LINK TO ORIGINAL ARTICLE
LINK TO AUTHOR'S REPLY

Corticotropin-releasing factor: innocent until proven guilty

William J. Giardino and Andrey E. Ryabinin

The recent Review article by Heilig *et al.* (Pharmacogenetic approaches to the treatment of alcohol addiction. *Nature Rev. Neurosci.* **12**, 670–684 (2011))[1] expertly discussed strategies towards the development of therapeutics for alcoholism. However, we noticed a serious omission in their discussion of the corticotropin-releasing factor (CRF) system.

The authors described evidence supporting a role for CRF receptor 1 (CRF_1) in alcohol-related behavioural traits, concluding that phenotypic screening may improve the clinical efficacy of CRF_1 antagonists. However, they did not acknowledge that in addition to CRF and CRF_1, this system includes three CRF-related ligands (the urocortins (UCNs): UCN_1, UCN_2 and UCN_3), an additional receptor (CRF_2) and the CRF binding protein (CRF_{BP})[2]. UCN_2 and UCN_3 bind CRF_2 selectively, whereas UCN_1 binds both CRF receptors and the CRF_{BP} with greater affinities than does CRF itself[2] (FIG. 1).

Although such information might be considered extraneous, we would like to correct a mistake in the authors' Review[1] that highlights precisely why it is necessary to acknowledge all CRF system components. Heilig *et al.* claimed that "blockade of stress-induced relapse is in part mediated by CRF_1 blockade in the median raphe nucleus (MRN)", citing a 2002 study[3]. In fact, those experiments used the non-selective[4] antagonist D-Phe CRF_{12-41}, leaving in question whether this effect was mediated by CRF_1 or CRF_2. On the surface, the error appears to be minor. However, because the authors neglected to mention all CRF system components, they not only falsely implicated CRF_1, but also implied that the underlying ligand must be CRF.

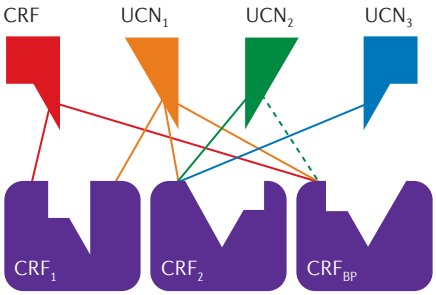

Figure 1 | **Relationships among corticotropin-releasing factor (CRF), urocortins and their targets.** CRF has high affinity for CRF receptor 1 (CRF_1) and CRF binding protein (CRF_{BP}), urocortin 2 (UCN_2) and UCN_3 are selective for CRF receptor 2 (CRF_2), and UCN_1 has high affinity for both receptors and the CRF_{BP}. Solid lines indicate high-affinity binding, dashed lines indicate species-dependent affinity.

This example illustrates a broader problem in the literature. Our analysis of the most recent 120 items retrieved by a PubMed search for CRF (or CRH) system involvement in alcoholism or addiction (excluding articles that focused solely on the hypothalamic–pituitary–adrenal axis) found that only 34.7% of these articles acknowledged UCN peptides. Furthermore, 53.3% of these articles implied a role for CRF without providing evidence against a role for UCNs.

We also identified several cases in which authors applied a ligand exogenously and inferred that the same ligand must mediate the effect endogenously. For example, the 2002 study discussed above found that intra-MRN CRF infusions reinstated alcohol-seeking, and the authors inferred that this mechanism mediated alcohol-seeking endogenously[3]. We should point out that many brain areas receive co-innervation by multiple ligands of the CRF system[2,5,6], complicating this interpretation.

Heilig *et al.* probably excluded CRF_2 and urocortins because orally available CRF_2-specific drugs do not exist. However, we might argue that the slower development of CRF_2-targeted therapies is a by-product of the issues outlined above. In fact, CRF_2-selective agonists are potent inhibitors of alcohol intake[7,8], and their therapeutic potential has been discussed[9]. Aside from the authors' exclusion of CRF_2, we remind them that UCN_1 also exhibits high affinity for CRF_1. Furthermore, genetic deletion of UCN_1 dampened alcohol preference and alcohol-induced reward[10], justifying the inclusion of UCNs in future conversation.

It is not our intent to diminish the role of CRF in alcohol-related behavioural traits. Rather, we hope that investigators will give careful thought to the endogenous mechanisms by which the CRF system influences behaviour and consider all suspects in order to generate a nuanced dissection of CRF system involvement in stress- and addiction-related disorders.

William J. Giardino and Andrey E. Ryabinin are at the Department of Behavioural Neuroscience, Oregon Health and Science University, 3181 SW Sam Jackson Park Road, Portland, Oregon 97219, USA.

Correspondence to A.E.R.
e-mail: ryabinin@ohsu.edu

doi:10.1038/nrn3110-c1

1. Heilig, M., Goldman, D., Berrettini, W. & O'Brien, C. P. Pharmacogenetic approaches to the treatment of alcohol addiction. *Nature Rev. Neurosci.* **12**, 670–684 (2011).
2. Reul, J. M. & Holsboer, F. Corticotropin-releasing factor receptors 1 and 2 in anxiety and depression. *Curr. Opin. Pharmacol.* **2**, 23–33 (2002).
3. Le, A. D., Harding, S., Juzytsch, W., Fletcher, P. J. & Shaham, Y. The role of corticotropin-releasing factor in the median raphe nucleus in relapse to alcohol. *J. Neurosci.* **22**, 7844–7849 (2002).
4. Perrin, M. H., Sutton, S. W., Cervini, L. A., Rivier, J. E. & Vale, W. W. Comparison of an agonist, urocortin, and an antagonist, astressin, as radioligands for characterization of corticotropin-releasing factor receptors. *J. Pharmacol. Exp. Ther.* **288**, 729–734 (1999).
5. Bittencourt, J. C. *et al.* Urocortin expression in rat brain: evidence against a pervasive relationship of urocortin-containing projections with targets bearing type 2 CRF receptors. *J. Comp. Neurol.* **415**, 285–312 (1999).
6. Deussing, J. M. *et al.* Urocortin 3 modulates social discrimination abilities via corticotropin-releasing hormone receptor type 2. *J. Neurosci.* **30**, 9103–9116 (2010).
7. Sharpe, A. L. & Phillips, T. J. Central urocortin 3 administration decreases limited-access ethanol intake in nondependent mice. *Behav. Pharmacol.* **20**, 346–351 (2009).
8. Funk, C. K. & Koob, G. F. A CRF_2 agonist administered into the central nucleus of the amygdala decreases ethanol self-administration in ethanol-dependent rats. *Brain Res.* **1155**, 172–178 (2007).
9. Lowery, E. G. & Thiele, T. E. Pre-clinical evidence that corticotropin-releasing factor (CRF) receptor antagonists are promising targets for pharmacological treatment of alcoholism. *CNS Neurol. Disord. Drug Targets* **9**, 77–86 (2010).
10. Giardino, W. J., Cocking, D. L., Kaur, S., Cunningham, C. L. & Ryabinin, A. E. Urocortin-1 within the centrally-projecting Edinger-Westphal nucleus is critical for ethanol preference. *PLoS ONE* **6**, e26997 (2011).

Acknowledgements
Authors are supported by US National Institutes of Health grants F31 AA021023 (W.J.G.) and AA013738, AA016647, AA010760 (A.E.R.).

Competing interests statement
The authors declare no competing financial interests.

FURTHER INFORMATION
Andrey Ryabinin's homepage: http://tinyURL.com/RyabininLab
ALL LINKS ARE ACTIVE IN THE ONLINE PDF