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Cardiovascular Responses to Naloxone Challenge in Opiate-Dependent Individuals

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NEWLIN, D. B., C. J. WONG AND L. J. CHESKIN. *Cardiovascular responses to naloxone challenge in opiate-dependent individuals.* PHARMACOL BIOCHEM BEHAV 43(2) 357-360, 1992.—Vagally mediated tachycardia appears to be a common response to abused drugs and, therefore, has implications for abuse liability. To test the specificity of this common factor, we determined whether the tachycardia to naloxone in opiate-dependent individuals has a significant vagal component. Naloxone challenge (0.4 mg, IM) in 19 opiate-dependent men and women was associated with highly reliable tachycardia, but no significant change in vagal tone index, a noninvasive measure of parasympathetic inhibitory control of the heart. We conclude that tachycardia during naloxone-precipitated withdrawal is not vagally mediated. Thus, there is some degree of specificity to the common factor of vagally mediated tachycardia to abused drugs because it was ruled out in at least one drug (naloxone) with aversive subjective effects.

Naloxone Opiate withdrawal Heart rate Vagal tone Parasympathetic Sympathetic Abused drugs

WE have reported that a broad range of abused drugs produce tachycardia that is vagally mediated. Cocaine (17), marijuana (16,24), alcohol (15), morphine (22), pentobarbitol (24), methylphenidate (20), and diazepam (1) all increase heart rate and decrease tonic vagal inhibition of the heart. Withdrawal of cardiac vagal tone, which normally suppresses heart rate, produces tachycardia that is mediated by the parasympathetic nervous system (3). Therefore, vagally mediated tachycardia may be a "common factor" to most abused drugs. Because these drugs are very different from one another pharmacologically (11), common factors are likely to play mechanistic roles in the abuse potential of these drugs. The purpose of this research was to determine the precise autonomic mechanisms of tachycardia produced by an aversive drug, naloxone, in opiate-dependent humans.

Several common factors among drugs of abuse have been identified. At a behavioral level, virtually all substances that are abused by humans are self-administered (7,12) and show place preference conditioning (14), and produce hyperlocomotion (23) in animal models. In human studies, these substances induce rewarding subjective effects (9). In the CNS recent evidence from microdialysis studies (8,10) in rats indicates that abused drugs preferentially increase dopamine efflux in the nucleus accumbens. Taken together, these findings suggest a common mechanism of drug-induced reward/reinforcement: activation of the mesolimbic dopaminergic reward system (10).

Based upon these common factors, we hypothesize that there is central linkage between drug reward processes and drug-induced withdrawal of vagal tone. In this sense, vagally mediated tachycardia is conceptually similar to hyperlocomotion. Both processes are activated by drugs of abuse. The brain circuitry of this linkage is not clear at the present time. This hypothesis assumes *central* as opposed to peripheral linkage. Therefore, drugs that produce tachycardia by peripheral mechanisms alone would not be expected to have reinforcing properties. For example, atropine, a potent peripheral vagal blocker (3), produces strong tachycardia and vagal tone decreases (6) but is not reinforcing (11).

This central linkage hypothesis would be directly contradicted if drugs that have *aversive* subjective effects also produce vagally mediated tachycardia. We chose to study the autonomic mechanisms of naloxone-precipitated withdrawal in opiate-dependent individuals because this is a well-characterized syndrome (11) with a parallel animal literature (4,5). Naloxone is not an abused drug. In fact, naloxone-precipitated withdrawal from opiates is uniformly described as aversive by heroin addicts and individuals maintained on methadone (13). Therefore, we reasoned that our linkage hypothesis would be proved false if naloxone-precipitated withdrawal were found to be associated with vagally mediated tachycardia (using similar recording procedures to those that have been used with abused drugs).

In our studies of abused drugs, we have used vagal tone index as a noninvasive measure of vagal inhibition of the heart to measure parasympathetic influences (21). Vagal tone index is derived from the electrocardiogram (EKG) using time series analysis of successive R-wave to R-wave intervals (19). It

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quantifies respiratory sinus arrhythmia, or heart rate variability in the respiratory frequency band. This variability has been viewed as a relatively pure measure of cardiac vagal tone (20).

Therefore, we measured heart rate and two different frequency components of heart rate variability to determine the precise autonomic mechanisms of naloxone-precipitated withdrawal in humans. On the basis of our central linkage hypothesis, we predicted that the tachycardia from naloxone in opiate-dependent individuals would *not* be associated with changes in vagal inhibition of the heart.

METHOD

Subjects

Subjects were 19 opiate-dependent individuals (6 men and 13 women) who were paid volunteers. Subjects' mean age was 34 years (range 26–45 years). Although five subjects had a history of methadone maintenance, they were free of methadone when tested. All subjects had at least three recent urine samples that were positive for opiates other than methadone and were negative for cocaine. Their mean period of reported use of opiates was 9.9 years (range 1–24 years).

Apparatus

Consecutive interbeat intervals (R-wave to R-wave on the EKG) were recorded with ms accuracy using a computerized recording system. The EKG signal was recorded with silver/silver chloride electrodes on the chest, amplified by a custom-built EKG preamplifier, and routed to the analog/digital converter on a Microstar Data Acquisition Processor (Redmond, WA) mounted in a microcomputer. The system detected consecutive R-waves and stored these data on-line. Heart rate (bpm) was derived from this data, as well as two different heart rate variability measures: vagal tone index (log ms^2) and the THM wave (log ms^2).

Vagal tone index and the THM wave were quantified using patented (19) software (MXEDIT) from Delta-Biometrics (Bethesda, MD). This software takes as input the successive R-wave to R-wave intervals in ms. Computerized editing with a human operator is performed on this train of intervals to recover the original heart rate signal in the case of artifact. Editing was performed by a technician who was blinded to the experimental hypothesis. MXEDIT then quantifies vagal tone index using time series analysis in which the frequency components above and below the respiratory band (0.12–0.40 Hz) are removed by moving polynomial filters. The remaining band variance is log transformed to yield the vagal tone index (19). Similar procedures are used to derive the THM wave, but the frequency band is 0.06–0.10 Hz.

Procedure

Subjects signed a consent form that had been approved by the Frances Scott Key Medical Center Institutional Review Board that described the procedure. The subject was seated in a quiet room during testing. Following a resting period of approximately 5 min, a 1-min baseline recording was performed. The 1-min baseline was adequate to obtain a stable measure of heart rate and heart rate variability (i.e., vagal tone index); this would allow approximately 20 completed respiratory cycles at the normal breathing rate of 0.3 Hz for the computation of vagal tone index. Subjects were then injected with 0.4 mg naloxone HCl (Du Pont, Wilmington, DE) intramuscularly. Subjects were observed for 30 min during continuous electrocardiographic recordings.

During this 30-min interval, subjects were rated on the Clinical Institute Narcotic Assessment Scale (CINA) (18) by medical personnel skilled on this instrument. The CINA consists of 11 observer-rated items concerning classical opiate withdrawal signs and symptoms such as nausea, gooseflesh, sweating, tremor, lacrimation, and yawning. All subjects whose results are reported here had scores above 20, the recommended cutoff for the abstinence syndrome. The mean score on the CINA was 33.1 (SEM = 2.0).

Systolic blood pressure (mm Hg) was recorded every 10 min during this 30-min period as part of the CINA. Only a subset (n = 14) of the 19 subjects had systolic blood pressure data.

Subjects received an intramuscular injection of 15 mg morphine sulphate at the end of this recording interval to relieve the opiate withdrawal symptoms. Recordings were not taken during the response to this morphine injection.

RESULTS

Statistical analyses proceeded using repeated-measures analyses of variance (ANOVA). The resting baseline before injection of naloxone was compared to the mean of the period of peak heart rate response from 10–20 min after injection. This peak response was selected to provide a strong test of concomitant variation in vagal tone (i.e., vagal tone would not be expected to change except when heart rate increased). The delayed tachycardic response was consistent with the slow distribution of intramuscular naloxone.

The cardiovascular response to naloxone in opiate-dependent individuals is illustrated in Fig. 1 for heart rate, vagal tone index, and the THM wave. Heart rate increased significantly, $F(1, 18) = 10.3, p < 0.005$, from baseline. The mean increase for the period from 10–20 min after injection was 5.1 bpm. In contrast, there was no concomitant variation in vagal tone index, $F(1, 18) = 1.6, p < 0.20$. Vagal tone changed less than 0.18 log units in response to naloxone during the same period from 10–20 min after injection.

Heart rate variability in frequencies much lower than the respiratory bandwidth (i.e., THM) actually increased. The THM wave increased significantly, $F(1, 18) = 6.8, p < 0.02$, during the period in which heart rate increased, from a baseline mean in THM of 4.9–5.3 log units during this same period.

Systolic blood pressure (for the 14 subjects on whom this measure was recorded) showed a mean increase of 10.5 mm Hg 10 min after naloxone, from a baseline of 117.0. The increase was 8.0 mm Hg 20 min after drug. This change was tested in a repeated-measures ANOVA and was found to be significant, $F(1, 13) = 18.2, p < 0.001$.

DISCUSSION

The primary result was that naloxone administered to opiate-dependent individuals produced tachycardia that did not have a significant vagal component. Despite highly reliable increases in heart rate, vagal tone index did not change. The tachycardia, which peaked approximately 12 min after intramuscular injection, reached a maximum mean increase of 7 bpm with considerable variability between individual subjects (SEM = 2.6 bpm). In contrast, vagal tone index decreased only 0.17 units, not a significant difference. Nineteen subjects provided adequate statistical power to detect reliable changes in vagal tone (had they occurred), indicating that the failure to find a significant difference in parasympathetic influences could not be attributed to false negative error.

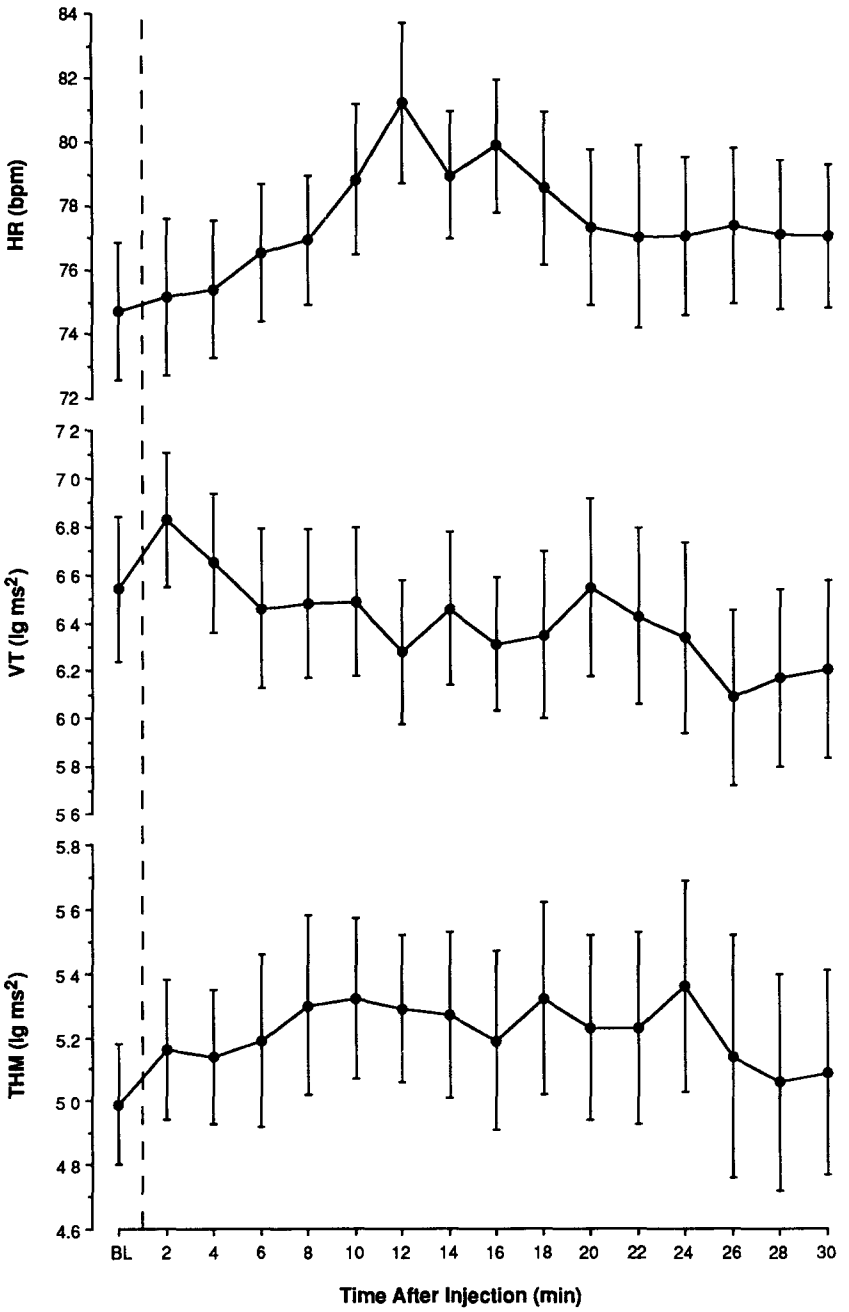

FIG. 1. Cardiovascular responses to intramuscular naloxone (0.4 mg) in 19 opiate-dependent individuals. Baseline (BL) was recorded before naloxone injection, and recording of heart rate (HR), vagal tone index, and the THM wave was continuous for 30 min after injection. Displayed are means (±SEM) of 2-min duration each. Naloxone-precipitated withdrawal was associated with significant increases in heart rate and the THM wave, but there was no change in vagal tone index.

These results indicate that the tachycardia from naloxone-precipitated withdrawal is not vagal in origin. Therefore, parasympathetic influences on the heart appear unimportant in the cardiovascular response to naloxone in opiate addicts. We are unaware of other studies in which parasympathetic cardiac influences have been assessed in naloxone-precipitated withdrawal.

The lower frequency rhythm in heart rate variability, the THM wave, increased significantly. We have not observed an increase in the THM wave with any abused drug we have studied. While there is agreement that vagal tone index is primarily vagal in origin (20), the THM wave has not been studied as intensively. Some authors have interpreted the THM wave as reflecting primarily sympathetic influences on the heart (2). In the context of the present results, this would indicate that the cardiovascular changes during naloxone-

precipitated withdrawal were primarily sympathetic rather than parasympathetic nervous system effects.

A recent clinical report (13) concerning the naloxone-precipitated withdrawal in individuals maintained on methadone tends to confirm this conclusion. They reported similar magnitude increases in systolic blood pressure (15 mm Hg) and heart rate (10 bpm) to 0.20 mg IV naloxone compared to placebo (which had little effect). Moreover, they found strong evidence of dysphoric mood states following infusion of naloxone.

The animal literature tends to support this interpretation. Although parasympathetic influences have not been studied, recent research in rodents indicates that naloxone-precipitated withdrawal is associated with tachycardia, increased mean arterial pressure, increased renal and adrenal sympathetic nerve activity, and increased levels of plasma catecholamines (4,5). Taken together with the present data, these results strongly implicate sympathetic mechanisms in naloxone-precipitated withdrawal in both humans and animals. Although it has been assumed that the cardiovascular response to naloxone in opiate-dependent individuals was sympathetic in origin (11), this same assumption (11) has proven false with many different drugs of abuse (see above).

In conclusion, these results effectively rule out vagal mediation of the tachycardia produced by naloxone administered to opiate-dependent individuals. The results with the heart rate variability index (the THM wave) at a dominant frequency that is lower than that of vagal tone, when combined with supportive animal literature, led to the conclusion that this cardiovascular response is primarily sympathetic rather than parasympathetic in origin. Therefore, our central linkage hypothesis was not proved false by discrepant data. Vagally mediated tachycardia may be a common factor in the response to abused drugs that is *not* shared by at least one drug (naloxone) with aversive subjective effects. Moreover, tachycardia alone is insufficient to produce reward/reinforcement, either through peripheral or central mechanisms. Only central, vagally mediated tachycardic responses to drugs of abuse appear to be associated with reward reinforcement. Further efforts to test the limits of this linkage hypothesis are currently underway with other abused drugs and other aversive drugs, as well as drugs with CNS effects that are subjectively neutral.

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