Published in final edited form as:

Behav Pharmacol. 2011 February ; 22(1): 87–90. doi:10.1097/FBP.0b013e3283423d55.

Naltrexone decreases d-amphetamine and ethanol self-administration in rhesus monkeys

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Abstract

Amphetamines are the second most highly abused illicit drugs worldwide, yet there is no pharmacological treatment for amphetamine abuse and dependence. Preclinical studies and, more recently, human studies, suggest that the opioid receptor antagonist naltrexone might be useful in the treatment of amphetamine abuse. Naltrexone, an opioid receptor antagonist, is currently used for the treatment of alcohol dependence. The purpose of this study was to explore the ability of naltrexone to modify self-administration of amphetamine or ethanol in rhesus monkeys. Monkeys were trained to respond for intravenous injections of either d-amphetamine (0.003 mg/kg/injection) or ethanol (0.05 g/kg/injection) on a fixed-ratio 30 schedule. Naltrexone (0.01–1 mg/kg) was administered intramuscularly 30 min prior to the start of treatment test sessions. Naltrexone dose-dependently decreased both amphetamine and ethanol self-administration. These findings support the potential use of naltrexone as therapy for amphetamine and polydrug abuse.

Keywords

amphetamine; ethanol; naltrexone; opioid receptor antagonist; self-administration; rhesus monkey

Introduction

Approximately 1% of the world population report past-year abuse of either illicit and/or prescription amphetamines (e.g., Adderall; SAMHSA, 2009; UNODC, 2009). Despite this number being greater than that for heroin and cocaine combined, to date there is no approved pharmaceutical therapy for the treatment of amphetamine abuse.

Drug abuse and dependence often are treated with agonists (e.g., methadone) that activate the same receptors stimulated by the particular drug of abuse (e.g., heroin). Although proven useful in the clinic, this approach may be limited by the addictive properties of the treatment drugs themselves, as well as being limited to treating dependence to specific drugs.

Receptor antagonists, conversely, might be useful for treating dependence to drugs from different classes. For instance, opioid receptor antagonists attenuate the rewarding effects of both opiates and alcohol in rats (e.g., Jimenez-Gomez and Shahan, 2007; Roberts and Bennett, 1993). This has been extended to the clinic, where naltrexone has been effective in reducing the use of heroin in detoxified, compliant individuals (Sullivan et al., 2007), as well as treating alcohol dependence (O'Malley et al., 2002).

Opioid receptor antagonists also may be useful for treating amphetamine abuse and dependence. In rodents, opioid antagonists impact the neurochemical and behavioral effects of amphetamine. For instance, naloxone pretreatments decrease amphetamine-induced dopamine release in the nucleus accumbens and striatum, and amphetamine-induced increase in locomotor activity in rats (Schad et al., 1995). More recently, naltrexone decreased reinstatement of amphetamine seeking in rats (Haggkvist et al., 2009). In humans, naltrexone decreased the reported subjective effects of amphetamine and amphetamine consumption in amphetamine-dependent individuals seeking treatment (Jayaram-Lindstrom et al., 2008a, 2008b). Together, these findings suggest that opioid receptor antagonists such as naltrexone may be useful in treating amphetamine abuse. No preclinical study to date, however, has investigated whether naltrexone decreases behavior maintained by amphetamine self-administration.

The purpose of the present study was to assess the effects of naltrexone on d-amphetamine and ethanol self-administration in rhesus monkeys. The use of rhesus monkeys is beneficial when assessing the potential therapeutic value of naltrexone given the extensive drug self-administration literature with this species, as well as the neuropharmacological and neurochemical similarities of nonhuman primates and humans (Weerts et al., 2007).

Methods

Subjects

Five adult rhesus monkeys (1 female, 4 males) were used. Three monkeys had prior ethanol self-administration experience, and one had experience with opioid antagonists. Monkeys were fitted with a chronic, indwelling catheter (Moxmed, Portage, WI) surgically implanted in the jugular, femoral, or brachial vein. Catheters passed subcutaneously to an exit site at the intrascapular region of the monkeys' backs. Here, the catheter connected through a flexible tether to the outside rear of the housing cage to an infusion pump. Monkeys wore a protective jacket attached to the flexible tether to keep the catheter-tether connection in place.

Water was freely available at all times. Monkeys were fed twice per day with Purina monkey chow, approximately 2 h prior and after the daily experimental session. Fresh fruit and enrichment toys also were provided daily.

The present study was conducted in AAALAC accredited facilities and the experimental protocol was approved by the University of Michigan Committee for Use and Care of Animals.

Apparatus

Experimental sessions were conducted in the individual housing cages, which were custom built with three solid stainless steel walls and a front barred wall (Research Equipment Co., Bryan, TX). The caging system was constructed with two cages (top and bottom) each. Cages were arranged in a large room, allowing visual access to other monkeys. Each cage was 76.2 x 83.8 x 91.4 cm (W x H x D). Three response levers (BRS-LVE, Beltsville, MD) were located on a side panel, mounted 25.4 cm above the barred floor. A 2.5-cm diameter cue light was located above each lever. Only the rightmost lever, right and center cue lights were used for this experiment. Drug infusions were delivered with pump speed of 1 cc per 5 s by a roller pump (Watson-Marlow, Falmouth, UK).

Programming and recording of experimental events was controlled with Med Associates (St. Albans, VT) software and interfacing connected to a computer in an adjacent room.

Procedure

Monkeys had extensive prior experience in drug self-administration studies and required no preliminary training. A baseline of intravenous (i.v.) d-amphetamine (0.003 mg/kg/inj) or ethanol (0.05 g/kg/inj) self-administration was established. During once daily, 90-min afternoon sessions, a red stimulus light was illuminated above the right lever signaling drug availability. Drug deliveries were arranged according to a fixed ratio 30 timeout 10 s schedule of drug reinforcement. Thirty responses on the active right lever turned off the red light and turned on a green light above the center lever and the infusion pump. A 10-s time out period followed each infusion, during which all lights were extinguished and responses had no consequence. The red light was then turned on and drug again was available.

Once a stable baseline of drug self-administration was established, determined by three consecutive sessions with no increasing or decreasing trend in responding, the effects of naltrexone (0.01–1.0 mg/kg) were evaluated. The 0.1 or 0.3 mg/kg dose was tested first, with other doses tested in ascending or descending order. A single dose of naltrexone was delivered intramuscularly 30 min prior to the beginning of the drug self-administration session. At least 3 sessions separated each naltrexone pretreatment, contingent on a return to baseline levels of responding.

Drugs

D-amphetamine sulfate (Abbott laboratories, Chicago, IL), ethanol (Pharmco, Brookfield, CT), and naltrexone hydrochloride (provided by the National Institute on Drug Abuse, Bethesda, MD) were dissolved in 0.9 % saline.

Data analysis—A linear mixed model with compound symmetry (SPSS, 17.0.2) was used, allowing analysis of repeated-measures data sets with missing values (e.g., not all subjects exposed to all doses). The test of least significant difference (LSD) was used for pairwise comparisons. Statistical analyses were considered significant when $p < 0.05$.

Results

Pretreatments with naltrexone dose-dependently decreased amphetamine [$F(5, 25.48) = 3.29, p < 0.05$] and ethanol [$F(5, 34.98) = 3.38, p < 0.05$] self-administration. Figure 1 shows the average effect of naltrexone pretreatment on response rates (top) and number of injections earned per session (bottom). For amphetamine ($n = 3$) and ethanol ($n = 4$) self-administration, the 0.3 and 1 mg/kg doses of naltrexone significantly decreased response rates and injections earned per session.

Given the disparity in control levels of self-administration between the two agents, with higher response rates for amphetamine, response rates during naltrexone pretreatment sessions were transformed to proportion of control. By normalizing levels of responding, the relative potency of naltrexone could be assessed. Figure 2 shows the proportion of control responses per min during amphetamine and ethanol sessions as a function of naltrexone dose. Naltrexone decreased responding for amphetamine to the same extent that it decreased responding for ethanol, indicating similar potency [$F(1, 10.26) = 0.36, NS$].

Discussion

It has been reported that naltrexone decreases the rewarding effects of self-administered alcohol and opiates (e.g., Jimenez-Gomez and Shahan, 2007; Roberts and Bennett, 1993). The present experiment found that pretreatment with naltrexone dose-dependently decreased responding for amphetamine infusions to the same extent that it decreased responding for ethanol infusions. The present findings, along with the studies of Jayaram-Lindstrom et al. (2008a,b) showing that naltrexone reduced the subjective effects, craving, and consumption of amphetamine in humans, suggest that naltrexone should be considered further as a therapy for treating amphetamine abuse and dependence.

One of the benefits of using naltrexone for treating drug abuse is its ability to decrease the rewarding effects of a variety of drugs. In this experiment, naltrexone decreased responding for different drugs at doses previously reported to decrease oral and i.v. ethanol self-administration in rhesus monkeys (Williams et al., 1998). Thus far, naltrexone has been useful for treating single-drug abuse or dependence; however, little is known about its usefulness for treating polydrug abuse. Given that most individuals who abuse drugs report intake of more than one drug class (e.g., heroin and cocaine; Leri et al. 2003), it would be of interest to investigate the effectiveness of naltrexone in treating polydrug abuse.

Williams et al. (1998) found that the effects of naltrexone were not surmountable with increases in ethanol dose, suggesting that the mechanism through which naltrexone decreases ethanol self-administration, and perhaps also amphetamine self-administration, differs from typical opioid agonist/antagonist interaction. It has been suggested that decreases in dopaminergic responses to drugs of abuse produced with opioid receptor antagonists is responsible for the reduction in the rewarding effects of non-opioid drugs (Di Chiara and Imperato, 1988). It also is possible, however, that this reduction is a result of non-opioidergic aversive effects of naltrexone. The specific mechanism has yet to be elucidated.

Oral naltrexone has been useful in treating alcohol dependence (Srisurapanont and Jarusuraisin, 2005), but its success has been limited by problems with medication noncompliance. Sustained-release formulations of naltrexone circumvent this problem and show promise for long-term success of the treatment of individuals dependent on opiates and alcohol (Comer et al., 2007; Soyka and Rösner, 2008). Given the present findings, the use of sustained-release formulation of naltrexone for treating amphetamine abuse and dependence also should be evaluated.

Acknowledgments

We thank Amy Hall, Kathy Carey, and Susan Pouliot for technical assistance conducting the experiment and Joe Kazemi of the University of Michigan Center for Statistical Consultation and Research for assistance with statistical analyses. We also thank Chris Podlesnik for useful comments on this document. This research was supported by Alkermes, Inc. and United States Public Health Service Grant DA 015449 (GW). CJ was supported by the National Institutes of Health under Ruth L. Kirschstein National Service Research Service Award T32 DA007267.

References

- Comer SD, Sullivan MA, Hulse GK. Sustained-release naltrexone: Novel treatment for opioid dependence. *Expert Opin Investig Drugs*. 2007; 16:1285–1294.
- Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Neurobio*. 1988; 85:5274–5278.
- Haggkvist J, Londholm S, Franck J. The opioid antagonist naltrexone attenuates reinstatement of amphetamine drug-seeking in the rat. *Behav Brain Res*. 2009; 197:219–224. [PubMed: 18793682]
- Jayaram-Lindström N, Konstenius M, Eksborg S, Beck O, Hammarberg A, Franck J. Naltrexone attenuates the subjective effects of amphetamine in patients with amphetamine dependence. *Neuropsychopharmacol*. 2008a; 33:1856–1863.
- Jayaram-Lindström N, Hammarberg A, Beck O, Franck J. Naltrexone for the treatment of amphetamine dependence: A randomized, placebo-controlled trial. *Am J Psychiatry*. 2008b; 165:1442–1448. [PubMed: 18765480]
- Jimenez-Gomez C, Shahan TA. Resistance to change of alcohol self-administration: Effects of alcohol-delivery rate on disruption by extinction and naltrexone. *Behav Pharmacol*. 2007; 18:161–169. [PubMed: 17351423]
- Leri F, Bruneau J, Stewart J. Understanding polydrug use: Review of heroin and cocaine co-use. *Addiction*. 2003; 98:7–22. [PubMed: 12492751]
- O'Malley SS, Krishnan-Sarin S, Farren C, Sinha R, Kreek MJ. Naltrexone decreases craving and alcohol self-administration in alcohol-dependent subjects and activates the hypothalamo-pituitary-adrenocortical axis. *Psychopharmacol*. 2002; 160:19–29.
- Roberts DCS, Bennett SAL. Heroin self-administration in rats under a progressive ratio schedule of reinforcement. *Psychopharmacol*. 1993; 111:215–218.
- Substance Abuse and Mental Health Services Administration [SAMHSA]. NSDUH Series H-36, HHS Publication No. SMA 09-4434. Office of Applied Studies; Rockville, MD: 2009. Results from the 2008 National Survey on Drug Use and Health: National Findings.
- Schad CA, Justice JB, Holtzman SG. Naloxone reduces the neurochemical and behavioral effects of amphetamine but not those of cocaine. *Eur J Pharm*. 1995; 275:9–16.
- Soyka M, Rösner S. Opioid antagonists for pharmacological treatment of alcohol dependence: A critical review. *Curr Drug Abuse Rev*. 2008; 1:280–291. [PubMed: 19630726]
- Srisurapanont M, Jarusuraisin N. Opioid antagonists for alcohol dependence. *Cochrane Database of Systematic Reviews*. 2005; 1 Art. No.: CD001867.
- Sullivan MA, Garawi F, Bisaga A, Comer SD, Carpenter K, Raby WN, Anen SJ, Brooks AC, Jiang H, Akerele E, Nunes EV. Management of relapse in naltrexone maintenance for heroin dependence. *Drug Alcohol Dep*. 2007; 91:289–292.

- United Nations Office on Drugs and Crime [UNODC]. World drug report 2009. United Nations Publications Sales No. E.09.XI.12; Vienna, Austria: 2009.
- Weerts EM, Fantegrossi WE, Goodwin AK. The value of nonhuman primates in drug abuse research. *Exp Clin Psychopharm*. 2007; 15:309–327.
- Williams KL, Winger G, Pakarinen ED, Woods JH. Naltrexone reduces ethanol-and sucrose-reinforced responding in rhesus monkeys. *Psychopharmacol*. 1998; 139:53–61.

Figure 1.

Mean ($\pm$ SEM) responses per min and injections earned during amphetamine and ethanol self-administration sessions as a function of naltrexone dose. Each data point represents the average of all determinations for each dose across all monkeys. Symbols denote statistical significance in LSD pairwise comparisons (* $p<0.05$; ** $p<0.01$).

Figure 2.

Mean ($\pm$ SEM) proportion of control responses per min for amphetamine (closed symbols) and ethanol (open symbols) infusions as a function of naltrexone dose. Proportion of control responses per min were calculated for individual monkeys using their average control level of responses and then averaged across monkeys.