigrostriatal dopamine neurons by nicotine. Neuropharamacology, 21, 963-968.

Liebman, J. M. (1983). Discriminating between reward and performance: A critical review of intracranial self-stimulation methodology. Neuroscience and Biobehavioral Reviews, 7, 45-72.

Lindsmith, A. R. (1947). Opiate Addiction. Bloomington , IN: Principia Press.

Lukas, R. J. (1991). Effects of chronic nicotinic ligand exposure on functional activity of nicotinic acetylcholine receptors expressed by cells of the PC12 rat pheochromocytoma or the TE671/RD human clonal line. Journal of Neurochemistry, 56(4), 1134-1145.

Lyness, W. H., Friedle, N. M., & Moore, K. E. (1979). Destruction of dopaminergic nerve terminals in nucleus accumbens: effect on d-amphetamine self-administration. Pharmacology Biochemistry and Behavior, 11, 553-556.

Mackey, W. B., & van der Kooy D. (1985). Neuroleptics block the positive reinforcing effects of amphetamine but not of morphine as measured by place conditioning. Pharmacology Biochemistry and Behavior, 22, 101-106.

Maisonueuve, I. M., Ho, A., & Kreek, M. J. (1995). Chronic administration of a cocaine "binge" alters basal extracellular levels in male rats: An in vivo microdialysis study. Journal of Pharmacology and Experimental Therapeutics, 272(2), 652-657.

Malin, D. H., Lake, J. R., Newlin-Maultsby, P., Roberts, L. K., Lanier, J. G., Carter, V. A., Cunningham, J. S., & Wilson, O. B. (1992). Rodent model of nicotine abstinence syndrome. Pharmacology Biochemistry and Behavior, 43 779-784.

Martino-Barrows, A. M., & Kellar, K. J. (1986). [3H]acetylcholine and [3H](-)nicotine label the same recognition site in rat brain. Molecular Pharmacology, 31, 169-174.

Markou, A., & Koob, G. F. (1991). Postcocaine anhedonia: An animal model of cocaine withdrawal. Neuropsychopharmacology, 4(1), 17-26.

Markou, A., & Koob, G. F. (1992). Bromocriptine reverses the elevation in intracranial self-stimulation threshold observed in a rat model of cocaine withdrawal. Neuropsychopharmacology, 7(3), 213-224.

Martin-Iverson, M. T., Szostak, C., & Fibiger, H. C. (1986). 6-Hydroxydopamine lesions of the medial prefrontal cortex fail to influence self-administration of cocaine. Psychopharmacology, 88, 310-314.

McGregor, A., Baker, G., & Roberts, D. C. S. (1994). Effect of 6-hydroxydopamine lesions of the amygdala on intravenous cocaine self-administration under progressive ratio schedule of reinforcement. Brain Research, 646, 273-278.

Mereu, G., Yoon, K. -W., Boi, V., Gessa, G. L., Naes, L., & Westfall, T. C. (1987). Preferential stimulation of ventral tegmental area dopaminergic neurons by nicotine. European Journal of Pharmacology, 141, 395, 400.

Mifsud, J. C., Hernandez, L., & Hoebel, B. G. (1989). Nicotine infused into the nucleus accumbens increases synaptic dopamine as measured by in vivo microdialysis. Brain Research, 478, 365-367.

Miliaressis, E., Rompre, P. -P., Laviolette, P., Philippe, L., & Coulombe, D. (1986). the curve-shift paradigm in self-stimulation. Physiology and Behavior, 37, 85-91.

Mogenson, G. J., Takigawa, M., Robertson, A., & Wu, M. (1979). Self-stimulation of the nucleus accumbens and ventral tegmental area of Tsai attenuated by microinjections of spiroperidol into the nucleus accumbens. Brain Research, 171, 247-259.

Morency, M. A., & Beninger. R. J. (1986). Dopaminergic substrates of cocaine-induced place conditioning. Brain Research, 399, 33-41.

Morrison, C. F. (1974). Effects of nicotine and its withdrawal on the performance of rats on signalled and unsignalled avoidance schedules. Psychopharmacologia, 38, 25-35.

Museo, E., & Wise, R. A. (1994). Place preference conditioning with ventral tegmental injections of cytisine. Life Sciences, 55(15), 1179-1186.

Nakahara, D., Fuchikami, K. Ozaki, N., Iwasaki, T., & Nagatsu, T. (1992). Differential effect of self-stimulation on dopamine release and metabolism in the rat medial frontal cortex, nucleus accumbens and striatum studied by in vivo microdialysis. Brain Research, 574, 164-170.

Nakajima, S., & Wise R. A. (1987). Heroin self-administration in the rat suppressed by SCH 23390. Society for Neuroscience Abstract, 13, 1545.

Nisell, M., Nomikos, G. G., & Svensson, T. H. (1994). Systemic nicotine-induced dopamine release in the rat nucleus accumbens is regulated by nicotinic receptors in the ventral tegmental area. Synapse, 16, 36-44.

North, R. A. (1992). Cellular actions of opiates and cocaine. Annals of the New York Academy of Sciences, 654, 1-6.

Olds J., & Milner, P. (1954). Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. Journal of Comparative and Physiological Psychology, 47, 419-427.

Olds, M. E., (1982). Reinforcing effects of morphine in the nucleus accumbens. Brain Research, 237, 429-440.

Parsons, L. H., Smith, A. D., & Justice, J. B. (1991). Basal extracellular dopamine is decreased in the rat nucleus accumbens during abstinence from chronic cocaine. Synapse, 9, 60-65.

Pettit, H. O., & Justice, J. B. (1989). Dopamine in the nucleus accumbens during cocaine self-administration as studied by in vivo microdialysis. Pharmacology, Biochemistry and Behavior, 34, 899-904.

Pettit, H. O., & Justice, J. B. (1991). Effect of dose on cocaine self-administration behavior and dopamine levels in the nucleus accumbens. Brain Research, 539, 94-102.

Phillips, A. G., Broekkamp, C. L. E., & Fibiger, H. C. (1983). Strategies for studying the neurochemical substrates of drug reinforcement in rodents. Progress in Neuro-psychompharmacology and Biological Psychiatry, 7, 585-590.

Phillips, A. G., Coury, A., Fiorino, D., LePiane, F. G., Brown, E., & Fibiger, H. C. (1992). Self-stimulation of the ventral tegmental area enhances dopamine release in the nucleus accumbens: A microdialysis study. Annals of the New York Academy of Sciences, 654, 199-206.

Phillips, A. G, & Fibiger, H. C. (1978). The role of dopamine in maintaining intracranial self-stimulation in the ventral tegmentum, nucleus accumbens, and medial prefrontal cortex. Canadian Journal of Physiology, 32, 58-66.

Phillips, A. G., & LePiane, F. G. (1980). Reinforcing effects of morphine microinjections into the ventral tegmental area. Pharmacology Biochemistry and Behavior, 12, 965-968.

Phillips, A. G., LePiane, F. G., & Fibiger, H. C. (1983). Dopaminergic mediation of reward produced by direct injection of enkephalin into the ventral tegmental area of the rat. Life Sciences, 33, 2505-2511.

Pothos, E., Rada, P., Mark, G. P., & Hoebel, B. G. (1991). Dopamine microdialysis in the nucleus accumbens during acute and chronic morphine, naloxone-precitated withdrawal and clonidine treatment. Brain Research, 566, 348-50.

Pocock, D., Leeb, K., & Wise, R. A. (1994). Elevations and phasic fluctuations in nucleus accumbens dopamine (DA) during IV heroin self-administration. Society for Neuroscience abstract, 20, 1234.

Pradhan, S. N., & Bowling, C. (1971). Effects of nicotine on self-stimulation in rats. Journal of Pharmacology and Experimental Therapeutics, 176, 229-243.

Reilly M. A., Lapin, E. P., Maker, H. S., & Lajtha, A. (1987). Chronic nicotine administration increases binding of [3H]domperidone in rat nucleus accumbens. Journal of Neuroscience Research, 18, 621-625.

Risner, M. E., & Jones, B. E. (1976). Role of noradrenergic and dopaminergic processes in amphetamine self-administration. Pharmacology Biochemistry and Behavior, 5, 477-482.

Rivest, R., Bauco, P., Wang., & Wise, R. A. (1993). Extracellualr dopamine and metabolite levels during rewarding lateral hypothalamic brain stimulation: Effect of fixed and variable "dose" of brain stimulation. International Symposium on Microdialysis and Allied Analytical Techniques.

Rivest, R., Leeb, K., Leone, P., & Wise, R. A. (1993). Microdialysis assessment of nucleus accumbens dopamine and metabolites during IV heroin self-administration: Changes with unit dose. Society for Neuroscience Abstract, 19, 1023.

Roberts, D. C. S., Corcoran, M. E., & Fibiger, H. C. (1977). On the role of ascending catecholaminergic systems in intravenous self-administration of cocaine. Pharmacology Biochemistry and Behavior, 6, 615-620.

Roberts, D. C. S., & Koob. G. F. (1982). Disruption of cocaine self-administration following 6-hydroxydopamine lesions of the ventral tegmental area in rats. Pharmacology Biochemistry and Behavior, 17, 901-904.

Roberts D. C. S., Koob. G. F., Klonoff, P., & Fibiger, H. C. (1980). Extinction and recovery of cocaine self-administration following 6-OHDA lesions of the nucleus accumbens. Pharmacology Biochemistry and Behavior, 12, 781-787.

Robertson, M. W., Leslie, C. A., & Bennett, J. P. (1991). Apparent synaptic dopamine deficiency induced by withdrawal from chronic cocaine treatment. Brain Research, 538, 337-339.

Rompre, P. -P., & Miliaresis, E. (1985). Localization of reward-relevant neurons in the pontine tegmentum: A moveable electrode mapping study. Brain Research, 496, 295-302.

Rompre, P. -P., & Wise, R. A. (1989). Opioid-neuroleptic interaction in brainstem self-stimulation. Brain Research, 477, 144-151.

Rossetti, Z. L., Hmaidan, Y., & Gessa, G. L. (1992). Marked inhibition of mesolimbic dopamine release: A common feature of ethanol, morphine, cocaine and amphetamine abstinence in rats. European Journal of Pharmacology, 221, 227-234.

Schacter, S. (1978). Pharmacological and psychological determinants of smoking. Annals of Internal Medicine, 88, 104-114.

Schaefer, G. J., & Michael, R. P. (1986). changes in response rates and reinforcement thresholds for intracranial self-stimulation during morphine withdrawal. Pharmacology Biochemistry and Behavior, 25, 1263-1269.

Schaefer, G. J., & Michael, R. P. (1988). An analysis of the effects of amphetamine on brain self-stimulation behavior. Behavioral Brain Research, 29, 93-101.

Schenk, S., Horger, B. A., Peltier, R., & Shelton, K. (1991). Supersensitivity to the reinforcing effects of cocaine following 6-hydroxydopamine lesions to the medial prefrontal cortex in rats. Brain Research, 543, 227-235.

Shiffman, S. (1979). The tobacco withdrawal syndrome. In N. A. Krasnegor (Ed.), Cigarette Smoking as a Dependence Process, National Institute on Drug Abuse Research Monograph. 158-184. Washington, DC: U.S. Government Printing Office.

Shoaib, M., Stolerman, I. P., & Kumar, R. C. (1994). Nicotine-induced place preferences following prior nicotine exposure in rats. Psychopharmacology, 113, 445-452.

Simasko, S. M., Soares, J. R., & Weiland, G. A. (1986). Two components of carbamylcholine-induced loss of nicotinic acetylcholine receptor function in the neuronal cell line PC12. Molecular Pharmacology, 30, 6-12.

Slifer, B. L., & Balster, R. L. (1985). Intravenous self-administration of nicotine: With and without schedule-induction. Pharmacology Biochemistry and Behavior, 22, 61-69.

Solomon, R. L., & Corbit, J. D. (1973). An opponent-process theory of motivation: II. Cigarette addiction. Journal of Abnormal Psychology, 81(2), 158-171.

Solomon, R. L., & Corbit, J. D. (1974). An opponent-process theory of motivation: I. Temporal dynamics of affect. Psychological Reviews, 81, 119-145.

Spyraki, C., Fibiger, H. C., & Phillips, A. G. (1982). Dopaminergic substrates of amphetamine-induced place preference conditioning. Brain Research, 253, 185-193.

Stellar, J. R., & Corbett, D. (1989). Regional neuroleptic microinjections indicate a role for nucleus accumbens in lateral hypothalamic self-stimulation reward. Brain Research, 477, 126-143.

Stewart, J., & de Wit, H. (1987). Reinstatement of drug-taking behavior as a method of assessing incentive motivational properties of drugs. In M. A. Bozarth (Ed.), Methods of Assessing the Reinforcing Properites of Abused Drugs, (211-227). New York: Springer Verlag.

Stewart, J., & Wise R. A. (1992). Reinstatement of heroin self-administration habits: Morphine prompts and naltrexone discourages renewed responding after extinction. Psychopharmacology, 108, 779-784.

Stolerman, I. P., Goldfarb, T., Fink, R., & Jarvik, M. E. (1973). Influencing cigarette smoking with nicotine antagonists. Psychopharmacologia, 28, 247-259.

Stolerman, I. P., & Shoaib, M. (1991). The neurobiology of tobacco addiction. Trends in Pharmacological Sciences, 12, 467-773.

Stinus, L., Le Moal, M., & Koob, G. F. (1990). Nucleus accumbens and amygdala are possible substrates for the aversive stimulus effects of opiate withdrawal. Neuroscience, 37(3), 767-773.

Swanson, L. W., Simmons, D. M., Whiting, P. J., & Lindstrom, J. (1987). Immunohistochemical localization of neuronal nicotinic receptors in the rodent central nervous system. Journal of Neuroscience, 7, 3334-3342.

Tennant, F. S., Tarver, A. L., & Rawson, R. A. (1984). Clinical evaluation of mecamylamine for withdrawal from nicotine dependence. In L. S. Harris (Ed.), Problems of Drug Dependence, National Institute on Drug Abuse Research Monograph, 49 (239-246). Washington, DC: U.S. Government Printing Office.

Ulett, J. A., & Itil, T. M. (1969). Quantitative electroencephalogram in smoking and smoking deprivation. Science, 164, 969-970.

Valenstein, E. S. (1964). Problems of measurement and interpretation with reinforcing brain stimulation. Psychological Review, 71(6), 415-437.

van der Kooy, D., Mucha, R. F., O'Shaughnessy , M., & Bucenieks, P. (1982). Reinforcing effects of brain microinjections of morphine revealed by conditioned place preference. Brain Research, 243, 107-117.

Wada, E., Wada, K., Boulter, J., Deneris, E., Heinemann, S., Patrick, J., & Swanson, L. W. (1989). Distribution of alpha2, alpha3, alpha4 and beta2 neuronal nicotinic receptor subunit mRNA in the central nervous system: A hybridization histochemical study in the rat. Journal of Comparative Neurology, 284, 314-335.

Wei, E. T, Loh, H. H., & Way E. L. (1973). Brain sites of precipitated abstinence in morphine-dependent rats. Journal of Pharmacology and Experimental Therapeutics, 185, 108-115.

Wei, E. T., & Loh, H. H. (1976). Physical dependence on opiate-like peptides. Science, 193, 1262-1263.

Weiss, F., Hurd, Y. L., Ungerstedt, U., Markou, A., Plotsky, M., & Koob, G. F. (1992). Neurochemical correlates of cocaine and ethanol self-administration. Annals of the New York Academy of Sciences, 654, 220-241.

Weiss, F., Markou, A., Lorang, M. T., & Koob, G. F. (1992). Basal extracellular dopamine levels in the nucleus accumbens are decreased during cocaine withdrawal after unlimited-access self-administration. Brain research, 593, 314-318.

Welzl,. H., Kuhn, G., & Huston, J. P. (1989). Self-administration of small amounts of morphine through glass micropipettes into the ventral tegmental area of the rat. Neuropharmacology, 28, 1017-1023.

West, R. J., Jarvis, M. J., Russell, M. A. H., Carruthers, M. E., & Feyerabend, C. (1984). Effect of nicotine replacement on the cigarette withdrawal syndrome. British Journal of Addiction, 79, 213-219.

West, R., & Schneider, N. (1988). Drop in heart rate following smoking cessation may be permanent. Psychopharmacology, 94, 566-568.

West, T. E. G., & Wise, R. A. (1988). Nucleus accumbens opioids facilitate brain stimulation reward. Society for Neuroscience Abstracts, 14, 1102.

Wilson, M. C., & Schuster, C. R. (1972). The effects of chlorpromazine on psychomotor stimulant self-administration on the rhesus monkey. Psychopharmacologia, 26, 115-126.

Wise, R. A. (1982). Neuroleptics and operant behavior: The anhedonia hypothesis. Behavioral Brain Sciences, 5, 39-87.

Wise R. A., (1987). Intravenous drug self-administration: A special case of positive reinforcement. In M. A. Bozarth (Ed.), Methods of Assessing the Reinforcing Properties of Abused Drugs, (pp. 117-141). New York: Springer Verlag.

Wise, R. A., (1988). The neurobiology of craving: Implications for the understanding and treatment of addiction. Journal of Abnormal Psychology, 97(2), 118-132.

Wise R. A. (1989). The brain and reward. In J. M. Liebman, & S. J. Cooper (Eds.), The Neuropharmacological Basis of Reward, (377-424). Oxford: Oxford University Press.

Wise, R. A., Bauco, P., Carlezon W. A., & Trojniar, W. (1992). Self-stimulation and drug reward mechanisms. Annals of the NewYork Academy of Sciences, 654, 192-198.

Wise, R. A., Newton, P., Leeb, K., Burnette, B., Pocock, D., & Justice, J. B. (1994). Elevations and phasic fluctuations in nucleus accumbens dopamine during IV cocaine self-administration. Society for Neuroscience Abstract, 20, 1626.

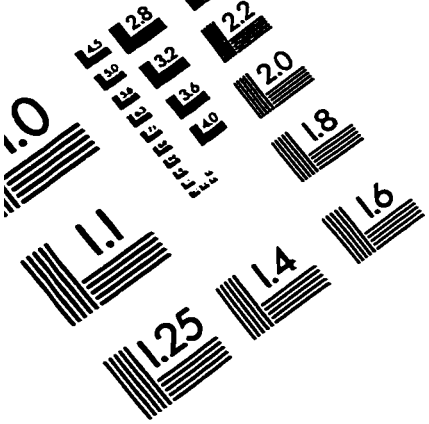
Wise, R. A., & Munn, E. (1995). Withdrawal from chronic amphetamine elevates baseline intracranial self-stimulation thresholds. Psychopharmacology, 117, 130-136.

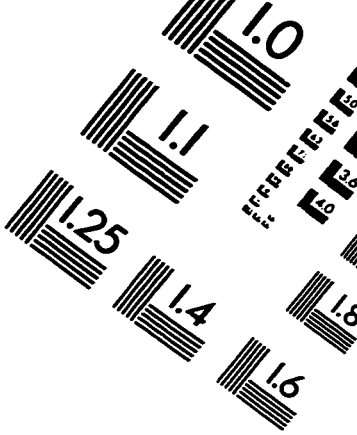
Wise R. A., & Rompre, P. -P. (1989). Brain dopamine and Reward. Annual Reviews of Psychology, 40, 191-225.

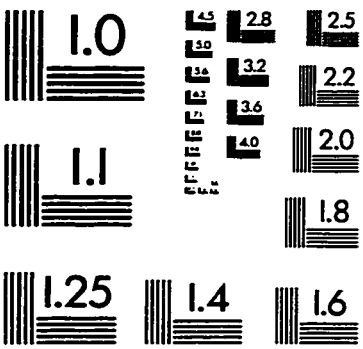
Yokel R. A., & Wise, R. A. (1975). Increased lever pressing for amphetamine after pimozide in rats: Imlications for a dopamine theory of reward. Science, 187, 547-549.

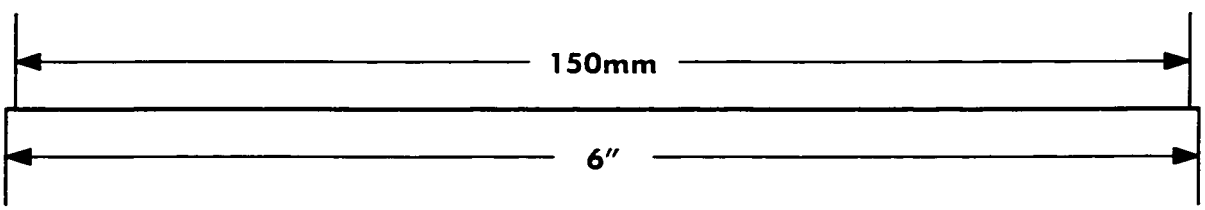
Yokel R. A., & Wise, R. A. (1976). Attenuation of intravenous amphetamine reinforcement by central dopamine blockade in rats. Psychopharmacology, 48, 311-318.

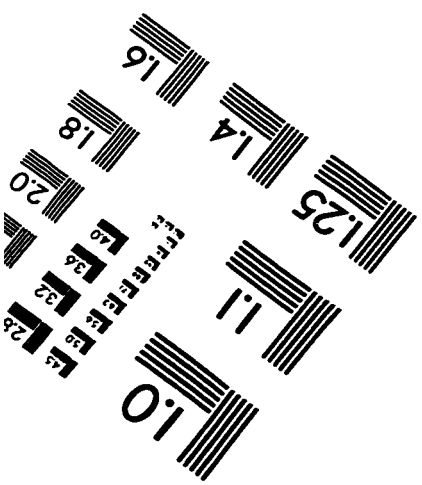
Zito, K. A., Vickers, G., & Roberts, D. C. S. (1985). Disruption of cocaine and heroin slef-administration following kainic acid lesions of the nucleus accumbens. Pharmacology Biochemistry and Behavior, 25, 1029-1036.

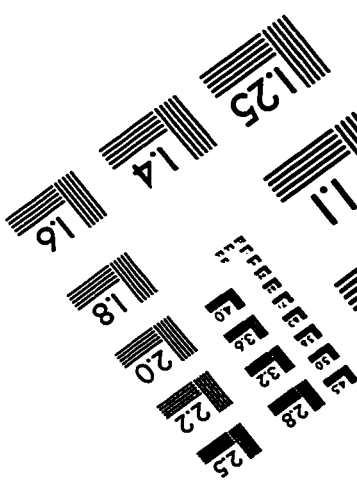












APPLIED IMAGE, Inc
1653 East Main Street
Rochester, NY 14609 USA
Phone: 716/482-0300
Fax: 716/288-5989