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CRF, vasopressin, and NPY effects on cellular function in the rat CeA (Huber et al., 2005; Roberto & Siggins, 2006; and unpublished data from our lab).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


