The cholinergic-dopaminergic reward link and addictive behaviours -special emphasis on ethanol and ghrelin

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson salen, Academicum, Medicinaregatan 3, Göteborg, torsdagen den 7 juni 2007 kl 13.00

av

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This thesis is based on the following research papers:

I. Jerlhag E, Grøtli M, Luthman K, Svensson L, Engel JA (2006) Role of the subunit composition of central nicotinic acetylcholine receptors for the stimulatory and dopamine-enhancing effects of ethanol in mice. Alcohol and Alcoholism 41(5): 486-493.

II. Jerlhag E, Egecioglu E, Dickson SL, Andersson M, Svensson L, Engel JA (2006) Ghrelin stimulates locomotor activity and accumbal dopamine overflow via central cholinergic mechanisms: implications for its involvement in brain reward. Addiction biology 11: 45-54.

III. Jerlhag E, Egecioglu E, Dickson SL, Douhan A, Svensson L, Engel JA (2007) Ghrelin administration into Tegmental Areas stimulates locomotor activity and increases extracellular concentration of dopamine in the nucleus accumbens. Addiction biology 12: 6-16.

IV. Jerlhag E, Egecioglu E, Dickson SL, Svensson L, Engel JA (2007) Alpha-conotoxin MII-sensitive nicotinic acetylcholine receptors are involved in mediating the ghrelin-induced locomotor stimulation and dopamine overflow in nucleus accumbens. Manuscript.

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Abstract

An important part of the reward systems is the cholinergic-dopaminergic reward link. This reward link has been proposed to be involved in reward and motivated behaviours. It encompasses a cholinergic input from the laterodorsal tegmental area (LDTg) to the mesolimbic dopamine (DA) system that originates in the ventral tegmental area (VTA) and projects to the nucleus accumbens. Previous results demonstrate that nicotinic acetylcholine receptors (nAChRs), especially those located in the VTA, are involved in mediating the stimulatory, rewarding and DA enhancing properties of ethanol. One aim of the present thesis was therefore to investigate the functional role of different nAChR subtypes for the behavioural and neurochemical effects of ethanol. In Paper I a slightly modified method was used to synthesize α-conotoxins with various subunit selectivity; α-conotoxin MII (αCtxMII) and a α-conotoxin PIA-analogue. Furthermore, it was demonstrated that αCtxMII-sensitive (*i.e.* the $\alpha_3\beta_2$*, β_3* and/or α_6* subtypes), rather than αPIA-analogue-sensitive (the α_6* subtype), nAChRs in the VTA are involved in mediating the stimulatory and accumbal DA enhancing properties of ethanol. Given that ethanol concomitantly increases ventral tegmental ACh and accumbal DA levels and that some of the effects of ethanol are mediated via the $\alpha_3\beta_2$* and/or β_3*, rather than α_6* subtypes in the VTA, we hypothesize that ethanol activates the cholinergic-dopaminergic reward link. There appears to be a neurochemical overlap between the reward systems and the systems regulating energy balance. Ghrelin is an orexigenic peptide, which *e.g.* via the hypothalamus increases food intake. Given that ghrelin is involved in energy balance regulation, the role for ghrelin in brain reward was investigated in Papers II, III, IV. It was demonstrated that intracerebroventricluar administration of ghrelin increases locomotor activity and accumbal DA overflow in mice, suggesting that ghrelin activates the mesolimbic DA system. In subsequent experiments it was found that administration of ghrelin into either the LDTg or the VTA (reward nodes expressing growth hormone secretagougue receptors (GHSR-1A)) increases the locomotor activity as well as accumbal DA overflow. Thus indicating that ghrelin, via GHSR-1A in the LDTg and/or VTA, activates the cholinergic-dopamine reward link. Further, the stimulatory and DA enhancing properties of ghrelin (intracerebroventricluar) were antagonized by systemic administration of the unselective nicotinic antagonist, mecamylamine, implying that cholinergic mechanisms are involved in mediating the stimulatory and DA enhancing effects of ghrelin. Additionally, it was showen that the stimulatory and DA enhancing effects of ghrelin administration (into either the VTA or LDTg) were mediated via αCtxMII-sensitive nAChRs, *i.e.* the $\alpha_3\beta_2$* and/or β_3* subtypes, in the VTA, implying neurochemical analogies between ethanol and ghrelin. These findings provide the first indication that ghrelin has a role in brain reward and that ghrelin is a part of the neurochemical overlap between systems regulating energy balance and reward. We hypothesize that ghrelin stimulates the cholinergic-dopaminergic reward link and thereby increases the incentive values of signals associated with motivated behaviours such as food searching/foraging. Thus ghrelin drives animals (and man) to work and to seek for food. High plasma levels of ghrelin have been associated with some aspects of binge eating/compulsive overeating as well as alcoholism. Additionally, a deranged reward system has been implicated in overeating and alcoholism. We therefore hypothesizes that hyperghrelinemia, via activation of the cholinergic-dopaminergic reward link, may be a part of the pathophysiology of binge eating and alcoholism. The findings in the present thesis demonstrate that the $\alpha_3\beta_2$* and/or β_3* subtypes are involved in mediating the stimulatory and DA enhancing effects of ethanol and ghrelin. It is therefore suggested that these subunits might be novel pharmacological targets for treatment of compulsive overeating as well as alcoholism.

Key words: ethanol, ghrelin, reward, food-seeking, ventral tegmental area, laterodorsal tegmental area, nucleus accumbens, dopamine, nicotinic acetylcholine receptors, *in vivo* microdialysis, locomotor activity, mice, addictive behaviours.

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