Cognition and social behaviour in schizophrenia

An animal model investigating the potential role of nitric oxide

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This thesis is based on the following papers:

I. Effects of phencyclidine on spatial learning and memory: Nitric oxide-dependent mechanisms. Wass C, Arher T, Palsson E, Fejgin K, Klamer D, Engel J. A. & Svensson L. Behavioural Brain Research 2006 Jul 15; 171(1): 147-53

II. Phencyclidine affects memory in a nitric oxide-dependent manner: Working and reference memory. Wass C, Arher T, Palsson E, Fejgin K, Alexandersson A, Klamer D, Engel J. A. & Svensson L. Behavioural Brain Research 2006 Nov 1; 174(1):49-55

III. Effects of phencyclidine on cognitive load: Targeting the nitric oxide system. Wass C, Svensson L, Fejgin K, Palsson E, Arher T, Engel JA & Klamer D. Submitted.

IV. The importance of nitric oxide in social dysfunction. Wass C, Fejgin K, Palsson E, Engel JA, Arher T, Svensson L & Klamer D. Manuscript.

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Abstract

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Cognitive deficits are the single strongest predictor of functional outcome in patients with schizophrenia. Furthermore, these deficits are not satisfactorily alleviated by available antipsychotic treatment. Functional outcome is also dependent upon social functioning and patients with schizophrenia display social dysfunctions including specific impairment in social cognition. Thus, cognitive deficits and social dysfunctions make up core symptoms of schizophrenia that needs to be further investigated in order to find novel treatment targets. Phencyclidine (PCP) is a psychotomimetic compound that produces symptoms in humans that closely resemble schizophrenia. Consequently, the PCP-model is consistently used for studying schizophrenia in experimental animals. Previous studies from our lab demonstrate that PCP-induced deficits in several translational animal models of schizophrenia can be blocked by inhibition of nitric oxide (NO) production. Such PCP-induced deficits range from impairment in pre-cognitive (pre-attentive) sensory information processing and habituation of acoustic startle to selective attention. In addition, several clinical studies indicate that the NO-signalling pathway may be involved in the pathophysiology of schizophrenia. The overall aim of this thesis was to investigate the effects of PCP and NO synthase (NOS) inhibition on higher order cognitive functions, i.e. memory, and social interaction. Therefore, we investigated the effects of PCP and the NOS-inhibitor, N^G-nitro-L-arginine methyl ester (L-NAME) on; (1) spatial learning, working memory, long-term memory, and cognitive flexibility using different versions of the Morris water maze, and (2) social function and memory using a social interaction paradigm. The results demonstrate that acute PCP-treatment impaired spatial learning, working memory, long-term memory, and cognitive flexibility in rats. These PCP-induce deficits were normalized by pretreatment with the NOS-inhibitor, L-NAME. Furthermore, PCP-treatment decreased time spent in social interaction, a deficit that was independent of motor activity and frequency of interactions. This social interaction deficit was blocked by NOS-inhibition. Taken together these results suggest that the effects of PCP, on cognitive functioning and social interaction, depend on the NO-signalling system. In addition, several studies from our research group show that systemic PCP-treatment in fact seems to increase NO production in the rodent brain. Based on these findings, in addition to the results from this thesis, we propose a "NO-dysregulation hypothesis for schizophrenia". Moreover, this hypothesis suggests that the NO-signalling pathway may be a potential new treatment target for schizophrenia.

Key words: schizophrenia, cognition, memory, Morris water maze, social function, social interaction, phencyclidine, nitric oxide, L-NAME, rat.

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