

# Cognitive dysfunction studied in animal models of schizophrenia

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This thesis is based on the following papers:

- I. Habituation of acoustic startle is disrupted by psychotomimetic drugs: differential dependence on dopaminergic and nitric oxide modulatory mechanisms. Klamer D, Pålsson E, Revesz A, Engel JA, Svensson L. *Psychopharmacology* 2004 Nov;176(3-4):440-50
- II. The effects of phencyclidine on latent inhibition in taste aversion conditioning: differential effects of preexposure and conditioning. Pålsson E, Klamer D, Wass C, Archer T, Engel JA, Svensson L. *Behavioural Brain Research* 2005 Feb 10;157(1):139-46.
- III. Antagonism of the nitric oxide synthase inhibitor, L-NAME, of the effects of phencyclidine on latent inhibition in taste aversion conditioning. Klamer D, Pålsson E, Wass C, Archer T, Engel JA, Svensson L. *Behavioural Brain Research* 2005 Jun 3;161(1):60-8.
- IV. The amino acid, L-lysine, blocks the disruptive effect of phencyclidine on prepulse inhibition in mice. Pålsson E, Fejgin K, Wass C, Engel JA, Svensson L, Klamer D. Manuscript.



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## Abstract

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Cognitive dysfunction is considered a core deficit of schizophrenia, which currently lacks effective pharmacological treatment. In order to identify novel and more effective drug treatments, translational experimental animal models of cognitive dysfunction are required. Schizophrenia-like symptoms can be induced in humans by phencyclidine (PCP). PCP also induces schizophrenia-like behavioural changes in experimental animals and several of these effects can be ameliorated by pretreatment with nitric oxide (NO) synthase inhibitors. This suggests an important role of NO in the effects of PCP. The general aim of the present thesis was to further investigate the effects of PCP, and the role of NO in these effects, in translational experimental animal models of cognitive dysfunction. Three behavioural models in rodents with relevance to schizophrenia were used. Pre-attentive information processing and non-associative learning were studied using the prepulse inhibition and habituation of the acoustic startle response models respectively. Additionally, selective attention was investigated using latent inhibition in taste aversion conditioning. Systemic administration of PCP to mice caused a deficit in habituation of the acoustic startle response. This effect of PCP was attenuated by pretreatment with the NO synthase inhibitor NG-nitro-L-arginine methyl ester (L-NAME). Furthermore, systemic administration of PCP potentiated latent inhibition in taste aversion conditioning. This effect could be normalized by pretreatment with L-NAME. Finally, acute and sub-chronic inhibition of NO synthase substrate (L-arginine) availability, using the amino acid L-lysine, attenuated the deficit in prepulse inhibition induced by PCP. In the present thesis PCP was shown to induce deficits in three translational animal models of cognitive dysfunction associated with schizophrenia. Additionally, blocking NO production ameliorated the deficits induced by PCP. These findings lend further support to the notion that drugs targeting central NO production could be of therapeutic value in the treatment of cognitive dysfunction in schizophrenia. In addition, they indicate that L-arginine availability may be an important regulatory mechanism of NO production in the brain.

*Key words:* phencyclidine, nitric oxide, prepulse inhibition, habituation, latent inhibition, NMDA receptor, rat, mouse, schizophrenia, cognition

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