J R Coll Physicians Edinb 2008; 38:131–2

Medication for alcohol dependence: the silver bullet?

JS Kelly
Editor, Clinical Section, Journal of the Royal College of Physicians of Edinburgh, Edinburgh, UK

TITLE Neurokinin 1 receptor antagonism as a possible therapy for alcoholism

AUTHORS George DT, Gilman J, Hersh J et al.

JOURNAL *Science* 2008; 319:1536–9.

KEYWORDS Acamprosate, alcohol use and relapse, naltrexone, substance P type 1 (NK1R) antagonists, UKATT study

DECLARATION OF INTERESTS The author has shares in pharmaceutical companies and has in the past received grants and fees from Fujisawa.

Published online ***May 2008***

Correspondence to ***JS Kelly, Division of Neuroscience, University of Edinburgh, 1 George Square, Edinburgh EH8 9JZ, UK***

tel. ***+44 (0)131 444 0512***
fax. ***+44 (0)131 650 3519***
e-mail ***J.S.Kelly@ed.ac.uk***

This paper follows on from studies in man[1] that showed the neurokinin 1 receptor (NK1R) antagonist GR205171 to reduce symptoms of social anxiety and to attenuate brain responses to the Trier Social Stress Test, and studies in rats that showed deletion of NK1Rs to change the response to opiate administration. The authors argue that pharmacological blockade of NK1Rs in humans might reduce the stress and reward related processes that underlie excessive alcohol use and relapse. The peptide, substance P (SP), and its receptors are concentrated in the dorsal roots of mammalian spinal cord. Results of numerous animal studies and in vitro experiments supported the role of SP as integral to the nociceptive process, potentiating excitatory inputs to nociceptive neurons. Over the past 70 years additional studies have shown the presence of the peptide and its receptors throughout the central peripheral and nervous system, where they are thought to have a role in the regulation of mood disorders, anxiety, stress, reinforcement, neurogenesis, respiratory rhythm, neurotoxicity and nausea/emesis.

Since SP type 1 (NK1R) antagonists are known to have limited activity in mice and rats, the authors based their preclinical behavioural studies on NK1R null mice. Using a free choice system, wild-type littermates consumed 10g of alcohol/kg of body weight per day at the end of the 60-day escalation period. Not only did the null mice consume less than half as much, but they were more sensitive to the sedative effects of alcohol.

To assess the clinical application of this finding the orally available and brain penetrant NK1R antagonist LY686017 was tested in a randomised controlled study on 50 hospitalised recently detoxified alcohol-dependent patients using two instruments, the Alcohol Urge Questionnaire (AUQ) and the Combined Global Impression Scale. As expected in an inpatient environment, the cravings of the majority of patients declined over time, yet weekly ratings by a blinded observer showed LY686017 in this four-week study to have a significant effect on craving but no effect on ratings for anxiety or depression. Additional tests in the fourth week showed LY686017 to suppress the rise in serum cortisol levels to stress and cue exposure, and an attenuation of brain activation in response to negative affective images of beverages using functional magnetic resonance imaging.

OPINION

The authors claim they have used a translational approach guided by animal data to show, using a variety of measures in humans, that NK1R antagonism might be of value in the treatment of alcoholism. They draw parallels between their work and experiments that suggest specific corticotrophin-releasing hormone (CRH) receptor 1 antagonists may also have a role in the attenuation of alcohol dependence.[2–4] This is in line with the hypothesis that the neuropeptide antagonists will only prove efficacious when a neural pathway is subjected to pathological activation. However, I am not sure I can follow their argument that the need for pathological activation explains the high-profile failure of SP-NK1R antagonists[5,6] to prove their worth as antidepressants when tested in a proper clinical as opposed to a translational study.

It is not clear to me why these proof-of-concept studies warrant space in high-profile journals. Although it is no doubt interesting to be able to describe human experiments that are consistent with the animal studies using high-tech methods to identify a specific target, the facts suggest that, at most, these highly publicised studies have failed to deliver. Recent publications[7–9] in *Nature*, *Nature Medicine* and *The Lancet* concerning new treatments are short and tailored to highlight the novelty of the work. However, in the present study and others the authors omit a lot of the detail, which is only found in the 'supporting online material'. For instance, in

this paper, the patients are described in the text at one point as detoxified and elsewhere as having fully recovered from alcohol withdrawal; only after reading the online material do we discover that seven patients had been withdrawn from benzodiazepines, that 40 out of 50 were smokers, 13 had been cannabis users and 17 cocaine users. In addition, a screen was used to exclude patients who had an equal response to alcohol and water in a reaction test. Although one might argue that this was an ideal group on which to test treatments to relieve craving, it could be that these patients had additional reasons to be unusually co-operative and anxious to please. Side effects are also listed only in the supporting material, with 44% of the treated group reporting fatigue as opposed to 20% of the placebo group.

The authors avoid reviewing the long list of failures of attempts to develop silver bullets that would relieve alcohol dependence. However, a recent review by Spanagel and Kiefer[10] carefully draws attention to a number of drugs that have proved clinically effective in preventing relapse, including naltrexone and acamprosate, and discusses the role of dopamine D3 receptor antagonists, CRH antagonists and the cannacinoids in the future. Spanagel and Kiefer carefully highlight the inconsistency of the outcomes of medication and in addition draw attention to the possible prejudice of health professionals against long-term medication and the hesitancy of the pharmaceutical industry to enter this field. Luty[11] has published a rather more pragmatic review, which claims that community-based treatments are just as effective as intense residential treatments and that acamprosate may prevent relapse in the medium to long term. Ideally, trials of treatments for alcohol dependence should follow up more than 70% of the participants for one year, confirm alcohol consumption using relatives or confidantes and confirm the patients' status and at interview using biochemical markers such as breathalysers and blood levels of gamma glutamyl or carbohydrate transferase to confirm their status. However, the authors of the United Kingdom Alcohol Treatment Trial (UKATT) study[12] doubt the value of this type of marker. The UKATT study compared social behaviour and network therapy with motivational therapy and found that both groups of clients reported that alcohol consumption had decreased by 45% and alcohol-related problems had halved at 12 months.

There must be very few pharmaceutical companies that did not develop orally active and tissue-penetrant neuropeptide antagonists and, in the mid-nineties, did not make claims for their value in the clinic as advanced treatments for pain relief, hay fever, asthma, depression, schizophrenia and cognitive decline. Today, almost nothing survives. Better and more explicit animal models based on knockout and knock-in genetics will make the science much more exciting, but may do little to bring these compounds into the clinic.

REFERENCES

1 Furmark T, Appel L, Michelgard A et al. Cerebral blood flow changes after treatment of social phobia with the neurokinin-1 antagonist GR205171, citalopram, or placebo. *Biological Psychiatry* 2005; 58(2):132–42.

2 Heilig M, Koob GF. A key role for corticotropin-releasing factor in alcohol dependence. *Trends Neurosci* 2007; 30(8):399–406.

3 Richardson HN, Zhao Y, Fekete EM et al. MPZP: A novel small molecule corticotropin-releasing factor type 1 receptor (CRF1) antagonist. *Pharmacol Biochem Behav* 2008; 88(4):497–510.

4 Ji D, Gilpin NW, Richardson HN et al. Effects of naltrexone, duloxetine, and a corticotropin-releasing factor type 1 receptor antagonist on binge-like alcohol drinking in rats. *Behav Pharmacol* 2008; 19(1):1–12.

5 Holmes A, Heilig M, Rupniak NMJ et al. Neuropeptide systems as novel therapeutic targets for depression and anxiety disorders. *Trends Pharmacol Sci* 2003; 24(11):580–8.

6 Kramer MS, Cutler N, Feighner J et al. Distinct mechanism for antidepressant activity by blockade of central substance P receptors. *Science* 1998; 281(5383):1640–5.

7 Knabl J, Witschi R, Hösl K et al. Reversal of pathological pain through specific spinal GABAA receptor subtypes. *Nature* 2008; 451(7176):330–4.

8 Patil ST, Zhang L, Martenyi F et al. Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized Phase 2 clinical trial. *Nature Med* 2007; 13:1102–7.

9 Addolorato G, Leggio L, Ferrulli A et al. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, doubleblind controlled study. *Lancet* 2007; 370(9603):1915–22.

10 Spanagel R, Kiefer F. Drugs for relapse prevention of alcoholism – 10 years of progress. *Trends Pharmacol Sci* 2008; 29(3):109–15.

11 Luty J. What works in alcohol use disorders? *Adv Psychiatr Treat* 2008;12:13–22.

12 UKATT Research Team. Effectiveness of treatment for alcohol problems: findings of the randomised UK alcohol treatment trial (UKATT). *BMJ* 2005; 331(7516):541.