J. Behav. Ther. & Exp. Psychiat. 50 (2016) 245–249

Contents lists available at ScienceDirect

Journal of Behavior Therapy and Experimental Psychiatry

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

Short report

Reactivating addiction-related memories under propranolol to reduce craving: A pilot randomized controlled trial

Michelle Lonergan [a, b], Daniel Saumier [a], Jacques Tremblay [a, b], Brigitte Kieffer [a, b], Thomas G. Brown [a, b], Alain Brunet [a, b, *]

[a] Research Center of the Douglas Mental Health University Institute, 6875 boul. Lasalle, Montreal, Qc, H4H 1R3, Canada
[b] Department of Psychiatry, McGill University, Ludmer Research & Training Bldg., 1033 Pine Ave. West, Montreal, Qc, H3A 1A1, Canada

ARTICLE INFO

Article history:
Received 2 July 2015
Received in revised form
21 September 2015
Accepted 28 September 2015
Available online 22 October 2015

Keywords:
Propranolol
Memory reconsolidation
Substance dependence
Craving
Clinical trial

ABSTRACT

Background: The reconsolidation blocker propranolol abolishes alcohol and drug-seeking behavior in rodents and attenuates conditioned emotional responses to drug-cues in humans in experimental settings. This suggests a role for its use in the treatment of substance dependence. In this translational pilot study, we explored the feasibility and efficacy of this procedure as an adjunct treatment for addiction. We hypothesized that guided addiction-related memory reactivation under propranolol would significantly attenuate tonic craving, a central element in relapse following addiction treatment.
Methods: Seventeen treatment-seeking adults diagnosed with substance dependence were randomized to receive double-blind propranolol ($n = 9$) or placebo ($n = 8$) on six occasions prior to reading a personalized script detailing a drug-using experience. The primary outcome measure was self-reported craving intensity.
Results: After controlling for baseline craving scores, intent-to-treat analysis revealed a time by group interaction, $F(1, 14) = 5.68$, $p = .03$, $\eta^2 = 0.29$; craving was reduced in the propranolol-treated group (Cohen's $d = 1.40$, $p < .05$) but not in the placebo group ($d = 0.06$, n.s.).
Limitations: The usual limitations related to small sample size and the lack of a follow-up apply here.
Conclusion: Drug-related memory reactivation under propranolol can subsequently reduce craving among substance-dependent individuals. Considering the relapse rate among individuals treated for substance dependence, our study highlights the feasibility of, and need for, more comprehensive trials of this treatment approach.

1. Introduction

Substance dependence is a chronically relapsing psychiatric disorder characterized by uncontrollable drug use despite significant adverse physical and psychosocial consequences (Diagnostic and Statistical Manual [DSM], American Psychiatric Association [APA], 2000, 2013). Recent perspectives on the neurobiological pathophysiology of addiction suggest that prolonged use of addictive drugs induces neuroplastic changes and altered neurotransmitter activity in brain regions associated with reward-related learning, effectively usurping normally adaptive associative memory mechanisms (Milton & Everitt, 2010; Torregrossa, Corlett, & Taylor, 2011). Consolidated long-term, drug-related memory cues in drug users can subsequently trigger conditioned responses (i.e., craving) that increase their risk of relapse, even after successful initial treatment and/or protracted abstinence (e.g., Torregrossa et al., 2011). However, reconsolidation theory posits that retrieval induces a transient period of memory lability where additional neurochemical processes are required for memory re-stabilization. Reconsolidation mechanisms putatively serve to enhance, impair, or update existing memories (Agren, 2014; Exton-McGuinness, Lee, & Reichelt, 2015; Sandrini, Censor, Mishoe, & Cohen, 2013). From a treatment-relapse perspective, decreasing the strength of alcohol- and drug-related memories by impairing their reconsolidation would be a highly desirable outcome.

When administered during the time-dependent reconsolidation

* Corresponding author. 6875 LaSalle Boulevard, Montreal, H4H 1R3, Canada.
E-mail addresses: michelle.lonergan@mail.mcgill.ca (M. Lonergan), saumierd@gmail.com (D. Saumier), jacques.tremblay@douglas.mcgill.ca (J. Tremblay), brigitte.kieffer@douglas.mcgill.ca (B. Kieffer), thomas.brown@mcgill.ca (T.G. Brown), alain.brunet@mcgill.ca (A. Brunet).

http://dx.doi.org/10.1016/j.jbtep.2015.09.012
0005-7916/

window, the β_2-adrenergic blocker propranolol has been shown to attenuate drug-seeking behavior in alcohol (Schramm, Everitt, & Milton, 2015; Wouda et al., 2010), cocaine (Milton, Lee, & Everitt, 2008), and morphine (Robinson & Franklin, 2007) dependent rodents. These animal paradigms, which model the motivational/rewarding effects of drug-related stimuli, suggest that disrupting the reconsolidation of underlying drug-related memories can reduce drug-seeking behavior akin to the relapse process in humans. In experimental settings, memory retrieval combined with propranolol administration attenuates memory for positive and negative drug-related words in abstinent heroin-dependent patients, as well as subjective craving and conditioned responses to drug-related cues in abstinent cocaine-dependent patients (Saladin et al., 2013; Zhao et al., 2011). These results were not replicated however in a sample of nicotine-dependent participants (Pachas et al., 2015). Nevertheless, impairment of the reconsolidation of drug-related memories with propranolol may facilitate treatment of substance dependence, as has been accomplished for traumatic memories in post-traumatic stress disorder (Brunet et al., 2008; Brunet, Poundja et al., 2011).

Low ecological validity limits existing studies by (i) a focus on addiction to a single drug, which is rather uncommon in clinical settings, and (ii) by use of a single memory retrieval session (iii) performed in a non-clinical experimental setting, following which the results were not sustained (Pachas et al., 2015; Saladin et al., 2013). No study to date has evaluated multiple sessions of reconsolidation impairment with personalized drug-use narratives as retrieval cues in individuals in treatment for various drug dependencies. This pilot, double-blind, randomized placebo-controlled trial tested the hypothesis that drug-related memory retrieval under propranolol is safe, tolerable, and produces a significant decrease in tonic (i.e., basal) craving.

2. Materials and method

2.1. Inclusion/exclusion criteria

Participants were recruited from a private residential (05/2011–06/2012) and a community outpatient (10/2012–05/2013) addiction treatment programs. Candidate participants were adults (18–65 years old) with a DSM-IV-TR (APA, 2000) diagnosis of substance dependence and enrolled in an addiction rehabilitation program. Participants with a past or current diagnosis of bipolar or psychotic disorder, actively suicidal, pregnant or breast-feeding women, with asthma, cardiovascular disease, diabetes, low blood pressure (<100 systolic), a resting heart rate of 55 bmp or lower, or with any other medical condition contraindicating the use of propranolol (i.e., use of other beta-blockers, insulin, antiarrythmics, clonidine, calcium channel blockers) were excluded. Participants taking selective serotonin reuptake inhibitors or selective norepinephrine reuptake inhibitors were not excluded if they had medical clearance to skip/postpone their dose on their treatment day (Kinzl, 2009).

2.2. Outcome measures

Primary efficacy outcomes were severity of alcohol/drug craving as measured by reliable and valid self-report questionnaires. Feasibility of the treatment and study protocols was assessed by a participant retention rate around 60%. Participants were assessed for their main substance of abuse. The Cocaine Craving Questionnaire (Tiffany, Singleton, Haertzen, & Henningfield, 1993) and Heroin Craving Questionnaire (Tiffany, Fields, Singleton, Haertzen, & Henningfield, in preparation) each contain 45 items that assess five dimensions of craving (desire, intent, positive/negative anticipation, and lack of control). The Marijuana Craving Questionnaire (Heishman, Singleton, & Liguori, 2001) contains 47 items assessing the same five dimensions, while the Alcohol Craving Questionnaire-revised (Singleton, Tiffany, & Henningfield, 2003) contains 30 items assessing two dimensions (urge/intention and reinforcement). All questionnaires measure current craving severity using a 7-point agree/disagree Likert scale, with statements such as “I crave (…) right now”. Averaging all items provides a general craving index, with higher scores indicative of stronger craving.

2.3. Procedure

The protocol was approved by McGill University's ethics committee and Health Canada. After obtaining signed informed consent, sociodemographic and clinical history information was obtained. The Mini International Neuropsychiatric Interview (Sheehan et al., 1998) was used to assess substance dependence and comorbid psychiatric disorders, and the number of days in the previous month that substance use interfered with the ability to fulfill home, work, or school obligations was used as an additional measure of the level of substance involvement. Participants then prepared a one-page narrative detailing a personal drug-using experience. In order to reactivate drug–cue associations that precipitate craving, participants were instructed to include as many details as possible of a typical drug-using episode including people, places, and environmental cues present during the anticipation, (over)use, and withdrawal stages. Prior to the first treatment visit, interviewers transcribed the script ensuring it was in the first person, present tense. All participants then underwent a medical examination to confirm study eligibility.

Included participants who returned for the first treatment visit (i.e., baseline) were randomized in a double-blind fashion to receive either propranolol hydrochloride or look-alike placebo for the whole duration of the study using an allocation ratio of 1:1. Due to variability in body mass, the medication dose was set to 1 mg/kg, as done in prior research (see Brunet, Poundja et al., 2011). This dosing strategy also reduces drug overexposure in low weight patients often seen in the addiction population. Propranolol hydrochloride is a synthetic noradrenergic beta-blocker that crosses the blood–brain barrier (Dey et al., 1986) and exerts central as well as peripheral effects (O'Carroll, Drysdale, Cahill, Shajahan, & Ebmeier, 1999). The randomization list was created by a third party unrelated to the study who used a randomized block design (Fleiss, 1986) with a block size of six. The list was achieved using a random number generator and was stratified according to type of addictive substance. The placebo and propranolol capsules were manufactured and coded by the Douglas Institute pharmacy to ensure blinding.

Each treatment session began by administering the psychometric evaluation of craving severity and giving the study drug under medical supervision. One hour after ingesting either propranolol or placebo, participants read aloud their personalized craving script to the interviewer, who probed for further clarification if needed. The interviewer's role was limited to ensuring that participants were emotionally engaged in the script-reading procedure; no attempts were made to interpret or re-structure the meaning of the narrative. If participants required therapeutic support following this procedure, they were to be referred to their case manager. Six bi-weekly sessions (separated by no less than 48 h) were provided over a period of 3 weeks. Treatment sessions took place either at the treatment site or at the Douglas Institute.