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# Dopaminergic Interference for Treatment of Schizophrenia and Alcohol Use Disorder

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Europa, Wallenberg Konferenscentrum, Medicinaregatan 20, fredagen den 17 juni, klockan 13:00

av

Klara Danielsson

Fakultetsopponent:

Göran Engberg, Professor

Karolinska Institutet, Sverige

**Avhandlingen baseras på följande delarbeten**

I. Söderpalm, B, **Danielsson, K**, de Bejczy, A, Adermark, L, Ericson, M. Combined administration of varenicline and bupropion produces additive effects on accumbal dopamine and abolishes the alcohol deprivation effect in rats. *Addiction Biology* 2020

II. **Danielsson, K**, Lagström, O, Ericson, M, Söderpalm, B, Adermark, L. Subregion-specific effects on striatal neurotransmission and dopamine-signaling by acute and repeated amphetamine exposure. *Neuropharmacology* 2021

III. **Danielsson, K**, Stomberg, R, Adermark, L, Ericson, M, Söderpalm, B. Differential dopamine release by psychosis-generating and non-psychosis-generating addictive substances in the nucleus accumbens and dorsomedial striatum. *Translational Psychiatry* 2021

IV. **Danielsson, K**, Stomberg, R, Adermark, L, Ericson, M, Söderpalm, B. Sub-region-specific modulation of striatal dopamine in Wistar rats. *Manuscript*

**SAHLGRENSKA AKADEMIN**
**INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI**

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# Dopaminergic Interference for Treatment of Schizophrenia and Alcohol Use Disorder

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**Abstract**

The neurotransmitter dopamine is involved in several different physiological functions as well as pathological conditions. Two conditions that have been suggested to be related to a low dopaminergic tone in the ventral striatum are substance use disorder, and negative symptoms in schizophrenia, both of which are difficult to treat. In this thesis we aim to investigate the possibility of selectively elevating dopamine in the ventral striatum (nucleus accumbens, nAc) in a rat model. To this end, we utilize use *in vivo* microdialyisis to sample and analyse extracellular dopamine, *ex vivo* electrophysiological field potential recordings to analyse effects on primarily excitatory neurotransmission, as well as behavioural methods to study ethanol consumption and behavioural sensitisation. In paper I, we show that the combination of the smoking cessation agent varenicline and the anti-depressant bupropion has an additive effect on nAc dopamine, and eliminates the alcohol deprivation effect in an ethanol consumption study. In paper II, we showcased the effects of protracted amphetamine treatment on both ventral and dorsal striatal (dorsomedial striatum, DMS) dopaminergic signalling using. Results show that the nAc appears more sensitive to both acute and sustained amphetamine challenge. In paper III, we investigated the effects of psychosis-generating and non-psychosis-generating addictive substances with regards of their effect on nAc and DMS dopamine. Key findings showed a distinct difference between amphetamine and cocaine, both strongly pro-psychotic, and nicotine, which has low psychosis-generating potential. Whereas amphetamine and cocaine both produces robust and similar elevations in dopamine in both the nAc and DMS, nicotine only had a noticeable effect in the nAc. In paper IV, findings from previous papers were combined in an effort to propose a way to selectively elevate dopamine in the nAc, without affecting DMS dopamine. We show that combining ethanol and nicotine does produce an additive effect on nAc dopamine, with no marked interference on DMS dopamine, findings that we could then reproduce using varenicline and the glycine transport inhibitor OR 24598.

**Keywords**: Dopamine, striatum, addiction, schizophrenia

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