Glycine receptors in the central nervous system
– development, distribution, and relation to actions of alcohol

Akademisk avhandling

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Professor Richard W. Olsen
University of California, Los Angeles, Ca, USA

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I. **Jonsson S**, Kerekes N, Hyytiä P, Ericson M, Söderpalm B. (2009) Glycine receptor expression in the forebrain of male AA/ANA rats Brain Res. 2009 Dec 11;1305 Suppl:S27-36

II. **Jonsson S**, Morud J, Pickering C, Adermark L, Ericson M and Söderpalm B (2012) Changes in glycine receptor expression in forebrain regions of the Wistar rat over development Brain Res. 2012 Mar 29;1446:12-21.

III. **Jonsson S**, Ericson M, Söderpalm B. (2012) The effects of long-term ethanol consumption on the expression of neurotransmitter receptor genes in the rat nucleus accumbens *Manuscript*

IV. **Jonsson S**, Adermark L, Stomberg R, Morud J, Ericson M and Söderpalm B (2012) Glycine receptors are involved in mesolimbic dopamine release induced by drugs of abuse *Manuscript*

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ABSTRACT

Glycine receptors in the central nervous system
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The widespread consumption of alcohol and the great socioeconomic impact of alcohol abuse and addiction have contributed to the extensive investigations of this substance. Despite great efforts there is still uncertainty concerning how alcohol exerts its effects and the mechanisms behind the transition from consumption to addiction. However, substantial evidence proposes involvement of the mesolimbic dopamine system in the rewarding and reinforcing effects of the drug. Alcohol is known to affect several neurotransmitter systems and the glycine receptor (GlyR) is among its primary targets. Previous studies from our group have strongly suggested that GlyRs in the nucleus accumbens (nAc, a key region in the mesolimbic dopamine system) are involved in the dopamine elevating and reinforcing effects of alcohol. Based on a number of studies a hypothesis of a neuronal circuit mediating these effects of alcohol, where the GlyR is a key component, has been proposed. The aim of this thesis was therefore to further examine the GlyR and its role in the actions of ethanol. Gene expression of GlyR subunits was measured in animals selectively bred based on alcohol preference (Alko-Alcohol, AA, and Alko Non-Alcohol, ANA, rats) with and without exposure to alcohol (Paper I), during development (Paper II) and in response to long-term alcohol consumption (Paper III). The main method, quantitative polymerase chain reaction (qPCR), was complemented by monitoring of consumption behaviour (Paper I and III) and immunohistochemical studies (Paper II and III). The effect of accumbal GlyR blockade on the dopamine elevating effect of alcohol and other drugs of abuse was investigated using *in vivo* microdialysis (Paper IV). In this study immunohistochemistry and retrograde tracing were also utilised to explore the proposed neuronal circuit. The results of the work presented in this thesis suggest: (1) that based on gene expression the glycinergic system seems robust, (2) the disparate alcohol consumption of AA and ANA rats is not due to differences in forebrain GlyR gene expression, (3) α2 appears to be the dominating α-subunit in the rat brain and α2β should be the dominating GlyR receptor composition in the adult brain, (4) the commonly accepted developmental shift from α2 to α1β is not a general effect, (5) GlyRs are mainly located in the nAc shell-region, (6) accumbal GlyRs are involved in the dopamine-elevating effect of nicotine and tetrahydrocannabinol in addition to alcohol, and (7) the possible addition of the lateral septum in the neuronal circuit mediating ethanol's dopamine-elevating effect.

Key words: glycine receptor, nucleus accumbens, alcohol, gene expression, dopamine

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