LINK TO ORIGINAL ARTICLE
LINK TO INITIAL CORRESPONDENCE

Our focus on the pharmacogenetics of CRF_1 antagonists is simply because they are in clinical development

Markus Heilig

We recently reviewed accumulating evidence that pharmacotherapies for alcohol addiction will have to be personalized, with the genetic make-up of the individual probably being one of the key variables for identifying responsive patients (Pharmacogenetic approaches to the treatment of alcohol addiction. *Nature Rev. Neurosci.* **12**, 670–684 (2011))[1]. Corticotropin-releasing factor (CRF) receptor 1 (CRF_1) is an emerging treatment target for alcoholism that has a compelling preclinical validation. Findings that support this receptor as a candidate target have been obtained using systemic administration of CRF_1-selective non-peptide antagonists. The predictive validity of these observations does not rely on any assumptions about the nature of the endogenous ligand (or ligands) whose actions are blocked by this class of drugs. Owing to the existence of orally available, brain-penetrant molecules in this class that are also safe and well tolerated for human use, CRF_1 antagonists have recently entered clinical development for alcohol addiction. Functional genetic variation at the gene locus that encodes CRF_1 has therefore become of immediate relevance for personalizing treatments that target this receptor.

Giardino and Ryabinin (Corticotropin-releasing factor: innocent until proven guilty. *Nature Rev. Neurosci.* 14 Dec 2011 (doi:10.1038/nrn3110-c1))[2] point out the exquisite complexity of the CRF family of peptides and their receptors, which extend well beyond CRF_1 and may influence alcohol consumption in multiple ways. The Ryabinin laboratory has made important contributions to this literature[3]. Other data also suggest that activation of CRF receptor 2 (CRF_2) by one of its endogenous urocortin ligands or an analogue might result in effects on alcohol intake similar to those seen when CRF_1 is blocked[4]. These data predict that synthetic CRF_2 agonists with drug-like properties may have the potential to become medications for alcoholism, much like CRF_1 antagonists. Such a prediction is consistent with recent data indicating that urocortins, presumably through their ability to activate CRF_2, are required for effective recovery from stress[5].

We share the hope that the discovery of urocortins and their CRF_2-mediated actions will ultimately lead to new opportunities for the development of treatments for addictive disorders. However, as Giardino and Ryabinin point out, no small molecules currently exist that target CRF_2 and are suitable for human use. Against that background, it is perhaps reasonable to focus a pharmacogenetic review on targets for which medications are actually in clinical development. CRF_1 is such a target, whereas CRF_2 is currently not. Giardino and Ryabinin argue that the slower development of CRF_2-targeted therapies is a result of the field neglecting them. The reality is, unfortunately, quite different. There is no lack of potentially attractive targets for alcoholism pharmacotherapies[6]. The main barrier to bringing forward novel pharmacotherapies is instead the difficulty in developing molecules that are suitable for human use. For reasons that are unclear, no non-peptide agonists for any member of the secretin family of G-protein-coupled receptors have been successfully developed. We certainly hope for breakthroughs in this area. Until those are achieved, however, we continue to believe patients are best served by focusing on targets with demonstrated potential for clinical development.

Markus Heilig is at the Laboratory of Clinical and Translational Studies, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, Maryland 20892, USA.

e-mail: markus.heilig@mail.nih.gov

doi:10.1038/nrn3110-c2

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. Giardino, W. J. & Ryabinin, A. E. Corticotropin-releasing factor: innocent until proven guilty. *Nature Rev. Neurosci.* 14 Dec 2011 (doi:10.1038/nrn3110-c1).
3. Ryabinin, A. E. & Weitemier, A. Z. The urocortin 1 neurocircuit: ethanol-sensitivity and potential involvement in alcohol consumption. *Brain Res. Rev.* **52**, 368–380 (2006).
4. 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).
5. Neufeld-Cohen, A. *et al*. A triple urocortin knockout mouse model reveals an essential role for urocortins in stress recovery. *Proc. Natl Acad. Sci. USA* **107**, 19020–19025 (2010).
6. Heilig, M. & Egli, M. Pharmacological treatment of alcohol dependence: target symptoms and target mechanisms. *Pharmacol. Therapeut.* **111**, 855–876 (2006).

Competing interests statement
The author declares no competing financial interests.

FURTHER INFORMATION
Markus Heilig's homepage: http://www.niaaa.nih.gov/ResearchInformation/IntramuralResearch/AboutDICBR/LCTS/Pages/default.aspx

ALL LINKS ARE ACTIVE IN THE ONLINE PDF