NeuroImage 78 (2013) 176–185

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Extended-release naltrexone (XR-NTX) attenuates brain responses to alcohol cues in alcohol-dependent volunteers: A bold FMRI study

Scott E. Lukas [a,b,c,*], Steven B. Lowen [a,b,c], Kimberly P. Lindsey [a,c], Nina Conn [a], Wendy Tartarini [a], John Rodolico [a,c], Gopi Mallya [a,c], Christopher Palmer [a,c], David M. Penetar [a,c]

[a] Behavioral Psychopharmacology Research Laboratory, McLean Hospital, Belmont, MA, USA
[b] Brain Imaging Center, McLean Hospital, Belmont, MA, USA
[c] Harvard Medical School, Department of Psychiatry, Boston, MA, USA

ARTICLE INFO

Article history:
Accepted 20 March 2013
Available online 6 April 2013

Keywords:
Naltrexone
Alcoholism
fMRI
Magnetic resonance imaging
Craving

ABSTRACT

Oral naltrexone reduces heavy drinking, but is less consistent as an abstinence promoter, whereas once-monthly extended-release naltrexone (XR-NTX) also maintains abstinence. The present study sought to determine if alcohol cue reactivity is attenuated by XR-NTX. Twenty-eight detoxified alcohol-dependent adult male and female volunteers received a single i.m. injection of either XR-NTX or placebo under double-blind conditions. An fMRI/cue reactivity procedure was conducted immediately before and two weeks after injection. At baseline, alcohol-related visual and olfactory cues elicited significant increases in orbital and cingulate gyri, inferior frontal and middle frontal gyri. Subsequently, brain activation was significantly altered in XR-NTX-treated individuals. These affected brain regions are associated with the integration of emotion, cognition, reward, punishment, and learning/memory, suggesting that XR-NTX attenuates the salience of alcohol-related cues. Such an effect on brain function may interrupt the processes associated with "slips" and relapse, which may account for XR-NTX's ability to maintain abstinence.

Introduction

Oral naltrexone has a long record of safe clinical use in the treatment of opioid addiction and alcohol dependence. This drug exhibits a low level of toxicity, and in clinical use, adverse events (AEs) are generally mild or moderate and reversible (McEvoy, 1999). In addition, when combined with various treatment programs, naltrexone has been found to decrease drinking rates, prolong abstinence, and hinder relapse to uncontrolled drinking among abstinent alcoholics who sampled alcohol during treatment (Anton, 1999; Kranzler, 2000; O'Malley et al., 1992; Volpicelli et al., 1992). However, shortcomings related to compliance and adverse effects limit the utility of oral naltrexone for the treatment of alcohol dependence. Meta-analyses of placebo-controlled trials of oral naltrexone (n = 19), have failed to find significant benefit for complete abstinence rates during treatment (Bouza et al., 2004; Srisurapanont and Jarusuraisin, 2005) and some have raised the possibility that naltrexone's benefit may even require "sampling" alcohol in order to facilitate extinction (Sinclair, 2001).

In April 2006, Vivitrol® (naltrexone for extended-release injectable suspension or XR-NTX) was approved in the United States for the treatment of alcohol dependence in subjects who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment (Gastfriend, 2011). This extended-release, microsphere formulation of naltrexone is administered by intramuscular (IM) gluteal injection every 4 weeks and in abstinent alcohol dependent adults receiving psychosocial therapy, has demonstrated efficacy in prolonging initial abstinence and maintaining total (i.e., 6-month) abstinence compared to placebo — i.e., in the absence of "sampling" alcohol (O'Malley et al., 2007). XR-NTX is generally well tolerated and only infrequent treatment-related AEs have been reported (nausea, injection site reaction and headache). This raises the question as to what is the mechanism by which XR-NTX might exert its clinical effect on abstinence.

It has been suggested that exposure to cues may lead to the activation of certain "automatic" cognitive functions, resulting in repetitive, unwanted thoughts about alcohol. These automatic thoughts are the cognitive equivalent of unconscious craving (Anton, 2000). Craving also may arise in part from persistent nervous system changes (i.e., neuroadaptation) that leave the alcoholic's brain vulnerable to relapse drinking (Koob, 2000). These changes persist in the absence of alcohol, and may result in conscious or unconscious physical and mental distress. This phenomenon could account for the craving alcoholics experience soon after the cessation of drinking, which makes them vulnerable to relapse for a protracted period of time.

A comprehensive understanding of craving requires the integration of unconscious and cognitive mechanisms (Rohsenow and Monti, 1999). Among the concepts of craving discussed here, both the social learning and cognitive processing models implicate cognitive learning in the development of harmful drinking patterns and

* Corresponding author at: 115 Mill Street, Neuroimaging Center, Belmont MA, 02478, USA. Fax: +1 617 855 3711.
E-mail address: slukas@mclean.harvard.edu (S.E. Lukas).

1053-8119/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neuroimage.2013.03.055

stress the importance of teaching conscious coping strategies in alcoholism therapy. Both of these models are also consistent with the involvement of other causal mechanisms, including reinforcement and other unconscious processes (Anton, 1999; Tiffany, 1999).

Craving studies based on a wide-range of imaging technologies of humans have identified specific regional changes in brain cell activity in response to alcohol-related cues (Anton et al., 2001; George et al., 2001; Hommer, 1999). Because these findings alone do not prove that the observed brain changes actually *cause* the subjective sensation of craving (Sayette et al., 2000), a more precise method to monitor how these urges affect the brain and is needed, and fMRI is well suited to provide this metric.

Echo-planar fMRI increases the temporal resolution for acquiring functional neuroanatomical images beyond what has been available with radionuclide scanning. Compared to other imaging modalities, fMRI is more likely to identify transient drug-induced changes in regional cerebral blood flow (CBF) or metabolism. Spatial resolution is excellent with fMRI, which contains connectivity and functional information in the same image.

The use of fMRI to track the effects of alcohol-related stimuli on central nervous system function has been well-validated. Braus et al. (2001) demonstrated that the ventral striatum (VS) was activated by presenting recently detoxified alcoholics with alcohol-associated visual cues. This research team later showed that this cue activation in the striatum and medial prefrontal cortex was associated with subsequent relapse in abstinent alcoholics (Grusser et al., 2004), while Kareken et al. (2004) demonstrated that olfactory cues activated nucleus accumbens and ventral tegmental areas in high risk drinkers. Finally, Myrick et al. (2008) demonstrated that oral naltrexone alone, and in combination with ondansetron, decreased alcohol cue-related activation of the VS in alcohol-dependent individuals. Only visual cues were studied and the analyses were confined to the VS.

Here, we tested the ability of a single i.m. injection of XR-NTX to alter whole-brain activation patterns (as measured by BOLD fMRI) associated with the delivery of alcohol-related visual and olfactory cues in individuals who are being treated for their alcohol dependence.

Methods

General

The present study was a double-blind, placebo-controlled between-subject design to test whether XR-NTX attenuates brain responses to alcohol-related olfactory and visual cues in treatment-seeking alcohol-dependent individuals. The protocol was reviewed and approved by the McLean Hospital Institutional Review Board (IRB); all participants read and signed an informed consent form before receiving a physical exam and psychiatric screen to participate in the study. A total of 31 adult (age 46.6 ± 9.2 years, mean ± S.D.) male (N = 21) and female (N = 10), recently detoxified individuals passed the screening protocol and were randomized to the protocol. Medication randomization was stratified by sex and age. A total of 24 were Caucasian and 7 were African American. The participants reported drinking on average a total of 82.8 ± 10.8 drinks per week during their most recent drinking period prior to their detoxification. A separate drug use questionnaire was used to collect information of drug and alcohol use histories and patterns. Mean age of initiation of heavy drinking was reported to be 24.7 ± 10.8 years (range 16–55). Nineteen did not smoke tobacco and those who did smoke reported smoking 17.3 ± 7.4 cigarettes per day. Thirteen reported using no other drug of abuse, while the remainder reported occasional (or past) use of cannabis (N = 11), cocaine (N = 10) and opioids (N = 1); some participants reported using more than one drug. All received a diagnosis of alcohol dependence via DSM-IV criteria and none received a diagnosis of dependence on any other drug including opiates, stimulants or sedative/hypnotics.

Medication treatment

The fMRI results are based on 28 individuals who successfully completed both fMRI sessions, yielding valid pre and post treatment data. Of these 28 participants, a total of 15 were randomized to receive XR-NTX (380 mg, i.m.), while 13 received placebo injection. XR-NTX is a microsphere formulation of naltrexone for suspension that is available in dose strength of 380 mg naltrexone per vial. The XR-NTX microspheres contain approximately 34% (w/w) naltrexone incorporated into a 75:25 matrix of poly (*D,L*-lactide co-glycolide) polymer (PLG). PLG is a common, biodegradable medical polymer having a history of safe human usage in sutures, bone plates and slow-release pharmaceuticals (e.g., Risperdal Consta®, Zoladex®, Lupron Depot®, Decapeptyl® SR and Sandostatin LAR® Depot). Placebo for XR-NTX microspheres consists of a sterile, white, powder of 75:25 PLG.

Behavioral treatment

All participants attended weekly relapse prevention counseling sessions conducted by a trained clinician—this was done to ensure that placebo-treated participants received some form of therapy. The sessions lasted approximately 60 min. A cognitive strategy was used with an emphasis on self-management and coping skills. The goal of the treatment was to develop coping skills that would help the participants maintain abstinence from alcohol. A Clinical Global Impressions (CGI) was also performed at each study visit to assess therapeutic effect.

The day after the fMRI scan (Day 1), subjects were contacted via telephone by site personnel to offer support following cue exposure. In addition, weekly visits were conducted for the first month after dosing and included the following assessments: laboratory tests, adverse events (AEs), vital signs, questionnaire responses and urine toxicology. Pregnancy tests were conducted as applicable on a monthly basis.

Experimental procedure

Data were acquired using a Siemens 3 T Trio whole body scanner with a transmit-receive quadrature birdcage head coil. A baseline fMRI scan/cue reactivity assessment was conducted at Visit 2 (Day 0) prior to randomization. Subject responses were collected via a keypad device in response to a computerized visual analog questionnaire. Visual stimuli were delivered using a projector, translucent screen, and mirrors; a custom-built olfactometer based on Lowen and Lukas (2006) provided olfactory stimuli. See Fig. 1 for a layout of the room configuration. The participants were instructed to use a MR compatible, fiber optic response pad (FORP, Current Designs, Inc., Philadelphia, PA) to move the cursor on the screen. An identical procedure was performed two weeks later.

Olfactory/visual cues

The MR-compatible olfactometer device (Lowen and Lukas, 2006) delivered one of the three odorants [alcohol, phenyl ethyl alcohol (rose scent) and humidified air (no odor)] automatically via computer control through a disposable nasal cannula. The three odorant streams converged near the subject to minimize delay due to dead space. Participants were exposed to their *preferred* brand of alcohol. For those who preferred beer, a thin layer of canola oil (1 mL) was floated on this odorant to retard foaming. Pictures of alcohol- and non alcohol-related images were presented to the participants via the translucent screen. The alcohol-related images depicted various types of beer, wine and distilled spirits in standard glasses and/or bottles while the non-alcohol images were photos of water, milk and tea in their various containers. Fig. 2 depicts the experimental procedure. All participants viewed the same series of images, regardless of their preferred alcoholic beverage.