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Commentary

Acamprosate: An Alcoholism Treatment That May Not Be What We Thought

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Occasionally, a paper comes along that fundamentally challenges what we thought we knew about a drug mechanism. The burden of proof in these cases is high, but if done in the right manner, these papers are particularly important. They have the potential of allowing us to go beyond incremental insights and may point to important, previously unrecognized processes. In this issue, Spanagel *et al* (2013) do just that, with regard to the FDA-approved alcoholism medication acamprosate and its mechanism of action.

Acamprosate belongs to a small but growing group of centrally acting medications that have modest but well-supported beneficial effects in the treatment of alcohol addiction (Mason and Lehert, 2012). Together, these pharmacotherapies represent two decades of progress. Over this time span, a widespread dogma that 'you can't cure a chemical addiction with yet another chemical' has in the alcohol field been replaced by a landscape in which acamprosate, as well as the mu-opioid receptor antagonist naltrexone, is approved by the FDA and is available to patients, whereas several additional compounds, such as ondansetron, topiramate, baclofen, and varenicline, have accumulated evidence for efficacy in well-designed academic trials. A feature shared by several of these medications is that their activity was first identified in animal models. This observation suggests that animal models, despite their limitations may in fact have a useful degree of predictive validity, and provides encouragement for translational research efforts.

Acamprosate, the calcium salt of N-acetyl-homotaurin, was initially shown to suppress alcohol drinking in experimental animals. This was followed by findings showing its ability to promote abstinence in large, well-designed trials. Subsequent preclinical studies pointed to an interesting profile with potentially important clinical implications. Specifically, when administered to non-dependent rats, acamprosate did not suppress alcohol consumption. However, when voluntary consumption was escalated, as happens both in experimental animals and patients following a prolonged history of physical dependence, acamprosate treatment was able to bring drinking levels back to normal, non-escalated levels (Rimondini *et al*, 2002). This profile may help understand subsequent clinical findings. Acamprosate has been consistently found to be efficacious in European studies, which tend to include highly dependent patients recruited from publicly funded treatment programs. It has fared less well in studies in the United States, which tend to rely on newspaper advertisements and typically recruit less severely dependent patient populations.

Multiple lines of research have linked the effects of acamprosate to glutamatergic transmission. Specifically, it has been argued that acamprosate is somehow able to normalize a hyperglutamatergic state that arises over time as alcohol addiction becomes increasingly severe. Particularly elegant support for this theory of action was provided by the Spanagel group several years back. In a landmark paper that used null mutants for the clock gene *Per2*, they found elevated extracellular levels of glutamate in the mutants due to impaired expression of one of the glutamate transporters, GLAST. As a result, the *Per2* mutants mimic animals with a history of alcohol dependence, not only with regard to their extracellular glutamate levels but also in that they display escalated alcohol consumption. Most importantly, both these phenotypes are rescued by acamprosate (Spanagel *et al*, 2005). These observations seem to translate to the human situation, as it was recently found that central glutamate levels, measured using magnetic resonance spectroscopy, become elevated in alcoholics entering abstinence. This rise was prevented by acamprosate (Umhau *et al*, 2010).

Throughout the years, however, the molecular target of acamprosate has remained elusive. Because of structural similarities, initial hypotheses centered on the possibility that acamprosate may act as a GABA-mimic or otherwise modulate GABA-ergic transmission. There is, however, little in the *in vivo* profile of acamprosate to suggest similarities with drugs known to enhance GABA-ergic transmission. In fact, a lack of sedative–ataxic or addictive properties is among the clinical advantages of acamprosate. Once it

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became clear that acamprosate's mechanism of action is likely to involve modulation of glutamatergic function, several potential mechanisms were explored. For instance, acamprosate was shown to possess some partial agonist activity on the NMDA receptor complex via actions at its polyamine site. This would potentially allow it to act as a functional antagonist during hyperglutamatergic states. However, experiments failed to demonstrate this kind of functional activity. More recently, focus shifted to potential activity of acamprosate at metabotropic glutamate receptors (mGluRs). This was prompted, for example, by observations that acamprosate blocked neurotoxicity induced by trans-ACPD, an mGluR agonist with affinity for mGluR1 and mGluR5 receptors (Kiefer and Mann, 2010).

Over the years, the notion has become widely accepted that, although we may not know its exact mechanism of action, acamprosate is 'a functional glutamate antagonist'. The paper by Spanagel *et al* (2005) in this issue fundamentally challenges this notion. The paper presents multiple lines of evidence that the reason it has been difficult to pin down the molecular site of acamprosate action may simply be because it does not exist. Instead, the authors propose that the activity attributed to acamprosate has all along reflected actions of the Ca^{++} it carries. The authors first thoroughly excluded agonist as well as antagonist activity of acamprosate at the glycine or glutamate sites of the NMDA receptor, respectively, as well as at the mGluR5 receptor. They then went on to demonstrate *in vivo* that, in contrast to the Ca^{++} salt, the sodium salt of acamprosate did not suppress relapse-like drinking. Conversely, the delivery of comparable amounts of Ca^{++} using a different carrier, gluconate, replicated suppression of relapse-like drinking. These animal findings are supported by secondary analyses of clinical trial data, which indicate that in acamprosate-treated patients positive outcomes are strongly correlated with plasma Ca^{++} levels. No such correlation exists in placebo-treated patients.

Although by no means final, these findings are highly provocative. A definitive proof of this notion will require ambitious randomized controlled clinical trials. One approach with a potential to generate a conclusive answer would be to directly compare the sodium and calcium salts of acamprosate in a trial. Perhaps better still would be to evaluate other means of the Ca^{++} delivery as an approach to treat alcohol addiction. Data in support of a therapeutic role of calcium would open fascinating clinical possibilities and would also provide an impetus for the field to re-examine the nature of neuroadaptations that occur following a history of alcohol dependence.

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