Cognitive function studied in animal models of schizophrenia

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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 pre-treatment 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 pre-treatment 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 pre-treatment with L-NAME. Finally, acute and sub-chronic inhibition of NO 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

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals;

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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LIST OF ABBREVIATIONS

AMPA	α-amino-3-hydroxy-5-methyl-4-isoaxole propionic acid
ASR	Acoustic startle response
cAMP	Cyclic adenosine monophosphate
CAT	Cationic amino acid transporter
CER	Conditioned emotional response
cGMP	Cyclic guanosine monophosphate
CS	Conditioned stimulus
CSF	Cerebrospinal fluid
CTA	Conditioned taste aversion
d-AMP	d-amphetamine
eNOS	Endothelial nitric oxide synthase
GTP	Guanosine triphosphate
i.p.	Intraperitoneally
iNOS	Inducible nitric oxide synthase
LI	Latent inhibition
L-NAME	N^G-nitro-L-arginine methyl ester
LTP	Long-term potentiation
NAC	Nucleus accumbens
PFC	Prefrontal cortex
NMDA	N-methyl-D-aspartic acid
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
NOS	Nitric oxide synthase
NPE	Non-preexposed
PCP	Phencyclidine
PE	Preexposed
PET	Positron emission tomography
PPI	Prepulse inhibition
s.c.	Subcutaneously
sGC	Soluble guanylyl cyclase
US	Unconditioned stimulus

BACKGROUND

Schizophrenia

When the 20th century was still young Eugene Bleuler renamed the disease then known as dementia praecox, a term introduced by Emil Kraepelin. Bleuler chose to call the disorder schizophrenia, from the Greek words schizo (split) and phreno (mind), as it appeared to him that the key feature of the disease was a shattered mind (Bleuler 1911). Now, almost a century later science is still struggling to solve the puzzle of schizophrenia. More importantly, approximately 1% of the people in the world, irrespective of gender, class or ethnic background (Jablensky et al. 1992), are struggling to cope with an illness that in ways lacks an effective treatment. Although the individual prognosis varies many patients face a lifetime of disability, stricken in the prime of life as schizophrenia usually manifests during young adulthood. Furthermore, around 10% of afflicted individuals will take their own life as a result of the disorder (Tandon 2005).

Since no biological marker for schizophrenia has yet been found, diagnosis is based on the assessment of the symptoms of each patient. Over the years criterion based diagnostic instruments have been developed to aid clinicians. One of the most widely used is the fourth edition of the American Psychiatric Association's Diagnostic and Statistic Manual (DSM-IV). In this diagnostic definition of schizophrenia, symptoms are divided into two main categories: positive and negative symptoms. The third category of cognitive deficits is recognized although not considered characteristic for diagnostic purposes. The positive symptoms are episodic in nature and associated with acute psychosis; they include hallucinations, delusions, disorganized speech and behaviour. Negative symptoms generally represent a loss of function and include social withdrawal, slowness of thinking and movement, emotional blunting and lack of drive. Both the negative symptoms and cognitive deficits are aspects of schizophrenia that are associated with the chronic state of the disorder. Generally, the specific symptomatology of schizophrenia varies significantly between patients and this heterogeneity complicates both diagnosis and research questions.

Recent years have seen a shift in schizophrenia research towards recognizing cognitive dysfunction as a core deficit of schizophrenia. Consequently, a large body of research is now aimed at delineating the neurobiology of the cognitive deficits associated with schizophrenia. The cognitive deficits associated with schizophrenia span a number of cognitive domains, including abstraction, verbal memory, attention, working memory and executive functions (Andreasen 1995; Häfner and an der Heiden 2003), and are often quite pronounced with patients scoring more than one standard deviation lower than control subjects on cognitive tasks (Keefe et al. 2005). Importantly, cognitive functionality has been shown to

be a predictor of community outcome in both cross-sectional (Green 1996; Green et al. 2000) and longitudinal studies (Green et al. 2004). However, the specific cognitive deficits associated with schizophrenia vary substantially within the patient population (Fioravanti et al. 2005). A number of neurological signs and subtle cognitive deficits have been found in children who were later to develop schizophrenia (Ellison et al. 1998). Similarly, mild cognitive dysfunction and psychomotor abnormalities have been demonstrated in relatives to schizophrenic patients implying that the cognitive impairment is more than a reflection of a poor functionality as a result of other symptoms (Flyckt et al. 2000; Heydebrand 2006; Sitskoorn et al. 2004). It has been suggested that cognitive deficits could represent endophenotypes of schizophrenia but so far no pathognomonic deficit has been identified. Although present during the prodromal stage, the level of cognitive impairment seems to markedly worsen as the patient progresses to the fully manifested disorder (Lencz et al. 2006). However, further neuropsychological decline, as seen in neurodegenerative disorders, does not seem present in the general patient population (Heaton et al. 2001), although further studies are needed.

Schizophrenia hypotheses

It is widely accepted that the pathophysiology of schizophrenia is likely to be complex in nature. Not surprisingly, formulating a theoretical framework that can account for the observed heterogeneity has proved difficult. Two such models have recently been proposed, both of which suggest early disturbances in the development of the central nervous system (Glenthoj and Hemmingsen 1997; Lieberman et al. 1997; Weinberger 1987). These disturbances are proposed to give rise to a dysfunction of the glutamate system, compromising communication between cortical and sub-cortical structures. Later, this defiency in neural modulatory capacity and rigidity in neural circuitry leads to a dysbalance of the dopamine system during adolescence and manifestation of psychotic symptoms. In addition a framework encompassing neurodevelopmental abnormalities and dysfunctions in information processing has been put forward (Braff 1993). Broadly, abnormal neurodevelopmental processes are proposed to lead to dysfunction of neural circuits and neurotransmitter systems. In a domino effect, these dysfunctions lead to an impaired information processing, cognitive dysfunction and overt psychotic symptoms (Andreasen 2000).
Models such as these are still incomplete but if schizophrenia is ever to be fully understood they must be formulated and tested as it is painstakingly clear that there is no magic bullet that will solve the enigma of schizophrenia in one well-aimed shot.

DOPAMINE AND SCHIZOPHRENIA

Dopamine remains the neurotransmitter most strongly associated with schizophrenia. Arvid Carlsson and co-workers first described the role of dopamine as a messenger molecule in the central nervous system in the late 1950s (Carlsson et al. 1957; Carlsson et al. 1958). Dopamine exerts its action through five different dopamine receptors that are G-protein coupled and modulate the activity of adenylyl cyclase and its second messenger cyclic adenosine triphosphate (cAMP). The D_1 and D_5 receptors stimulate while the D_2, D_3 and D_4 receptors inhibit adenylyl cyclase (Garau et al. 1978; Gingrich and Caron 1993; Kebabian and Calne 1979; Kebabian and Greengard 1971).
During the last fifty years dopamine has been implicated in a number of physiological processes *e.g.* motor control, reward mechanisms and cognition but also in pathophysiologial conditions such as Parkinson's disease (Carlsson 1959; Ehringer and Hornykiewicz 1960), drug abuse (Engel 1977; Engel et al. 1992; Koob 1992; Wise 1996) and schizophrenia (Carlsson and Lindqvist 1963; Seeman et al. 1976).

The link between dopamine and schizophrenia rests heavily on the fact that all antipsychotic drugs with proven clinical effect block dopamine receptors and there is a correlation between clinical potency and affinity for the D_2 receptor among these drugs (Nordstrom et al. 1993; Seeman et al. 1976). In addition the dopamine releasing agent d-amphetamine (d-AMP) can induce a paranoid psychosis in healthy individuals (Angrist and Gershon 1970; Randrup and Munkvad 1967) as well as an exaggerated dopamine response in drug free schizophrenic patients (Breier et al. 1997; Laruelle et al. 1996). This heightened dopamine response exacerbates positive but not negative symptoms, an effect likely due to an increased D_2 receptor stimulation (Breier et al. 1997; Laruelle et al. 1996). This selective effect on positive symptoms indicates that increased dopaminergic activity cannot be the only neurochemical substrate of schizophrenia as was originally suggested (Keefe et al. 1999). Both negative symptoms and cognitive deficits have been related to the prefrontal cortex (PFC), a brain region that has been shown to be hypoactive in schizophrenic patients (see general discussion). Since the PFC receives significant dopaminergic input, it was hypothesized that instead of dopamine hyperactivity this region would suffer from dopamine hypoactivity in schizophrenic patients. This would lead to a reduced stimulation of D_1 receptors, the predominant form of dopamine receptor in the frontal cortex (Goldman-Rakic et al. 2000; Goldman-Rakic and Selemon 1997; Jentsch et al. 1997b; Jentsch et al. 1999b). Furthermore, it has been demonstrated that reduced prefrontal activity leads to increased striatal dopaminergic transmission in schizophrenic patients (Meyer-Lindenberg et al. 2002).
Thus the predominant view today is that schizophrenia is associated with an imbalance in the dopamine system that ultimately results in a heightened reactivity in mesolimbic dopamine neurons, associated with an increased D_2 receptor stimulation and positive symptoms, coupled with a reduced activity in the

dopamine neurons projecting to the frontal cortex, in turn associated with D_1 receptor hypostimulation and negative symptoms and cognitive dysfunction (Davis et al. 1991; Weinberger 1987).

GLUTAMATE AND SCHIZOPHRENIA

The association between dopamine and schizophrenia is supported by empirical data but whether a dysfunctional dopamine system is a primary causative factor in the pathophysiology of schizophrenia or rather a consequence of another dysfunction remains an open question. A prime candidate for another underlying dysfunction is the glutamate system. In the CNS, L-glutamate binds and activates four different types of receptors; α-amino-3-hydroxy-5-methyl-4-isoaxole propionic acid (AMPA), kainate, N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate receptors. The first three are ionotropic receptors that upon activation allow the passage of Na^+, Ca^{2+} and K^+ through the cell membrane while the metabotropic receptors are coupled to G-proteins and intracellular second messenger systems. The receptor type with the strongest association to schizophrenia is undoubtedly the NMDA receptor. It has been linked to long-term potentiation (LTP), a cellular process believed to be crucial in learning and memory, and possesses several interesting biophysical properties. In order to be activated it requires the simultaneous binding of L-glutamate and L-glycine or D-serine in conjunction with a depolarising event that will remove a Mg^{2+} that blocks the channel at resting potentials. Activation will lead to an influx of Ca^{2+} and to a lesser extent Na^+ and K^+. It is also subject to regulation by Zn^{2+} and polyamines (Ozawa et al. 1998; Thornberg and Saklad 1996). Constituting part of the neurochemical backbone of the central nervous system, the NMDA receptor is located throughout the brain with the highest densities in the frontal cortex, hippocampus and nucleus accumbens (NAC) (Monaghan and Cotman 1985).

In the 1950s an effective yet troublesome anaesthetic agent called phencyclidine (PCP, "angel dust") was briefly introduced. The trouble lay in the unpleasant psychic side effects of the drug and its use was soon discontinued. However, PCP re-emerged as a recreational drug in certain social strata. A number of such users were admitted to psychiatric clinics diagnosed with schizophrenia. Clinical studies confirmed that PCP could induce a psychotic state very similar to schizophrenia in healthy individuals (Allen and Young 1978; Luby et al. 1959; Pearlson 1981; Yesavage and Freman 1978) and when given to schizophrenic patients it exacerbated their symptoms (Itil et al. 1967). It was suggested that the pharmacological effects of PCP were mediated by its non-competitive inhibition of the NMDA receptor and this hinted at a possible hypoglutamatergic mechanism in the pathophysiology of schizophrenia (Javitt and Zukin 1991; Lodge and Anis 1982). Later, the PCP-analogue ketamine was also reported to produce symptoms in healthy volunteers that resemble those seen in schizophrenia as well as worsen aspects of the disorder in schizophrenic patients

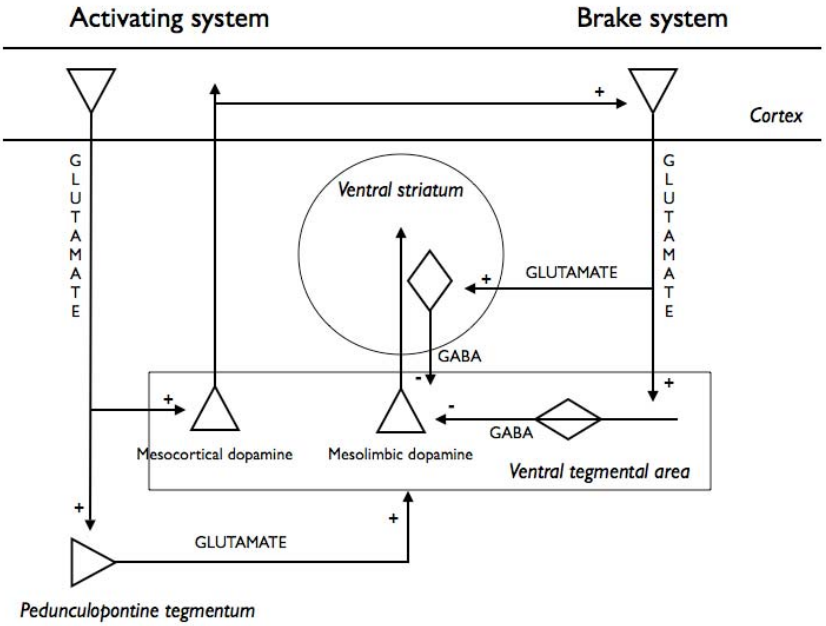
(Abi-Saab et al. 1998; Krystal et al. 2003; Krystal et al. 1994; Lahti et al. 1995). In agreement with the effects of PCP, a study by Kim and co-workers reported reduced levels of glutamate in the cerebrospinal fluid of schizophrenic patients (Kim et al. 1980). However, later studies could not replicate this finding (Gattaz et al. 1982; Perry 1982), although a post mortem study did show reduced levels of glutamate in the prefrontal and hippocampal regions of schizophrenic patients (Tsai et al. 1995). Interestingly, the endogenous NMDA receptor antagonist kynurenic acid has been shown to be elevated in CSF (cerebrospinal fluid) and post mortem brain samples of schizophrenic patients, further supporting an involvement of the glutamate system in the pathophysiology of schizophrenia (Erhardt et al. 2001; Nilsson et al. 2005; Schwarcz et al. 2001).
Additionally, it has been reported that glycine, the co-agonist of glutamate at the NMDA receptor, is lowered in plasma from schizophrenic patients (Sumiyoshi et al. 2004) and glycine or glycine site agonists have been tried as adjuvant treatment of schizophrenia in combination with antipsychotics with some success (Javitt 2006). Genetic studies have not shown any direct link between schizophrenia and the NMDA receptor but a number of genes that have been associated with schizophrenia *e.g.* Neuregulin 1, RGS4 and dysbindin, code for proteins that are known to interact with the NMDA receptor (Chowdari et al. 2002; Chumakov et al. 2002; Moghaddam 2003; Stefansson et al. 2003; Straub et al. 2002).

DOPAMINE AND GLUTAMATE

Interestingly, dopaminergic and glutamatergic neurons in the brain communicate extensively with each other. This ties in with a concept of schizophrenia as a neural circuits dysfunction disorder, emphasising the importance of communication between brain regions. In a model (figure 1) proposed by Carlsson and collaborators (1999b), the PFC modulates the activity of midbrain dopamine neurons via both an activating and an inhibitory pathway. The activating pathway consists of direct projections to midbrain dopaminergic neurons, which in turn, project back to the cortex, and indirect projections to mesolimbic dopamine neurons. The inhibitory pathway is indirect and involves GABAergic neurons. This dual modulation of PFC dopamine activity has been demonstrated in rodents (Jackson et al. 2001). Furthermore, it seems that there is glutamate mediated tonic inhibitory regulation of mesolimbic dopaminergic neurons and a concomitant excitatory regulation of mesoprefrontal dopaminergic neurons (Takahata and Moghaddam 2000). This neural circuit model predicts that a loss of NMDA receptor function in the PFC would result in a reduced activity in neurons projecting to the cortex as well as unpredictable effects on baseline activity in mesolimbic dopamine projections. However, the loss of glutamatergic regulatory activity would render the mesolimbic dopaminergic neurons more vulnerable to stressors. Or in other words, predispose them to dysfunction. This model is based mainly on rodent findings but does find some support in primate and human

studies (Laruelle et al. 2003) and illustrates the potential consequences of neural circuit dysfunctions in schizophrenia.

Figure 1. *Proposed model of modulation of dopaminergic activity by cortical projections (adapted from Laruelle et al, 2003).*



NEURODEVELOPMENT

The importance of genetic factors in the pathophysiology of schizophrenia is evident from twin and family studies and the heritability of schizophrenia is estimated to 70-85%. The genetic risk depends on the degree of biological relatedness, *i.e.* first-degree relatives of an affected individual have a higher risk of developing schizophrenia than do second-degree relatives (Lewis and Levitt 2002). Similarly, a monozygotic twin is at greater risk than a dizygotic twin. This genetic liability seems to be transmitted in a polygenic, non-Mendelian fashion. A number of loci as well as gene variants have been associated with schizophrenia (Norton et al. 2006). However, many such findings have not been replicated. Aside from methodological issues, one explanation to some of these non-replications may be that there are several pathogenetic paths that all terminate in a similar manifestation of symptoms. Thus, different patterns of genetic predisposition would be expected in different populations. Despite the high heritability, the concordance of schizophrenia among monozygotic twins is only about 50% (Lewis and Levitt 2002). This suggests that environmental factors play an

important role in the pathophysiology of schizophrenia. Indeed, a number of environmental factors that increase the risk of schizophrenia have been identified. These include, but are not limited to, maternal nutritional status, maternal infection, season of birth, urban birth and obstetrical complications (Dean and Murray 2005). Several of the identified risk factors are associated with pre- or perinatal life. Consequently, neurodevelopmental insults may be involved in the pathophysiology of schizophrenia. Associations between schizophrenia and genes involved in neurodevelopmental processes support this idea (Rapoport et al. 2005). The concept of neurodevelopmental pathology in schizophrenia is not new since already the work of *e.g.* Kraepelin and Bleuler, pointed out that premorbid signs of schizophrenia could be detected early in life. However, more specific conceptualizations of schizophrenia as a disorder of neurodevelopment appeared in the 1980s. Weinberger (1987) suggested that schizophrenia could involve a fixed brain lesion during brain development which remains silent until certain brain maturational events bring it "on line". Other investigators proposed that this was only applicable to a subset of individuals with schizophrenia (Murray et al. 1992). In contrast, Feinberg (1982) thought that the central pathogenic process was altered cortical synaptic pruning during adolescence. Thus, both early and late disturbances in neurodevelopment have been suggested to be involved in the pathophysiology of schizophrenia. However, these views can be united into single theory, suggesting that disturbances in both early and late processes in neurodevelopment interact in the pathophysiology of schizophrenia (Rapoport et al. 2005). These disturbances in turn, could be caused by an interaction of genetic predisposition and environmental factors. The exact mechanism by which subtle pre- or perinatal disturbances could interact with brain maturation during adolescence to generate the manifest disorder remains unknown. The identified genetic and environmental risk factors are small in effect size and an increased understanding of their interactions is likely needed in order to understand the role of neurodevelopment in schizophrenia.

Additionally, it should be noted that not only the dopaminergic and glutamatergic systems have been associated with schizophrenia. A number of other hypotheses on the pathophysiology of schizophrenia, that address the role of neurodevelopment and neuronal connectivity, have been proposed, see *e.g.* (Berger et al. 2006; Davis et al. 2003; Lewis et al. 2005).

Pharmacological treatment of schizophrenia

A major breakthrough in the treatment of schizophrenia came during the 1950s when chlorpromazine was introduced (Delay et al. 1952). In 1958 haloperidol was added as a treatment option for schizophrenia and it was five years later that Carlsson and Lindqvist (1963) suggested that chlorpromazine and haloperidol blocked central dopamine receptors and that this effect was responsible for the antipsychotic action of these agents. Since then, all novel antipsychotics introduced share the common denominator of being D_2 receptor blockers. PET

(positron emission tomography) studies indicate that a receptor occupancy of 70% is needed to induce an antipsychotic effect (Wiesel 1994). This type of treatment has been found to reduce symptom severity in many patients, although a significant population are non-responders. Specifically, positive symptoms are greatly alleviated while negative symptoms and cognitive deficits are relatively unaffected. Antipsychotic drugs are usually divided into two categories: first-generation (typical) and second-generation (atypical) antipsychotics. First-generation compounds, *e.g.* haloperidol and chlorpromazine, are distinguished by a highly potent D_2 receptor antagonism and a propensity to cause extrapyramidal side effects and dysphoria (Farde et al. 1992; Lewander 1994). The introduction of clozapine gave birth to the term atypical antipsychotics. PET studies indicate that clozapine exerts an antipsychotic effect at a D_2 receptor occupancy of around 50% (Farde et al. 1994). This may explain the reduced propensity of clozapine to cause extrapyramidal side effects. Clozapine has been suggested to be more effective in treatment refractory patients and in treating negative symptoms and certain cognitive deficits (Lieberman 1996). Apart from its D_2 receptor antagonism, clozapine also shows a high affinity for a number of other receptors, *e.g.* adrenergic and serotonergic receptors, which are thought to contribute to the clinical profile of clozapine (Marcus 2005). A number of other second-generation compounds have been introduced since clozapine. They generally cause less extrapyramidal side effects but are prone to cause hyperprolactinemia and weight gain. Their binding profile for non-D_2 receptors vary and it remains unclear how non-D_2 receptor interactions may contribute to clinical effect.

Recently, a novel second-generation antipsychotic, aripiprazole, was introduced. Aripiprazole is a partial dopamine receptor agonist (Tamminga and Carlsson 2002) and its receptor binding profile is suggested to normalize both hyper- and hypo-dopaminergic states, but whether this is actually the case in the clinical setting is uncertain. Aripiprazole binds to several receptor types and to date most data would indicate a similar efficacy as other compounds and that any advantage would be in tolerability (Christensen et al. 2006; Kasper et al. 2003; Pigott et al. 2003). This is not to be belittled, but after more than 50 years of drug development no novel rationale for the treatment of schizophrenia has been successfully introduced in the clinic. Consequently, there is considerable room for improvement, especially when it comes to treatment of negative and cognitive symptomatology (Hagan and Jones 2005).

Deficits in pre-attentive information processing and selective attention

As already described there have been a number of attempts to outline a unified theory explaining the symptoms manifested in schizophrenic patients. The experiments presented within these pages have been especially influenced a hypothesis suggesting that impairments in pre-attentive filtering, *i.e.* the

preconscious processing of external and internal stimuli, and attention may constitute core deficits of schizophrenia. A relative inability to filter or gate information could result in sensory flooding and a subsequent cognitive fragmentation. The breakdown of basal cognitive mechanisms would spill over and lead to a deterioration of higher order cognitive functions producing the manifested symptoms of schizophrenia (Braff et al. 1978; Braff 1993; Freedman et al. 1987; McGhie and Chapman 1961).

Animal models of schizophrenia

The pivotal question could be put like this: Animals do not become schizophrenic, how then can the study of them tell us anything about a disorder that seems so uniquely human? It is true that animal models cannot fully mimic the complexity nor manifest all the symptoms of schizophrenia. However if the disorder can be disassembled into mechanisms like a sensitized mesolimbic dopamine system or a deficit in information processing, animal models can provide considerable information. More generally, animal models remain a necessity to 1) test theories of the disorder 2) uncover pathophysiological mechanisms and 3) develop new treatment strategies. Naturally, the potential as well as the shortcomings of every animal model must be kept in mind when one studies a multi-faceted reality. One way to address this issue is to evaluate the construct, face and predictive validity of a model.

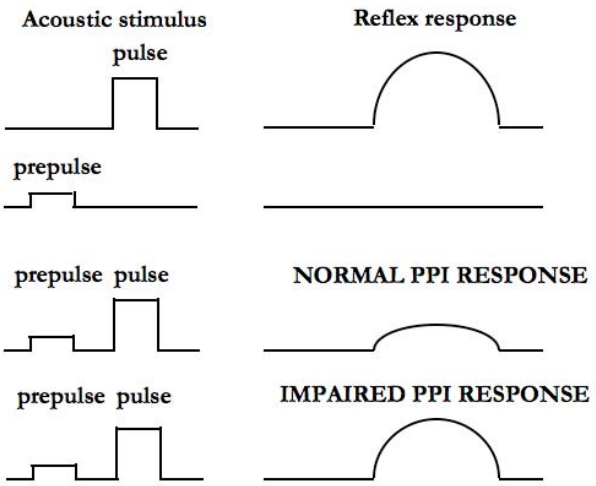
Animal models of psychiatric disorders can be classified as having construct-, face-, or predictive validity (Willner 1984)

Construct validity	Similar underlying neurophysiological concept
Face validity	Similar endpoint measurements in clinical and experimental models
Predictive validity	Similar pharmacological profile in clinical and experimental studies

When modelling schizophrenia in an experimental animal at least two things should be considered. Firstly, brain function must be altered to resemble schizophrenia pathophysiology. This can be accomplished using *e.g.* acute or chronic administration of psychotomimetic drugs, interference with neurodevelopmental processes and genetic manipulation. Secondly at least one measurable parameter related to schizophrenia is needed. This thesis will focus on the PCP model and the behavioural parameters of prepulse inhibition (PPI) of the acoustic startle response (ASR), habituation of the ASR and latent inhibition (LI). However, the reader should be aware that a number of other approaches are available when using animal models to study schizophrenia.

Pre-attentive sensory information processing can be assessed by the PPI of the ASR paradigm. PPI is defined as the reduction in reflex response to an intense stimulus when this stimulus is immediately preceded (30-500 ms) by a weaker prestimulus (Graham 1975; Hoffman and Ison 1980). The prestimulus, set to an intensity low enough as not to elicit a measurable startle response by itself, evokes a short lasting inhibitory process in the brain which is manifested by the attenuated response to the following more intense stimulus (figure 2).

Figure 2. *Schematic drawing showing normal and impaired prepulse inhibition of the acoustic startle response.*



Human studies

PPI is readily observed in humans (Graham 1975) and provides a means to quantify complex sensorimotor gating processes in the brain. In 1978 Braff and colleagues showed that PPI was disrupted in schizophrenic patients (Braff et al. 1978), *i.e.* patients displayed lower levels of PPI -interpreted as a less efficient gating mechanism- than control subjects. These findings have been replicated a number of times (Braff et al. 1992; Grillon et al. 1992; Kumari et al. 2000; Parwani et al. 2000; Weike et al. 2000) and extended to include studies of drug-naïve patients (Ludewig et al. 2003a; Mackeprang et al. 2002). However, an impaired PPI response is not pathognomonic to schizophrenia as this deficit is also found in other brain disorders, *e.g.* obsessive-compulsive disorder (Swerdlow et al. 1993), Huntington's disease (Swerdlow et al. 1995), Tourette's syndrome and attention deficit hyperactivity disorder (Castellanos et al. 1996).
The effects of antipsychotic medication on PPI deficits in schizophrenic patients have been studied extensively. Unfortunately, the results are not entirely uniform.

A number of studies support a positive effect of antipsychotic medication on PPI deficits with a superior efficacy of second-generation antipsychotics (Kumari and Sharma 2002; Kumari et al. 1999; Leumann et al. 2002). However, there are studies that do not support these findings (Quednow et al. 2006; Weike et al. 2000). Interestingly, some studies demonstrate a significant improvement in symptom severity without a concomitant restoration of PPI (Duncan et al. 2003; Mackeprang et al. 2002; Parwani et al. 2000), although a recent study does not support this observation (Minassian et al. 2006). However, taken together with the fact that PPI-deficits have been reported in first-degree relatives of schizophrenic patients (Cadenhead et al. 2000) it is possible that PPI is a stable trait marker of impaired sensory information processing. A recent publication states the heritable variance in PPI to over 50% (Anokhin et al. 2003) and it has been hypothesized that separate anatomical substrates might underlie a state- versus a trait-dependent PPI-deficit (Swerdlow et al. 2000a).

Animal studies

PPI is well preserved across species and can be tested using similar parameters in both animals and humans (Swerdlow and Geyer 1998). This provides some interesting opportunities for cross-species explorations of pre-attentive information processing. There are a variety of pharmacological, anatomical and genetic manipulations of neurotransmitter systems or brain regions hypothesized to be involved in the pathophysiology of schizophrenia that will induce an impaired PPI in the laboratory setting. Both PCP and d-AMP have been shown to cause a decrease in PPI in experimental animals. A number of antipsychotics reverse this deficit in monkeys (Linn et al. 2003), rats (Bakshi and Geyer 1995; Bakshi et al. 1994; Depoortere et al. 1997; Johansson et al. 1995; Swerdlow et al. 1994) and mice (Curzon and Decker 1998; Fejgin et al. 2006; Ouagazzal et al. 2001). There seems to be a differential effect of first and second-generation antipsychotics in that the former primarily block the deficit induced by dopamine receptor agonists while the latter seem to ameliorate deficits induced both by dopamine receptor agonists and NMDA receptor antagonists. However there are studies that do not support this general view (Geyer et al. 2001; Johansson et al. 1995; Swerdlow et al. 1998).

The primary prepulse inhibition circuit

The primary acoustic startle circuit constitutes a very small number of synaptic couplings as pointed out by the very short latency, 8 ms in the rat, of the electromyographic response after tone onset (Ison et al. 1973). Extensive anatomical tracing, lesion and electrical stimulation experiments indicate that the primary acoustic startle circuit in the rat consists of the auditory nerve, the ventral cochlear nucleus, the nucleus of the lateral lemniscus, the caudal pontine reticular nucleus, spinal interneurons and lower motor neurons (Davis et al. 1982). Despite

its relative simplicity, the ASR can be modified as exemplified by habituation and PPI. In the PPI situation the prepulse may intersect with the ASR at the pontine reticular nucleus, which receives projections from the peduculopontine nucleus. This nucleus is in turn modulated by a number afferents descending from the forebrain circuitry (Koch 1999; Swerdlow et al. 2001).
PPI is generally not considered to involve learning mechanisms *i.e.* increases or decreases in response following repeated testing. Rather it has been viewed as a hard-wired sensorimotor gating process. The data to date indicate that PPI is modulated by the cortico-striato-pallido-thalamic neural circuitry (Koch 1999; Swerdlow et al. 1994) and a deficit in this circuit is hypothesized to result in a sensory over-stimulation of the cerebral cortex (Carlsson et al. 1999a; Carlsson and Carlsson 1990; Glenthoj 1995). A modified circuit was recently proposed where the thalamus plays a more central role (Zhang 1999). All sensory signals must pass through the thalamus before reaching the cortex where they activate a number of inhibitory feedback loops to a number of subcortical regions, including the striatum and thalamus, possibly recruiting these regions in sensorimotor gating.

Dopaminergic influence on prepulse inhibition

Both indirect (d-AMP) and direct (apomorphine) dopamine receptor agonists dose-dependently decrease PPI in rats and mice when administered systemically (Johansson et al. 1995; Mansbach et al. 1988; Ralph et al. 2001; Swerdlow et al. 1986; Varty et al. 2001). A similar effect following administration of d-AMP has been shown in humans (Hutchison and Swift 1999), although a subsequent study failed to replicate this finding (Swerdlow et al. 2002).
As already mentioned, the mesocorticolimbic dopamine system is intimately involved in the regulation of PPI and systemic administration of d-AMP increases dopamine levels paralleled in time and duration by a decrease in PPI in rats (Zhang et al. 2000). Other studies have tried to determine which dopamine receptor subtypes are involved in the PPI modulating effect of dopamine. An apomorphine-induced deficit in PPI was reversed by the D_2 receptor antagonists haloperidol and raclopride, but not by the D_1 receptor antagonist SCH 23390 (Mansbach et al. 1988; Swerdlow et al. 1991). Also, a selective D_2 agonist, quinpirole, but not a selective D_1 agonist, SKF 38393 disrupted PPI (Peng et al. 1990) and this effect of quinpirole was reversed by haloperidol (Wan and Swerdlow 1993). These studies point to a major role of the D_2 receptor in the modulation of PPI in rats. In addition, it seems that this receptor exerts a tonic effect on PPI as administration of haloperidol and raclopride increases PPI *per se* (Depoortere et al. 1997; Johansson et al. 1995). Under certain experimental conditions PPI has been shown to be reduced by systemic (Swerdlow et al. 1991; Swerdlow et al. 2005; Wan et al. 1996) and intra-medial PFC (Ellenbroek et al. 1996; Shoemaker et al. 2005; Swerdlow et al. 2005) administration of D_1 receptor antagonists. The importance of the medial PFC in this effect is supported by a

study showing that reduction of medial PFC dopamine levels decreases PPI (Bubser and Koch 1994). It has been suggested that D_1 blockade in the medial PFC leads to a reciprocal increase in dopamine in the NAC and a decreased PPI. In addition, a recent study showed that local administration of the D_1 receptor antagonist SCH 23390 into the PFC can potentiate the PPI disruptive effect of systemically administered apomorphine (de Jong and van den Buuse 2006). However, the mechanism of D_1 receptor mediated modulation of PPI remain inconclusive as one study showed that a disruption of PPI following SCH 23390 administration was insensitive to amelioration by haloperidol (Swerdlow et al. 2005) and dopaminergic lesions in the medial PFC in rats have produced inconsistent results (Swerdlow et al. 2006).
Recent data from receptor knockout mice lacking differing subtypes of the dopamine receptor have suggested that the D_2 subtype is essential for the PPI disruption induced by d-AMP (Ralph et al. 1999; Ralph-Williams et al. 2002) while the D_1 subtype is necessary for the effects of apomorphine. These data also point to a potential difference in the dopaminergic regulation of PPI in mice and rats. In addition there are strain specific differences in the effects of pharmacological manipulations in the PPI model and methodological issues such as basal level of PPI, prepulse intensity and inter-stimulus interval (Dulawa and Geyer 2000; Ralph et al. 2001; Swerdlow and Geyer 1998; Swerdlow et al. 2000b; Varty et al. 2001) has to be considered.

Glutamatergic influence on prepulse inhibition

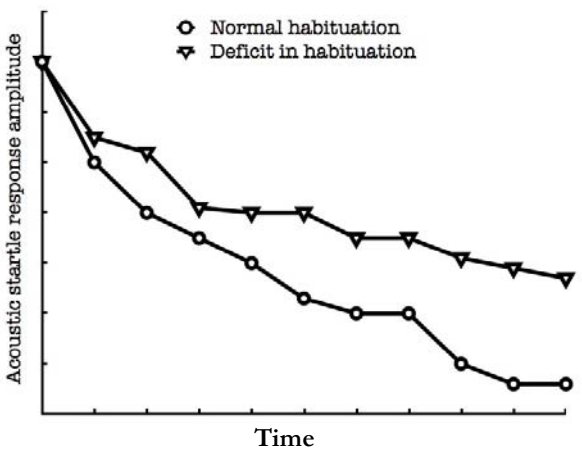
A large body of evidence point to a central role of glutamatergic neurotransmission as a modulator of PPI in experimental animals. The non-competitive NMDA receptor antagonist PCP and its analogues, MK-801 and ketamine, dose-dependently disrupt PPI in rodents (Brody et al. 2003; Curzon and Decker 1998; Johansson et al. 1995; Mansbach and Geyer 1989; 1991). PCP also decreases PPI in non-human primates (Linn and Javitt 2001; Linn et al. 2003). Data from human studies using ketamine are more inconsistent, published studies include observations of decreased, increased or no change in PPI (Abel et al. 2003; Duncan et al. 2001; Karper et al. 1994; van Berckel et al. 1998; Vollenweider et al. 2000). Clearly, further studies are needed to clarify these effects.
Glutamate transmission influences the neural substrates of PPI in a complex manner (Swerdlow et al. 2001). Glutamate and dopamine have been shown to interact at the level of the NAC to regulate PPI. Local infusion of AMPA into the NAC disrupts PPI and this effect can be blocked by systemic administration of haloperidol (Wan et al. 1995). A lesion in the medial PFC has been shown to render rats insensitive to the disruptive effect of MK-801 on PPI while not affecting the response to apomorphine (Schwabe and Koch 2004). Possibly, descending glutamatergic projections from the PFC increases dopamine transmission in the NAC leading to a disruption of PPI. However, local infusion of AP-5 and 7-chlorokynurenate (a synthetic analogue of an endogenous NMDA

receptor antagonist) also reduce PPI without affecting dopamine levels in the NAC as measured by microdialysis (Kretschmer and Koch 1997). This suggests that manipulations of the glutamatergic system can affect PPI without increasing dopamine transmission. The interaction between glutamate and dopamine was also shown to differ between the core and shell subregions of the NAC (Wan and Swerdlow 1996), and the functional differences between the NAC subregions may provide an explanation to the somewhat contradictory data.

DEFICITS IN HABITUATION OF THE ACOUSTIC STARTLE RESPONSE

A likely consequence of impaired pre-attentive sensory information processing would be a relative inability to screen out irrelevant stimuli (Geyer and Braff 1987) leading to a deficit in habituation response (figure 3). Habituation refers to the decrease in response that is observed when an identical stimulus is presented repeatedly, and it is considered to be the simplest form of learning (Petrinovich and Peeke 1973). Interestingly, a deficit in this form of non-associative learning has been demonstrated in schizophrenic patients, including drug-naïve patients (Akdag et al. 2003; Bolino et al. 1992; Braff et al. 1992; Ludewig et al. 2003a; Meincke et al. 2004; Parwani et al. 2000; Taiminen et al. 2000).

Figure 3. *Schematic drawing showing normal and impaired habituation (adapted from Geyer and Braff, 1987).*



The neural circuit that mediates habituation of ASR primarily involves the giant neurons of the caudal pontine formation that in turn project directly onto motor neurons in the spinal cord (Davis 1980; Fendt et al. 2001). Thus, different brain circuits most likely control habituation and PPI (Koch 1999). An association between a deficit in habituation of the eye-blink response and negative and cognitive symptomatology has been demonstrated in one study (Taiminen et al.

2000), while another found no such association (Meincke et al. 2004). Additionally, antipsychotic drug treatment has not been shown to normalize a deficit in habituation response (Bolino et al. 1992; Meincke et al. 2004; Taiminen et al. 2000). Further studies are clearly needed to elucidate the role of the observed habituation deficit in the pathophysiology of schizophrenia.

DEFICITS IN LATENT INHIBITION

Imagine trying a new brand of soda just before going on a rollercoaster ride that makes you violently ill. Now, when being offered that brand of soda you might recoil in disgust as it triggers the memory of being ill. You have been conditioned to a stimulus (soda) and consequence (illness) contingency. However if you instead drank a soda that you had tasted numerous times before without any adverse consequences before that ill-fated ride, the association between taste and illness would be much less likely to occur. This would constitute LI, a phenomenon first described by Lubow and Moore (Lubow and Moore 1959). LI is usually defined as the retardation in learning a conditioned stimulus (CS, *e.g.* a flavour) and unconditioned stimulus (US, *e.g.* nausea) contingency when the subject has prior experience of the CS. It is a psychological phenomenon that has been documented in all mammals tested and it seems to generalize well across sensory modalities (Lubow 1973).

There is still debate over what LI reflects in terms of cognitive function (figure 4). The most popular theory states that LI is a measure of selective attention and that during CS pre-exposure the test subject learns to ignore this stimulus, thus decreasing its associability (Lubow 1997; Pearce and Hall 1980). Based on a large number of animal studies, Weiner and Feldon have suggested an alternative "switching" theory of LI (Weiner 1990; Weiner and Feldon 1997). According to this theory a CS + no US association is learnt during pre-exposure that continues to control behaviour during the conditioning phase. In order to behaviourally express the CS + US association the animal must switch from the CS + no US strategy to the new CS + US one. Another theory, that takes the effect of context into account, suggests that learning the CS + US pairing is not disrupted in LI paradigms but rather the expression of this learning (Escobar et al. 2002). Context is essentially the learning situation and can comprise both external and internal cues. A context + CS association learnt during pre-exposure masks the CS + US relationship subsequently learnt but does not interfere with learning *per se*. This theory serves well to explain LI disruption due to a long delay between learning and test phases. In short, the main controversy concerns whether LI reflects attention processes during pre-exposure that retards learning during conditioning, or if LI is to be seen as a failure to express associations learned during conditioning due to pre-exposure (Escobar et al. 2002; Lubow 1997).

Figure 4. *Hypotheses on the latent inhibition effect.*

Preexposure	Conditioning	LI mechanism
	SELECTIVE ATTENTION MODEL	
Learned inattention to the CS	Reduced strength of CS and US pairing due to inattention to CS.	Less association between CS and US.
	SWITCHING MODEL	
CS + no US association is formed.	Learning CS + US association requires a switch from the CS + no US association.	Switch mechanism retards formation of the CS + US association.
	CONTEXT MODEL	
CS + context association is formed.	Normal formation of the CS + US association.	The CS + context association masks expression of the CS + US association.
Mechanism proposed to be impaired in acute schizophrenia		

Human studies

LI entered schizophrenia research when Solomon (Solomon et al. 1981) and Weiner (Weiner et al. 1984) suggested that decreased LI might provide an animal model of the widely described inability of schizophrenic patients to ignore irrelevant stimuli. It was then shown that acute schizophrenic patients indeed displayed a lowered level of LI (Baruch et al. 1988) *i.e.* they learned the preexposed CS + US contingency faster than healthy controls. This finding has been replicated in a number of studies (Guterman et al. 1996; Kathmann et al. 2000; Rascle et al. 2001; Vaitl et al. 2002) but has also been confounded by negative findings (Leumann et al. 2002; Swerdlow et al. 1996) and reports of abnormally strong LI in chronic schizophrenic patients (Cohen et al. 2004; Rascle et al. 2001). In parallel to these findings it has been shown that low to moderate doses of d-AMP lowers LI in healthy control subjects (Gray et al. 1992; Swerdlow et al. 2003). A critical review of the work done suggests that there is a dichotomy between acute and chronic schizophrenic patients in that the former show reduced LI and the latter intact or increased LI (Gray and Snowden 2005). An explanation for this discrepancy may be the effect of antipsychotic medication. Antipsychotic drugs have been shown to increase LI in both human (Williams et al. 1996; Williams et al. 1997) and animal studies (Dunn et al. 1993; Shadach et al. 1999; Weiner et al. 1996b). The clinical picture is also scattered by differences in experimental protocols, making the exact relationship of LI and schizophrenia

unclear. Possibly, a relative lack of LI is a state marker associated with the acute phase of the disorder, rather than a trait marker of schizophrenia psychopathology. However, several studies have shown decreased LI in otherwise healthy subjects scoring high on questionnaires measuring schizotypy (Braunstein-Bercovitz and Lubow 1998; Della Casa et al. 1999; Lubow and De la Casa 2002; Lubow et al. 2001) indicating that deficits in LI may indeed be trait dependent. To validate this supposition the confounding effects of antipsychotic medication would have to be disentangled. Others have suggested that the chronic state is associated with a potentiated LI (Rascle et al. 2001). A similar abnormality of LI has been observed in patients with obsessive-compulsive disorder (Swerdlow et al. 1999) and in rats treated with NMDA receptor antagonists (see below).

Animal studies

The test procedures used in experimental animals differ substantially from those used in clinical studies, complicating the comparison of data. Human studies currently require the use of a masking task to prevent the test subject from deductively solving the test (Lubow and Gewirtz 1995), although alternatives to masking are being explored (Escobar et al. 2003). Two procedures are routinely used in experimental animals, the conditioned emotional response (CER) model and the conditioned taste aversion (CTA) model (Welzl et al. 2001). The CER model is by far the most common and uses an electric foot shock as the US and a tone or a light as the CS. The measured parameter is the time to complete a certain number of licks from a water bottle in the presence of the CS. CTA on the other hand utilizes an aversive pharmacological agent lithium chloride (LiCl) as the US and a sweet (sucrose or saccharine) solution as the CS. In this case the measured parameter is the amount of sweet solution ingested during a test session. There are a number of parameters to be considered when designing and analyzing LI experiments:

1) The properties of the CS must be considered and normally neutral stimuli are used to mimic human studies and to reduce the potential confounding factor that rewarding or aversive stimuli may represent. In CTA the use of a neutral stimulus is not possible and while both sucrose and saccharine can produce LI, stimuli with more complex taste properties are unsuitable and can produce the opposite outcome *i.e.* latent facilitation (Bennett et al. 1996).

2) Similarly, the choice of US warrants consideration, the foot-shock in the CER model and LiCl in CTA, are approaches with little similarity to human study protocols. Yet LI using CTA has been demonstrated in humans (Arwas et al. 1989).

3) The impact of experimental manipulations, pharmacological or otherwise, on the experience of the CS and US must also be addressed; *e.g.* it has been shown that the administration of d-AMP may influence the perceived intensity of foot-shock in rats (Killcross et al. 1994) and rewarding drugs, such as d-AMP, can induce conditioned taste avoidance *per se* (Parker 1995).

4) Furthermore the amount of pre-exposure to the CS and the number of CS + US pairings during conditioning exert opposite effects on the level of LI. More pre-exposure to the CS increases LI while more CS + US pairings decrease it.
5) Another important parameter is that of context. A change in *e.g.* test environment between pre-exposure and conditioning effectively disrupts LI, demonstrating a key role of context in the LI effect.
6) Lastly, the time frame of the experiments must be considered, as it has been shown that *e.g.* long delays between conditioning and testing can both disrupt (Rosas and Bouton 1997) and enhance LI (De la Casa and Lubow 2002) *per se*.

The latent inhibition circuitry

The primary locus of LI in experimental animals seems to be the NAC. This brain region constitutes an interface between motivational and motor systems and plays a vital role during the conditioning stage of LI (Young et al. 2005). Local administration of d-AMP into the NAC during conditioning disrupts LI (Solomon and Staton 1982) whereas administration of haloperidol or lesions in dopaminergic terminals in the NAC leads to persistent LI (Gray et al. 1997; Joseph et al. 2000). Measurements of extra-cellular dopamine levels confirm these findings as conditioning is associated with an increase in dopamine levels in the NAC and preexposure to the CS abolishes this increase (Young et al. 1993). The NAC can be functionally subdivided in a core and shell region and several studies indicate that these regions exert differential effects on LI (Gal et al. 2005; Weiner et al. 1996a).

Lesions in the hippocampus have been shown to both disrupt (Schmajuk et al. 1994; Solomon and Moore 1975) and spare (Clark et al. 1992) LI. Further studies have revealed that a hippocampal lesion renders LI insensitive to manipulation of context (Holt and Maren 1999; Honey and Good 1993). The disruption of LI after hippocampal lesions seems to be due to the destruction of axons passing through the hippocampus (Weiner 2003). These axons likely originate in the entorhinal cortex, as supported by lesions in this region (Coutureau et al. 1999). In summary, the hippocampus plays an important role in the contextual modulation of LI and the entorhinal cortex in the general expression of LI.
Both the medial PFC and the basolateral amygdala provide extensive input to the NAC and disturbances of both regions can modify ventral striatal dopamine function (Groenewegen et al. 1996; Groenewegen et al. 1999; Louilot et al. 1985). Indeed, the basolateral amygdala seems to be involved in evaluating the impact of reinforcement in LI (Cardinal et al. 2002; Holland et al. 2000). The role of the medial PFC however, remains elusive. No study has been able to detect a change in LI following medial PFC lesions (Lacroix et al. 1998; Lacroix et al. 2000b) or local administration of dopamine agonists and antagonists (Broersen et al. 1999; Ellenbroek et al. 1996; Lacroix et al. 2000a). However, lesions in the orbitofrontal PFC has been shown to produce abnormally persistent LI (Schiller and Weiner

2004; Schiller et al. 2006). Thus, the described LI circuitry primarily involves the NAC, the hippocampus and entorhinal cortex, the basolateral amygdala and possibly also regions of the PFC.

Dopaminergic influence on latent inhibition

Numerous studies show that LI can be disrupted by the systemic administration of d-AMP to rats in an inverse dose-related manner (Ellenbroek et al. 1997; Solomon et al. 1981; Weiner et al. 1987; Weiner et al. 1984; 1988). This parallels data from human studies in which also only low to moderate doses of d-AMP disrupts LI (Gray et al. 1992; Swerdlow et al. 2003). Initially it was suggested that d-AMP had to be administered at least twice, both before preexposure and conditioning phases, to disrupt LI. It was then shown that d-AMP could disrupt LI when administered only before conditioning provided that the rats either were sensitized by a d-AMP injection 24 hours earlier (Weiner et al. 1988) or if the conditioning session took place at least 45 minutes after the administration of d-AMP (Gray et al. 1997). It has been hypothesized that the dopamine release induced by d-AMP needs to be Ca^{2+} dependent to disrupt LI and that with repeated administration or the passage of time the d-AMP effect on dopamine release goes from being relatively Ca^{2+} independent to Ca^{2+} dependent. The direct dopamine agonist apomorphine does not disrupt LI and this lack of effect extends to the D_1 agonist SKF 38393 and the D_2 agonist quinpirole (Feldon et al. 1991). Haloperidol increases LI with remarkable consistency across studies (Moser et al. 2000) and this seems to generalize to a number of other antipsychotic agents (Dunn et al. 1993), although this is based on a single study. The noteworthy exception is clozapine where most studies have shown an increase in LI after clozapine administration (Moran et al. 1996; Trimble et al. 1998) but a number of negative findings (Dunn et al. 1993) and reports of disrupted LI after high doses of clozapine (Christison et al. 1991) complicate matters. Generally though, both first and second-generation antipsychotics reverse d-AMP-induced disruption of LI (Gosselin et al. 1996; Millan et al. 1998; Warburton et al. 1994), supporting the involvement of D_2-receptors in the effect of d-AMP on LI.

Glutamatergic influence on latent inhibition

Early reports on the effects of NMDA receptor antagonists on LI indicated that neither PCP nor MK-801 disrupts LI (Schroeder et al. 1998; Turgeon et al. 2000; Turgeon et al. 1998; Weiner and Feldon 1992). Since only acute schizophrenic patients show lowered LI it was hypothesized that disruption of LI modelled mainly positive symptomatology associated with acute psychosis and aberrations primarily in dopamine signalling. A few studies did find that high doses of PCP and MK-801 (Turgeon et al. 2000; Turgeon et al. 1998) and continuous delivery of PCP (Schroeder et al. 1998) disrupted LI in rats. However, NMDA receptor antagonists are known to induce perseverative behaviour or impair the ability to

alter behavioural strategy (Carlsson and Carlsson 1989; Moghaddam et al. 1997; Svensson 2000) and in analogy might not disrupt LI but rather potentiate it, reflecting an inability to disregard from the context of preexposure when subjected to conditioning (Weiner and Feldon 1992). In line with this it has been shown that MK-801-treatment leads to a persistent LI (Gaisler-Salomon and Weiner 2003), *i.e.* LI is still displayed under conditions that disrupt LI in control rats. The mechanism of LI potentiation by NMDA receptor antagonists can at present only be speculated upon. Conditioning-based potentiated LI has been associated with reduced dopamine transmission in the NAC whereas LI disruption seems to require impulse dependent dopamine release within the NAC (Warburton et al. 1996). A number of studies show that PCP increases accumbal dopamine release (Adams and Moghaddam 1998; Jentsch et al. 1997a; Johansson et al. 1998), however this is likely due to an increase in tonic activity in ventral tegmental area dopaminergic neurons accompanied by a decrease in phasic activity (Svensson 2000). An alternative mechanism may be an increase of glutamate release in the PFC, as this effect has been related to perseverative behaviour in rats (Adams and Moghaddam 1998).

The phencyclidine model of schizophrenia

As mentioned PCP was developed as an anaesthetic agent but was withdrawn due to its side effects that included hallucinations and a psychotic state that incorporated the full symptomatology of schizophrenia (Allen and Young 1978; Javitt and Zukin 1991; Luby et al. 1959; Pearlson 1981; Yesavage and Freman 1978). The observation that PCP could induce positive symptoms, negative symptoms and cognitive deficits associated with schizophrenia launched PCP-administration as a model of schizophrenia. It seemed likely that PCP altered brain function in a manner resembling the schizophrenic brain and that the PCP-model could unmask some of the pathophysiology of the disorder (Farber 2003; Olney et al. 1999; Thornberg and Saklad 1996). Administration of PCP to rodents and non-human primates causes certain behavioural abnormalities similar to those observed in schizophrenic patients *e.g.* information processing deficits (Geyer et al. 1984; Mansbach and Geyer 1989) and cognitive dysfunction related to the frontal cortex (Adams and Moghaddam 1998; Jentsch et al. 1997b). In addition, PCP induces hyperlocomotion, behavioural stereotypy and social withdrawal, all of which are thought to be relevant for clinical aspects of schizophrenia (Jentsch and Roth 1999; Lipska and Weinberger 2000).

Neurochemical effects of phencyclidine

The psychotomimetic effect of PCP is attributed to, *i.a.* its action at the glutamatergic NMDA receptor. PCP acts as a non-competitive inhibitor of this receptor via a binding site inside the channel complex (Javitt and Zukin 1991; Lodge and Anis 1982). Somewhat paradoxically, PCP has been shown to increase

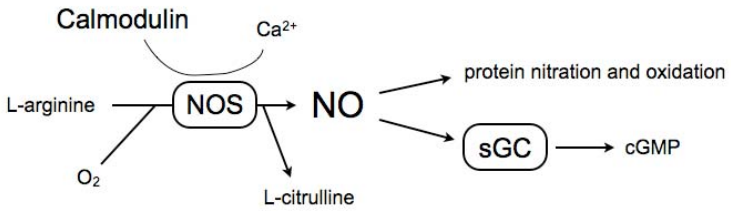
glutamate release in the PFC and NAC (Adams and Moghaddam 1998). This glutamatergic hyperstimulation may explain some of the behavioural effects of PCP (Moghaddam and Adams 1998) and could be caused by a loss of inhibitory drive, via a blockade of NMDA receptors on GABAergic interneurons, and ensuing disinhibition of primary corticolimbic neurons leading to a complex circuit dysbalance (Farber 2003; Olney et al. 1999; Thornberg and Saklad 1996). Several studies also indicate that PCP alters the activity of dopaminergic, noradrenergic and serotonergic neurotransmitter systems, particularly in the frontal cortex and NAC (Adams and Moghaddam 1998; Jentsch et al. 1997a; Jentsch et al. 1999a; Johansson et al. 1998). The receptor binding profile of PCP also includes D_2- and 5-HT_2-receptor agonistic properties (Callado et al. 2000; Kapur and Seeman 2002; Seeman and Lasaga 2005), σ receptor affinity (Sonders et al. 1988) and dopamine transporter inhibition (Rothman 1994). Additionally, PCP has been shown to increase intracellular Ca^{2+}, likely by inhibition of voltage-gated K^+ channels or release from intracellular stores (Bartschat and Blaustein 1986; 1988; Mattson et al. 1992). As a whole, these observations suggest that the neurochemical effects of PCP depend on several neurotransmitter systems and brain regions implicated in current hypotheses on the pathophysiology of schizophrenia.

Nitric oxide

Nitric oxide (NO) was first recognized as the endothelial-derived relaxing factor in the cardiovascular system and as a mediator of the tumoricidal and bactericidal action of macrophages (Hibbs et al. 1987; Palmer et al. 1987). Later, evidence for a neural role of NO emerged, linking it to LTP and thus to learning and memory (Bredt and Snyder 1989; Garthwaite et al. 1989). NO serves as a messenger molecule in a number of physiological processes and possesses several interesting qualities. Being a gas, it can diffuse freely through cell membranes and may serve as a retrograde messenger in synaptic plasticity events such LTP. As it cannot be stored in the cell, release is dependent on ongoing synthesis. NO has a half-life of seconds and as a free radical it can react directly with proteins and also form several cytotoxic moieties (Dawson et al. 1992). In the brain, NO coexists with classical neurotransmitters and is probably involved in the modulation of neuronal signal transmission. *In vivo* data suggests that NO can modulate every major neurotransmitter system, *i.e.* dopamine, glutamate, 5-HT, noradrenalin and GABA (Kano et al. 1998; Prast and Philippu 2001; Segovia and Mora 1998; Smith and Whitton 2000; 2001; Wegener et al. 2000), hypothesized to be involved in the pathophysiology of schizophrenia (Carlsson et al. 2001; Roth et al. 2004; Tamminga et al. 2003).

NO is formed by a two-step oxidation reaction between the amino acid L-arginine and molecular O_2 catalyzed by nitric oxide synthase (NOS) (figure 5).

Figure 5. *Schematic drawing of nitric oxide synthesis and signal transduction.*



Three isoforms of the NOS enzyme have been described, NOS-1 or neuronal NOS (nNOS), NOS-2 or endothelial NOS (eNOS) and NOS-3 or inducible NOS (iNOS), which differ in their cellular localization and regulatory mechanisms (Steinbusch et al. 2000). The nNOS isoform is predominantly present in neurons, eNOS in endothelial cells and iNOS in macrophages. Activation of nNOS and eNOS is dependent on above ambient Ca^{2+} levels whereas the activation of iNOS is not (Ruan et al. 1996). The latter has been described as inducible whereas the former two are constitutive. However, it has been shown that iNOS is indeed constitutively expressed and the expression of both eNOS and nNOS can be induced, thus this division becomes more a matter of degree than principle. In the brain NO is proposed to be a key link between NMDA receptor mediated increases in cytoplasmic Ca^{2+} and activity dependent long-term changes such as differentiation and synaptic plasticity (Karatinos et al. 1995; Snyder and Ferris 2000).

Once released NO binds to the heme moiety of soluble guanylyl cyclase (sGC) to cleave guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) and organic phosphate. The cGMP cascade affects *e.g.* phosphodiesterase and protein kinase activity. Known targets of cGMP-dependent protein kinases include DARPP-32 (Tsou et al. 1993), the inositol 1,3,4-triphosphate receptor (Koga et al. 1994), G-substrate (Detre et al. 1984), NOS (Bredt et al. 1992) and the $GABA_A$ receptor (Leidenheimer 1996). NO exerts its action mainly through cGMP, but also through direct nitration of proteins, phosphoinositides and cAMP.

G-protein-coupled receptors have also been shown to regulate NO. Hormones and neurotransmitters can activate these receptors and thereby stimulate intracellular Ca^{2+} mobilization, via the phospholipase C/inositol triphosphate systems and thus increase cGMP and cAMP levels via NO production.
The distribution of nNOS in the brain has been studied extensively in several different species, including rats, mice and humans. Generally the localization of nNOS in rodents is restricted to limited populations of neurons in the cerebral

cortex, hypothalamus, brain stem, cerebellum, basal forebrain, striatum, hippocampus, olfactory bulb and thalamus (Cork et al. 1998; Forstermann et al. 1990; Hara et al. 1996; Kidd et al. 1995; Vincent and Hope 1992). In humans, the highest levels of NOS activity are found in the cerebral cortex, limbic system, striatum and the brain stem (Blum-Degen et al. 1999; Downen et al. 1999; Egberongbe et al. 1994). There are apparent differences in the distribution and activity of nNOS across mammalian species. Nevertheless, the distribution of nNOS suggests an extensive neuromodulatory role for NO in the brain.

NITRIC OXIDE AND SCHIZOPHRENIA

A tentative link between NO metabolism and schizophrenia was first made in Russia in the 1960s (Averbukh et al. 1966), but it was not until the early 1990s that work began in detail. Histochemists had introduced NADPH diaphorase histochemistry as a tool to label neuronal populations expressing NOS (Vincent et al. 1982) and the importance of NO was beginning to sink in, it was even named "molecule of the year 1992". Overall, the human data supporting a role of NO in the pathophysiology of schizophrenia have found both increases and decreases in NO levels (Bernstein et al. 2005). Thus both possibilities must be taken into consideration when discussing NO as a potential pathophysiological agent in schizophrenia.

Genetic associations between nitric oxide and schizophrenia

A single nucleotide polymorphism (Shinkai et al. 2002) as well as a repeat polymorphism (Reif et al. 2006) in the nNOS gene have been associated with schizophrenia, although the former finding was not replicated in a second study (Liou et al. 2002). Interestingly, the repeat polymorphism also impacted on prefrontal functioning in schizophrenic patients demonstrating a functional role for this gene variant (Reif et al. 2006). Two independent studies have also found significant associations between single nucleotide polymorphisms in the CAPON (a protein closely linked to nNOS) gene and schizophrenia (Brzustowicz et al. 2004; Zheng et al. 2005).

Biochemical links between nitric oxide and schizophrenia

An increase in nNOS mRNA in PFC samples from schizophrenic patients has been shown (Baba et al. 2004), but a decrease in nNOS activity in the same brain region has also been reported (Xing et al. 2002). Supporting the latter lowered NO metabolites (nitrite and nitrate) were found in the CSF of schizophrenic patients (Ramirez et al. 2004) but again higher levels of metabolites have been found in the caudate nucleus (Yao et al. 2004). Furthermore, higher levels of NOS protein have been demonstrated in the cerebellar vermis (Karson et al. 1996). In addition, a number of studies have investigated NOS activity using blood samples and the

predominant finding is an increase in NOS activity, NO or metabolite levels in the blood of schizophrenic patients (Das et al. 1996; Das et al. 1995; Herken et al. 2001; Taneli et al. 2004; Zoroglu et al. 2002). However, the demonstration of lower nNOS activity and NO metabolite levels in schizophrenic patients complicate these findings (Srivastava et al. 2001; Suzuki et al. 2003). Additional observations include increased levels of ADMA (Das et al. 1996), an endogenous NOS-inhibitor, and lowered levels of arginase (Yanik et al. 2003), which competes with NOS for substrate, in blood samples from schizophrenic patients.

Histochemical correlates of nitric oxide dysfunction in schizophrenia

An increase in NADPH-expressing neurons in the brain stem and elevated levels of nNOS in the cerebellar vermis of schizophrenic patients has been reported (Bernstein et al. 2001). Furthermore, a displacement of prefrontal and temporal lobe cortical grey and white matter neurons has been demonstrated, with fewer neurons in superficial and more in deep layers in schizophrenic patients (Akbarian et al. 1993a; Akbarian et al. 1996; Akbarian et al. 1993b). Finally, a reduction in NOS containing neurons in the hypothalamus has been shown (Bernstein et al. 2000; Bernstein et al. 1998). Collectively, this data supports an abnormal NO system in the brain of schizophrenic patients that may be linked to aberrations in neurodevelopment.

NITRIC OXIDE SYNTHASE INHIBITORS BLOCK THE BEHAVIOURAL EFFECTS OF PHENCYCLIDINE

As described the mechanism of action of PCP is not fully understood but several studies show that the NOS inhibitor N^G-nitro-L-arginine methyl ester (L-NAME) can block the effects of PCP on PPI, locomotion and stereotyped behaviour in rats (Johansson et al. 1997; Johansson et al. 1998; Klamer et al. 2005b; Klamer et al. 2005c). Recently, the effect of L-NAME was replicated in mice using the PPI model (Klamer et al. 2001). L-NAME was also shown to attenuate PCP-induced alterations in the dopaminergic and serotonergic systems in rats (Johansson et al. 1998). A recent study indicated that L-NAME might be more effective in ameliorating the effects of PCP on locomotor activity and PPI as compared to similar effects induced by the PCP-analogue MK-801 (Klamer et al. 2005c). As the main difference between PCP and MK-801 is the higher affinity of the latter for the NMDA receptor complex it was suggested that L-NAME possibly interfered with the binding of PCP at the NMDA receptor. However, receptor-binding data did not show any interaction of L-NAME with the MK-801-sensitive NMDA receptor binding of PCP, indicating that the effect of L-NAME on PCP-induced behavioural changes cannot be explained by interactions at the NMDA receptor (Klamer et al. 2005c). In addition, selective nNOS inhibitors also attenuate behavioural effects of PCP in rats (Johansson et al. 1999; Wiley 1998) and mice (Klamer et al. 2004b). Transgenic mice lacking the nNOS gene show less

hyperlocomotion (Bird et al. 2001; Wiley et al. 1999) and an increase in PPI (Klamer et al. 2005a) in response to PCP. Since the effects of PCP likely encompass several neurotransmitter systems it is possible that PCP modulates PPI bidirectionally, the net effect usually being a decrease in PPI. Tentatively, PCP is disconnected from its PPI decreasing mechanism in nNOS knockout mice, yielding an increase in PPI instead. The mechanism of the interaction between PCP and the NO-system remains to be elucidated though a recent study showed a significant increase in hippocampal cAMP levels after both local and systemic PCP administration (Klamer et al. 2005b). This increase was temporally correlated to the disruptive effects of PCP on PPI and could be blocked by pre-treatment with L-NAME. Interestingly, the NOS and guanylyl cyclase inhibitor methylene blue have been shown to have clinical effect as adjuvant therapy in schizophrenic patients (Deutsch et al. 1997) and block PCP-induced behaviours in mice (Klamer et al. 2004a). These observations suggest that NO plays a role in the pharmacological effects of PCP and possible also in schizophrenia.

AIM OF THESIS

The general aim of the thesis was to further investigate the effect of PCP in animal models of cognitive function and the involvement of NO in these effects.
Specific aims

I. To investigate if inhibition of NOS could attenuate the deficits in habituation of acoustic startle induced by psychotomimetic drugs.
II. To study the effects of PCP and d-AMP on LI using CTA.
III. To investigate if a NOS inhibitor could block the potentiating effect of PCP on LI using CTA.
IV. To study if inhibition of NOS substrate (L-arginine) availability could serve as a novel means to block NO-dependent and PCP-induced disruption of PPI.

MATERIAL AND METHODS

Animals

Male Sprague-Dawley rats (B&K Universal AB, Sollentuna, Sweden, paper II and III), 250-300g, and male NMRI mice (B&K Universal AB, Sollentuna, Sweden, paper I and IV or Charles River, Sulzfeld, Germany, paper IV), 28-40 g, were used. The rodents arrived at the animal facilities at least five days prior to the start of the experiments. The rats were housed one per cage (26 x 42 x 15 cm) and the mice maximum eight per cage (Sealsafe IVC 2l, 365 x 207 x 140 mm) in a colony room under constant temperature (20±1°C) and humidity (55%). Food (Standard feed, Harlan Teklad, Norfolk, England) and tap water were available *ad libitum* all the time the animals spent in their home cages. The daylight cycle was maintained artificially (dark 18.00-06.00 hours). Experiments were performed during the light phase. All experiments were carried out in accordance with the Guide for the Care and Use of Laboratory Animals as adopted by the NIH, and was approved by the Ethics Committee for Animal Experiments, Göteborg, Sweden

Drugs

Drugs used in the experiments: d-AMP (dextroamphetamine sulphate) (RBI, Natick, USA), haloperidol (Sigma-Aldrich, Germany), L-NAME (RBI, Natick, USA), LiCl (Sigma Ultra, Sigma Chemicals CO, Stockholm, Sweden), L-lysine (Sigma-Aldrich, Germany), (+)MK-801 hydrogen maleate (dizocilpine) (RBI, Natick, MA, USA) and PCP (1-(1-phenylcyclohexyl)piperidine HCl) (RBI, Natick, USA). d-AMP, L-NAME, L-lysine and PCP were dissolved in saline (0.9% NaCl dissolved in distilled water), LiCl was dissolved in distilled water and haloperidol was dissolved with a minimal amount of glacial acetic acid (10 µl/mg) and then diluted with lukewarm 5.5% D-glucose, to a final pH of around 6. Saccharine (Sigma Chemical CO, USA) was dissolved in tap water. Injections were given subcutaneously (s.c.) to rats in a volume of 2 ml/kg (d-AMP, L-NAME, PCP) or 5 ml/kg (LiCl) and intraperitoneally (i.p.) to mice in a volume of 10 ml/kg.

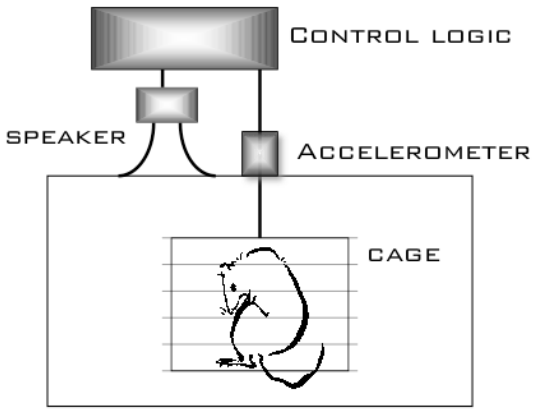
Prepulse inhibition and habituation of acoustic startle

APPARATUS

Acoustic startle recordings were only performed in mice in the present thesis. A MOPS 2b startle response recording system (Metod och Produkt, Svenska AB, Göteborg, Sweden) was used (figure 6). Each mouse was placed in a small wire-mesh cage (5.5 x 10 x 5.5 cm) made of stainless steel, which was suspended at one point at the top to a piston in such way that it could freely move under the piston. A sudden movement of the rodent inside the cage caused a displacement of the

piston, the acceleration of which was converted to an analogue signal by a moving coil transducer. This signal was sampled and digitalised with a 12-bit digital resolution by a microcomputer, which also served to control the delivery of acoustic stimuli. Startle amplitude was defined as the maximum signal amplitude (digital units) that occurred during the first 40 ms after delivery of the startle-eliciting stimulus. Three cages were used simultaneously and each cage was housed in a separate, dimly lit and sound-attenuated cabinet (52 x 42 x 38 cm). The cages were calibrated for equal sensitivity before test and mice tested more than once were always tested in the same cage. The acoustic signal consisted of white noise delivered to the rodent by two high-frequency loudspeakers built into the ceiling of the cabinet. A continuous acoustic signal provided a background white noise level of 62 dB (A) inside the cabinet.

Figure 6. *Schematic drawing of the apparatus used in the prepulse inhibition and habituation acoustic startle experiments.*



TESTING PROCEDURE

Habituation of acoustic startle

The mice were placed in the startle cages in the enclosure for a 10-min accommodation period exposed to the 62 dB background noise only. After the accommodation period they were presented with 20 pulse-alone trials. The time interval between the trials was always 10 s. Pulse intensity was set to 105 dB and the duration of each pulse was 20 ms. After the pre-test, the mice were matched and randomized into homogenous groups according to their mean startle response amplitude.

The mice used in the habituation test were again placed in the startle cages in the enclosures for a 10-min accommodation period exposed to the 62 dB background noise only. After this period they were presented with 121 pulse-alone trials. The time interval between the trials was always 10 s. Pulse intensity was set to 105 dB and the duration of each pulse was 20 ms.

Prepulse inhibition of acoustic startle

The mice were first placed in the startle cages for a 10 min acclimatization period as described above. After this period, they were presented with a series of five startle pulse-alone trials followed by a series of five prepulse-alone trials. The pulse-alone trials served only to accustom the mice to the sudden change in stimulus conditions and were omitted from the data analysis and the prepulse-alone trials were analysed only to ensure that these stimuli did not evoke any startle responses on their own. Thereafter the mice were presented, three times repeatedly, with a series of five prepulse + pulse trials followed by a series of five pulse-alone trials, *i.e.*, a total of 30 trials. The time between trials was always 10 s and the time between any series of trials was 70 s. Startle pulse intensity was set to 105 dB and prepulse intensity to 70 dB. The prepulse was 60 ms in duration and presented immediately before the startle pulse, which was 20 ms in duration. The startle pulse was set to 105 dB, since this intensity was found to evoke a robust startle response that showed a minimum of habituation and at the same time did not cause a ceiling effect. Similarly, prepulse intensity was set to 70 dB (8 dB above background noise) to produce a robust PPI. The mice were subjected to a pre-test containing no drug treatments. After the pre-test the mice were matched into homogenous groups using their mean PPI and startle response amplitudes.

STATISTICAL ANALYSIS

Habituation of acoustic startle

The first startle pulse response was omitted from statistical analysis due to marked variability. Hence, 120 startle pulse trials were used in the analysis. The 120 pulses were divided into six blocks, each block containing 20 pulses. The mean response amplitude for the first 20 startle response trials (block number 1) was calculated for each mouse and treatment condition and used to assess possible drug-induced changes in basal startle response reactivity. Habituation, the change in mean response amplitude over time, was calculated using the formula:

Habituation= [block number x/block number 1 * 100] - 100

Using this formula, a 0% value denotes no difference in startle response amplitude between block number 1 and block number x, and consequently no habituation. Negative values indicate a decreased response over time, *i.e.* a habituation of the

ASR. Habituation was also calculated as the difference in startle response between block number 1 and block number 6. The statistical analysis using this definition was compared with habituation over time to avoid false positive or false negative significances. Statistical analysis was performed by factorial ANOVA with treatment as between-subjects factor followed by Fisher's PLSD test for difference between groups. Two-tailed levels of significance were used and $p<0.05$ was considered statistically significant.

Prepulse inhibition of acoustic startle

The mean response amplitude for startle pulse-alone trials (P) was calculated for each mouse and treatment condition and was used in the statistical analysis to assess drug-induced changes in startle reactivity. The mean response amplitude for prepulse + pulse trials (PP) was also calculated and used to express the percent PPI using the formula:

$$PPI\ (\%) = 100 - [(PP/P) * 100]$$

Using this formula, a 0% value denotes no difference between the pulse-alone and prepulse + pulse response amplitudes and consequently no PPI. Statistical analysis was performed by one- or two-way ANOVA followed by Bonferroni's Multiple Comparison Test for difference between treatment conditions. Two-tailed levels of significance were used and $p<0.05$ was considered statistically significant.

Latent inhibition

WATER BOTTLES

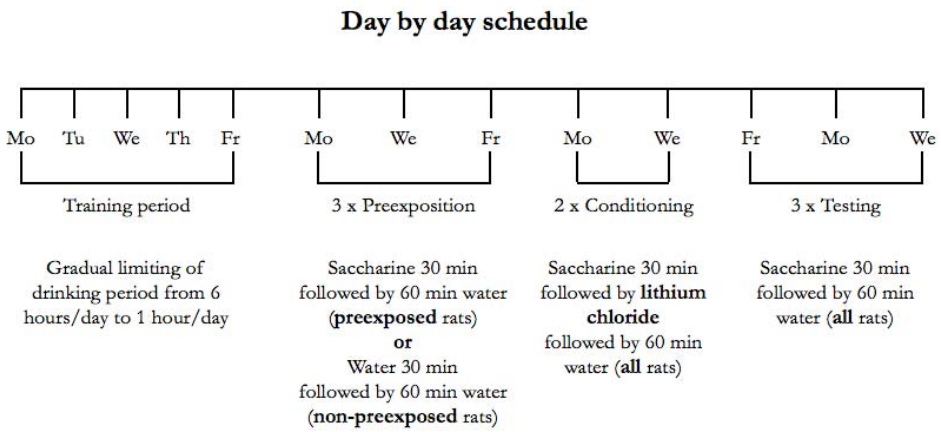
Water was presented to the rats in a standard 500 ml plastic bottle with a metal nozzle. Saccharine (0.1%) was presented in a standard 300 ml plastic bottle with a metal nozzle equipped with a metal ball that produced a distinctive clicking sound (noisy bottle) during licking. All bottles were individually marked to assure identification.

EXPERIMENTAL DESIGN

LI was assessed using a CTA procedure in which the taste of saccharine was conditioned to nausea induced by LiCl. All experiments except Experiment 1 used four groups of animals with eight animals in each group. After arrival at the animal facility the rats were allowed to acclimatize for five days with unlimited access to drinking water. They were then put on a 5-day limited access schedule, gradually reducing access to drinking water to 1 hr (09.30-10.30) per day. All experiments were performed with the rats in their home cages. A 3-preexposure/ 2-conditioning trials experimental design was used followed by 3 test trials (figure 7).

At preexposure two groups of rats were given access to 0.1% saccharine in noisy bottles (preexposed (PE) rats) and two groups to water bottles (non-preexposed (NPE) rats) for 30 minutes. All bottles were then replaced with water bottles for 60 minutes. During conditioning trials all rats were given access to noisy saccharine bottles only. After 30 minutes the rats were injected with LiCl (0.3 mol/l, 5 ml/kg) and the saccharine bottles were replaced with water bottles for 60 minutes. During test trials all rats were given access to noisy saccharine bottles for 30 minutes. The bottles were then replaced with water bottles for 60 minutes. On days in between sessions the animals were allowed to drink water for 1 h (09.30-10.30). The bottles were weighed, with an accuracy of 0.1 g, before and after each drinking period to assess the amount of liquid consumed (converted to ml).

Figure 7. *Experimental design used in the latent inhibition experiments.*



STATISTICAL ANALYSIS

Statistical analysis was performed by ANOVA with treatment and preexposure as between-subjects factors and trial as within-subjects factor followed by Fisher's PLSD test for pair wise comparisons. Each experiment was divided into three parts: Preexposure (3 trials), Conditioning (2 trials) and Test (3 trials), and each part was analysed separately in the ANOVA analysis. A separate 2-way analysis of Test 3 was also performed with treatment and preexposure as between-subjects factors. A few data points were lost due to leaking bottles and omitted from the statistical analysis. Two-tailed levels of significance were used and $p<0.05$ was considered as statistically significant.

RESULTS AND DISCUSSION

Paper I

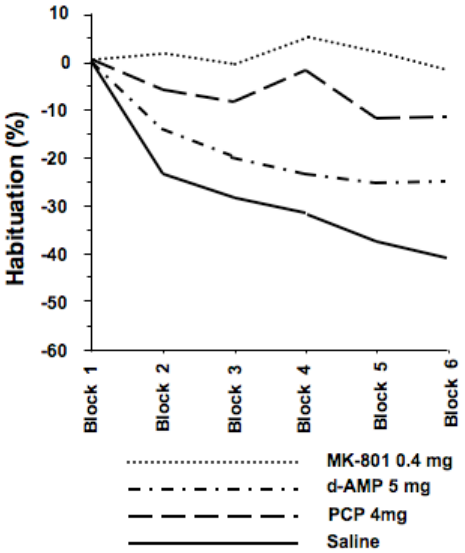
Habituation of acoustic startle is disrupted by psychotomimetic drugs: differential dependence on dopaminergic and nitric oxide modulatory mechanisms.

A deficit in information processing has been considered a central feature in schizophrenia, which might lead to stimulus overload and cognitive fragmentation (Braff 1993; Geyer and Braff 1987). In line with this general idea, schizophrenic patients display a relative inability to gate or filter incoming stimuli. A functional outcome of this deficit is a reduced habituation response to repeated acoustic stimuli compared to control subjects (Bolino et al. 1992; Braff et al. 1992; Geyer and Braff 1982).

Habituation is defined as a decrease in response to an identical stimulus when it is presented repeatedly. It has been viewed as the simplest form of learning (Petrinovich and Peeke 1973). In paper I, habituation is measured as the reduction in ASR to repeated startle-eliciting stimuli presented to mice. The dual-process theory (Groves and Thompson 1970) postulates the existence of two opposite processes, habituation and sensitization, the sum of which will determine the direction of a change in response after repeated stimulus presentations. In the present study, PCP (4 mg/kg), MK-801 (0.4 mg/kg) and d-AMP (5 mg/kg) had no effect on ASR reactivity *per se* but impaired habituation (figure 8).
These psychotomimetic drugs have been shown to produce sensitization in experimental animals and it is conceivable that the effect seen in the present study is due to increased sensitization rather than decreased habituation. The deficit in habituation observed here is in accordance with previous studies showing deficits in habituation due to an increased availability of dopamine or NMDA receptor hypofunction (Davis et al. 1975; Geyer et al. 1984; Kokkinidis 1986; Wang et al. 2003).

Habituation of acoustic startle may represent an animal model for certain aspects of information processing and non-associative learning, situated somewhere between PPI and more complex models of cognitive function. It has been demonstrated that drug naïve schizophrenic patients exhibited a significant deficit in PPI as well as a deficit in habituation of acoustic startle (Ludewig et al. 2003b), further supporting that deficits in PPI and habituation could serve as behavioural markers of information processing deficits in schizophrenia (Ludewig et al. 2003b; Nuechterlein et al. 1994).

Figure 8. *MK-801, d-amphetamine and phencyclidine induced a deficit in habituation of the acoustic startle response (for details, see paper I).*



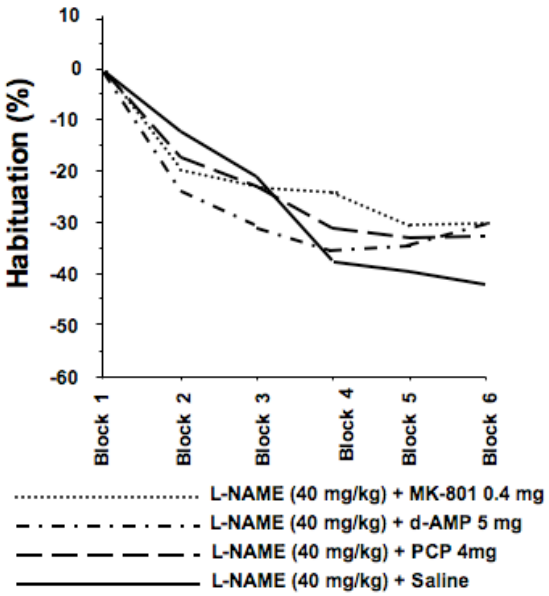
NITRIC OXIDE SYNTHASE INHIBITION REVERSES THE IMPAIRMENT IN HABITUATION INDUCED BY PSYCHOTOMIMETIC DRUGS

The NOS inhibitor, L-NAME, blocked the deficits in habituation induced by PCP, MK-801 and d-AMP at a dose that did not affect ASR or habituation *per se* (figure 9). This suggests that psychotomimetic drugs with different modes of action may converge on an intracellular pathway involving NO. This concept of converging signalling is supported by the fact that transgenic mice lacking a downstream signalling protein, DARPP-32, do not respond to PCP, d-AMP and lysergic acid (LSD) when tested for PPI and repetitive movements (Svenningsson et al. 2003).

As expected, haloperidol (0.4 mg/kg) was effective in blocking the impairment in habituation induced by the indirect dopamine agonist, d-AMP. This is in agreement with the effects of d-AMP on PPI and other behavioural studies. Notably, the reduced habituation after PCP administration was also blocked by haloperidol pre-treatment, which is not the case in the PPI model. However, habituation and PPI of acoustic startle are most likely modulated by different brain circuits (Koch 1999) and changes in PPI have been shown to occur independent of changes in startle amplitude (Johansson et al. 1995; Olivier et al. 2001; Ouagazzal et al. 2001; Swerdlow and Geyer 1998). In addition the effect of MK-801 was not blocked by haloperidol suggesting a difference in dependence on D_2 signalling between PCP and MK-801 in their effects on habituation of acoustic

startle. This discrepancy is not easily explained as recent data indicate that both compounds can act as D_2 receptor agonists, although an earlier study would suggest that MK-801 has little effect on the dopaminergic system (Callado et al. 2000) whereas interactions between PCP and D_2-receptors (Kapur and Seeman 2002) and the dopamine transporter (Rothman 1994; Rothman et al. 1989) have been reported. The finding that L-NAME, but not haloperidol reverses the deficit in habituation induced by MK-801 suggests that this effect does not primarily involve the dopaminergic system, but rather other neurotransmitters *e.g.* NO. The present findings suggest that targeting a common intracellular pathway, instead of dopamine receptors, may be an alternative approach to block the effect of psychotomimetics. Further, the observed effect of L-NAME on a PCP-induced impairment in pre-attentive sensory information processing and non-associative learning should be tested in models of higher order learning and selective attention. If the present findings can be extended to cover a wider range of cognitive functionality this would significantly strengthen the proposed NO-dependence for the schizophrenia-like behavioural effects of PCP.

Figure 9. *L-NAME blocked a psychotomimetic-induced deficit in habituation of the acoustic startle response (for details, see paper I).*



Paper II

The effects of phencyclidine on latent inhibition in taste aversion conditioning: differential effects of preexposure and conditioning.

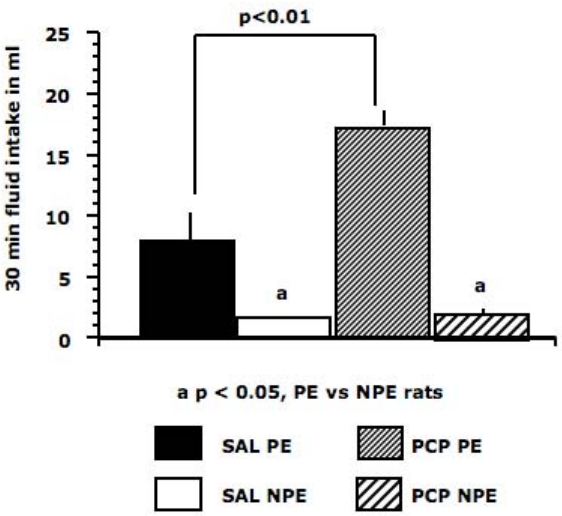
LI is one procedure for studying selective attention (Lubow 1973), an aspect of cognitive function with greater complexity as compared to habituation of ASR. LI is usually defined as the retardation in learning a conditioned stimulus (CS, *e.g.* a flavour) and unconditioned stimulus (US, *e.g.* nausea) contingency when the subject has prior experience of the CS (see introduction). Several studies have shown that LI is altered by compounds that increase dopaminergic neurotransmission and putatively by compounds that decrease glutamatergic neurotransmission (Mohammed et al. 1986; Thornberg and Saklad 1996; Weiner 2003). Much interest for these studies derive from recent concepts of the pathophysiology of schizophrenia in which a weakened glutamatergic activity together with an exaggerated responsiveness in the dopaminergic systems are thought to constitute a major pathophysiological mechanism (Carlsson et al. 1997). Furthermore, since information processing and attention deficits are frequently observed in schizophrenia, the LI procedure has been used in attempts to model these deficits and investigate their dependency on dopaminergic and glutamatergic activity.

In the present study PCP (2 mg/kg) was found to potentiate LI when administered during conditioning *i.e.* preexposed PCP-treated animals consumed significantly more saccharine solution than saline treated counterparts during test sessions (figure 10). This "super"-LI effect has been associated with the chronic phase of schizophrenia (Rascle et al. 2001) although the effects of antipsychotic medication constitute a potential confounder (Williams et al. 1996; Williams et al. 1997). In contrast, d-AMP (1 and 0.33 mg/kg) did not alter LI in the present study but seemed to disrupt learning of the CS + US contingency during conditioning. Specifically, both preexposed and non-preexposed d-AMP-treated animals consumed significantly more saccharine solution than their saline treated counterparts during test sessions. An ancillary finding was that both compounds disrupted LI when administered during the preexposure phase, as there was no significant difference in intake during test sessions between PE and NPE rats.

LI has been explained by attention, switching and recall mechanisms (see figure 4) (Gray and Snowden 2005). The disruptive effect of PCP and d-AMP on LI in paper II when administered only during preexposure, could be explained by a lack of attention to the CS during preexposure. However, drug effects on saccharine intake and the potential role of the drug to act as a contextual cue confound the observed effect. Similarly, the disruptive effect of d-AMP on conditioned learning makes it difficult to ascertain any specific effects on LI. The potentiation of LI observed after administration of PCP during conditioning could be explained by a

deficit in switching or recall. NMDA receptor antagonists are known to induce perseverative behaviour or impair the ability to alter behavioural strategy (Carlsson and Carlsson 1989; Moghaddam et al. 1997; Svensson 2000), which in our study translates to an increased tendency to let the CS-no US pairing of the preexposure phase guide behaviour during test phases as compared to control animals. Conclusively, LI using the CTA model could provide a useful model to study behavioural effects of PCP on cognitive flexibility and selective attention. However, it may be less well suited to study effects related to alterations in dopaminergic activity as suggested by the confounding effects of d-AMP on conditioned learning.

Figure 10. *Phencyclidine potentiated latent inhibition (for details, see paper II)*



Paper III

Antagonism by the nitric oxide synthase inhibitor, L-NAME, of PCP-induced effects on latent inhibition in taste aversion conditioning.

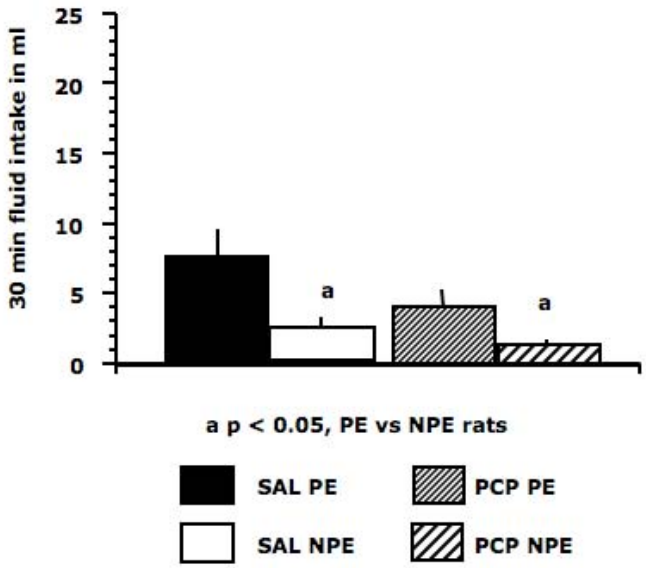
Previous studies have shown that the NOS inhibitor L-NAME, can block the effects of PCP but not d-AMP on PPI and locomotor activity in rodents (Johansson et al. 1997; Klamer et al. 2001; Klamer et al. 2005b; Klamer et al. 2005c). This finding has been interpreted as a potential antipsychotic effect of NOS inhibition with a preferential effect on negative symptoms and cognitive dysfunction (Klamer 2004). As discussed in paper II, we found that PCP (2 mg/kg) increases LI in CTA whereas d-AMP (1 and 0.33 mg/kg) disrupts conditioned learning. LI has been considered to reflect aspects of attention and cognitive flexibility (Weiner 2003), and the study presented in paper III was conducted to investigate the effects of NOS inhibition in this context.
In analogy with the findings using the PPI and locomotor activity models, L-NAME (10 mg/kg) was found to attenuate PCP (2 mg/kg)-induced increase in LI (figure 11) while the same dose had no effect on the impairment induced by d-AMP (0.5 mg/kg). Additionally, L-NAME (10 mg/kg) *per se* exerted a disruptive effect on LI (see below).

Findings in schizophrenic patients using a LI procedure show that LI is disrupted during the acute phase of the disorder, but replaced by normal or potentiated LI during the chronic phase (Gray and Snowden 2005). Disruption of LI has been linked to a hyperdopaminergic state since d-AMP can disrupt LI in healthy controls and experimental animals (Weiner 2003). Possibly potentiation of LI is indicative of cognitive dysfunctionality that entails an inability to change behavioural strategy in response to altered contingencies. Such an inability has been demonstrated in schizophrenic patients using *e.g.* the Wisconsin Card Sorting Test. Unfortunately, the presence of a potentiated LI in chronic schizophrenic patients is difficult to ascertain since treatment with D_2-antagonists is known to potentiate LI and many studies are designed to detect disruption of LI rather than potentiation. However, one study has shown that LI correlates with the negative dimension in both acute and chronic schizophrenic patients (Rascle et al. 2001). This indicates that a potentiated LI in schizophrenic patients may reflect a cognitive dysfunction.

The disruptive effect of L-NAME on LI observed in the present paper is difficult to reconcile with the notion of potentiated LI as a consequence of administration of antipsychotics. This effect however, is most likely linked to D_2 receptor blockade and L-NAME does not seem to primarily interact with the dopaminergic system in its effects on LI, since it did not block the effect of d-AMP. As the present experiments use a CTA paradigm as opposed to a CER paradigm,

methodological differences may well account for the observed discrepancies. Further studies using antipsychotic drugs in our experimental setup are needed to clarify this notion. We have demonstrated that several behavioural effects of PCP can be attenuated by directly blocking the NOS enzyme (see introduction), thus interfering with NO production. However this may not be the only, or indeed the best, means to decrease NO signalling. NO utilizes several second messenger systems, all constituting potential targets for pharmacological interventions. In addition, data is accumulating indicating substrate availability as an important regulatory mechanism in NO production (Bae et al. 2005; Closs et al. 1997). A transport system, termed y^+, seems to be critical in mediating the influx of L-arginine across the blood-brain barrier (O'Kane et al. 2006). This implies that interference with the transport of L-arginine may have functional effects on NO levels in the brain.

Figure 11. *L-NAME attenuates a phencyclidine-induced potentiation of latent inhibition (for details, see paper III).*

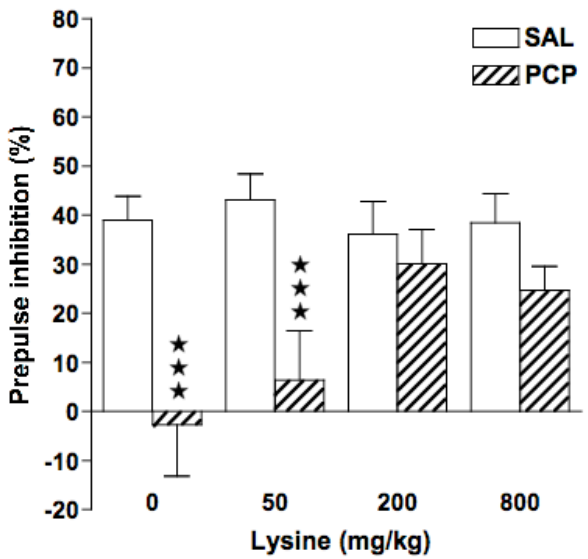


Paper IV

The amino acid, L-lysine, reduces the disruptive effect of phencyclidine on prepulse inhibition in mice.

NO is produced from the amino acid L-arginine and O_2 in a reaction catalyzed by NOS. L-arginine and L-lysine share a membrane bound transport system, the cationic amino acid transporter (CAT) (White et al. 1982). Studies have shown that saturation with L-lysine can inhibit transport of L-arginine (Closs et al. 1997), deplete intra-cellular stores of L-arginine (Closs et al. 1997) and reduce NO production (Carter et al. 2004) *in vitro*. The main finding of Paper IV was that sub-chronic (200 and 800 mg/kg) (figure 12) and acute (800 mg/kg) pre-treatment with L-lysine attenuated the effects of PCP on PPI.

Figure 12. *Sub-chronic pre-treatment with L-lysine dose-dependently attenuated a phencyclidine-induced disruption of prepulse inhibition of the acoustic startle response (for details, see paper IV).*



A competitive antagonism of L-arginine transport across the blood-brain barrier and a depletion of L-arginine supply may explain these findings. A relative lack of substrate for NO production would prevent a hypothesized PCP-induced increase in NO levels and thus the disruptive effect of PCP on PPI. Notably, the intra- and extra-cellular concentrations of L-arginine normally exceed the saturation level of

the NOS enzyme, although administration of exogenous L-arginine has been shown to elevate NO production in several studies (Arnal et al. 1995; Wu and Meininger 2000). This paradox remains unresolved and the importance of substrate transport as a regulator of NO production warrants further study. In particular inter-species and inter-organ differences in amino acid transporter expression could help to clarify the "L-arginine paradox". There are several isoforms of the CAT enzyme and a number of other transport proteins that can shuttle L-arginine across the cell membrane, albeit with lesser specificity than CAT (Closs et al. 2004).

It cannot be excluded that other mechanisms may contribute to the effect observed in paper IV as both L-lysine and L-arginine can be converted to metabolites with neuromodulatory properties *e.g.* α-aminoadipic acid (Wu et al. 1995) and agmatine (Halaris and Piletz 2003). However, preliminary data indicate that the attenuation of the PCP (5 mg/kg)-induced deficit in PPI by subchronic L-lysine (200 mg/kg) pre-treatment can be reversed by an acute administration of L-arginine (800 mg/kg, unpublished data) supporting a proposed depletion of NOS substrate as the active mechanism. These observations further support an important role of NO in the behavioural effects of PCP.

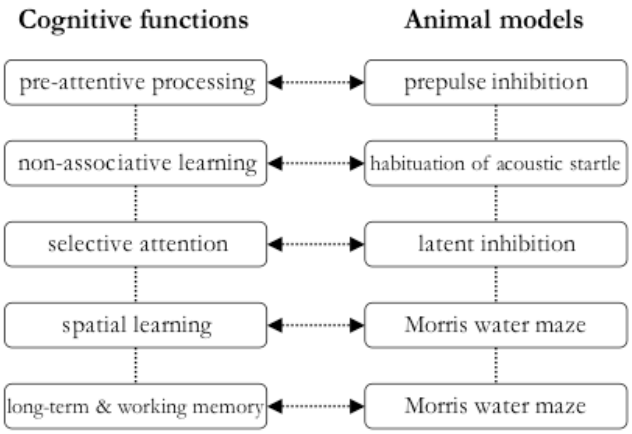
GENERAL DISCUSSION

Animal models of cognitive dysfunction

There are a number of different experimental animals available for the study of cognitive dysfunction in schizophrenia, ranging from mice to non-human primates. Although, generally advantageous some important issues are raised. Not only are the minds of rats and monkeys structurally and functionally different from our own, they are also different from each other. This makes cross-species comparisons both vital and difficult as the literature on the study of cognitive function contains a number of non-replications across species. In addition, there are documented behavioural differences between strains within a particular species. Despite this, significant progress has been made on the neurobiology of cognition. There are in fact many commonalities across species and even complicated aspects of cognitive function such as working memory can be modelled in both non-human primates and rats. Mice are useful for primary screening, mainly due to genetic manipulation, but remain somewhat limited in their behavioural repertoire. Rats and non-human primates are well suited for studies using more complicated cognitive models such as the 5-choice serial reaction time task or attentional set-shifting paradigms (Hagan and Jones 2005). Again, making cross-species comparisons can disclose important information on the evolutionary stability or diversity of cognitive functions.

Our aim has been to establish a ladder of cognitive models that encompasses several integrative levels of cognitive function (figure 13). While covering far from all of the cognitive deficits linked to schizophrenia it does provide a means to study cognition of different levels. Importantly, the original finding that L-NAME can block the behavioural effects of PCP has been extended to all the models in figure 13. Most recently, impairments in spatial reference and working memory induced by PCP were shown to be sensitive to pre-treatment with L-NAME (Wass et al. 2006; Wass et al. 2005). Naturally, it still remains to be shown that these behavioural data can be translated into clinically effective treatments. However, they do indicate that the cognitive dysfunction induced by PCP seems to involve NO signalling across several levels of cognitive task complexity.

Figure 13. *Overview of translational experimental animal models of cognitive function.*



HABITUATION OF ACOUSTIC STARTLE

All three psychotomimetics tested led to a robust decrease in habituation of acoustic startle. Thus, the habituation of acoustic startle model does not differentiate dopaminergic (d-AMP) from glutamatergic (MK-801, PCP) pharmacological manipulation. This may have implications for its utility in identifying novel treatments for cognitive dysfunction in schizophrenia (see below). The fact that haloperidol blocked the effects of PCP on habituation was unexpected, as first-generation antipsychotics are relatively poor at blocking PCP-induced deficit in PPI. Again, there seems to be differences in the pharmacological profile of PCP and MK-801. The lower dose of L-NAME was only effective against a MK-801-induced disruption of habituation while the higher dose of L-NAME blocked the effect of all three psychotomimetics. This is opposite to what was observed in an earlier study in the rat where L-NAME was more effective in attenuating PCP-induced deficits as compared to MK-801(Klamer et al. 2005c). This discrepancy between PCP and MK-801 remains difficult to adequately explain at present, but raises the issue of dissimilarities in pharmacological effect of these compounds. However, the results of paper I indicate that not only the behavioural effects of PCP, but also those of MK-801 and d-AMP, may involve alterations in NO signalling.

LATENT INHIBITION

Compared to the habituation model, our LI setup seems more successful in discriminating between the psychotomimetic effects of d-AMP and PCP. However, the usefulness of the LI paradigm needs to be explored further. Disruption of LI is present only during the acute phase of the disorder and may primarily be related to positive symptomatology. Potentiated LI, as have been reported in chronic patients, has not been studied in depth. Few studies are designed to detect this effect and antipsychotic medication constitutes a major confounding factor. In rats, a lesion in the orbital PFC has been shown to produce abnormally persistent LI (Schiller and Weiner 2004). Recently, this potentiation of LI was normalized by treatment with clozapine but not by haloperidol (Schiller et al. 2006). This suggests that potentiated LI may be an index of certain PFC-dependent cognitive dysfunction that may respond more readily to treatment with second-generation antipsychotics.

One advantage of the PPI and habituation of acoustic startle as well as the LI model is that they translate relatively well between the pre-clinical and clinical setting. In addition, the neural circuitries of all three models are relatively well described. This brings us to the question of the anatomical substrate of cognitive functionality. Clearly, this involves a network consisting of several brain regions that will differ in character depending on the cognitive task at hand.

AMINO ACID TRANSPORT AND METABOLISM IN SCHIZOPHRENIA

It is theoretically conceivable that subtle alterations in the trafficking and metabolism of amino acids could impair the function of neurotransmitter systems and constitute a risk factor for schizophrenia. There are two studies to date that have demonstrated an increased frequency of schizophrenia in populations where pregnant mothers were exposed to famine (St Clair et al. 2005; Susser and Lin 1992). Tentatively, prenatal malnutrition, and consequently a deficit in availability of several essential amino acids *e.g.* L-arginine, L-tyrosine and L-tryptophan, increases the risk of developing mental disorders, such as schizophrenia.

Indeed, there is some evidence that aberrations in transport and metabolism of amino acids may be linked to schizophrenia. L-tyrosine serves as the substrate for the biosynthesis of both dopamine and noradrenalin. Interestingly, alterations in L-tyrosine transport in schizophrenic patients have been reported (Flyckt et al. 2001; Hagenfeldt et al. 1987; Wiesel et al. 1994) and a low K_m for L-tyrosine has been positively correlated to poor cognitive functioning in schizophrenic patients (Wiesel et al. 2005). Additionally a lack of dietary L-tyrosine seems to attenuate dopamine signalling and aspects of cognitive function (Harmer et al. 2001; McLean et al. 2004). The essential amino acid L-tryptophan is the substrate for the neurotransmitter 5-HT, but it can also be converted to kynurenic acid using a different metabolic pathway. Kynurenic acid is synthesized in brain tissue and

functions as a NMDA- and nicotinic α7-receptor antagonist. Kynurenic acid levels have been shown to be elevated in the cerebrospinal fluid (Erhardt et al. 2001; Nilsson et al. 2005) and post mortem brain samples (Schwarcz et al. 2001) of schizophrenic patients. In addition, increased levels of kynurenic acid disrupts PPI in rats (Erhardt et al. 2004) and alters the firing pattern of midbrain dopaminergic neurons (Erhardt and Engberg 2002), resembling that seen after administration of NMDA receptor antagonists.
Taken together the above observations indicate that the transport and metabolism of amino acids may serve as an alternative approach in finding the neurochemical basis of schizophrenia symptomatology and to find new treatment possibilities.

The prefrontal cortex and schizophrenia

A brain region that has received special interest in the context of cognitive function is the PFC. Selective damage to this part of the brain impairs function across several cognitive domains. The PFC has been suggested to orchestrate higher levels of information processing and is extensively interconnected with many other brain structures (Goldberg 2002) including the basal ganglia. Ingvar and Franzen (1974) published an imaging study demonstrating hypofrontality in schizophrenic patients. The study was performed during a resting state and has never been replicated, but numerous studies have shown hypofrontality in schizophrenic patients on a number of working memory and executive function tasks (Andreasen et al. 1992; Spitzer 1993; Weinberger et al. 1986; Yurgelun-Todd et al. 1996). This finding has been interpreted as a relative inability of schizophrenic patients to activate the PFC during tasks that require working memory. Most studies have focused on the dorsolateral PFC but a recent meta-analysis indicates that abnormal activation patterns may not be restricted to this region, but may include *e.g.* the anterior cingulate region (Glahn et al. 2005). Furthermore, some studies have found no difference (Honey et al. 2002) or even increased activation (Callicott et al. 2000; Manoach et al. 1999) in the dorsolateral PFC of schizophrenic patients during working memory tests.

NO AND THE PREFRONTAL CORTEX

Neurons expressing nNOS constitute only 0,5-2% of the total number of cortical neurons, but are found in networks with extensive connections (Vincent and Kimura 1992). These cortical NOS neurons have been shown to be mainly GABAergic (Chesselet and Robbins 1989; Gabbott and Bacon 1995) and are scattered throughout lamina II-VI and the subcortical white matter. nNOS is primarily expressed presynaptically (Faber-Zuschratter and Wolf 1994) but released NO might also diffuse and interact with postsynaptic targets. Others and we have shown that NO seems to be a key mediator in several behavioural effects of PCP, although the exact mechanism of this NO-dependent effect has not been elucidated. In this context, precise dopamine and NMDA receptor interactions play an important role for cognitive dysfunction involving the PFC (Yang and

Chen 2005). Interestingly the NMDA receptor is closely coupled to nNOS via the PSD-95 protein and activation of the NMDA receptor leads to NO and cGMP formation (Brenman and Bredt 1997). Furthermore several studies show that NO is involved in the modulation of dopamine release (Spatz et al. 1995; Strasser et al. 1994; Zhu and Luo 1992) and a recent study showed that the D_1 and NMDA receptors have synergistic effects on cGMP production in striatal neurons (Tukey et al. 2005).

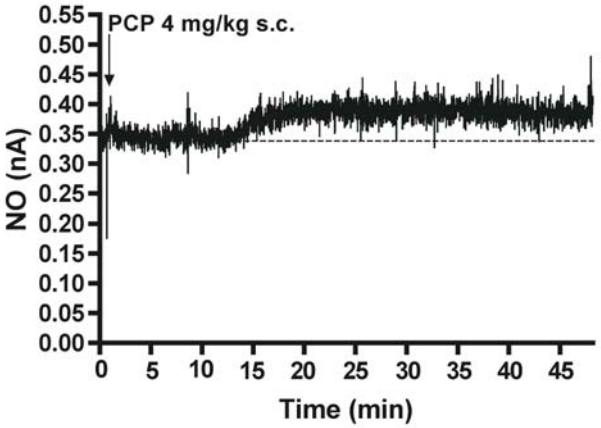
A number of studies have found abnormalities in subpopulations of GABAergic neurons in the dorsolateral PFC in schizophrenic patients (Akbarian et al. 1995; Benes et al. 1996; Hashimoto et al. 2003; Mirnics et al. 2000), suggesting that neural disinhibition and lack in cortical tuning may play a role in the pathophysiology underlying cognitive impairment in schizophrenia (Lewis et al. 2005). In analogy, it has been suggested that PCP inhibits GABAergic neurons in the PFC by blocking NMDA receptors on these neurons. The resulting lack of inhibitory tonus decreases the signal to noise ratio in the PFC and could explain the increase in glutamate levels observed in the PFC in rats after systemic PCP administration (Adams and Moghaddam 1998). The PCP-induced increase in glutamate release could in turn result in an increase in NO production.

Furthermore, the neuronal localisation of nNOS seems to differ with respect to brain region. As noted above, nNOS expression in the cortex seems restricted to GABAergic interneurons, whereas localisation in the cerebellum also includes cholinergic interneurons and in the hippocampal CA1 region nNOS is expressed in pyramidal neurons. This indicates a potential difference in the functional role of nNOS depending on brain region. If the "pro-cognitive" effect of NOS inhibitors in animal models of schizophrenia can be related to a particular brain region it may be possible to identify more specific targets for future drug development. Interestingly, NO dependent cGMP production in the PFC may be independent of NMDA receptor activation. Instead it has been shown that inhibition of $GABA_A$ and $GABA_B$ receptors in the PFC increases NO-dependent cGMP signalling (Ishizuka et al. 2000; Pepicelli et al. 2004).

We have found that systemic administration of PCP leads to an increase in extra-cellular cGMP levels in the medial PFC of mice as measured by microdialysis. This increase in cGMP levels is blocked by pre-treatment with a NOS inhibitor (unpublished data). In addition, inhibition of cGMP production in the mouse medial PFC dose-dependently attenuates the effects of PCP on PPI (unpublished data). However, it was also found that an ibotenic acid lesion in the mouse medial PFC did not alter basal PPI levels or interfere with a PCP-induced disruption of PPI but rendered this deficit insensitive to amelioration by pre-treatment with L-NAME (unpublished data). Thus, a functional medial PFC does not seem to be required for the disruptive effect of PCP on PPI in the mouse but appears to be critical for a NO-dependent modulation of such an effect. Preliminary findings using a NO-sensitive micro-electrochemical sensor developed by the research

group of professor John Lowry, National University of Irleand Maynooth, indicate that systemic administration of PCP leads to an increase in NO levels in the rat PFC (figure 14, unpublished data). This further supports the notion of an interaction between PCP and NO situated in the PFC.

Figure 14. *Phencyclidine increases nitric oxide levels in the prefrontal cortex of rats.*



Ultimately, there seems to be a complex interaction of glutamate, dopamine and GABA in controlling the activity of cortical pyramidal neurons and disturbances in recurrent networks may consequently provide an explanation for the cognitive deficits of schizophrenia (Goldman-Rakic 1999; Rao et al. 2000; Trantham-Davidson et al. 2004; Tseng and O'Donnell 2004). NO is well positioned to play an important role in such interactions, putatively positioned at key synapses in the PFC and with the ability to modulate glutamatergic, dopaminergic and GABAergic activity. In conclusion, a prefrontal NO/sGC/cGMP signalling pathway may constitute an interesting target for novel pharmacological treatments aimed at restoring cognitive function in schizophrenic patients.

Developing cognitive enhancers

As mentioned, the cognitive deficit observed in schizophrenic patients is heterogeneous and it remains uncertain whether any specific form of cognitive impairment can explain the symptoms of the disorder. Nonetheless improvement of cognitive function has become an important goal in the treatment of schizophrenia. A number of compounds have been shown to enhance cognition in animal models but the transition into the clinical setting has proven a difficult hurdle (Hagan and Jones 2005). One problem may be that the clinical goal is to identify agents that normalize an impaired functionality, not agents that improve cognitive function *per se*. This necessitates a clear understanding of the deficits within the patients and access to good translational animal model of these deficits. Clearly this approach warrants a consensus on how the cognitive dysfunction associated with schizophrenia should be categorized and understood. Even

further, it is not clear whether improved cognitive performance also translates into significant clinical effects.

Recently the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia, www.matrics.ucla.edu) initiative launched by the NIMH tried to identify the cognitive domains affected in schizophrenia and the result was a list of 7 primary domains; attention/vigilance, speed of processing, working memory, verbal learning and memory, reasoning and problem solving and social cognition (Robbins 2005). Of these only verbal learning and memory are downright impossible to model in animals and they might be approximated by *e.g.* visual learning and memory tests. The MATRICS program was launched to identify means to make research into cognitive enhancers for schizophrenia more effective. This includes a division between psychosis and cognitive deficits as pharmacological target areas (Geyer 2006). The underlying premise being that rather than looking for an antipsychotic agent that is also a cognitive enhancer, one should focus on finding pro-cognitive therapies that can be used in adjunct with existing antipsychotic drugs. However, this also infers that animal models aimed specifically at predicting antipsychotic efficacy become less useful. Thus, some behavioural models such as the conditioned avoidance response and locomotor activity models may be less suited to detect compounds capable of restoring cognitive functionality in schizophrenic patients. This line of reasoning is relevant to animal models based primarily on the dopaminergic hyperactivity hypothesis, such as the acute administration of d-AMP. Evidence to date links increased dopamine transmission to positive symptoms in schizophrenia rather than cognitive dysfunction (Abi-Dargham 2004).

Predictive validity for animal models of schizophrenia commonly relies on the effect of known antipsychotic drugs in the model compared to the patient population. The problem with cognitive enhancers is that there are no positive controls, *i.e.* drugs effective in ameliorating cognitive dysfunction in schizophrenic patients, in the clinical setting. Ascertaining whether an animal model will have any predictive validity in identifying "pro-cognitive" drugs will thus be difficult. A compromise may be to use models that respond to second-generation antipsychotics, but not to first-generation as certain compounds such as clozapine, seem to have at least a modest positive effect on cognitive deficits (Woodward et al. 2005).

Another problem is that the cognitive deficits associated with schizophrenia span a number of cognitive domains and display a great deal of heterogeneity across the patient population. Thus, the questions arise whether one "pro-cognitive" compound suffices or if different profiles of cognitive dysfunction require tailored pharmacological treatment? If a pathophysiological core deficit can be identified that is linked to a number of specific deficits, a single drug may indeed be of benefit to most patients. As no single cognitive deficit is unique to schizophrenia there is a certain commonality in dysfunction to other brain disorders. Can these

deficits have similar pathophysiology or are they merely similar endpoints of differential pathological processes? On a broader scale one might speculate as to whether a future pro-cognitive drug that is effective in schizophrenia patients will also be effective in treating cognitive deficits of *e.g.* dementias. Possibly, the fundamental issue is whether schizophrenia should be regarded as psychotic disorder accompanied by negative symptoms and cognitive deficits, or as a cognitive disorder accompanied by psychotic episodes. The latter view might petition for a return to the term dementia praecox as defined by Kraepelin; then again to define schizophrenia we need to more fully understand the neurobiological basis of the disorder. Hopefully, the development of "pro-cognitive" pharmacological treatments will provide both aid for the patients and insight into the pathophysiological mechanisms of schizophrenia.

CONCLUDING REMARKS

The development of "pro-cognitive" drugs aimed at treating the disabling cognitive dysfunctionality associated with schizophrenia is a difficult task. The cognitive dysfunction varies in both severity and nature between patients, and so far no effective pharmacological treatment exists in the clinic. Despite this, the potential benefit of such drugs is large enough to warrant a directed and thorough research effort. We have found that NOS inhibition is effective in ameliorating schizophrenia-like cognitive dysfunction in experimental animals. This is supported by the findings in the present thesis and the thesis of Daniel Klamer (2004). This suggests that the NO system could be an interesting target for "pro-cognitive" drugs. However, to fully evaluate this idea a more detailed understanding of how NO can impact on neuronal activity and networks is needed. To this end translational animal models used in conjunction with biochemical measurements of neuronal activity and transmitter release will play an important role. This could further elucidate the potential role of NO in the pathophysiology and the treatment of cognitive dysfunction in schizophrenia.

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