Neuropsychopharmacology (2016) 41, 659–660

www.neuropsychopharmacology.org

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Does Acamprosate Really Produce its Anti-Relapse Effects via Calcium? No Support from the PREDICT Study in Human Alcoholics

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Neuropsychopharmacology (2016) **41,** 659–660; doi:10.1038/npp.2015.175

Spanagel *et al* (2014) argue that calcium ion alone is the active moiety of acamprosate. This finding contravenes the conventional wisdom on the action of acamprosate in relapse prevention in alcoholism (Littleton, 1995). In closing, the authors request that their findings be independently replicated; in particular, there is a need for validation in humans. To this end, we analyze the impact of calcium levels on drinking behavior in the framework of a large RCT, the PREDICT study (Mann *et al*, 2012).

The paper by Spanagel e*t al* is based on three preclinical studies that support the conclusion that calcium rather than *N*-acetylhomotaurinate is the active moiety of acamprosate. The authors argue that, compared with calcium, the sodium salt of *N*-acetylhomotaurinate is ineffective at reducing excessive alcohol drinking, alcohol-seeking, or relapse-like drinking behavior. In addition, they show animal brain profiles 30 min after single i.p. injections of both calcium and sodium *N*-acetylhomotaurinate, each dosed at 200 mg/kg. As similar concentrations of each compound reached the entire brain, the authors argue that differences of bioavailability do not have a role in the observed behavioral effects.

Finally, the authors present data in humans from a monocentric RCT conducted in the 1990s (Kiefer *et al*, 2003). Unfortunately, only a limited number of plasma samples were available, resulting in $N=12$ patients assigned to placebo and $N=19$ treated with acamprosate. Calcium plasma concentrations were measured before treatment and 1, 2, and 3 months after treatment. A statistical trend of enhanced calcium plasma levels in acamprosate-treated patients *vs* placebo was found. Moreover, when correlating three primary efficacy parameters—time to first drink, time to severe relapse, and cumulative abstinence duration—with calcium plasma levels, no significant correlation in the placebo group emerged, whereas in the acamprosate group the first two parameters (first drink and cumulative abstinence) were significantly correlated. This would seem to indicate that patients whose plasma calcium levels had been elevated due to acamprosate treatment showed better relapse prevention results.

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Results from our Human Analyses

We report data of a larger cohort of alcohol-dependent patients that countervail the above results. We conducted our analysis retrospectively based on the German PREDICT study (Mann *et al*, 2012). Data on calcium levels were available from a randomized clinical sample of $N=101$ alcohol-dependent patients (76 assigned to acamprosate at 1998 mg/day *vs* 25 patients to placebo). Neither subsample differed significantly from the full sample on any of the observed parameters. Patients' plasma calcium concentrations were measured at months 1 and 3. We compared differences in calcium plasma concentration between groups using *t*-tests, and applied Cox regressions to estimate the influence of calcium plasma concentration on treatment outcomes.

First, we found that acamprosate-treated patients did not significantly differ from those treated with placebo in terms of their calcium levels at either month 1 or 3 ($P\geqslant 0.12$). Second, the effect of calcium plasma concentrations (at months 1 or 3) on severe relapse was always non-significant ($P\geqslant 0.340$).

Discussion

Our results do not support the conclusions drawn by Spanagel *et al.* In a larger sample of acamprosate-treated patients, we found no indication of an interaction between calcium plasma levels and time to first heavy relapse. We also did not find any difference in calcium plasma levels between acamprosate- and placebo-treated patients. One might argue that our sample is not well suited for investigating the role of calcium as a mediator of successful treatment as acamprosate was not found to be significantly more effective than placebo.

We argue that this concern is unfounded. The reason why the PREDICT study did not show a significant treatment effect for acamprosate (plus brief intervention) was the good response in the placebo (plus brief intervention) group. Although this makes it a 'negative' study for approval, this does not exclude it from further analyses such as comparing patients with good and poor responses. Indeed, PREDICT patients displayed a wide variation in both their calcium levels and their treatment outcomes, which were found to be unrelated to each other. In other words, acamprosate-treated patients relapsed independently of their calcium levels.

We offer two potential explanations for the differences between our findings and the conclusions drawn by Spanagel *et al*:

(1) Evidence shows that the pharmacological activity of sodium acamprosate is dependent on the application site. Whereas Spanagel *et al* used i.p. application exclusively, others have shown that the effects of intracerebral microinjection of sodium acamprosate are site and dose dependent. Morse and Koob (2002) demonstrated bilateral microinjections of sodium acamprosate into the bed nucleus of the stria terminalis to be effective at decreasing free-choice ethanol-response rates in alcohol-dependent rats, whereas injections to other brain sites yielded no such effect. These data provide evidence that sodium acamprosate is an active molecule affecting ethanol self-administration. We suggest that the data of Spanagel *et al* show that, although their i.p. injections did reach the brain, the levels of sodium acamprosate were not high or site-specific enough (or both) to be effective. Thus the measured brain levels of calcium and *N*-acetylhomotaurinate may not have been sufficiently high to translate into behavioral outcomes.

(2) It may be that reductive models are of limited translational validity in addiction research. For example, Crabbe (2012) stated that 'despite more than 50 years of research with genetically preferring rats and mice, it is rare that even high preferrers will drink enough alcohol to become intoxicated.' It is thus questionable whether valid levels of intoxication are reached while testing a molecule for its anti-relapse effect, as the concept of 'relapse' implies that an intoxicated state has been established before.

The study by Spanagel *et al* is a valuable preclinical contribution, helping to reassess the mechanisms by which acamprosate affects alcohol consumption in rodents. As no data to date preclude an interaction between calcium and homotaurinate, calcium may yet have an important role in relapse prevention, and this could be a fruitful area for future research. However, the authors' generalization of their findings to humans—stating unequivocally that 'acamprosate produces its anti-relapse effects via calcium'—seems premature. Such a statement can only be verified through a RCT in humans.

FUNDING AND DISCLOSURE

The PREDICT Study was performed between 2000 and 2008. It was funded by the German Government (01EB0410). Acamprosate medication was provided for free by Merck Serono. The authors declare no conflict of interest.

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