Nicotine sensitization and the effects of extended withdrawal

- behavioral, neurochemical and electrophysiological studies in the rat

Akademisk avhandling

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Avhandlingen baseras på följande delarbeten:

I. **Morud J***, Adermark L*, Perez-Alcazar M, Ericson M, Söderpalm B. (2015). Nicotine produces chronic behavioral sensitization with changes in accumbal neurotransmission and increased sensitivity to re-exposure. *Addiction Biology,* 21(2):397-406

II. Adermark L**, Morud J**, Lotfi A, Jonsson S, Söderpalm B, Ericson M. (2015). Age-contingent influence over accumbal neurotransmission and the locomotor stimulatory response to acute and repeated administration of nicotine in Wistar rats. *Neuropharmacology,* 97:104-12

III. **Morud J**, Strandberg J, Andrén A, Ericson M, Söderpalm B, Adermark L. Extended nicotine withdrawal induces spontaneous disinhibition and alters accumbal neurotransmission. Submitted 2016.

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Abstract

Tobacco use is one of the primary factors for global burden of disease and often results in life-long nicotine addiction, only a small percentage users are able to maintain cessation. The life-long addiction together with a high relapse risk might be connected to drug-induced altered neural circuits. However, there is still uncertainty concerning the mechanisms involved in the progressive changes of neuronal function induced by repeated nicotine exposure. The rewarding effects of nicotine have been attributed to increased dopamine (DA) levels in the nucleus accumbens, (nAc) after stimulation of nicotinic acetylcholine receptors (nAChRs) in the ventral tegmental area (VTA). To explore long-term and age-dependent effects by nicotine, Wistar rats were exposed to nicotine daily for three weeks, followed by different withdrawal periods after which locomotor stimulatory effects and behavioral disinhibition were assessed by means of activity boxes and the elevated plus-maze, respectively. In addition, neurotransmission was studied in brain slices from the nAc utilizing field potential recordings and whole-cell patch clamp. Histological procedures were also used for estimation of dendritic spine density. The results show that nicotine-induced locomotor sensitization is sustained for up to seven months, concomitant with decreased synaptic function in nAc and increased response to the dopamine D2 receptor agonist quinpirole in nAc shell. We demonstrate that young animals display a faster response to nicotine and rapid tolerance development to the rearing depressing effect of nicotine. In addition, young animals exhibited lowered accumbal synaptic activity ten days into withdrawal. Moreover, nicotine induces behavioral disinhibition that is not fully developed until three months into withdrawal. These behavioral effects develop in parallel with changes in accumbal synaptic activity, GABAergic transmission and spine density. In addition, gene expression of $GABA_A$ receptor subunits is altered at this time point. Finally, we show that local manipulation of GABAergic transmission in the nAc in drug naïve rats results in disinhibitory behavior. In conclusion, limited exposure to nicotine causes long lasting to chronic alterations in behavior and accumbal neurotransmission. In particular the response to dopaminergic and GABAergic acting drugs is not fully developed until after extended abstinence.

Keywords: Abstinence, dopamine, elevated plus-maze, GABA, inhibitory control, nucleus accumbens, sensitization

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