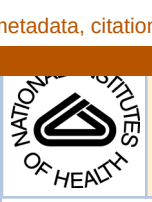

Published in final edited form as:

Alcohol Clin Exp Res. 2012 February ; 36(2): 193–196. doi:10.1111/j.1530-0277.2011.01734.x.

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

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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

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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.

Acknowledgments

This work was supported by NIH grants AA013573, AA015148, and AA017803.

REFERENCES

Bachtell RK, Weitemier AZ, Ryabinin AE. Lesions of the Edinger-Westphal nucleus in C57BL/6J mice disrupt ethanol-induced hypothermia and ethanol consumption. Eur J Neurosci. 2004; 20(6): 1613–1623. [PubMed: 15355328]

Chen AC, Manz N, Tang Y, Rangaswamy M, Almasy L, Kuperman S, Nurnberger J Jr, O'Connor SJ, Edenberg HJ, Schuckit MA, Tischfield J, Foroud T, Bierut LJ, Rohrbaugh J, Rice JP, Goate A, Hesselbrock V, Porjesz B. Single-nucleotide polymorphisms in corticotropin releasing hormone receptor 1 gene (CRHR1) are associated with quantitative trait of event-related potential and alcohol dependence. Alcohol Clin Exp Res. 2010; 34(6):988–996. [PubMed: 20374216]

Crabbe JC, Harris RA, Koob GF. Preclinical studies of alcohol binge drinking. Ann N Y Acad Sci. 2011; 1216:24–40. [PubMed: 21272009]

Fan AZ, Russell M, Stranges S, Dorn J, Trevisan M. Association of lifetime alcohol drinking trajectories with cardiometabolic risk. J Clin Endocrinol Metab. 2008; 93(1):154–161. [PubMed: 18029458]

Funk CK, O'Dell LE, Crawford EF, Koob GF. Corticotropin-releasing factor within the central nucleus of the amygdala mediates enhanced ethanol self-administration in withdrawn, ethanol-dependent rats. J Neurosci. 2006; 26(44):11324–11332. [PubMed: 17079660]

Funk CK, Zorrilla EP, Lee MJ, Rice KC, Koob GF. Corticotropin-releasing factor 1 antagonists selectively reduce ethanol self-administration in ethanol-dependent rats. Biol Psychiatry. 2007; 61(1):78–86. [PubMed: 16876134]

Goudriaan AE, Grekin ER, Sher KJ. Decision making and binge drinking: a longitudinal study. Alcohol Clin Exp Res. 2007; 31(6):928–938. [PubMed: 17403069]

Hingson R, Heeren T, Winter M, Wechsler H. Magnitude of alcohol-related mortality and morbidity among U.S. college students ages 18–24: changes from 1998 to 2001. Annu Rev Public Health. 2005; 26:259–279. [PubMed: 15760289]

Kaur S, Li J, Stenzel-Poore MP, Ryabinin AE. Corticotropin-releasing factor acting on corticotropin-releasing factor receptor type 1 is critical for binge alcohol drinking in mice. Alcohol Clin Exp Res. (in press).

Koob GF. Alcoholism: allostasis and beyond. Alcohol Clin Exp Res. 2003; 27(2):232–243. [PubMed: 12605072]

Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology. 2001; 24(2):97–129. [PubMed: 11120394]

Lowery EG, Spanos M, Navarro M, Lyons AM, Hodge CW, Thiele TE. CRF-1 antagonist and CRF-2 agonist decrease binge-like ethanol drinking in C57BL/6J mice independent of the HPA axis. Neuropsychopharmacology. 2010; 35(6):1241–1252. [PubMed: 20130533]

Lowery EG, Thiele TE. Pre-clinical evidence that corticotropin-releasing factor (CRF) receptor antagonists are promising targets for pharmacological treatment of alcoholism. CNS Neurol Disord Drug Targets. 2010; 9(1):77–86. [PubMed: 20201818]

Lyons AM, Lowery EG, Sparta DR, Thiele TE. Effects of food availability and administration of orexigenic and anorectic agents on elevated ethanol drinking associated with drinking in the dark procedures. Alcohol Clin Exp Res. 2008; 32(11):1962–1968. [PubMed: 18782340]

Miller JW, Naimi TS, Brewer RD, Jones SE. Binge drinking and associated health risk behaviors among high school students. Pediatrics. 2007; 119(1):76–85. [PubMed: 17200273]

Naimi TS, Brewer RD, Mokdad A, Denny C, Serdula MK, Marks JS. Binge drinking among US adults. JAMA. 2003; 289(1):70–75. [PubMed: 12503979]

NIAAA. National Institute on Alcohol Abuse and Alcoholism Council approves definition of binge drinking, in NIAAA Newsletter. Vol. vol 3. 2004.

Okoro CA, Brewer RD, Naimi TS, Moriarty DG, Giles WH, Mokdad AH. Binge drinking and health-related quality of life: do popular perceptions match reality? Am J Prev Med. 2004; 26(3):230–233. [PubMed: 15026103]

Rhodes JS, Best K, Belknap JK, Finn DA, Crabbe JC. Evaluation of a simple model of ethanol drinking to intoxication in C57BL/6J mice. Physiol Behav. 2005; 84(1):53–63. [PubMed: 15642607]

Rhodes JS, Ford MM, Yu CH, Brown LL, Finn DA, Garland T Jr, Crabbe JC. Mouse inbred strain differences in ethanol drinking to intoxication. Genes Brain Behav. 2007; 6(1):1–18. [PubMed: 17233637]

Ryabinin AE, Weitemier AZ. The urocortin 1 neurocircuit: ethanol-sensitivity and potential involvement in alcohol consumption. Brain Res Rev. 2006; 52(2):368–380. [PubMed: 16766036]

Shepherd JP, Sutherland I, Newcombe RG. Relations between alcohol, violence and victimization in adolescence. J Adolesc. 2006; 29(4):539–553. [PubMed: 16863892]

Sparta DR, Sparrow AM, Lowery EG, Fee JR, Knapp DJ, Thiele TE. Blockade of the corticotropin releasing factor type 1 receptor attenuates elevated ethanol drinking associated with drinking in the dark procedures. Alcohol Clin Exp Res. 2008; 32(2):259–265. [PubMed: 18162072]

Treutlein J, Kissling C, Frank J, Wiemann S, Dong L, Depner M, Saam C, Lascorz J, Soyka M, Preuss UW, Rujescu D, Skowronek MH, Rietschel M, Spanagel R, Heinz A, Laucht M, Mann K, Schumann G. Genetic association of the human corticotropin releasing hormone receptor 1 (CRHR1) with binge drinking and alcohol intake patterns in two independent samples. Mol Psychiatry. 2006; 11(6):594–602. [PubMed: 16550213]