MASTER THESIS PROJECT

The role of nitric oxide in pharmacological animal models of schizophrenia

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Rationale

Schizophrenia is a severely debilitating brain disorder that poses a serious healthcare problem worldwide. Recent theories concerning the pathophysiology of schizophrenia stress the importance of the cognitive impairment associated with the disorder. These impairments span a number of cognitive domains and impact on the social and professional life of patients with schizophrenia (Green et al. 2004). Furthermore, cognitive dysfunctions do not generally respond well to treatment with traditional antipsychotics and consequently, novel treatment options are needed.

To find new treatments and to better understand the underlying pathophysiology of schizophrenia, several methods to model schizophrenia in humans and experimental animals have been developed. Pharmacological challenge with phencyclidine (PCP) has been shown to produce a psychotic condition in humans that encompasses all symptoms of schizophrenia (Javitt 2007), including cognitive deficits. This model of schizophrenia has proved to be a valuable tool to increase our knowledge of this brain disorder.

We, and others, have demonstrated that PCP induces deficits in a number of cognitive functions that are similarly impaired in patients with schizophrenia (Johansson et al. 1997; Klamer et al. 2001; Wiley 1998; Klamer et al. 2004c; Palsson et al. 2004; Wass et al. 2006b; Wass et al. 2006a). These cognitive dysfunctions can all be normalized by inhibition of nitric oxide (NO) synthase, as demonstrated by our original preclinical findings at University of Gothenburg (Klamer et al. 2001; 2004a; b; Klamer et al. 2005a; Klamer et al. 2004c; Klamer et al. 2005b; Wass et al. 2006a; Wass et al. 2006b).

NO is pleiotropic signalling molecule that can act as a neuromodulator in the brain. Accumulating clinical data also suggest that NO may play a role in schizophrenia pathophysiology (for a review see Bernstein et al. 2005). Additional evidence has been derived from the observations that methylene blue, which blocks NO synthase and NO-dependent soluble guanylyl cyclase-mediated intracellular signalling, shows a certain efficacy as an adjuvant to established antipsychotics in the treatment for schizophrenia (Deutsch et al. 1997) and attenuates PCP-induced behavioural effects in mice (Klamer et al. 2004a).

As discussed above, it is plausible that alterations in NO production may play an important role in the schizophrenia-like behavioural effects of PCP and in the pathophysiology of the disorder. However, direct evidence for such an interaction requires monitoring of in vivo NO levels which has been a difficult technical hurdle, as NO is a gaseous signalling molecule with a half-life of only a few seconds. Presently, Professor John Lowry’s research group at National University of Ireland, Maynooth has developed microelectrochemical sensors, which represent a completely new concept for the determination of NO in living tissue. The direct measurement, in real time, of NO levels in the brain of freely moving animals represents a potentially ground breaking methodological achievement. NO has been implicated in e.g. drug dependence, regulation of food intake and neurodegenerative processes in the brain which means that once established, this methodology may be a valuable tool in a number of research areas.

The aim of this project will be to use in vivo voltammetry to further study the role of NO in schizophrenia. This will answer important questions regarding the role of NO in the pathophysiology of schizophrenia as well as the potential of the NO signalling pathway as a target for novel pharmacological treatments for schizophrenia.

Work plan

The work plan is preliminary and may be subject to change prior to project start.

The project will compare the effect of 4 psychosis-inducing drugs that are used to model aspects of schizophrenia symptomatology in experimental animals, on NO levels in the medial prefrontal cortex and nucleus accumbens.

The experimental outline is as follows.
1. Surgical implantation of NO sensors into the prefrontal cortex and nucleus accumbens in rats.
2. Following recovery after surgery, NO will be monitored using an in vivo voltammetry unit following administration of saline or different doses of psychotomimetic agents.
The experiment will include 4 different treatment groups
A) saline, PCP (1, 2 and 4 mg/kg)
B) saline, MK-801 (0.05, 0.1 and 0.2 mg/kg)
C) saline, ketamine (5, 10 and 20 mg/kg)
D) saline, amphetamine (0.5, 1 and 2 mg/kg)

Animals will be randomized to the different treatment groups and the animal will receive all doses of the treatment in a balanced cross-over design with a 2 day wash-out period between administrations.

The project involves the following experimental procedures (training in these techniques will be provided)
- Handling of rats and subcutaneous injections
- Stereotaxic surgery and sensor implantation
- Basic voltammetry methodology

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References