STRESS, ENDOGENOUS OPIOID PEPTIDES, AND THE REINFORCEMENT VALUE OF NICOTINE

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Submitted to the Faculty of the
Graduate College of the
Oklahoma State University
in partial fulfillment of
the requirements for
the Degree of
DOCTOR OF PHILOSOPHY
July, 1995

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THE REINFORCEMENT VALUE OF NICOTINE

Thesis Approved:

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ACKNOWLEDGMENTS

I wish to express gratitude to my major advisor, Dr. Frank L. Collins, Jr., for his advice and guidance throughout graduate school. I am also grateful to Dr. John R. Tassey for providing me with the opportunity to initiate this research. I would like to thank my other committee members for their helpful comments and suggestions. More over, I wish to express gratitude to DuPont Pharma and the Oklahoma University Department of Psychiatry and Human Behavior for their generous financial support.

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Several recent reviews of the neurobiology of drug abuse implicate common biological mechanisms as serving a prominent role in drug reinforcement and addiction. For example, Wise and Bozarth (1987) offer the theory that positive reinforcement and psychomotor stimulation rely on a common biological mechanism. According to this theory, reinforcing and stimulating properties of a given drug employ common dopaminergic pathways that project from the midbrain through the medial forebrain bundle (MFB) to the cortical regions. This theory is founded on numerous studies that have established a dopaminergic link among many drugs of abuse, such as amphetamines, cocaine, opiates, alcohol, and nicotine. Izenwasser and Kornetsky (1992) also identify dopaminergic activity as the main contributor to the neurochemical basis of drug reinforcement. Like Wise and Bozarth (1987), Izenwasser and Kornetsky implicate the mesolimbic dopaminergic pathway which begins in the ventral tegmental area (VTA) and projects to several frontal areas including the nucleus accumbens (NA). Most recently, Robinson and Berridge (1993) have described the importance of the mesolimbic pathways. According to Robinson and Berridge (1993), repeated activation of these pathways powerfully enhances the attribution of incentive salience to drugs and drug related cues, which leads to pathological craving.

Endogenous Opioid Peptides, Stress, and the Reinforcement Pathways

In addition to discussing the dopaminergic reinforcement pathways, Izenwasser and Kornetsky (1992) emphasize the involvement of endogenous opioid peptides (EOPs) as a biological correlate of the dopaminergic activity. Several studies using an intracranial self-stimulation (ICSS) paradigm have shown that the administration of drugs that activate the dopaminergic pathways often results in an increase in the ICSS rate as well as a decrease in the threshold at which the ICSS is reinforcing. EOPs are suspected of playing an important role in drug reinforcement because of the high number of enkephalins and opioid binding sites along the reinforcement pathways and because opioid antagonists, such as naloxone, often prevent an increase in the ICSS rate and prevent a decrease of the reinforcement threshold.

Stress is often believed to be associated with the initiation and maintenance of drug abuse. A sizable literature has associated stress and negative affect with the initiation and maintenance of drug abuse. For example, Fulmer & Lapidus (1980) found that negative emotional states are involved in the maintenance of use and to a lesser degree in the initiation of use. Some have attributed this association to the ability of drugs, such as alcohol and nicotine, to reduce negative affect. However, studies that directly test this model have provided inconsistent findings. With alcohol for example, some studies have supported a reduction of negative affect (Josephs & Steele, 1990; Levenson, Sher, Grossman, Newman, & Newlin, 1980) and other studies refute this idea

(Rohsenow, 1982; Sayette & Wilson, 1991). These inconsistencies may be a result of different methodology and different definitions of negative emotional states (e.g., as anxiety, tension, hostility, anger, or depression). Alternatively, the tension reduction model may not be a sufficient description of the relationship between stress and drug abuse. Other researchers believe that stress results in individual mood states which mediate the relationship between stress and drug abuse (Hussong & Chassin, 1994). Negative mood states have also been conceptualized as internal cues for drug administration (Childress et. al., 1994; Powell et. al., 1990).

In terms of the pharmacology of stress, it has been widely accepted for some time that stress results in EOP activity in animals and in humans (for reviews see Przewlocki, 1993; McCubbin, 1993; Olson & Olson, 1993). According to McCubbin (1993), exposure to aversive stimuli which require a coping response that is only partially effective results in the release of EOPs. Different laboratory procedures have been used to produce a stress induced release of EOPs, such as mental arithmetic (Bandura, Cioffi, Taylor, & Brouillard, 1989), exam stress (Meyerhoff, Oleshansky, & Mougey, 1988), and exposure to loud noise while solving visual spatial problems (Fertig, Peters, Meuller, Kamimori, & Human, 1992). In summary, stress is an important behavioral variable in drug addiction, which is biologically mediated, at least in part, by EOPs.

Sensitization of the Dopaminergic Pathways to Drugs and Stress

Another important dimension of the neurophysiological conceptualization of drug addiction is the long-term sensitization of these reinforcement pathways (for review see Kalivas & Stewart, 1991; Stewart, 1992; Robinson & Berridge, 1993). Sensitization may be defined as an increase in response over repeated presentations of a stimulus and is thought to be a result of interneuronal plasticity (Eikelboom & Stewart, 1982). With repeated administration of a given dose of a drug, an organism will demonstrate increases in dopaminergic activity along the reinforcement pathways and increases in behavioral activity. For example, with repeated systemic injections of amphetamine or opiates, dopamine is released from both cell bodies and terminals and both sensitization and stimulus control over the sensitization develops (see Stewart, 1992). Likewise, when opiates were injected into the VTA, dopamine is released from the cell bodies and terminals and both sensitization and stimulus control develops.

Numerous authors have also demonstrated that stress can sensitize an organism to the effects of drugs via EOP activity in the VTA (e.g. Deroche et. al., 1992; Kalivas, Duffy, Abhold, & Dilts, 1988; Kalivas & Duffy, 1989; Deutch & Roth, 1990). For example, Kalivas and Stewart (1991), indicate that both drugs and stressors stimulate D1 receptors in the somatodendritic regions of the A10/A9 neurons in the VTA, which leads to the development of cross-sensitization. Furthermore, Kalivas and Abhold (1987) demonstrated that stress

led to an increase in enkephalins in the A10 neuronal region and projections to the NA and prefrontal cortex. Over repeated administrations of the footshock stressor, this pathway was sensitized to later injections of an enkephalin analogue. The sensitization was reversed by injections of naltrexone into the VTA. Thus, the cross-sensitization of these pathways to stress and drugs may be largely due to a stress induced EOP facilitation of these reinforcement pathways.

A Biobehavioral Model for Stress, Reinforcement, and Drug Abuse

In summary, drugs which enhance dopaminergic transmission between the ventral tegmental area (VTA), nucleus accumbens (NA), amygdala (AMG), and other frontal and prefrontal structures along the mesolimbic pathways are rewarding and promote approach and appetitive behavior (see Robinson & Berridge, 1993). Studies have demonstrated that alcohol, opiates, cocaine, amphetamines, and nicotine enhance transmission along these pathways. Stress also enhances transmission along these pathways through endogenous opioid peptide (EOP) mechanisms, possibly indirectly through an inhibition of GABA interneurons which releases dopaminergic neurons from the inhibitory action of the GABA interneurons (Kalivas & Stewart, 1991). These pathways also become sensitized to the effects of drugs such that equivalent doses elicit greater behavioral activity and greater release of dopamine from cell bodies. Stress also cross-sensitizes these pathways such that an animal which is repeatedly stressed demonstrates an enhanced transmission of dopamine when

challenged with a drug. In addition, these pathways also come under the control of conditioned stimuli in the environment such that these stimuli enhance or inhibit the sensitization to the drug (Stewart, 1992).

We propose that environmental stress initiates EOP activity which partially activates the dopaminergic reinforcement pathways, and in a manner similar to the effect of opiates on the ICSS threshold, increases the reinforcement value and lowers the threshold for reinforcement for subsequent drug administrations. With repeated activation by stress or drugs, these pathways become more sensitized to environmental cues, the effect of stress, and the effect of the drug on these pathways. Thus, the organism becomes increasingly vulnerable to the reinforcing effects of stress and drugs.

Nicotine and a Biobehavioral Model

Similar to the drugs mentioned above, the reinforcement of nicotine also seems to be biologically related to dopaminergic activity and stress. Several articles provide evidence that there is an interaction between the mesolimbic dopamine pathways and nicotine (Ksir & Cline, 1987; Calabresi, Lacey & North, 1989; Imperato, Mulas, & Di Chiara, 1986; Balfour, 1994). Furthermore, lesions targeted to deplete dopamine in the NA reduce the rate of nicotine self-administration in rats (Singer, Wallace, and Hall, 1982).

The research on nicotine also provides evidence that EOPs are involved in nicotine administration. In a review of the neurobiology of smoking, Pomerleau and Pomerleau (1984) describe several important neuroregulators of smoking,

including dopamine and EOPs. They indicate that these neuroregulators may be important in terms of initially increasing arousal and attention and reducing negative affect. Other researchers have also noted increases in EOP activity as a result of smoking (Fertig, Pomerleau, & Sanders, 1986; Gilbert, Meliska, Williams, & Jensen, 1992; Wewers, Tejwani, & Anderson, 1994). In a study on the effects of opioid antagonists on smoking behavior, Karras & Kane (1980) reported that naloxone reduced the desire to smoke and smoking behavior after nicotine deprivation in a work setting. In a laboratory replication, Gorelick, Rose, and Jarvik (1989) found that naloxone decreases smoking behavior. However, Nemeth-Coslett & Griffiths (1986) indicated that naloxone does not decrease smoking in a relaxed, naturalistic environment.

Similar to other drugs, stress also plays an important role in the use of nicotine (for reviews see Pomerleau & Pomerleau, 1990, 1984; Carmody, 1989). Smokers are often reported to smoke more or desire to smoke more while under stress (Spielberger, 1986; Pomerleau & Pomerleau, 1987). A common explanation for the relationship is that smoking reduces stress and negative affect (e.g., Carmody, 1989). Some studies support this explanation (Perkins, Grobe, Fonte, & Breus, 1992; Gilbert & Spielberger, 1987; Jarvik, Caskey, Rose, Herskovic, & Sadeghpour, 1989; Rose, Ananda, & Jarvik, 1983), while others do not (e.g., Fleming & Lombardo, 1987; Jarvik, Caskey, Rose, Herskovic, & Sadeghpour, 1989). Pomerleau and Pomerleau (1991) indicate that anxiety reduction may be only indirectly related to smoking. A recent study by Kassel

and Shiffman (1995) suggests that the relationship may be mediated by the effects of nicotine on attention. Although the mechanisms by which stress and smoking are interrelated have not been fully explained, it seems clear that stress is an important variable.

One method of determining the reinforcement value of a drug is the behavioral economics paradigm (for review see Bickel, DeGrandpre, & Higgins, 1993). Two factors are important in the behavioral economics paradigm. First, subjects will work less for a reinforcer as the cost, in terms of the number of responses required to earn a reinforcer, increases. Secondly, response rate for the consumption of a reinforcer will also vary in relation to the availability of competing reinforcers. Thus, one measure of reinforcement value is the extent to which a subject will respond for a given reinforcer in the context of a concurrent reinforcer. Several recent studies have successfully used this paradigm to determine the reinforcement value of nicotine under different circumstances (Bickel, DeGrandpre, Hughes, & Higgins, 1991; Epstein, Bulik, Perkins, Caggiula, & Rodefer, 1991; Perkins, Epstein, Grobe, & Fonte, 1992; DeGrandpre, Bickel, Higgins, & Hughes, 1994). In addition, a recent study in our lab using a behavioral economics paradigm to examine the reinforcement value of nicotine after inducing stress, relaxation, or a no treatment control condition, suggested that stress had the effect of increasing the reinforcement value of nicotine (Quevedo & Collins, 1993).

The present study used a behavioral economics paradigm to examine the relationship between stress and the reinforcement value of nicotine. Theoretically, EOPs released after stressful events partially activate the dopaminergic pathways and change the reinforcement value of nicotine. Specifically, pre-treatment with stress may act to decrease the threshold of reinforcement and increase the reinforcement value of a subsequent administration of nicotine, just as pre-treatment with opioids decrease the threshold and increase the reinforcement value of subsequent administrations of ICSS. Based on this theory, naltrexone should prevent the increase in the reinforcement value of nicotine after stress, by preventing EOPs from activating the dopaminergic pathways and decreasing the threshold for reinforcement.

The first hypothesis of the present study was that stress would increase the reinforcement value of nicotine. Specifically, it was predicted that nicotine would be more reinforcing after stress and that participants who received stress and placebo would increase their responding for nicotine, relative to the no stress and placebo condition. The second hypothesis was that naltrexone would prevent stress from increasing the reinforcement value of nicotine and that participants would experience this effect as a loss of reinforcement. Thus, it was predicted that participants who receive stress and naltrexone would respond more for nicotine immediately after experiencing this loss of reinforcement, relative to the other combinations of stress and drug.

Method

Participants

Twenty male volunteers were recruited from patients who had expressed interest in smoking cessation groups at the VA hospital in Oklahoma City, Oklahoma. These subjects were given information about the research study when they called to inquire about smoking cessation groups. Participation in this study did not delay any smoking cessation treatment which they received. As compensation for their participation, each subject received $100 after completing the study. Of these twenty subjects, four quit after the first session because of the time committment. Three other subjects quit after reporting side effects, such as nausea and dysphoria, from the naltrexone. There were 2 other subjects who reported nausea on the evening after taking naltrexone for the first time, but these subjects did not drop out of the study. Of the 13 subjects who finished the study, 77% were White and 23% were Black. The mean age was 43.1 with a range of 24 to 53, while the mean education was 13.7 years with a range of 12 to 16. The mean number of cigarettes smoked daily was 27.25 with a range of 20 to 47.

The subjects were selected if they had smoked 16 or more cigarettes each day for the last year, and did not use other forms of tobacco (i.e. chewing tobacco, pipes, or cigars). To insure that each subject smoked regularly, carbon monoxide (CO) levels were at least 10 parts per million. Furthermore, subjects were not included if they had received treatment for a psychiatric disorder within

the last two years, as evidenced by a review of their medical charts at the VA. Subjects were also excluded if they scored more than a 47 on the Trait Anxiety form of the State Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, & Lushene, 1970) or by scoring 16 or more using the Beck Depression Inventory (BDI; Beck, Rush, Shaw, & Emery, 1979). Any subject who was excluded for one of these reasons was given information regarding the outpatient mental health services provided at the VA.

The STAI is a 40-item instrument comprised of two subscales which include Form Y-1 as a measure of state anxiety and Form Y-2 as a measure of trait anxiety. Form Y-2 was used for screening subjects. Scores on this subscale range from 20 to 80 with higher scores indicating greater levels of anxiety. In a normative sample of undergraduates the mean trait score for undergraduate men was 36.35 with a standard deviation of 9.67 (Spielberger et. al., 1970). Thus, subjects were excluded if their score of Form Y-2 was greater than one standard deviation above the mean. The STAI has proven to be a reliable and valid measure of anxiety (Spielberger et al., 1970).

The BDI is a 21-item instrument used to measure symptoms of depression (Beck & Steer, 1987). Scores range from 0 to 63 with scores greater than 16 indicative of moderate depression. Thus, subjects were excluded if their score on the BDI was equal to or more than 16. The BDI has also demonstrated reliability and validity (Beck & Steer, 1987).

Carbon monoxide (CO) levels were obtained using a handheld Vitalograph CO monitor. As mentioned previously, subjects were excluded if their CO level was below 10 p.p.m. This is consistent with research suggesting that less than 10 p.p.m. is a normal level for nondependent smokers (Lando et al., 1991).

Subjects were also excluded if naltrexone was contraindicated. This included subjects who: (1) were currently using or had used within the last month any form of exogenous opioid or tested positive for any other drug on a urine drug screen; (2) had a history of opioid abuse; (3) had any history of hepatic disease or other liver injury including cirrhosis; or (4) had any evidence of liver abnormalities as indicated by their medical records and laboratory blood tests.

A VA physician reviewed the medical data and prescribed the medication before each subject began the experimental manipulations. An experimenter randomly assigned subjects to the drug condition (naltrexone vs. placebo) and the stress condition (stress vs. no stress). A second experimenter who was blind to the drug assignment dispensed the medication to the subjects. Subjects were not administered naltrexone more than once within one week to insure the elimination of the naltrexone before the next administration.

Apparatus

The Concurrent VR Schedules of Reinforcement computer program (Collins & Carter, 1991) was used to measure the reinforcement value of nicotine. This program utilizes a concurrent VR schedule of reinforcement which is portrayed

as two slot machines displayed simultaneously on the computer screen. One slot machine is used to earn nickels as reinforcers and the other is used to earn cigarette puffs as reinforcers. In this program, there are 9 VR schedules which are divided into 3 blocks (Block1 = VR 7, VR 11, VR 15; Block 2 = VR 20, VR 25, VR 30; Block 3 = VR 41, VR53, and VR 70). The program automatically advances to the next schedule when two reinforcers (any combination of coins &/or puffs) are earned. At the end of each block, the program pauses to allow the participant to collect the reinforcers earned.

Procedure

Each subject initially attended a short screening session, during which he were generally informed about the nature and purpose of the study. The risks involved with the administration of naltrexone was carefully detailed, after which each subject was given an informed consent form to sign. Next, each subject completed the screening measures outlined above as well as a questionnaire on demographics. The medical data was passed to the physician, and those subjects who were approved for the study were scheduled for 4 more appointments over the course of two weeks to complete the experiment.

On each of their next 4 appointments, the subjects were given either 50 m.g. of naltrexone or a placebo in a plain bottle and instructed that "the bottle either contains naltrexone or an inactive pill." The subjects were then asked to smoke a cigarette to equate for deprivation level across subjects. The subjects waited a total of 90 minutes to begin the experiment after taking the pill to allow the

naltrexone to enter the blood stream and cross the blood-brain barrier. Subjects were allowed to leave the lab during this time. However, they were asked to leave their cigarettes and were instructed not to eat or drink beverages containing caffeine.

At the end of the 90 minutes, the subjects began the experiment by completing the first pre-manipulation measure of state anxiety (STAI). The subjects then engaged in the first 5-minute experimental manipulation. For the subjects in the stress condition, mental arithmetic was performed for 5 minutes. Subjects were informed prior to beginning that they were allotted an extra $2.50 for their performance during a mental arithmetic session and that $.25 would be deducted for each incorrect answer they gave. The mental arithmetic consisted of subtracting serial 17's from a four digit number. During the 5 minutes, the subjects were repeatedly instructed to answer as quickly and accurately as possible, and the subjects were informed whether each answer was correct or incorrect. Subjects in the no stress condition simply read magazines for 5 minutes without any pressure or constraints.

After the 5-minute manipulation, the participants completed the post manipulation measure of state anxiety. After completing the STAI, subjects rated their desire to smoke using a simple 10-point scale with 0 equal to no desire and 10 equal to extreme desire and then used the computer program to begin earning reinforcers for Block 1. After progressing through 3 schedules of Block 1, the subjects had 5 minutes to smoke the number of puffs earned and/or collect

the spare change earned. This cycle was repeated in Block 2 and 3. The amount of time necessary to complete a block depended on how fast the subject pushed the lever. A subject normally finished Block 1 in approximately 25 minutes, Block 2 in 45 minutes, and Block 3 in 1 hour 20 minutes (see Figure 1 for timeline of assessment administration).

Insert Figure 1 here

After the subjects completed all 4 appointments, they were asked to guess which days they received naltrexone. They were also debriefed and compensated with $100.

Design

A four factor within-subjects design (drug x stress x block x schedule) was utilized for the statistical analyses. The four factors included drug (naltrexone vs. placebo), stress (stress vs. no stress), block and schedule (each VR schedule). In addition, the design was counterbalanced across four treatment orders in a Latin square arrangement. The first treatment order consisted of placebo and stress on session 1, naltrexone and stress on session 2, placebo and no stress on session 3, and naltrexone and no stress on session 4. The second treatment order consisted of naltrexone and stress, placebo and stress, naltrexone and no stress, and placebo and no stress, respectively. The third treatment order consisted of placebo and no stress, naltrexone and no stress, placebo and

stress, and naltrexone and stress, while the fourth treatment order was naltrexone and no stress, placebo and no stress, naltrexone and stress, and placebo and stress, respectively. Each treatment order contained 3 subjects, except for the first, which contained 4 subjects.

Results

Each subject was asked to guess which days they had received the medication. If the subjects were guessing at random, they would be expected to guess correctly 50% of the time. The subjects guessed correctly on 52% of the sessions, indicating that they were unable to reliably discriminate between the naltrexone and placebo.

Data for two of the fifty-two experimental sessions were missing due to experimenter error. In both cases, the research assistant failed to administer the experimental manipulation (the mental arithmetic task). This occurred once during the naltrexone condition and once during the placebo condition. Various methods to estimate the missing data were considered, such as imputing unconditional means or using regression equations. However, according to Little and Rubin (1987), these methods are unreliable and often require ad hoc adjustments to provide accurate estimates. Instead, they recommend using the Expectation-Maximization (EM) algorithm to provide Maximum Likelihood estimates which are reliable and do not require ad hoc adjustments. The EM algorithm estimates the missing data, estimates the parameters of the data set, estimates the missing values again while assuming the new parameters are

correct, and continues to iterate until convergence. In this case, an EM computer program (EMCOV.EXE; Graham, Hofer, & Mackinnon, 1991) was used to estimate the missing data. This was done by holding the other factors (i.e., schedule, block, and drug) constant while entering the 13 data points for the no stress condition and the 12 data points for the stress condition. The last data point for the stress condition was then estimated using the EM algorithm.

Baseline Data

Analyses of the pre-experimental data were calculated using the baseline measure of expired CO as well as state anxiety (STAI) to check for any baseline differences between the experimental factors. A repeated measures ANOVA did not reveal any significant differences on level of expired CO for drug, stress, or an interaction. There were also no significant differences on state anxiety before the experimental session began for drug, stress, or an interaction. Thus, no baseline differences in anxiety or amount smoked were found.

Stress Manipulation

Analyses of the post-manipulation state anxiety were conducted for each block to verify that it was effective and to assess any habituation to the stress manipulation. These data are presented in Figure 2. A repeated measures ANOVA revealed that the stress manipulation was effective in Block 1. When subjects performed the mental arithmetic, they scored significantly higher on the STAI, $F(1,12) = 8.23$, $p < .05$, than when they did not. There were no significant main effects for the drug or interaction effects.

Insert Figure 2 here

Analyses of state anxiety in the Block 2 also indicated a significant difference for stress. When subjects performed the mental arithmetic, they scored significantly greater on the STAI, $F(1,12) = 10.88$, $p < .01$. There were no main effects for drug or interaction effects.

In Block 3, subjects did not report significantly greater anxiety when performing the mental arithmetic. There were also no main effects for drug, or interaction effects. Thus, the stress manipulation was effective during Block 1 and Block 2 and not effective in Block 3.

Effects on the Reinforcement Value of Nicotine

The reinforcement value of nicotine was operationally defined as the percentage of the total possible lever presses made at each schedule. A percentage was used to equate the value across the different VR schedules. Otherwise, the reinforcement value would rise simply as a function of the increase in the VR requirement. Figure 3 represents the percentage of lever presses for each combination of drug and stress at each schedule of reinforcement. A repeated measures ANOVA was conducted separately for each block. To control for a sphericity bias, the Huyhn-Feldt correction (Huynh & Feldt, 1976; SAS Institute, 1988) was used to adjust the significance levels as needed.

Insert Figure 3 here

In Block 1, the only significant finding was a main effect for schedule, $F(2,24) = 6.55$, $p < .01$. However, in Block 2, the analyses revealed a significant schedule by drug by stress interaction, $F(2,24) = 3.69$, $p < .05$. Post-hoc analyses indicated that the number of lever presses for nicotine by subjects receiving the naltrexone and stress combination was significantly greater at the first schedule of Block 2 as compared to the placebo and stress combination, $t(12) = 2.14$, $p < .05$, the placebo/ no stress combination, $t(12) = 2.83$, $p < .05$, and the naltrexone and no stress combination, $t(12) = 2.51$, $p < .05$. In Block 3, there were no significant effects for drug, stress, or an interaction.

Analyses were also conducted to determine if stress alone had the predicted impact on the reinforcement value of nicotine as it did in a previous study (Collins & Quevedo, 1993). For this analysis, the stress and placebo combination was compared with the no stress and placebo combination in each block. In Block 1, there were no significant effects at the $p < .05$ level, although there was a trend for an interaction between schedule and stress ($F(2,24) = 3.03$, $p = .06$). One-tailed dependent t tests revealed that when subjects received the stress manipulation, they worked more for puffs at the VR 11 schedule, $t(12) = 2.06$, $p < .05$. There were no significant differences at VR 7 or VR 15. In Blocks 2 and 3, there were also no significant effects.

Effects on Self-Reported Desire and Anxiety

A measure of desire to smoke was collected immediately after each stress manipulation. In Block 1, there were no significant effects for drug, stress, or an interaction. This was also true for Block 2 and Block 3,.

The STAI was administered at the beginning of Blocks 1-3. Thus, the instrument served as a measure of affect after subjects smoked at the end of Block 1 and Block 2. If the subjects who were given naltrexone were experiencing a reduction in the reinforcement value of nicotine, it might be expected that these subjects would report greater stress or negative affect immediately after smoking. Analyses were conducted on the STAI at Blocks 1-3 to test this hypothesis. Figure 4 represents STAI data for Block 1, Block 2, and Block 3. Analyses indicated a significant three way interaction between Block, Drug, and Stress, $F(2,24) = 3.60$, $p < .05$, suggesting that subjects receiving naltrexone and stress were experiencing more anxiety at Block 2. Post-hoc one-tailed t tests revealed that the naltrexone and stress combination resulted in greater anxiety when compared to the placebo and no stress combination, $t(12) = 2.10$, $p < .05$, and the naltrexone and no stress combination, $t(12) = 1.94$, $p < .05$. There was no significant difference between the naltrexone and stress combination and the placebo and stress combination at Block 2.

Insert Figure 4 here

Discussion

The Effect of Stress on the Reinforcement Value of Smoking

The results of this study indicated that the stress manipulation was effective in Blocks 1 and 2 but not in Block 3. The first hypothesis was that stress would result in an increase in the reinforcement value of nicotine which would lead to a consistent increase in responding across schedules by participants who received the stress and placebo combination as compared to the no stress and placebo combination. While there was a trend for participants who received stress and placebo to respond more for nicotine in Block 1, overall the results did not confirm this hypothesis.

There are three possible explanations for the absence of an effect for the stress and placebo combination. First, stress may not alter the reinforcement value of nicotine. However, this seems unlikely given the effect of the combination of stress and naltrexone, which will be discussed in the following paragraphs. Secondly, the behavioral economics paradigm used in this experiment may not be sensitive enough to detect changes in the reinforcement value of nicotine due to stress. This is consistent with our previous findings, which found only a marginal and inconsistent effect for stress (Quevedo & Collins, 1993). Finally, the sample used in this study may not have been large enough to detect changes in the reinforcement value of nicotine due to stress without the added effect of naltrexone. This explanation seems to be the most

likely because the interaction between stress and schedule in Block 1 was very close to being significant.

The Effect of Stress and Naltrexone on the Reinforcement Value of Smoking

The second hypothesis was that naltrexone would prevent stress from increasing the reinforcement value of nicotine and that participants would experience this as a loss of reinforcement and subsequently would respond more for nicotine. The data supported this prediction in Block 2 but not in Block 1 or 3.

At first glance, these results seem to be incongruous because the effects of stress and naltrexone were not consistent across blocks. However, this pattern of results is quite consonant with the underlying biobehavioral model. It is our assertion that this pattern of results can be attributed to a loss of reinforcement that only occurred when the participants of this study were able to experience, concurrently, the effects of naltrexone, stress, and nicotine.

After smoking at the end of Block 1, the demand for puffs decreased for the placebo and stress, placebo and no stress, and naltrexone and no stress groups. However, the demand for puffs when subjects received naltrexone and stress remained high. At the first schedule of Block 2, they worked significantly more for puffs when they received naltrexone and stress as compared to any of the other three combinations. Across the three schedules of Block 2, their demand drops while demand under the other three combinations increases.

This effect in Block 2 can be interpreted as a small extinction burst similar to what is observed when a reinforcer is diminished or taken away entirely. Participants seemed to have experienced a loss of reinforcement after smoking at the end of Block 1 which resulted in a increase in their response for nicotine in the subsequent VR schedule relative to the other combinations of drug and stress. This effect is probably due to the EOP antagonist properties of naltrexone which prevented stress from partially activating the dopaminergic pathways and prevented a decrease in the threshold for reinforcement. Participants experienced this as a reduction of reinforcement. As a result, they may have experienced more frustration and anxiety as indicated by their STAI scores immediately after smoking prior to Block 2 (see Figure 4).

The observation that this loss of reinforcement only occurred during Block 2 is important. Block 2 differs from Block 1 in that subjects did not have the opportunity to smoke just prior to beginning the schedules in Block 1. Thus, there was no opportunity for subjects in the naltrexone and stress combination to experience a loss of reinforcement in Block 1. The absence of a significant interaction in Block 1 supports the interpretation that subjects experienced a loss of reinforcement only after having a combination of stress, naltrexone, and nicotine.

Another important finding is that naltrexone without stress did not seem to have an effect on the reinforcement value of nicotine by itself, which would have been expected if naltrexone has a general suppressing effect on the

dopaminergic reinforcement pathways. Again, the effect of naltrexone seems to be specific to the combination of stress and smoking. Rather than a general effect, it seems to specifically prevent EOPs from activating these pathways. Nicotine receptors along these pathways would not be blocked and therefore it is not surprising that nicotine is still reinforcing. However, since smoking also produces increases in EOP activity (Pomerleau & Pomerleau, 1984), naltrexone might be expected to have a small effect by preventing this activity from stimulating the reinforcement pathways. Previous studies have shown that opioid antagonists may have a small effect on smoking (e.g., Gorelick et. al., 1989). It is possible that with more subjects or a self-report measure of the initial stimulatory and rewarding effects of nicotine, a small effect would have emerged.

Do the Findings Support the Underlying Biobehavioral Model?

The failure of the behavioral economics paradigm to demonstrate an effect for stress without naltrexone on the reinforcement value of nicotine was disappointing. It may be difficult to behaviorally detect changes in the reinforcement value of nicotine unless naltrexone is used. However, given the difficulty in detecting changes with the present paradigm, it was very encouraging to find an effect that was quite strong when stress, naltrexone, and nicotine were presented concurrently in Block 2. This pattern of data is consistent with a biobehavioral model in which stress, via EOPs, partially activates the dopaminergic reinforcement pathways and lowers the threshold for

reinforcement of a subsequent dose of nicotine, precipitating an increase in the reinforcement value of nicotine.

Future studies need to explore the effect of naltrexone and stress on the subjective experience of reward and self-reported affect. By including a measure of self-reported reward, future studies will be able to determine if stress does in fact increase the experience of reinforcement after smoking. These studies would also be able to test for the effects of naltrexone on self-reported reward obtained from smoking. Other researchers have found that naltrexone reduces certain self-reported rewarding properties of alcohol, especially the stimulatory effects on the ascending arm of the blood alcohol curve (Swift et. al., 1994). Smokers also report an initial stimulatory effect from smoking (e.g., Pomerleau & Pomerleau, 1984), and this effect may also be attenuated by naltrexone.

Future research should also continue to focus on neurophysiological components of nicotine addiction. For example, it has been well documented that EOP activity and dopaminergic activity are induced by smoking. Researchers have also demonstrated that smoking increases attention and that this increase in attention may be important in terms of affective regulation (Acri, 1994; Kassel & Shiffman, 1995). Interestingly, arousal in the form of neural activity along the mesolimbic pathways increases attention and increases in attention also correspond with increases in reinforcement and reward. Thus, there is a great deal of overlap among attention, affect, and reinforcement, and

more precise experimentation that includes psychophysiological assessment should lead to a model that accurately describes these pharmacological and behavioral processes as they relate to drug addiction.

Several problems with this study need to be addressed. These findings are based on a small number of subjects, and it is possible that the results are spurious, rather than representing a pattern that is consistent with the biobehavioral model reviewed previously. Furthermore, the generalizability of these results were limited because of the exclusion of women, the low number of subjects, and a subject pool that was limited to veterans without any comorbid substance use or psychiatric problems. Future studies need to replicate these results with women as well as with populations other than veterans.

An Integrative Model of Stress, Arousal, Attention, and Reinforcement

In summary, drugs which enhance dopaminergic transmission between the VTA, NA, Amygdala and other frontal and prefrontal structures along the mesolimbic pathways are rewarding and promote approach and appetitive behavior. Stress may also enhance transmission along these pathways through EOP mechanisms, possibly by inhibiting GABA interneurons which release dopaminergic neurons from the inhibitory action of the GABA interneurons. These pathways also become sensitized to the effects of drugs and stress such that equivalent doses elicit greater behavioral activity and greater release of dopamine from cell bodies. Thus, stress also cross-sensitizes these pathways such that an animal which is repeatedly stressed demonstrates an enhanced

transmission of dopamine when challenged with a drug. In addition, these pathways also come under the control of conditioned stimuli in the environment such that these stimuli enhance or inhibit the sensitization to the drug.

The neurophysiological pathways involved in affect, arousal, and attention overlap with the pathways involved in drug reinforcement. These pathways have also been studied extensively. Lang and associates (1993) have demonstrated on numerous occasions that the acoustic startle response (ASR) is influenced by ongoing affective and attentional states. In their paradigm, they measure the response of the obicularis muscle to acoustic startle probes. They have found that foreground stimuli with negative valence enhances the startle response. For example, exposure to shock or the threat of shock enhances the startle reflex (Greenwald, Bradley, Cuthbert, & Lang, 1990). In addition, picture stimuli, films and emotional imagery have all been found to modulate the ASR with the positive valence stimuli inhibiting and the negative valence stimuli enhancing the ASR. When the ASR is measured early (within 800-1000 m.s.), attentional modulation appears to be the dominating factor. Later in the viewing period, emotional modulation appears to be the dominating factor. Furthermore, while the startle response itself will habituate, the emotional modulation does not, and as arousal increases, the strength of the inhibition or enhancement of the ASR also increases.

Another important aspect of the emotional modulation of the ASR is that it has a demonstrable pathway. Davis (1992; Davis, Hitchcock, & Rosen, 1992)

has demonstrated that the obligatory pathway for the startle reflex involves the ear, the cochlear nucleus, reticularis pontis caudalis (RPC), and spine. The emotional modulation of this reflex by visual stimuli has been attributed to input from the retina and the lateral geniculate to the perirhinal cortex and then to the lateral and basolateral nuclei of the amygdala. The central nucleus of the amygdala connects to the obligatory circuit via monosynaptic projections to the RPC where it modulates the obligatory response. LeDoux (1990) has also described the importance of the lateral and central nuclei of the amygdala and its afferent connections to the sensory thalamus. Cortical structures also activate the amygdala when conditioned stimuli are complex.

In the drug literature, there is ample evidence of an association between stress and addiction. In the animal literature on drug reinforcement, stress is associated with the sensitization of the reinforcement pathways. In the animal literature on startle response, stress produces a long-term sensitization (enhancement) of the ASR (Davis, 1989). In addition, one of the major outputs of the amygdala during fear is to the VTA. Complex cues seem to gain neural access to the amygdala and enhance startle, just as drug related cues gain access to the reinforcement pathways. Thus, both startle and drug taking behavior involve some of the same neurophysiological structures and processes. Specifically, the amygdala serves a prominent role is negative affect and the emotional modulation of startle and has projections to the VTA where it may influence drug taking behavior. On the other hand, there are also dopaminergic

projections from the reinforcement pathways to the amygdala, which may in turn influence the emotional modulation of the ASR. Figure 5 summarizes these relationships. Because startle response and drug reinforcement share common neurophysiological mechanisms, this methodology may prove to be an important measure of sensitization to drugs and drug related cues as well as the effect of naltrexone on this sensitization.

Insert Figure 5 here

A series of experiments by Stewart (1992) demonstrated that activation of the VTA by opiates leads to the integration of sensory information and stimulus control over the sensitization of these pathways. This exemplifies the potential importance of EOPs in the activation of these pathways and the integration of sensory information. It also suggests that drugs such as naltrexone may prove to be important in the treatment of addictive behavior. ASR methodology would be critical in terms of testing these hypotheses.

To explain the implications of this overlap in terms of cognition, it may be helpful to apply a connectionistic learning model which defines itself by the desire to integrate neurophysiological properties, such as neuronal plasticity, with principles of learning theory (for review see Martindale, 1991; LeDoux, 1990, 1993). Basically, the dynamics of a neural network are such that learning is the result of changes in the strengths of connections between neural

elements. The connection strength is increased when either neural elements are activated concurrently for a long period of time or for repeated periods of time. Another postulate of this theory is that the arousal system has a multiplicative effect on the activation of connections, such that it functions to increase in a multiplicative fashion the activation of any given "node." This increase in activation and arousal also corresponds to an increase in attention and reinforcement. Neurophysiologically, this corresponds to the activation of the mesotelencephalic pathways. Cognitively, this serves to strengthen connections between sensory information about the environmental and the pathways themselves via projections to the cortex.

Thus, activation along the mesolimbic pathways that results from stress or from drugs would result in increased arousal, attention, and reinforcement. The strength of connections to cortical structures and the amygdala which encode sensory and affective information would be enhanced when these structures are repeatedly activated concurrently. The sensory and affective cues which gain access to these pathways are then able to modulate the activation. Recent studies have provided preliminary evidence that stress increases attention as does nicotine (Kassel & Shiffman, 1995; Acri, 1994; Steele & Josephs, 1990).

Implications for Clinical Treatment and the Use of Naltrexone

Naltrexone has proven to be a safe and effective pharmacological adjunct in the treatment of alcoholics and has been reported to reduce craving for alcohol, prevent one drink from priming a relapse, and to decrease the rewarding

stimulatory effects of alcohol (Volpicelli et al., 1992; O'Malley et al., 1992; Swift et al., 1994).

The action of alcohol on the dopaminergic reinforcement pathways is similar to that of nicotine. Alcohol stimulates the reinforcement pathways and this appears to be important in terms of its addictive liability (e.g., Littleton & Little, 1994). Elevated dopamine levels in the VTA and NA promote drinking while pre-treatment with pharmacological interventions modifies the reinforcing effects of alcohol (Samson & Harris, 1992). Furthermore, EOPs seem to play an important role in the reinforcing effects of alcohol. Low doses of alcohol induce a release of EOPs from the hypothalamus which seems to mediate the stimulatory rewarding effects of alcohol. These doses correspond to the typical alcohol concentration observed in the ascending arm of the blood alcohol curve (BAC) in humans. This observation is also consistent with research by Swift et. al. (1994) in which naltrexone attenuated the stimulatory reinforcing effects of alcohol during the ascending arm of the BAC. Naltrexone has also been shown to prevent the alcohol induced release of dopamine from the NA in rats (Benjamin, Grant, & Pohorecky, 1992).

Thus, nicotine and alcohol are similar in that both stimulate the release of EOPs from the hypothalamus which facilitates dopaminergic activity. This activity appears to increase the stimulatory and reinforcing aspects of the drug, especially at low doses shortly after administration. These effects appear to be blocked by naltrexone which further suggests that EOPs serve a critical role.

This is also consistent with the findings of the present study in which EOPs were prevented from priming these pathways and subjects experienced a subsequent loss of reinforcement from nicotine.

A sizable amount of research has also been devoted to investigating the role of stress and negative affect in cigarette smoking and smoking cessation treatment (Abrams et. al., 1987; Zelman, Brandon, Jorenby, & Baker, 1992; Tiffany & Drobes, 1990; Brandon, 1994) . Stress and negative affect appear to significantly increase the risk of relapse after smoking cessation treatment (Brandon, Zelman, & Baker, 1987; Coen & Lichtenstein, 1990; Pomerleau, Adkins, & Pertschuk, 1978). Stress also seems to potentiate reactivity to smoking cues (Niaura et al., 1992).

The effect of stress on the dopaminergic reinforcement pathways may potentiate the risk for relapse. From a clinical perspective, it would be most useful to prevent stress from accessing these pathways. Not only may naltrexone decrease the stimulatory reinforcement or reward associated with alcohol or nicotine induced EOP activity, this present study suggests that naltrexone may have an added prophylactic benefit in that it appears to prevent stress from activating these pathways which in turn may help to prevent relapse after treatment.

While naltrexone may help to prevent a relapse to smoking as it does with alcohol, the potential efficacy of naltrexone in smoking cessation treatment may be even greater. As reviewed previously, opiates administered in the VTA result

in the sensitization of these pathways as well as conditioned stimulus control over the activation of these pathways (e.g. Stewart, 1992), and stress has a similar action via EOP activity in this area (Kalivas & Abhold, 1987). The present study indicates that naltrexone may interfere with the activation of these pathways and subsequent reinforcement of nicotine after stress. This phenomenon may have important implications for a potentially useful treatment. Repeated activation of sensory and affective cues while blocking the ability of these cues to access the reinforcement pathways could potentially desensitize these pathways to the effects of stress and environmental cues. In other words, repeated presentation of stress and drug-related cues without the activation of the reinforcement pathways would decrease the strength of the neural connections. Thus, the ability of affective and environmental cues to prime subsequent drug-taking behavior would be minimized.

Future clinical studies should examine the efficacy of combining naltrexone with traditional smoking cessation treatment with the idea that naltrexone may facilitate smoking cessation by reducing the reinforcement value of nicotine after stress. Naltrexone may also help to prevent relapse once cessation is attained. In addition, future clinical trials should evaluate the utility of exploiting a combination of exposure to affective cues, smoking, and naltrexone and its effect on treatment outcome.

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	Experimental Session																
		Block 1					Block 2					Block 3					
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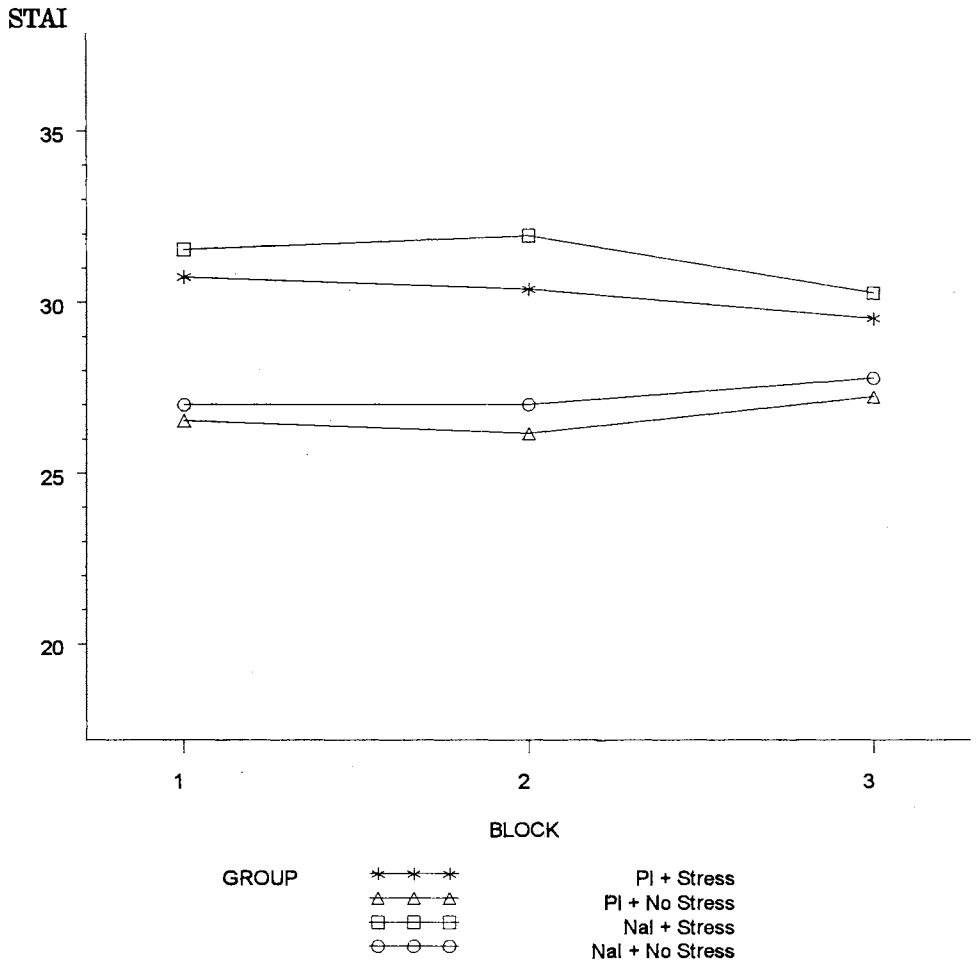
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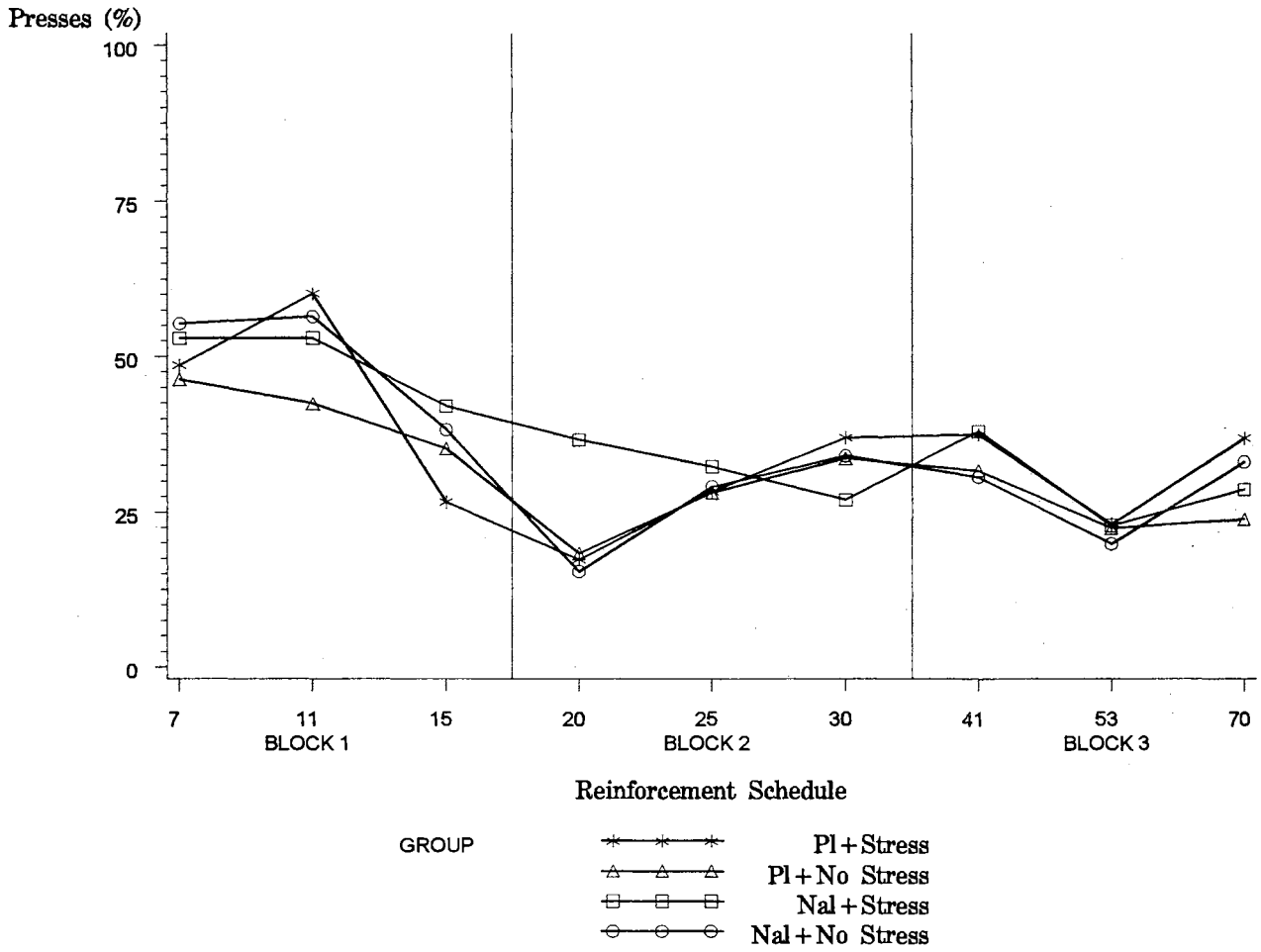
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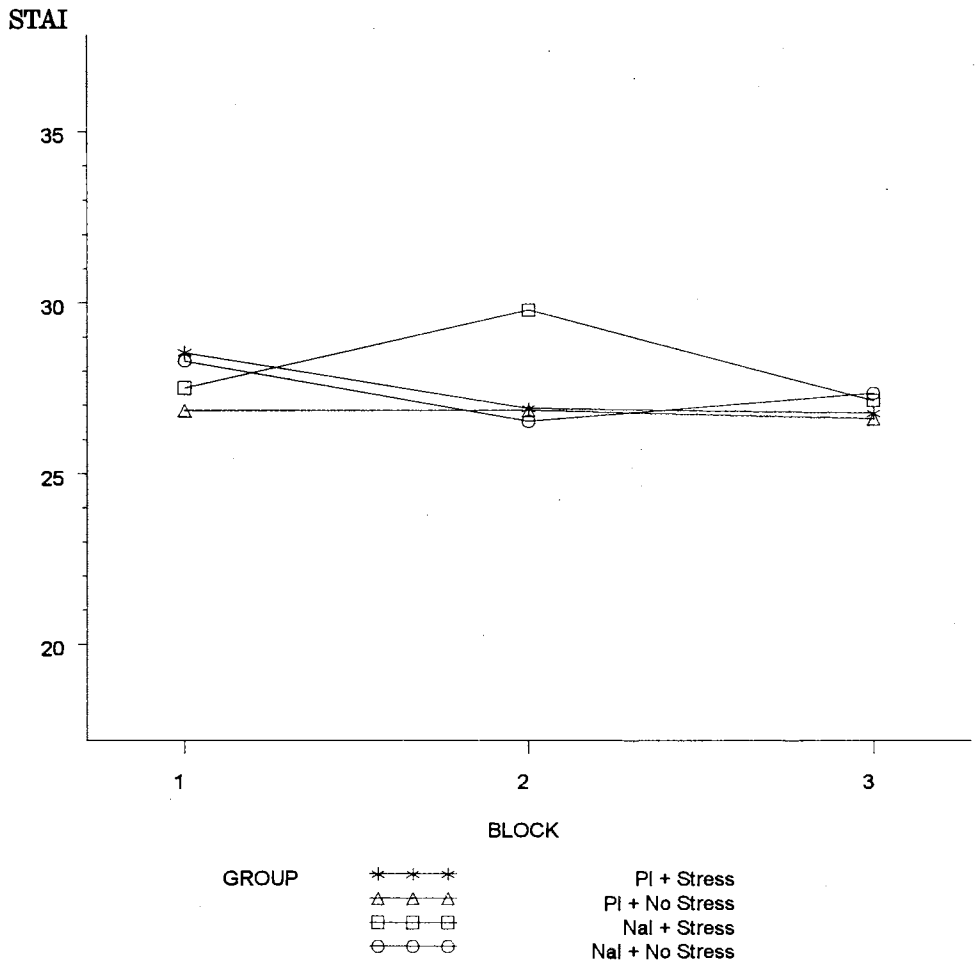
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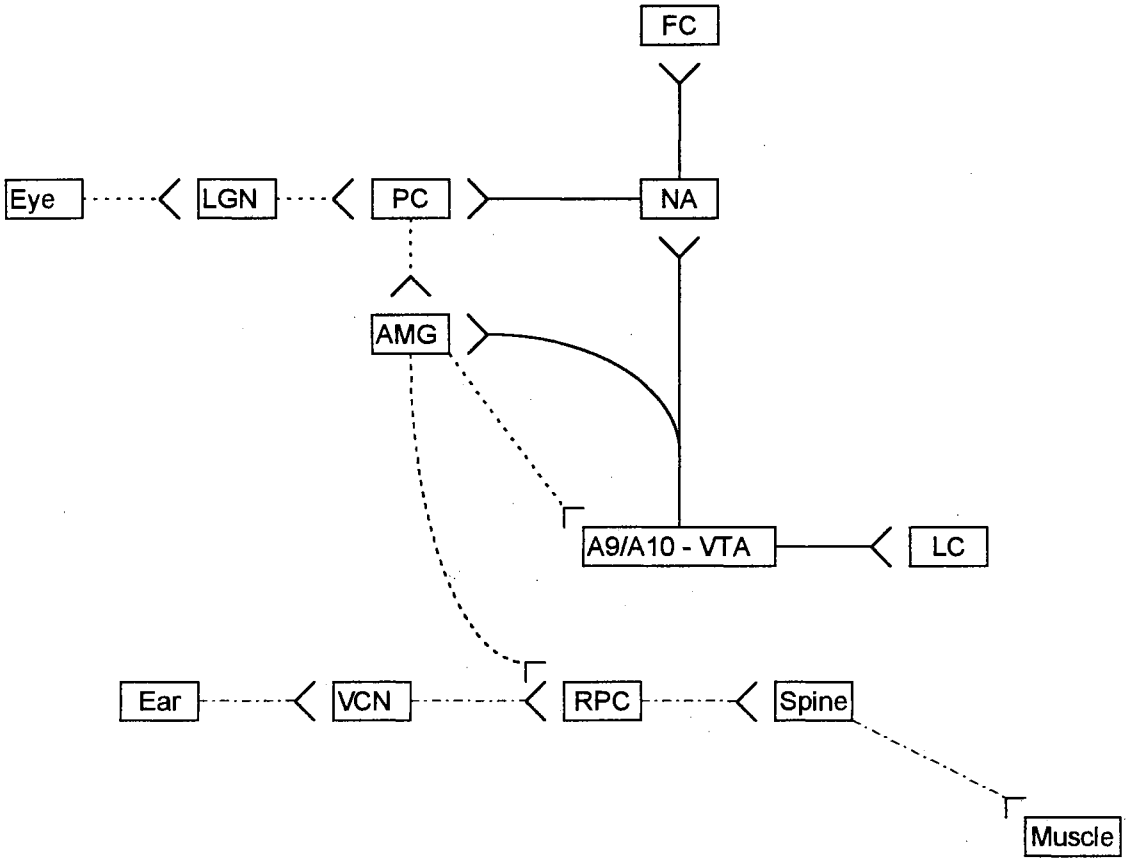

Obligatory ASR Circuit .....

Emotional / Cue modulation Circuit .....

Drug Sensitization / Reward Circuit _____

VITA

Kent E. Hutchison

Candidate for the Degree of

Doctor of Philosophy

Thesis: STRESS, ENDOGENOUS OPIOID PEPTIDES, AND THE REINFORCEMENT VALUE OF NICOTINE

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OKLAHOMA STATE UNIVERSITY
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Principal Investigator(s): Frank Collins

Reviewed and Processed as: Expedited

Approval Status Recommended by Reviewer(s): Approved

APPROVAL STATUS SUBJECT TO REVIEW BY FULL INSTITUTIONAL REVIEW BOARD AT NEXT MEETING.
APPROVAL STATUS PERIOD VALID FOR ONE CALENDAR YEAR AFTER WHICH A CONTINUATION OR RENEWAL REQUEST IS REQUIRED TO BE SUBMITTED FOR BOARD APPROVAL. ANY MODIFICATIONS TO APPROVED PROJECT MUST ALSO BE SUBMITTED FOR APPROVAL.

Comments, Modifications/Conditions for Approval or Reasons for Deferral or Disapproval are as follows:

Comment:
See attached memo.

Signature: _____ Date: October 21, 1993
Chair of Institutional Review Board