

The role of taurine-related compounds on the effects of ethanol in the rat mesolimbic dopamine system

Akademisk avhandling

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Torsdagen den 30 januari 2025, klockan 9.00

av **Karin Ademar**

Fakultetsopponent: Professor **David Engblom**, Linköpings Universitet, Sverige

Avhandlingen baseras på följande delarbeten:

- I. **Ademar K**, Ulenius L, Loftén A, Söderpalm B, Adermark L, Ericson M. Separate mechanisms regulating accumbal taurine levels during baseline conditions and following ethanol exposure in the rat. *Scientific Reports* 2024 Sep 26;14(1):24166
- II. **Ademar K**, Adermark L, Söderpalm B, Ericson, M. Sodium acamprostate and calcium exert additive effects on nucleus accumbens dopamine in the rat. *Addiction Biology* 2022 Sep;27(5):e13224
- III. **Ademar K**, Loftén A, Nilsson M, Domi A, Adermark L, Söderpalm B, Ericson M. Acamprostate reduces ethanol intake in the rat by a combined action of different drug components. *Scientific Reports* 2023 Oct 19;13(1):17863
- IV. **Ademar K**, Danielsson K, Söderpalm B, Adermark L, Ericson M. The effects of sub-chronic calcium treatment on ethanol-induced dopamine elevation and the alcohol deprivation effect in the rat. *Submitted 2024*.

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The role of taurine-related compounds on the effects of ethanol in the rat mesolimbic dopamine system

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Abstract

Alcohol use disorder (AUD) is a major contributor to the global burden of disease. The reinforcing properties of alcohol involve enhanced dopamine activity in the nucleus accumbens (nAc), an important part of the mesolimbic dopamine system. For ethanol to induce accumbal dopamine elevation, a concomitant increase in endogenous taurine within the nAc appears to be required. However, the cellular origin of this ethanol-mediated increase in extracellular taurine levels remains unknown. Interestingly, one of the available treatments for AUD is a homotaurine derivative, acamprosate (Campral®; calcium-bis(*N*-acetylhomotaurinate)). Although it has been used for decades, the exact mechanisms underlying acamprosate's anti-relapse effects are still controversial and unknown. The overall aim of this thesis was not only to define neurobiological mechanisms contributing to the rewarding properties of ethanol, but also to identify novel targets for pharmacological treatments. To this end, *in vivo* microdialysis, combined with pharmacological, chemogenetic and metabolic approaches, and behavioral paradigms were performed in male Wistar rats. We demonstrate that the ethanol-induced elevation of extracellular taurine levels in the nAc was blocked by local administration of an L-type calcium channel antagonist and not prevented by inhibition of action potential firing, while specific manipulation of astrocytes did not affect the evoked release. Acamprosate elevated nAc dopamine levels in a glycine receptor-sensitive manner, possibly through a simultaneous taurine release. Moreover, co-administration of calcium and *N*-acetylhomotaurine produced an enhanced dopamine and taurine output compared to the drugs administered alone, suggesting that the two components act in concert on a neurochemical level and that both parts of acamprosate in fact are biologically active. The acute effect of a combination of calcium and *N*-acetylhomotaurine administration abolished the alcohol deprivation effect (ADE), while long-term treatment did not. Following acute and repeated calcium treatment, the same effects on ADE outcome were observed. Additionally, the dopamine-elevating properties of calcium were lost after sub-chronic calcium administration. Thus, tolerance development was evident in long-term calcium-treated rats. In conclusion, the results indicate that ethanol-induced taurine elevation may originate from neurons in an action-potential-independent manner. Furthermore, this thesis shows that both calcium and the *N*-acetylhomotaurine in acamprosate have important roles in the mechanism of action of the drug, while calcium appears prominent for the tolerance development previously observed for acamprosate. Even if tolerance development is observed, the results implicate an important role of calcium on the acute effects of ethanol, and that it may serve as a treatment supplement for some patients with AUD.

Keywords: Acamprosate, dopamine, ethanol, nucleus accumbens, taurine

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