

Brain glycine receptors as a common target for alcohol and the relapse-preventing drug acamprosate

– a preclinical study

Akademisk avhandling

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av

PeiPei Chau

Fakultetsopponent: Professor Giancarlo Colombo
University of Cagliari, Italy

Avhandlingen baseras på följande arbeten:

- I. Chau P, Stomberg R, Fagerberg A, Söderpalm B, Ericson M. Glycine receptors involved in acamprosates' modulation of accumbal dopamine levels: an *in vivo* microdialysis study Alcohol Clin Exp Res. 2010 Jan;34(1):32-8.
- II. Chau P, Höifödt-Lidö H, Löf E, Söderpalm B, Ericson M. Glycine receptors in the nucleus accumbens involved in the ethanol intake-reducing effect of acamprosate Alcohol Clin Exp Res. 2010 Jan;34(1):39-45.
- III. Chau P, Söderpalm B, Ericson M. Acamprosate-induced dopamine elevation is associated with its' ethanol intake-reducing effect Submitted/Manuscript
- IV. Chau P, Söderpalm B, Ericson M. The mGluR5 antagonist MPEP elevates accumbal dopamine and glycine levels: interaction with strychnine-sensitive glycine receptors Submitted/Manuscript
- V. Ericson M, Chau P, Clarke RB, Adermark L, Söderpalm B. Rising taurine and ethanol concentrations in nucleus accumbens interact to produce dopamine release after ethanol administration Addiction Biology (E-pub ahead of print Aug 23 2010).



UNIVERSITY OF GOTHENBURG

Abstract

Brain glycine receptors as a common target for alcohol and the relapse-preventing drug acamprosate – a preclinical study

PeiPei Chau

Addiction Biology Unit, Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Alcohol abuse and dependence make up the most prevalent categories of substance use disorders in the world. Converging evidence from the current research group has identified two receptor populations, the glycine (GlyRs) and nicotinic acetylcholine receptors (nAChRs) in the mesolimbic dopamine system, as two potentially important targets for the development of new medication to treat alcohol dependence. It is suggested that ethanol primarily acts via GlyRs in the nucleus accumbens (nAc) with a secondary and indirect effect on nAChRs in the ventral tegmental area (VTA), subsequently activating dopaminergic neurons leading to an increase of extracellular dopamine in the nAc. Pharmacological modulation of these receptors alters the activity of the suggested nAc-VTA-nAc circuitry with prominent effects on ethanol-induced dopamine elevations as well as ethanol intake. The general aim of this thesis was to further investigate the role of these receptors for regulating ethanol-induced dopamine and consummatory actions, by using ethanol and substances with possible anti-alcohol effects in the rat. Measurements of extracellular dopamine and amino acid levels in the nAc were examined using *in vivo* brain microdialysis in awake, freely-moving male Wistar rats. In addition, a voluntary ethanol consumption paradigm with limited access was used to measure ethanol intake. The results indicate that the anti-relapse substance acamprosate has a similar dopamine-modulating profile as previously observed with ethanol and the endogenous GlyR ligand taurine. The acamprosate-induced dopamine elevation was demonstrated to be inhibited by pre-treatment with GlyR or nAChR-antagonists (Paper I). At a behavioral level, the ethanol intake-reducing effect of acamprosate was *reversed* by GlyR antagonism in the nAc (Paper II). In addition, the loss of the ethanol intake-reducing effect of chronic administration of acamprosate is potentially linked with its' dopamine-modulating property (Paper III). The influence of acamprosate-related substances, the metabotropic glutamate type 5 receptor (mGluR5) antagonist MPEP and taurine, were also investigated. We found that mGluR5 and GlyR may have a joint mechanism to activate the dopamine output (Paper IV). Also, an augmentation of extracellular taurine levels is required in order to obtain an ethanol-induced dopamine increase (Paper V). The findings of this thesis have revealed a new mechanism of action for the anti-relapse agent acamprosate. But, most importantly, the results have further confirmed the relevance of the nAc-VTA-nAc neuronal circuitry for alcohol addiction.

Keywords: acamprosate, alcohol, dependence, dopamine, glycine, nicotinic acetylcholine receptor

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