

The gut-brain axis and alcohol-mediated behaviours: the amylin story

Akademisk avhandling

Som för avläggande av medicinsk vetenskap doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligens försvaras i **hörsal Arvid Carlsson, Medicinaregatan 3, fredagen den 22 november 2019, kl. 09:00**

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Fakultetsopponent:
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Avhandlingen baseras på följande delarbeten

- I. **Kalafateli AL**, Vallöf D, Jerlhag E. Activation of amylin receptors attenuates alcohol-mediated behaviours in rodents. *Addiction Biology* 2019; 24(3): 388-402
- II. **Kalafateli AL**, Vallöf D, Colombo G, Lorrain I, Maccioni P, Jerlhag E. An amylin analogue attenuates alcohol-related behaviours in various animal models of alcohol use disorder. *Neuropsychopharmacology* 2019; 44(6): 1093-1102
- III. **Kalafateli AL**, Satir TM, Vallöf D, Zetterberg H, Jerlhag E. Behavioural responses to alcohol involve amylin receptor signalling within brain areas processing reward. *Submitted*
- IV. **Kalafateli AL**, Aranäs C, Jerlhag E. Effects of sub-chronic amylin receptor activation on alcohol-induced locomotor stimulation and monoamine levels in mice. *Submitted*
- V. **Kalafateli AL**, Vestlund J, Raun K, Egecioglu E, Jerlhag E. Effects of a selective long-acting amylin receptor agonist on alcohol consumption, food intake and body weight in male and female rats. *Manuscript*

**SAHLGRENKA AKADEMIN
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The gut-brain axis and alcohol-mediated behaviours: the amylin story

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Abstract

Alcohol use disorder (AUD) is a complex neuropsychiatric disorder with high rates of mortality and morbidity. The currently available pharmacotherapies show varied efficacy, leading to the investigation of new neurochemical targets for alcohol. Recently, gut-brain hormones involved in appetite regulation have been shown to modulate alcohol-mediated behaviours. However, the role of the anorexigenic gut-brain hormone amylin in such behaviours was until recently unknown. Therefore, this thesis aims at identifying how amylin signalling regulates behavioural responses to alcohol and suggests the underlying mechanisms of this modulation.

The studies in this thesis present novel data that, firstly, amylin receptor (AMYR) activation by the amylin analogue salmon calcitonin (sCT) attenuates the established acute effects of alcohol to increase locomotion and dopamine release in the nucleus accumbens (NAc) in mice. Secondly, acute sCT administration decreases alcohol consumption and alcohol relapse drinking in rats chronically exposed to alcohol. Notably, the gene expression of the AMYR components is different in the NAc of high, compared to low alcohol-consuming rats. In selectively bred Sardinian alcohol-preferring rats, sCT decreases the number of lever presses for alcohol reward in an operant self-administration paradigm. Thirdly, sCT crosses the blood-brain barrier and reaches reward-related areas, including the laterodorsal tegmental area, the ventral tegmental area and the NAc, whereby activates local AMYRs to decrease acute alcohol behaviours in mice and chronic in rats. Fourthly, repeated sCT treatment decreases alcohol-induced locomotion even after discontinuation of sCT administration and alters the levels of neurotransmitters in reward-related areas. Lastly, a selective AMYR synthetic amylin analogue decreases alcohol consumption in both male and female rats and alters monoamine levels in reward-related brain areas in both sexes.

The thesis attributes an entire new role to the amylin signalling, that of the regulator of alcohol-mediated behaviours. The commercial availability of amylin analogues for the treatment of other disorders could set the ground for the development of targeted pharmacotherapies for AUD and potentially for other addictive disorders.

Keywords: reward, mesolimbic dopamine system, addiction, calcitonin, IAPP