Göteborg, 2019

Glucagon-like peptide-1 and alcohol-mediated behaviors in rodents

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Karl Isaksson, Medicinaregatan 16, fredagen den 8 februari 2019, klockan 9.00

av
Daniel Vallöf

Fakultetsopponent:
Erika Roman, Docent
Uppsala universitet

Avhandlingen baseras på följande delarbeten

I. Vallöf D, Maccioni P, Colombo G, Mandrapa M, Jörnulf JW, Egecioglu E, Engel JA, Jerlhag E. The glucagon-like peptide-1 receptor agonist liraglutide attenuates the reinforcing properties of alcohol in rodents. Addict Biol. 2016, 21(2):422-37

II. Vallöf D, Kalafateli AL, Jerlhag E. Brain region specific glucagon-like peptide-1 receptors regulate alcohol-induced behaviors in rodents. *Submitted*

III. Vallöf D, Jerlhag E. Glucagon-like peptide-1 receptors within the nucleus of the solitary tract regulate alcohol-mediated behaviors in rodents. *Submitted*

IV. Vallöf D, Kalafateli AL, Jerlhag E. Alcohol intake in male and female rats following long-term treatment with a glucagon-like peptide-1 receptor agonist. *Manuscript*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

GÖTEBORGS UNIVERSITET

Göteborg, 2019

Glucagon-like peptide-1 and alcohol-mediated behaviors in rodents

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Abstract

Alcohol use disorder (AUD) is a serious cause of morbidity and mortality. However, due to the limited efficacy of existing pharmacotherapies, further investigations of potential neurochemical targets are required to define new pharmacological interventions. In recent years, a pivotal role of the appetite regulatory peptide glucagon-like peptide-1 (GLP-1) in drug reinforcement and addiction processes has been identified. However, the ability of GLP-1 receptors (GLP-1R) to influence various alcohol-related behaviors and the downstream mechanisms for this interaction remains to be further evaluated. The aim of the present thesis was to investigate the mechanisms of action of GLP-1R agonists on alcohol-mediated behaviors in rodents.

Our studies firstly investigated the GLP-1R agonist, liraglutide, which suppressed the well-documented effects of alcohol on the mesolimbic dopamine system, namely alcohol-induced accumbal dopamine release and conditioned place preference (CPP) in mice. Also, acute administration of liraglutide prevented the alcohol deprivation effect and reduced alcohol intake in outbred rats, while repeated treatment decreased alcohol intake in outbred rats and reduced operant alcohol self-administration in selectively bred Sardinian alcohol-preferring rats. Secondly, we found that injections of exendin-4 (Ex4) into brain regions of the cholinergic-dopaminergic reward link are important for regulating alcohol-induced behaviors. Ex4 into the nucleus accumbens shell blocked alcohol-induced locomotor stimulation and alcohol reward-dependent memory retrieval in the CPP model in mice as well as decreased alcohol intake in rats. Moreover, Ex4 did not alter alcohol-induced behaviors when infused into the anterior ventral tegmental area (VTA). On the other hand, Ex4 into the posterior VTA blocked alcohol-induced locomotor simulation without altering alcohol-CPP in mice or alcohol intake in rats. Furthermore, Ex4 into the laterodorsal tegmental area attenuated alcohol-induced locomotor stimulation in mice and reduced alcohol intake in rats, but did not affect alcohol reward-dependent memory retrieval in the CPP model in mice. Thirdly, obtained results showed that Ex4 into the nucleus of the solitary tract (NTS), a food-intake regulating area that is linked to the cholinergic-dopaminergic reward link, attenuated alcohol-induced locomotor stimulation, accumbal dopamine release and alcohol reward-dependent memory retrieval in the CPP model in mice. In addition, NTS-Ex4 decreased alcohol intake in rats consuming alcohol for 12 weeks. Fourthly, we found that both nine as well as five weeks of treatment with the GLP-1R agonist dulaglutide reduced alcohol intake in male and female rats. The decrease in alcohol consumption was prolonged in male rats following discontinuation of the nine-week dulaglutide treatment.

Collectively, findings in the present thesis demonstrated that different GLP-1R agonists attenuate various alcohol-mediated behaviors in rodents and that this involves subpopulations of central GLP-1R. As GLP-1 and its receptor seem to play an important role in the pathophysiology of alcohol-mediated behaviors, clinically available GLP-1R agonists deserve to be examined as potential treatments in patients with AUD

Keywords: Addiction, Dopamine, Gut-brain axis, Reward

ISBN: 978-91-7833-288-5 (TRYCK) http://hdl.handle.net/2077/57960
ISBN: 978-91-7833-289-2 (PDF)