Abstract

Role of Glycine Receptors in the Regulation of Dopamine Activity and Ethanol Intake in the Rat

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Alcoholism with its multitude of negative consequences to the afflicted, his/her relatives and the society remains a devastating disease. During the last few years new pharmacological treatments, such as naltrexone and acamprosate, have based on findings obtained in experimental animal models of alcoholism been introduced to combat this disorder. Unfortunately these drugs are, however, effective only in a fraction of patients and therefore new pharmacological treatments are warranted.

Acute ethanol administration enhances dopamine release in the nucleus accumbens (nAc) in rodents and in the ventral striatum in man. This dopamine elevation in a major target area of the mesolimbic dopamine system, a central part of the brain reward system, is believed to be involved in ethanol's positive reinforcing and rewarding effects. The mechanisms by which ethanol produces this effect are, however, not fully understood.

Previous findings indicate that nicotinic acetylcholine receptors (nAChRs) in the cell-body region of the mesolimbic dopamine system are involved in mediating the dopamine elevating effect of ethanol, but that activation of these receptors is secondary to some primary effect produced in the nAc. Here the possibility that ethanol produces its dopamine activating and reinforcing effects via a primary agonistic interference with strychnine-sensitive glycine receptors (GlyR) in the nAc of adult, male Wistar rats was examined.

First the ligand binding α-subunit and the scaffolding protein gephyrin of the GlyR were shown to be present in tissue samples from the nAc. Microdialysis experiments then showed that dopamine output in the nAc was concentration-dependently decreased after local perfusion with the GlyR antagonist strychnine, while local glycine instead increased dopamine output in a minority of rats. Both local strychnine and glycine antagonized the ethanol induced (300 mM) increase of dopamine output in the nAc, whereas local strychnine, but not glycine, antagonised also the dopamine elevating effect of systemic ethanol (2.5 g/kg, i.p.). Bilateral glycine or strychnine perfusion in the nAc of ethanol high-preferring male Wistar rats (ethanol preference >60 % in a two-bottle free-choice model) decreased and increased, respectively, ethanol preference or intake, and systemic treatment with a glycine reuptake inhibitor lowered both ethanol intake and preference in the same model. Finally, and in contrast to glycine, local perfusion of taurine increased dopamine output in all animals, and this effect was antagonized by strychnine.

These findings suggest that GlyRs in the nAc are involved both in regulating basal dopamine levels and in mediating the dopamine activating and reinforcing effects of ethanol. A hypothesis regarding how ethanol produces its dopamine activating effect that encompasses also our previous findings of nAChR involvement is presented. It is further suggested that taurine rather than glycine may be the endogenous ligand for GlyRs in the nAc. Finally, drug developmental and candidate genes studies focusing on taurine/glycine neurotransmission in relation to alcoholism and psychiatric disorders related to the mesolimbic dopamine system are warranted.

Key words: Strychnine-sensitive glycine receptor (GlyR), dopamine, ethanol, nucleus accumbens (nAc), glycine, taurine, glycine re-uptake inhibitor (GLYT1)

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