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Commentary: Studies on binge-like ethanol drinking may help identify the neurobiological mechanisms underlying the transition to dependence

Todd E. Thiele
Department of Psychology and Bowles Center for Alcohol Studies, University of North Carolina, Chapel Hill, NC, 27599-3270, USA

Abstract

The goals of this commentary are to discuss the important contributions of the work by Kaur et al. titled “Corticotropin releasing factor acting on corticotropin releasing factor receptor type 1 is critical for binge alcohol drinking in mice”, published in this issue of *Alcoholism: Clinical and Experimental Research*, and to highlight the importance of pre-clinical research aimed at identifying the neurobiology of binge ethanol drinking. The work by Kaur et al. provides an important extension of previous pharmacological evidence implicating corticotropin releasing factor (CRF) type-1 receptors (CRF1R) in binge-like ethanol drinking by verifying the role of the CRF1R using genetic tools, and by establishing that CRF, but not urocortin 1 (Ucn1), is the primary neuropeptide associated with the CRF system that modulates binge-like ethanol drinking in C57BL/6J mice. It is suggested that the evidence for a critical role of the CRF1R in excessive ethanol intake observed in both models of binge-like ethanol drinking and dependence-like ethanol intake indicates that overlapping mechanisms may be involved, and that studies that employ models of binge-like ethanol drinking may provide insight into the neurobiological mechanisms that underlie the transition to ethanol dependence.

Keywords

Binge; CRF; CRF-1 receptor; ethanol; knockout

Alcohol (ethanol) dependence and relapse in abstinent alcoholics are major health problems in the United States and neurochemical pathways that modulate these disorders are currently under investigation. However, heavy alcohol use and binge alcohol drinking patterns, which can emerge prior to the onset of dependence, have received far less attention. A ‘binge’ is defined by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as a pattern of drinking that produces blood ethanol concentrations (BECs) greater than 0.08% (80 mg/dl) (NIAAA, 2004). The pattern of alcohol drinking required to produce these BECs is about 5 and 4 drinks in 2-hours for the average adult male and female, respectively. Interestingly, while about 90% of the ethanol consumed by individuals under the age of 21 in the United States is in the form of binge drinking, 70% of binge drinking episodes in the US involve adults age 26 years and older (Naimi et al., 2003). Thus, binge drinking is not restricted to the young but is a risky behavior prevalent in adults. As with all abusive patterns of alcohol drinking, frequent binge drinking is associated with numerous negative short- and long-term consequences. Binge drinking increases the risk of mood disorders (Okoro et al., 2004), increases aggressive and violent behavior (Shepherd et al., 2006), and impairs decision

Address for Correspondence: Dr. Todd E. Thiele, Department of Psychology, University of North Carolina, Davie Hall CB# 3270, Chapel Hill, NC 27599-3270, Phone: (919) 962-1519, Fax: (919) 962-2537, thiele@unc.edu.

making and judgment (Goudriaan et al., 2007). Furthermore, heavy binge drinking has been linked to long-term health consequences including heart disease, high blood pressure, and type 2 diabetes (Fan et al., 2008). Perhaps most alarming is the finding of increased risk for developing alcohol dependence in individuals that binge drink early in life (Hingson et al., 2005; Miller et al., 2007). Thus, it is of paramount importance to identify neurochemical pathways in the brain that modulate binge drinking as such knowledge may provide insight into novel pharmaceutical treatments that could protect against this dangerous behavior. The manuscript by Kaur and colleagues (Kaur et al., in press) in the current volume of *Alcoholism: Clinical and Experimental Research* is an exciting example of recent work aimed at identifying the neurobiology of binge alcohol drinking.

CORTICOTROPIN RELEASING FACTOR(CRF) MODULATES EXCESSIVE BINGE-LIKE ETHANOL DRINKING: CONVERGENCE OF GENETIC AND PHARMACOLOGICAL DATA

Kaur et al. take advantage of a recently developed preclinical model to study the role of the CRF system in binge-like ethanol drinking (Rhodes et al., 2005). This procedure, typically referred to as “drinking in the dark” (DID), involves giving C57BL/6J mice 2–4 hours of limited access to 20% (v/v) ethanol beginning 3 hours into the animal’s dark cycle. Importantly, with DID procedures, C57BL/6J mice consume enough ethanol in a short period of time to achieve pharmacologically meaningful blood ethanol concentrations (BECs; >80 mg/dl) and exhibit evidence of behavioral intoxication (Rhodes et al., 2007), defining features of binge alcohol drinking. Further, C57BL/6J mice drink similar levels of ethanol with or without water concurrently available (Rhodes et al., 2007), and excessive drinking does not appear to be driven by caloric need (Lyons et al., 2008). As previous work has implicated CRF in the modulation of excessive ethanol drinking (Funk et al., 2006; Funk et al., 2007; Lowery et al., 2010; Sparta et al., 2008), Kaur et al. used DID procedures to assess binge-like ethanol drinking in genetically altered mice lacking components of the CRF system. Mutant mice maintained on a C57BL/6J genetic background lacked normal production of either CRF, CRF type-1 receptor (CRF1R), CRF type-2 receptor (CRF2R), or urocortin 1 (Ucn1). They found that while CRF2R and Ucn1 knockout (KO) mice did not show reliable alterations of binge-like ethanol drinking, CRF and CRF1R KO mice showed blunted ethanol intake and associated BECs relative to littermate wild-type mice. Importantly, while wild-type mice drank enough ethanol to achieve BECs considered meaningful to model binge drinking (Crabbe et al., 2011), CRF and CRF1R KO mice did not achieve BECs consistent with a binge. Thus, CRF and the CRF1R are necessary to maintain levels of binge-like ethanol drinking characteristic of normal C57BL/6J mice.

Several novel and important contributions come from the Kaur et al. work. First, using genetic tools they provided a verification of previous pharmacological evidence implicating CRF1R signaling in the modulation of binge-like ethanol drinking (Lowery et al., 2010; Sparta et al., 2008). Our group has previously shown that peripheral administration of the bioavailable and selective CRF1R antagonist, CP-154,526, significantly blunted binge-like ethanol drinking in C57BL/6J mice. On the other hand, peripheral administration of CP-154,526 did not alter non-binge-like ethanol drinking using alternate drinking procedures that resulted in moderate levels of ethanol intake (Sparta et al., 2008). Interestingly, Kaur et al. speculate that inconsistent and negative results from previous studies employing the KO mice that they used may be related to the fact that previous studies did not use drinking procedures that generated binge-like levels of ethanol intake. When taken together, our previous work and the present work by Kaur et al. provide strong converging evidence that CRF1R signaling modulates binge-like ethanol drinking, but is not involved in regulating non-binge-like intake.

Since CRF and Ucn1 both bind to CRF1R and CRF2R, the use of receptor-selective pharmacological tools does not allow one to differentiate the unique contributions of each ligand. A second important contribution from the work of Kaur et al. is that they were able to show the CRF, but not Ucn1, is the primary ligand associated with the central CRF system that modulates binge-like ethanol drinking. Kaur et al. make the important point that while CRF modulates binge-like ethanol drinking, previous work from their laboratory (Bachtell et al., 2004; Ryabinin and Weitemier, 2006) implicates Ucn1 in regulating alcohol acceptance and preference. Finally, although the CRF1R antagonist used in our previous work was highly receptor-selective, it is always possible that pharmacological tools can influence behavior via non-selective actions. By using CRF1R and CRF2R KO mice, Kaur et al. confidently argue the important role of the CRF1R in binge-like ethanol drinking. However, previous pharmacological evidence has implicated the CRF2R in binge-like ethanol drinking (Lowery et al., 2010), thus it would be premature to rule out an important role for the CRF2R. While these features of the Kaur et al. study provide important new insight into the role of the CRF system in the modulation of binge-like intake, this work, as well as previous studies directed at binge-like drinking, may actually do much more to advance the field of alcoholism research.

STUDIES OF BINGE-LIKE ETHANOL DRINKING MAY HELP US UNDERSTAND THE NEUROBIOLOGICAL MECHANISMS UNDERLYING THE TRANSITION TO DEPENDENCE

As noted above, a selective CRF1R antagonist was shown to significantly blunt binge-like ethanol drinking in C57BL/6J mice without altering low level, non-binge-like intake (Sparta et al., 2008). These observations suggest that CRF1R signaling is triggered when sufficient blood/brain ethanol levels are achieved, which may modulate continued binge-like ethanol drinking. In the Kaur et al. study, CRF and CRF1R KO mice showed blunted binge-like drinking while prior work (which employed procedures that generated moderate ethanol intake) failed to find lower drinking with CRF and CRF1R KO mice. These results parallel observations showing the CRF receptor antagonists blunt excessive dependence-like ethanol drinking in rats exposed to ethanol vapor but fail to influence low level ethanol intake by non-dependent animals (Funk et al., 2006; Funk et al., 2007). The ability of CRF receptor antagonists to blunt excessive dependence-like ethanol drinking without influencing non-dependent ethanol intake has been hypothesized to result from allostatic alterations (increases) of CRF signaling (Koob, 2003; Koob and Le Moal, 2001). Over the course of repeated cycles of ethanol exposure and abstinence, neuroplastic alterations are thought to develop in brain regions critical for modulating neurobiological responses to ethanol, reflecting ethanol dependence, which in turn triggers excessive ethanol intake.

The similarities between models of excessive binge-like ethanol drinking and dependence-like ethanol intake suggest that overlapping mechanisms may be present. An exciting possibility is that excessive binge-like drinking in non-dependent animals may trigger transient neurochemical alterations (e.g., increased CRF1R signaling) in critical neurochemical pathways analogous to what occurs after the development of dependence. These transient neurochemical changes are hypothesized to modulate binge-like drinking as do permanent neurochemical changes in modulating dependence-induced drinking. These alterations may worsen and fail to “normalize” with repeated binge episodes, ultimately contributing to the transition to dependence, consistent with the allostasis model (Koob and Le Moal, 2001). Clearly, much more work will be needed to verify this theoretical construct, and studies employing procedures that model binge drinking may help clarify this important gap in the literature. Importantly, gaining an understanding of how neuroplastic changes

gradually unfold as ethanol dependence emerges will greatly increase our understanding of this devastating disease, and may provide new insights into treatment approaches.

FINAL CONSIDERATIONS

The exciting work by Kaur et al. reinforces the idea the CRF1R signaling is critical in the modulation of binge-like ethanol drinking, and provides important new information by showing that CRF, but not Ucn1, is the critical neuropeptide within the CRF system that modulates binge-like intake. Ucn peptides appear to modulate ethanol preference in non-binge-like drinking animals. Future work is needed to determine the central CRF neurocircuitry involved and to more carefully characterize the potential role of the CRF system in the transition to ethanol dependence. Studies that examine changes in central CRF pathways over the course of repeated binge-like drinking episodes may help address these questions. Finally, it should also be noted that the previous pharmacological studies, and the work by Kaur et al., have potential clinical relevance. Pharmaceutical targets that are useful for curbing and/or preventing binge drinking could not only help individuals avoid many of the health consequences noted above, but may protect vulnerable individuals from progressing to the point of ethanol dependence. Because neuroplastic changes are thought to emerge in the brain with the development of dependence, and to be the underlying cause of uncontrolled excessive ethanol intake characteristic of dependent individuals (Koob, 2003; Koob and Le Moal, 2001), treating at-risk individuals suffering from alcohol abuse disorders before they have become dependent may be a more effective approach than treatments that are aimed at individuals that have already become dependent. CRF1R antagonists, in addition to potential treatments for dependence and relapse, may be attractive targets for treating problematic binge drinking, prior to the development of ethanol dependence (Lowery and Thiele, 2010). Recent human genetic linkage studies implicating the CRF1R gene in binge drinking (Treutlein et al., 2006) and alcohol dependence (Chen et al., 2010) bolster this concept.

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