Revisiting baclofen in the treatment of alcoholism: just a question of enantiomer?

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The benefit-risk balance of the GABA (γ-aminobutyric acid)-B receptor agonist baclofen in the treatment of alcohol addiction is still controversial not only because the efficacy has not been clearly demonstrated but also because of the recent safety concern. Thus it is a pressing need to better characterize the factors that modulate both the efficacy and the side effects and also the variability of the response depending on individuals. Most of the preclinical and clinical studies used the racemic baclofen [(±)-baclofen], however, recent data showed that the effect of baclofen on alcohol intake may be enantiomer dependent. In this sense, the doses of the more active enantiomer, R(+)-baclofen, which suppressed alcohol intake, did not produce effects in the case of S(-)-baclofen in alcohol-preferring rats, or even it showed the opposite effects in mice. Here we used the gold standard animal model of alcohol dependence: initial period of intermittent access to ethanol (20% v/v, 2-bottle choice), followed by training and maintenance in an operant ethanol (20% v/v) self-administration paradigm. Then, rats are exposed to chronic intermittent ethanol vapor (14 hours/day), and the self-administration session (30 minutes, fixed ratio 3 schedule) is performed 6 to 8 hours after the vapor is turned OFF. Dose-response curves for (±)-baclofen, R(+)-baclofen, and S(-)-baclofen were performed, showing that R(+)baclofen was more effective than racemic baclofen in suppressing alcohol intake, while S(-)-baclofen failed to affect alcohol consumption. Also, the effect size (Cohen's *d*) of (±)-baclofen (1 mg/kg), in both nondependent and dependent rats, was small (0.3 and -0.1, respectively), while the same dose of R(+)-baclofen showed larger effect sizes in both groups, being lower in dependent ($d = 0.6$) than in nondependent animals ($d = 1.5$). Our results suggest that R(+)-baclofen could be a potentially more effective medication than (±)-baclofen in the treatment of alcohol dependence. We are currently analyzing our data to see whether the efficacy may be dependent upon individual features such as the basal level of ethanol intake or pharmacokinetics. We will also investigate the efficacy on motivation, craving and relapse.

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