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Pharmacometabolomics and individualized reatment strategy: High serum glutamate level is associated with positive response to acamprosate treatment

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Abstract

Acamprosate is approved for treatment of alcohol dependence and is known to stabilize a glutamatergic imbalance in the brain. However, the efficacy of acamprosate is not universal in all patients. We identified potential predictors of acamprosate response using a pharmacometabolomics approach and revealed a mechanism for acamprosate action. To identify the blood metabolite markers of acamprosate response, 40 amino acid metabolites were screened using UPLC-MS/MS. We observed that glutamate levels were significantly higher at baseline in the 51 responders compared to the 39 non-responders [p = 0.007]. In addition, after adjustment for baseline PACS, increased glutamate was significantly associated with increased probability of a favorable acamprosate response (OR=1.047, p=0.010). This indicates that an escalated baseline glutamate level itself in the acamprosate responder group provides essential information regarding likelihood of a positive treatment outcome beyond clinical measures. We also identified glutamate-ammonia condensation by glutamine synthetase (GS) as an important pathway for acamprosate action in the acamprosate responder group. Consistent with glutamate, ammonia also showed a significant profile change at baseline and after acamprosate treatment in the responder group. To confirm whether acamprosate promotes GS metabolism, we measured serum glutamate levels after acamprosate treatment in mice. Interestingly, acute acamprosate treatment reduced serum glutamate levels for a period of time longer than its steady state in blood (30min), indicating a strong glutamate metabolism alteration in the serum by acamprosate treatment. Overall, these findings suggest that high baseline glutamate levels may be a biomarker to predict the efficacy of acamprosate treatment and glutamate regulation by GS metabolism may play an important role in pharmacological intervention of acamprosate in maintaining abstinence. Since GS is highly expressed in astrocytes, these data provide a possible mechanism underlying the pharmacological efficacy of acamprosate in stabilizing a hyper-glutamatergic state in the brain.

Biography

Dr. Doo-Sup Choi is a molecular biologist and neuroscientist. He graduated from the Department of Biochemistry at Yonsei University in Seoul, Korea with BS (1988) and MS (1990). Dr. Choi completed his Ph.D. at the Louis Pasteur University in Strasbourg, France in 1997. He performed a two-year postdoctoral research in the field of neuropharmacology of addiction (1997-1998) in the Department of Biopharmaceutical Sciences at University of California San Francisco (UCSF). Following that, he joined the Ernest Gallo Clinic and Research Center and the Department of Neurology at UCSF as a staff research scientist (1999-2004) and then a junior faculty member (2004-2005). He joined the College of Medicine, Mayo Clinic in 2005 and has established an innovative and cutting-edge research program by combining mouse genetics, behaviors, proteomics, neurochemistry, and imaging.