Molecular biological study of strychnine sensitive glycine receptors in the rat brain reward system after long-term ethanol consumption

Alcoholism & society
The problems of alcohol abuse are wide-ranging and far-reaching in society. The cost to society as measured by social, medical, occupational, and legal effects is exceedingly high and probably underestimated. The contributing factors that create alcoholics are many, and any combination can increase a person's chance of falling dependant on the substance. Some of the factors that contribute to alcoholism are age, gender, family history, family background, psychological disorders, and even personality traits. Any of these factors could increase chances of being an alcoholic.

The “brain reward system”
The reward pathway is primarily made up of core structures that are connected by the median forebrain bundle: the nAc, the VTA, the ventromedial and lateral nuclei of the hypothalamus, the medial prefrontal cortex and the amygdala. The mesolimbic dopamine system with cell-bodies in the VTA projecting mainly to the nAc has been implicated as an especially important part of the brain reward pathway and is known to interact with all addictive drugs of abuse.

Ethanol and the glycine receptor
Research in our group has demonstrated that ethanol elevates dopamine levels in the nAc by directly or indirectly interacting with the strychnine sensitive glycine receptor (GlyR). This receptor appears to tonically regulate the dopamine output in the same brain region by a neuronal loop involving the cell body region (VTA). We now have results indicating that the subunit composition of the GlyR may be genetically different in ethanol preferring versus non-preferring rats but further studies are required.
A recently suggested 2-alpha-3-beta stoichiometric composition of the pentameric ligand gated ion channel (GlyR) points towards the fact that quantitatively the beta subunit is dominant. In adult rats 3 subtypes of alpha-subunits are known (alpha-1, alpha-2, alpha-3) that show specific distribution in the central nervous system. Our preliminary results so far suggest that the dominant alpha subunit in the nAc and prefrontal cortex is the alpha-2 subtype and the more common alpha-1 subtype appears to be expressed very low. These preliminary studies are extremely interesting and have big potential for being clinically relevant for treatment of alcoholism.

**Questions to be answered with the proposed study:**

*Does long-term ethanol consumption alter the subunit composition of the GlyR in the brain reward system?*

*Do female rats express the same subtype composition of the GlyR in the brain reward system as male rats?*

*How female rats genetically predisposed towards enhanced EtOH consumption differ from female rats genetically predisposed towards low ethanol consumption?*

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