THE PREFRONTAL CORTEX AND INFORMATION PROCESSING:

NITRIC OXIDE SIGNALING STUDIED IN AN ANIMAL MODEL OF SCHIZOPHRENIA

Akademisk avhandling
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av
Kim Fejgin
Fakultetsopponent: Professor Leif Lindström
Institutionen för Neurovetenskap, Akademiska sjukhuset, Uppsala

Avhandlingen baseras på följande delarbeten:

I. Pålsson E, **Fejgin K**, Wass C, Engel JA, Svensson L, Klamer D (2007). The amino acid L-lysine blocks the disruptive effect of phencyclidine on prepulse inhibition in mice. *Psychopharmacology (Berl) 192(1): 9-15.*

II. **Fejgin K**, Pålsson E, Wass C, Svensson L, Klamer D (2008). Nitric oxide signaling in the medial prefrontal cortex is involved in the biochemical and behavioral effects of phencyclidine. *Neuropsychopharmacology 33(8): 1874-1883.*

III. Pålsson E*, Finnerty N*, **Fejgin K*,** Klamer D, Wass C, Svensson L, Lowry J. Increased cortical nitric oxide release after phencyclidine administration. *Under revision*

IV. **Fejgin K*,** Pålsson E*, Wass C, Finnerty N, Lowry J, Klamer D. Prefrontal $GABA_B$ receptor activation attenuates phencyclidine-induced impairments of prepulse inhibition: Involvement of nitric oxide. *Under revision*

UNIVERSITY OF GOTHENBURG

ABSTRACT

The prefrontal cortex and information processing:
nitric oxide signaling studied in an animal model of schizophrenia

The prefrontal cortex has been extensively linked to several cognitive domains that are severely compromised in schizophrenia. It has therefore become a key region for studies on the disabling cognitive dysfunction commonly observed in patients with schizophrenia. The absence of effective treatment options for cognitive deficits makes the identification of novel drug targets urgent, and this search is largely dependent on validated animal models. Administration of the NMDA receptor antagonist phencyclidine (PCP) has proven effective in mimicking several features of schizophrenia, including disrupted information processing and aberrant prefrontal cortex function. Previous studies show that a range of cognition-related behavioral deficits induced by PCP in experimental animals, including impaired pre-attentive information processing as measured by prepulse inhibition (PPI), can be blocked by inhibiting the production of nitric oxide (NO). The aim of the present thesis was to study the role of prefrontal NO signaling in the effects of PCP on information processing. Measurements of NO and its main effector, cGMP, were performed using *in vivo* voltammetry and microdialysis. This was combined with PPI and locomotor activity studies following pharmacological modulation of NO and GABA signaling. Systemic administration of PCP to mice disrupted PPI, which was blocked in a dose-dependent manner by inhibiting substrate availability for NO synthase using L-lysine, and by microinjections of an inhibitor of cGMP synthesis into the mouse medial prefrontal cortex. Furthermore, PCP caused an increase in prefrontal cGMP levels that was blocked by the NO synthase inhibitor, L-NAME. Similarly, prefrontal NO release, as measured by a novel microelectrochemical sensor, was increased by PCP, and this increase was blocked by pretreatment with L-NAME in the rat. Finally, systemic pretreatment with a combination of sub-threshold doses of the $GABA_B$ agonist baclofen, and L-NAME, increased PPI *per se*, and prevented the effects of PCP on PPI. On a regional level, prefrontal microinjections with baclofen fully blocked the effects of PCP on PPI in mice, and NO levels in the rat prefrontal cortex were decreased following systemic baclofen administration. In conclusion, the present thesis presents biochemical and behavioral support for the involvement of a prefrontal NO/cGMP signaling pathway in the effects of PCP. Furthermore, this mechanism may partly be explained by a decrease in inhibitory power of GABAergic interneurons, followed by increased NO signaling in the prefrontal cortex. Thus, studies of GABA/NO interactions in the prefrontal cortex may prove valuable when searching for novel treatment targets for cognitive dysfunction in schizophrenia.

Keywords: schizophrenia, nitric oxide, prepulse inhibition, phencyclidine, prefrontal cortex, cGMP, baclofen, cognition

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