Published in final edited form as:

Alcohol. 2009 November ; 43(7): 541–543. doi:10.1016/j.alcohol.2009.09.024.

Stress, Alcohol Craving and Relapse Risk: Mechanisms and Viable Treatment Targets

Barbara J. Mason¹, Yavin Shaham², Friedbert Weiss¹, and AD Le³

¹The Scripps Research Institute, La Jolla, CA, USA

²National Institute on Drug Abuse, Baltimore, MD, USA

³University of Toronto, Toronto, Ontario, CANADA

Stress and Relapse to Drug Seeking: An Update (Y Shaham)

In 1995 we reported that exposing rats to mild intermittent footshock stress reinstates heroin seeking after extinction of the drug-reinforced behavior (Shaham and Stewart, 1995). This finding led to a series of studies by us and other investigators on the behavioral and neuronal mechanisms involved in stress-induced relapse to drug seeking, as measured in an operant reinstatement model (Ghitza et al., 2006; Le et al., 2000; Shaham et al., 2000; Wang et al., 2005). In this lecture I summarized the main findings from these and related studies. My lecture covered four topics:

- (1) The generality of the phenomenon of footshock stress-induced reinstatement of heroin seeking in rats to other stressors, other procedures (CPP), other drug and non-drug reinforcers, and other species.
- (2) The effect of different pharmacological agents on stress-induced reinstatement of drug seeking.
- (3) The neuroanatomical sites involved in stress-induced reinstatement of drug seeking.
- (4) The application of the reinstatement model to the study of relapse to palatable food seeking.

Role and Treatment Target Potential of Group I and II Metabotropic Glutamate Receptors in Stress-Induced Drug-Seeking (F Weiss)

Stress is a major factor contributing to relapse in abstinent drug and alcohol abuse patients. Growing evidence supports a role of metabotropic glutamate receptors (mGluRs) in stress-associated drug use and drug-seeking. Moreover, neuroadaptation in the function of these receptors that develops during chronic drug exposure may play a significant role in the development of dependence and propensity to relapse (Aujla et al., 2008; Sidhpura et al., 2007; Sidhpura et al., 2008). To advance understanding of the role and treatment target potential of mGluRs in drug addiction, the effects of a selective mGlu₅ antagonist (MTEP) and a selective

© 2009 Elsevier Inc. All rights reserved.

Corresponding Author: Barbara J. Mason, Ph.D., The Scripps Research Institute, 10550 North Torrey Pines Road, TPC-5, La Jolla, CA 92037; Tel: 858-784-7324; Fax: 858-784-7340; mason@scripps.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

mGlu_{2/3} agonist (LY379268) were examined in tests of drug self-administration, reinstatement, and anxiety. LY379268 (0.3–3 mg/kg) as well as MTEP (0.3–3 mg/kg) dose-dependently reversed the effects of footshock stress on reinstatement of both cocaine and ethanol-seeking behavior (Sidhpura et al., 2007; Sidhpura et al., 2008; Zhao et al., 2006). Importantly, in the case of ethanol-seeking, rats with a history of ethanol dependence, tested after three weeks of abstinence, were more sensitive to the “anti-reinstatement” effects of LY379268 than MTEP and, conversely, non-dependent rats were more sensitive to the effects of MTEP than LY379268 (Hao et al., 2008; Sidhpura et al., 2007; Sidhpura et al., 2008; Zhao et al., 2007). In an animal model of anxiety (i.e., the “shock-probe” or “defensive burying” test), LY379268 (0.3–3 mg/kg) dose-dependently reduced anxiety-like behavior in rats with a history of escalated cocaine self-administration. In contrast, in rats without a history of cocaine escalation and in drug-naïve controls, this mGlu_{2/3} agonist reduced anxiety-like behavior only at the highest dose (Aujla et al., 2008). These findings confirm that Group I and II mGluRs represent a promising treatment target for stress-induced drug-seeking and relapse as well as general anxiety associated with protracted drug withdrawal. Additionally, these findings suggest that chronic ethanol and cocaine intoxication neuroadaptively alters the function of Group I and II mGluRs. These changes may be of significance for understanding the neurobiological basis of drug dependence and, in particular, vulnerability to stress-induced relapse associated with a history of drug dependence. Supported by AA10531 and DA07348.

Stress-Induced Reinstatement of Alcohol Seeking: Studies with the $\alpha 2$ Noradrenergic Receptor Antagonist Yohimbine (AD Le)

We have found that systemic injections of yohimbine (an $\alpha 2$ adrenoceptor antagonist that induces stress and anxiety like responses in humans and laboratory animals) potentially reinstate alcohol seeking in drug-free rats (Le et al., 2005). Unlike exposure to intermittent footshock stress, the original stressor found to reinstate alcohol seeking, yohimbine also increases ongoing alcohol self-administration. In an initial pharmacological study, we found that the CRF1 receptor antagonist antalarmin attenuated yohimbine-induced increases in alcohol self-administration and yohimbine-induced reinstatement (Marinelli et al., 2007). Although yohimbine is a prototypical $\alpha 2$ adrenoceptor antagonist, it also acts at other receptor types and subtypes, including 5-HT_{1A}, $\alpha 1$ and D₂-like receptors (Millan et al., 2000). Results from our recent studies with idazoxan (another prototypical $\alpha 2$ adrenoceptor antagonist) or RS-79948 (a highly selective $\alpha 2$ adrenoceptor antagonist) demonstrated that these compounds do not mimic the effects of yohimbine on alcohol self-administration or reinstatement. On the other hand, systemic injections of the 5-HT_{1A} receptor antagonist WAY 100,635 decreased yohimbine-induced increases in alcohol self-administration and yohimbine-induced reinstatement. Clonidine, the widely used $\alpha 2$ -agonist did not significantly affect Yohimbine-induced increases in alcohol self-administration but did attenuate reinstatement (Le et al., 2009, in press). The results of our studies suggest that $\alpha 2$ -antagonists properties of yohimbine may play a role in the reinstatement of alcohol seeking, but not self-administration. On the other hand, yohimbine's actions on 5-HT_{1A} receptors contribute to its effect on both alcohol self-administration and reinstatement.

A Human Laboratory Model of Risk Factors for Relapse in Alcohol Dependence and for Predicting Medication Efficacy (BJ Mason)

The protracted abstinence phase in alcohol dependence involves a state of heightened vulnerability to relapse following acute withdrawal that has been linked to prolonged activation of the brain stress arousal systems, and a heightened reactivity to internal cues, e.g. negative affect, and external cues, e.g. the sight and smell of alcohol, that are common precipitants of relapse in dependent subjects. We developed a human laboratory model of such risk factors

for relapse to provide an early phase screen for potential medications for protracted abstinence, as an alternative to human laboratory methods involving alcohol administration (Mason et al., 2008).

This human lab model involves initially classifying non treatment-seeking paid volunteers with alcohol dependence as cue reactive if their ratings of craving severity to in vivo alcohol cues exceed that to water cues by at least 50%. Cue reactors were randomly assigned to one week of double-blind gabapentin 1200 mg a day or matched placebo. At the end of the medication phase, subjects' subjective and physiological reactivity to pairs of affective (negative, neutral, positive) and beverage (alcohol, water) cues were measured to determine if gabapentin modified reactivity to these laboratory analogues of risk factors for relapse.

Subjects were 33 cue reactors (21% female, mean age of 39.7 years). Using mixed-effects modeling, gabapentin significantly reduced the effect of alcohol beverage exposure (relative to water) on ratings of both subjective strength of craving and also intention to drink. Gabapentin also significantly attenuated subjective arousal rating for both positive and negative affect-inducing image exposures, relative to neutral images.

This highly standardized laboratory assessment of reactivity to alcohol and affective cues offers a screen for potential anti-drinking relapse medications as an alternative to methods involving alcohol administration that violate the condition of protracted abstinence. Using this model, gabapentin was found to suppress craving to alcohol cues and arousal to affective cues often associated with relapse (Mason et al., 2009).

Acknowledgments

Supported by NIAAA grant numbers R01AA012602 and R37AA014028

References

- Aujla H, Martin-Fardon R, Weiss F. Rats with extended access to cocaine exhibit increased stress reactivity during acute and protracted abstinence. *Neuropsychopharmacology* 2008;33:1818–1826. [PubMed: 17895914]
- Ghitza UE, Gray SM, Epstein DH, Rice KC, Shaham Y. The anxiogenic drug yohimbine reinstates palatable food seeking in a rat relapse model: a role of CRF(1) receptors. *Neuropsychopharmacology* 2006;31:2188–2196. [PubMed: 16341025]
- Hao Y, Martin-Fardon R, Weiss F. Rats with extended access to cocaine exhibit differential sensitivity to pharmacological actions of LY37926 and MTEP: a progressive ratio study. *Abstr Soc Neurosci* 2008:359.1.
- Le AD, Funk D, Harding S, Juzysch W, Fletcher P. The role of noradrenaline and 5-hydroxytryptamine in yohimbine-induced increases in alcohol-seeking in rats. *Psychopharmacology*. 2009 in press.
- Le AD, Harding S, Juzysch W, Funk D, Shaham Y. Role of alpha-2 adrenoceptors in stress-induced reinstatement of alcohol seeking and alcohol self-administration in rats. *Psychopharmacology* 2005;179:366–373. [PubMed: 15551068]
- Le AD, Harding S, Watchus W, Juzysch W, Shalev U, Shaham Y. The role of corticotropin-releasing factor in stress-induced relapse to alcohol-seeking behavior in rats. *Psychopharmacology* 2000;150:317–324. [PubMed: 10923760]
- Marinelli PW, Funk D, Juzysch W, Harding S, Rice KC, Shaham Y, Le AD. The CRF1 receptor antagonist antalarmin attenuates yohimbine-induced increases in operant alcohol self-administration and reinstatement of alcohol seeking in rats. *Psychopharmacology* 2007;195:345–355. [PubMed: 17705061]
- Mason BJ, Light JM, Escher T, Drobos DJ. Effect of positive and negative affective stimuli and beverage cues on measures of craving in non treatment-seeking alcoholics. *Psychopharmacology* 2008;200:141–150. [PubMed: 18604601]

- Mason BJ, Light JM, Williams LD, Drobos DJ. Proof-of-concept human laboratory study for protracted abstinence in alcohol dependence: effects of gabapentin. *Addict Biol* 2009;14:73–83. [PubMed: 18855801]
- Millan MJ, Newman-Tancredi A, Audinot V, Cussac D, Lejeune F, Nicolas JP, Coge F, Galizzi JP, Boutin JA, Rivet JM, et al. Agonist and antagonist actions of yohimbine as compared to fluparoxan at alpha (2)-adrenergic receptors (AR)s, serotonin (5-HT)(1A), 5-HT(1B), 5-HT(1D) and dopamine D(2) and D(3) receptors. Significance for the modulation of frontocortical monoaminergic transmission and depressive states. *Synapse* 2000;35:79–95. [PubMed: 10611634]
- Shaham Y, Erb S, Stewart J. Stress-induced relapse to heroin and cocaine seeking in rats: a review. *Brain Res Brain Res Rev* 2000;33:13–33. [PubMed: 10967352]
- Shaham Y, Stewart J. Stress reinstates heroin self-administration behavior in drug-free animals: an effect mimicking heroin, not withdrawal. *Psychopharmacology* 1995;119:334–341. [PubMed: 7675970]
- Sidhpura N, Martin-Fardon R, Aujla H, Weiss F. Differential effects of a mGlu5 antagonist on suppressing stress-induced reinstatement of ethanol-seeking in ethanol-dependent vs. non-dependent rats. *Abstr Soc Neurosci* 2007;63.4.
- Sidhpura N, Martin-Fardon R, Aujla H, Weiss F. Ethanol dependant rats show differential sensitivities to the anti-relapse effects of mGlu2/3 and mGlu5 receptors ligands. *Alcohol Clin Exp Res* 2008; (Suppl 32):32A.
- Wang B, Shaham Y, Zitzman D, Azari S, Wise RA, You ZB. Cocaine experience establishes control of midbrain glutamate and dopamine by corticotropin-releasing factor: a role in stress-induced relapse to drug seeking. *J Neurosci* 2005;25:5389–5396. [PubMed: 15930388]
- Zhao Y, Dayas CV, Aujla H, Baptista MAS, Martin-Fardon R, Weiss F. Activation of Group II metabotropic glutamate receptors attenuates both stress and cue-induced ethanol seeking and modulates c-fos expression in the hippocampus and amygdala. *J Neurosci* 2006;26:9967–9974. [PubMed: 17005860]
- Zhao Y, Martin-Fardon R, Aujla H, Weiss F. Effects of LY379268, a mGlu2/3 receptor agonist, on ethanol self-administration in ethanol dependent vs. non-dependent rats. *Alcohol Clin Exp Res* 2007;(Suppl 31):85A. [PubMed: 18070245]