

REWARD-RELATED GENES AND ALCOHOL DEPENDENCE

Akademisk avhandling

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av

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- I. **Sara Landgren**, Jörgen A. Engel, Malin E. Andersson, Arturo Gonzalez-Quintela, Joaquin Campos, Staffan Nilsson, Henrik Zetterberg, Kaj Blennow, Elisabet Jerlhag. Association of nAChR gene haplotypes with heavy alcohol use and body mass. *Brain Research, 1305 Suppl: S72-9, 2009*
- II. **Sara Landgren**, Elisabet Jerlhag, Henrik Zetterberg, Arturo Gonzalez-Quintela, Joaquin Campos, Ulrica Olofsson, Staffan Nilsson, Kaj Blennow, Jörgen A. Engel. Association of pro-ghrelin and GHSR gene polymorphisms and haplotypes with heavy alcohol-use and body mass. *Alcoholism Clinical and Experimental Research, 32(12): 2054-61, 2008*
- III. **Sara Landgren**, Elisabet Jerlhag, Jarmila Hallman, Lars Orelund, Lauren Lissner, Elisabeth Strandhagen, Dag S. Thelle, Henrik Zetterberg, Kaj Blennow, Jörgen A. Engel. Genetic variation of the ghrelin signalling system in severe female alcohol dependence. *In press, Alcoholism Clinical and Experimental Research, 2010*
- IV. **Sara Landgren**, Jörgen A. Engel, Petri Hyytiä, Henrik Zetterberg, Kaj Blennow, Elisabet Jerlhag. Regulation of alcohol drinking by the ghrelin signalling system in rat lines selected for differential alcohol preference. *Submitted manuscript, 2010*



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Abstract

REWARD-RELATED GENES AND ALCOHOL DEPENDENCE

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Introduction: The rewarding properties of alcohol are mediated by the brain reward systems, specifically by the cholinergic-dopaminergic reward link, involving both nicotinic acetylcholine receptors (nAChRs) as well as the ghrelin signalling system. The susceptibility for developing alcohol dependence is influenced by genetic factors. Therefore, the aim of this thesis is to investigate the genes encoding nAChRs as well as ghrelin and its receptor (GHS-R1A) in human genetic association studies of alcohol dependence. Furthermore, various aspects of ghrelin signalling have been investigated in rats with different alcohol preference.

Observations: In the genetic association studies it was shown that; (1) nAChR gene variants influence alcohol consumption and body weight in alcohol-dependent individuals; (2) genetic variants of the ghrelin signalling system influence the risk of developing alcohol dependence, even though the effect size is small, and these variants might also affect body weight. The animal studies in this thesis showed that; (3) GHS-R1A antagonism reduces alcohol intake in a genetic rat model of high alcohol consumption; (4) GHS-R1A gene expression is higher in high alcohol consuming rats than in low alcohol consuming ones in reward-related brain areas; (5) alcohol counteracts the reduction of plasma ghrelin levels over time.

Conclusions: The data presented in this thesis suggest that genetic variations of reward-related genes may be involved in the pathogenesis of alcohol dependence, although not as major susceptibility genes. Rather, they contribute to increased vulnerability in the reward systems that, in combination with environmental factors, may lead to dependence.

Keywords: alcohol – dependence – reward – smoking – body weight – gene – polymorphism – nAChR – ghrelin – GHS-R1A

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