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Cue reactivity and opioid blockade in amphetamine dependence: A randomized, controlled fMRI study

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ABSTRACT

Background: The opioid antagonist, naltrexone, has been shown to reduce the risk of relapse in amphetamine dependence, but the mechanisms behind this effect are not well understood. We aimed to investigate if naltrexone attenuates cue reactivity and craving in amphetamine dependence.
Methods: Forty men with severe, intravenous amphetamine dependence were randomized to one dose of naltrexone (50 mg) or placebo. In a BOLD fMRI cue reactivity paradigm, they were exposed to drug-related and neutral films and gave subjective ratings of craving after each film. Twenty-nine patients left data of sufficient quality to be included in the final analysis.
Results: The drug-related films elicited strong subjective craving and BOLD activations of the striatum, cingulate cortex, and occipito-temporal visual attention networks. Longer history of amphetamine use was associated with greater activations of the prefrontal cortex. Naltrexone as compared to placebo had no significant effects on brain activations or subjective ratings.
Conclusion: Patients with severe stimulant use disorder exhibit strong neural cue reactivity, the patterns of which are modulated by duration of drug use. In this sample, we found no evidence for any effects of naltrexone on cue reactivity.

1. Introduction

Amphetamine use disorder is a global health problem for which there is still no approved pharmacological treatment. In Northern Europe, amphetamine has dominated injection drug use for decades (Hakansson et al., 2009). One of the few promising pharmacological treatments for amphetamine dependence is the opioid antagonist naltrexone (Karila et al., 2010), which is currently used clinically for the treatment of alcohol and opioid dependence (Lobmaier et al., 2011; Rösner et al., 2010). In a number of human laboratory studies, it has consistently been shown that pre-treatment with naltrexone attenuates the subjective effects of amphetamine (Jayaram-Lindström et al., 2004, 2008b; Marks et al., 2014; Ray et al., 2015). Interestingly, in randomized clinical trials, a significant effect of naltrexone has also been shown to prolong the time to first amphetamine use, a fact which obviously cannot be explained by naltrexone's modulation of amphetamine effects (Jayaram-Lindström et al., 2008a).

One hypothesis is that naltrexone might attenuate craving, which has long been recognized as an important cause of relapse in addictive disorders (Drummond, 2001). Craving serves as a diagnostic criterion for addiction in both DSM 5 and ICD 10 and is a central concept in most theoretical models of these disorders (Tiffany and Wray, 2012). For instance, the theory of incentive sensitization predicts that the drug-dependent subject's 'wanting' of drugs increases over time, while the 'liking' of the drug actually diminishes and eventually plays a minor role in relapse and maintenance of problematic drug use (Berridge et al., 2009). Therefore, attenuating craving might be an important treatment target in severe addiction. Since subjective ratings of craving are only weakly associated with time to relapse and other clinically important outcomes (Tiffany and Wray, 2012), an important research goal is to develop laboratory models that objectively assess the processes involved in craving and relapse.

The biological mechanisms of craving are not fully understood, but striatal dopamine release seems to be of importance, at least for

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stimulant drugs (Berger et al., 1996; Volkow et al., 2006). However, there is also evidence for the involvement of the brain opioid system, and in alcohol dependence naltrexone has been shown to attenuate cue-induced craving and neural cue reactivity as measured with BOLD fMRI (Lukas et al., 2013; Myrick et al., 2008).

This led us to hypothesize that naltrexone might also attenuate craving and neural cue reactivity in amphetamine dependent patients. At the start of this project, there were still no published studies of cue reactivity in amphetamine dependent patients. Since then, three fMRI studies with methamphetamine users have appeared (Courtney et al., 2016; Malcolm et al., 2016; Yin et al., 2012). However, two of these studies did not require the participants to fulfill diagnostic criteria for amphetamine dependence (Courtney et al., 2016; Yin et al., 2012), and their cases generally represent mild or moderate addiction severity. Courtney et al. also studied the effects of naltrexone vs. placebo using cross-over randomization and found that naltrexone attenuated activity in primary sensory and motor areas when viewing drug-related pictures (Courtney et al., 2016). In the present study, we only included patients with long histories of compulsive, intravenous amphetamine use and used a paradigm of movie cues designed to induce strong craving reactions in the participants.

2. Material and methods

This study was designed as a randomized, double-blind, placebo-controlled clinical trial with two parallel groups of amphetamine dependent patients. Each patient received one oral dose of naltrexone (50 mg) or identical placebo and then went through an fMRI examination with a paradigm of visual drug cues. The study was approved by the Stockholm Ethics Review Board and the Swedish Medical Products Agency. It was preregistered in the EU Clinical Trials Register (EudraCT 2010-021384-33) and performed according to International Conference on Harmonisation guidelines for Good Clinical Practice, with external monitoring by the Karolinska Trial Alliance. All participants provided their written, informed consent before participating in any study procedures.

2.1. Participants

40 male, non-treatment seeking amphetamine users aged 20–65 were recruited via advertisement and word of mouth at the needle exchange program and in shelters in the Stockholm region. The exclusion of female participants was based on earlier fMRI studies suggesting different neural patterns between male and female stimulant users (Kilts et al., 2004), and we therefore chose to include only the most prevalent sex in this patient group to avoid introducing sex as a confounding variable in this small, experimental study. All participants were screened by a study physician, including psychiatric assessment with the Structured Clinical Interview for DSM-IV, Axis 1 (SCID-1), and detailed assessment of substance use history and other background variables with the Addiction Severity Index (McLellan et al., 1992). Inclusion criteria included DSM-IV diagnosis of amphetamine dependence since at least two years prior, history of intravenous amphetamine use, amphetamine use for a minimum of 12 days in the last 12 weeks, and having been drug free 1–30 days (minimum 24 h). The study was started before the release of DSM-5, but all patients would qualify for a diagnosis of severe amphetamine use disorder according to DSM-5. Exclusion criteria were other ongoing substance dependence (except nicotine), schizophrenia or bipolar disorder I, left-handedness, clinical signs of amphetamine intoxication at the day of testing, traces of cannabis, opiates, cocaine, or benzodiazepines in the urine at the day of testing, traces of alcohol as measured by breathalyser at the day of testing, or presence of severe somatic disorder. Patients with contraindications to MRI or the study medication were also excluded.

2.2. Study procedures

After a first screening visit, eligible patients were scheduled for a test day. Having arrived in the clinic on the test day, the patients were asked for a supervised urine test to exclude current use of drugs other than amphetamine. If the result was negative and a breathalyser test showed no trace of alcohol, the patient was included in the study and randomized to one capsule of 50 mg naltrexone (naltrexone hydrochloride, APL, Stockholm) or an identical capsule with placebo. This dose was chosen based on our earlier laboratory work and clinical trials with amphetamine dependent patients, which have all used 50 mg of naltrexone (Jayaram-Lindström et al., 2005, 2008b, 2008a). Block randomization was performed by the providers of the study medication, and block size was unknown to the investigators. After an interval of at least 60 min following ingestion of the study medication, the fMRI procedures were started.

The experiment described here consisted of the patients seeing film clips depicting drug related scenes (i.e., people preparing and taking drugs, both nasally and by injecting) or neutral scenes (e.g., old people drinking coffee or chatting). The visual content of the film types was not matched in detail but was broadly similar in colour, luminance, and presence of humans and faces.

The drug related film clips had been developed in our lab, and pilot trials had shown them to elicit strong but transient craving responses in amphetamine dependent individuals (unpublished data). Nine film clips of each type, lasting 16 s each, were shown in a pseudo-randomized order. The films were separated by a short break in which the participants were asked to rate with a trackball their level of amphetamine craving on a Visual Analogue Scale on the screen, with 0 in one end representing no craving at all and 100 in the other end representing the maximum level of craving imaginable (Kober et al., 2016; Milella et al., 2016). This was followed by a brief fixation cross. In total, the experiment lasted for 7 min.

After the examination, the patients were debriefed and asked about lingering craving and possible adverse events. All patients were offered clinical follow-up.

2.3. Magnetic resonance imaging

MRI examinations were performed with a 3 T instrument (GE MR750 Discovery) with an 8-channel head coil at the Karolinska MR Research Center. Each subject went through a total of four fMRI paradigms and structural imaging (T1 and T2 flair) lasting for about 50 min in total. The experiment described here was the last to be performed before the structural imaging and was preceded by a resting state examination and two different paradigms with still pictures (none of which elicited any significant drug craving in the subjects). For this experiment, we used EPI with gradient echo, slice thickness = 2.9 mm, number of slices = 43, TR = 2500 ms, TE = 30 ms, flip angle = 75°, FOV = 230 mm.

2.4. Data analysis

fMRI data was analyzed with SPM 12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). The data was realigned, co-registered to the participant's structural image, segmented, and smoothed with a 7 mm FWHM Gaussian kernel. The images were then normalized to an MNI template. Since movement artifacts often represent a major problem in fMRI, we quantified this using frame-wise displacement (FD) (Power et al., 2012). The FD is computed for each frame (image volume) as the root-mean-squared difference between adjacent images in terms of rotational and translational movements (in total 6 movement parameters). We decided to set a limit for the level of movement allowed such that patients were excluded if more than 25% of their volumes had a FD > 0.3.

The functional data were analyzed as a block design using the