RESPONSE TO "ANXIOUS TO DRINK: GABAPENTIN NORMALIZES GABAERGIC TRANSMISSION IN THE CENTRAL AMYGDALA AND REDUCES SYMTPOMS OF ETHANOL DEPENDENCE

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We are pleased that the authors of this Journal Club article have chosen to review our article and we would like to take this opportunity to clarify and expand on a few important points.

First, Clemens and Vendruscolo (2008) correctly note that the electrophysiological profile of gabapentin is bi-directional as determined by the ethanol history of the animal (increases GABA transmission in CeA of non-dependent rats and decreases GABA transmission in CeA of alcohol-dependent rats). These effects are directly paralleled by behavioral data in this study: gabapentin infused into the CeA blocked dependence-induced increases in ethanol drinking, while gabapentin infused into the CeA of non-dependent rats produced a trend (p=0.08) toward an increase in ethanol drinking [figure not shown in Roberto et al., (2008)].

Second, the authors state that "…the link between GABA transmission in the CeA and anxiety in this study is quite puzzling…" It is important to re-emphasize here that electrophysiological recordings from the CeA are thought to be taken from GABA interneurons. Therefore, increases and decreases in GABA transmission in Roberto et al., (2008) do not necessarily imply that the net neural or functional output of the CeA is more or less inhibitory, respectively. In fact, it appears that quite the opposite may be true, such that increases in GABA transmission produce a disinhibition of downstream target regions whereas decreases in GABA transmission inhibit those regions. This

hypothesis is supported by not only the behavioral effects of gabapentin, but also by recent data regarding CRF, vasopressin, and NPY effects on cellular function in the rat CeA (Huber et al., 2005; Roberto & Siggins, 2006; and unpublished data from our lab). Further details of this circuitry remain to be elucidated.

Finally, the authors correctly note that relapse to alcohol drinking in humans typically occurs during protracted abstinence, rather than during acute withdrawal, and that the results of Roberto et al. (2008) should be extended to other withdrawal time points. While acute withdrawal is often conceptually "lumped together" with physical disturbances, our vapor exposure protocols typically involve doses low enough (125-225 mg/dl) to avoid severe physical withdrawal symptoms upon termination of vapor exposure. Furthermore, the motivational symptoms of withdrawal are traditionally linked with protracted abstinence because they are present at protracted time points (Gilpin et al., 2008; Roberts et al., 2000; Zhao et al., 2007). However, motivational symptoms of dependence are reliably present in rats at acute withdrawal time points as evidenced by increased anxiety-like behavior, alcohol drinking and willingness to work for alcohol early during acute withdrawal, even when animals still have alcohol in blood from vapor exposure (Funk et al., 2007; O'Dell et al., 2004; Roberts et al., 1996; Valdez et al., 2002; Walker et al., 2007; Zhao et al., 2007). Drugs that block relapse drinking in human alcoholics effectively suppress acute withdrawal-induced increases in alcohol drinking by rats and mice (e.g., acamprosate; Morse & Koob, 2002; Snelling et al., 2007), highlighting the predictive validity of this model.

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REFERENCES

Clemens KJ Vendruscolo LF (2008) Anxious to drink: gabapentin normalizes GABAergic transmission in the central amygdala and reduces symptoms of ethanol dependence. J Neurosci 28.

Funk CK, Zorrilla EP, Lee MJ, Rice KC, Koob GF (2007) CRF1 antagonists selectively reduce ethanol self-administration in ethanol-dependent rats. Biol Psychiat 61:78-86.

Gilpin, N.W., Richardson, H.N., Lumeng, L., Koob, G.F. (2008. Dependence-induced alcohol drinking by alcohol-preferring (P) rats and outbred Wistar rats. Alcohol Clin Exp Res Epub ahead of print.

Huber D, Veinante P, Stoop R (2005) Vasopressin and oxytocin excite distinct neuronal populations in the central amygdala. Sci 308:245–8.

Morse AC, Koob GF (2002) Intra-BNST acamprosate attenuates withdrawal-induced increases in ethanol consumption in dependent rats. Washington, DC: Abstract Society for Neuroscience.

O'Dell LE, Roberts AJ, Smith RT, Koob GF (2004) Enhanced alcohol self-administration after intermittent versus continuous alcohol vapor exposure. Alcohol Clin Exp Res 28:1676-82.

Roberto M, Gilpin NW, O'Dell LE, Cruz MT, Morse AC, Siggins GR, Koob GF (2008) Cellular and behavioral interactions of gabapentin with alcohol dependence. J Neurosci 28:5762-71.

Roberto M, Siggins GR (2006) Nociceptin/orphanin FQ presynaptically decreases GABAergic transmission and blocks the ethanol-induced increase of GABA release in central amygdala. Proc Natl Acad Sci USA 103:9715-20.

Roberts AJ, Cole M, Koob GF (1996) Intra-amygdala muscimol decreases operant ethanol self-administration in dependent rats. Alcohol Clin Exp Res 20:1289-98.

Roberts AJ, Heyser CJ, Cole M, Griffin P, Koob GF (2000) Excessive ethanol drinking following a history of dependence: animal model of allostasis. Neuropsychopharmacol 22:581-94.

Snelling CC Fretwell AM, Tanchuck MA, Finn DA (2007) Different effect of acamprosate and naltrexone on "withdrawal-associated" limited access ethanol consumption in C57BL/6 mice. Alcohol Clin Exp Res 31 Suppl:86A.

Valdez GR, Roberts AJ, Chan K, Davis H, Brennan M, Zorrilla EP, Koob GF (2002) Increased ethanol self-administration and anxiety-like behavior during acute

withdrawal and protracted abstinence: regulation by corticotropin-releasing factor. Alcohol Clin Exp Res 26:1494-501.

Walker BM, Koob GF (2007) The γ-aminobutyric acid-B receptor Agonist baclofen attenuates responding for ethanol in ethanol-dependent rats. Alcohol Clin Exp Res 31:11-18.

Zhao Y, Weiss F, Zorrilla EP (2007) Remission and resurgence of anxiety-like behavior across protracted withdrawal stages in ethanol-dependent rats. Alcohol Clin Exp Res 31:1505-15.