CONDITIONAL AND NON-CONDITIONAL REWARD-RELATED RESPONSES TO ALCOHOL – NICOTINIC MECHANISMS

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I. Löf E., Olausson P., deBejczy A., Stomberg R., McIntosh J.M., Taylor J.R., Söderpalm B. Nicotinic acetylcholine receptors mediate the dopamine activating and reinforcing properties of ethanol cues. Submitted.

II. Löf E., Olausson P., Taylor J.R., Söderpalm B. Nicotinic acetylcholine receptors are required for the conditioned reinforcing properties of sucrose associated cues. Manuscript.

III. Löf E., Ericson M., Stomberg R., Söderpalm B. Characterization of ethanol-induced dopamine elevation in the rat nucleus accumbens. In press, Eur. J. Pharmacol.

IV. Löf E., Chau P., Stomberg R., Söderpalm B. Ethanol-induced dopamine elevation in the rat - modulatory effects by subchronic treatment with nicotinic drugs. In press, Eur. J. Pharmacol.

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ABSTRACT

The mesolimbic dopamine system is believed to mediate the positive reinforcing and rewarding effects of addictive drugs by increasing dopamine levels in its terminal area, the nucleus accumbens (nAc). Nicotinic acetylcholine receptors (nAChRs) within this system appear important for the pharmacological actions of both alcohol and nicotine, which may explain the frequent co-abuse of these two drugs. Despite available pharmacological and psychological therapies, most addicts relapse to smoking and alcoholism, often due to the impact of drug-associated stimuli (cues) on craving and compulsive drug-seeking.

The first part of this thesis investigated the role of nAChRs in the effects of alcohol-associated as well as sucrose-associated cues on mesolimbic dopamine activity and/or behaviors related to drug-seeking (responding with conditioned reinforcement) in the rat. In the second part, *in vivo* microdialysis was utilized to characterize the ethanol-induced dopamine elevation in the rat nAc and the consequences thereon by subchronic pre-treatment with nicotinic drugs.

The data demonstrate that antagonism of ventral tegmental area (VTA) nAChRs abolishes the ethanol cue-induced dopamine elevations in the nAc and the conditioned reinforcing properties of ethanol cues. Moreover, nAChRs appear to mediate responding with conditioned reinforcement to sucrose. The results also indicate that the most important site of interference for ethanol-induced dopamine elevations is in the nAc, but that once the ethanol action is present in this brain region, ethanol may act also in the VTA to produce add-on effects. Furthermore, the decline in dopamine that is observed following the initial elevation after ethanol administration may be due to recruitment of dopamine inhibitory $GABA_A$ receptors in the nAc, as demonstrated by the ability of a $GABA_A$ antagonist to attenuate this effect. Pretreatment with a nicotinic drug abolished the dopamine declining phase.

We hypothesize a novel mechanism by which alcohol-associated cues stimulate mesolimbic dopamine activity and promote drug-seeking behavior by activation of VTA $\alpha3\beta2^*$ and/or $\alpha6^*$ nAChRs. Interestingly, the same nAChR subtypes were previously demonstrated to mediate the pharmacological effects of ethanol. This coincidence may play a critical role in the well known phenomenon of "loss of control" of drinking, a hallmark of alcoholism. Pharmacological manipulations of specific nAChR subtypes may thus be possible treatment strategies to prevent cue-induced relapse to alcoholism. The demonstration that nAChRs mediate responding with conditioned reinforcement also to sucrose, may explain the enhanced sugar intake associated with smoking cessation and alcohol abstinence.

The second part of the thesis suggests that recruitment of $GABA_A$-receptor activity is responsible for the second, declining phase with respect to nAc dopamine levels following ethanol administration and that pre-treatment with nicotinic drugs produces tolerance to this effect in the nAc and other brain regions. This phenomenon could be part of the explanation to why the sedative effects of ethanol are reduced in some nicotine users.

These results contribute with novel explanations for the common co-abuse of nicotine and alcohol and suggest specific nAChRs as potential targets for novel pharmacological interventions aimed at reducing cue-induced craving and relapse in alcoholism.

Key words: ethanol, nicotine, ventral tegmental area, nucleus accumbens, dopamine, nicotinic acetylcholine receptor, γ-amino-butyric acid receptor A, conditioned reinforcement, *in vivo* microdialysis, rat

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