Neonatal Phencyclidine (PCP) induced deficits in rats: A behavioural investigation of relevance to schizophrenia

This thesis is submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

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Abstract

Background: The main aim of the studies in this thesis is to provide insights into the neonatal phencyclidine (PCP) induced deficits in male and female rats as a neurodevelopmental animal model of schizophrenia.

Methods: Both male and female rats were treated with neonatal PCP on postnatal days (PNDs) 7, 9 and 11 or vehicle, followed by weaning on PND 21-22. The rats were then tested in behavioural paradigms such as novel object recognition, spatial memory and social interaction in their adolescent and adult stages and were also tested with acute treatment of typical and atypical antipsychotic agents.

Results: Neonatal PCP treatment (10 & 20 mg/kg in males and 10 mg/kg in females; once a day for 3 days on PND 7,9 and 11) caused novel object recognition and spatial memory impairment in male and female rats both in the adolescent (PND35-56) and in the adult stages (PND>56) (chapter 2) and robust deficits in social interaction behaviours in the adolescent stage. The SI deficits were observed in adulthood in female but not in male rats thereby establishing a sex-specific social behavioural deficit (chapter 3). The object memory and social interaction deficits induced by neonatal PCP treatment were reversed following acute risperidone but not haloperidol. Finally, the temporal profile of this treatment regime was investigated and the male and female animals were tested on PND 190 and PND 365. The animals did not have any challenge dose of PCP during their testing stage. The result showed that there was significant deficit in object and spatial recognition memory in both male and female animals at both time points, thereby establishing enduring deficits.

Conclusion: Given the heterogeneity of the schizophrenic disorder and its complex aetiology, it is understandably difficult to find animal models that completely mimic most or all of the symptoms associated with the disorder. However, data from the studies in this thesis support the use of neonatal PCP as a valid animal model of cognitive and negative symptoms, and explores the effect of antipsychotics in understanding the model. Also, in light of the efficacy of neonatal PCP to produce robust object, spatial memory and social interaction deficits in rats, it appears that this model may be a useful tool to investigate the potential of novel therapeutic candidates that may help improve therapy and understand the illness.
List of papers and refereed proceedings arising from this thesis


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<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>5-HT:</td>
<td>5-hydroxytrytamine or serotonin</td>
</tr>
<tr>
<td>5-HT1-7:</td>
<td>5-hydroxytryptamine receptor subtypes 1-7</td>
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<tr>
<td>Acb:</td>
<td>Nucleus accumbens</td>
</tr>
<tr>
<td>AMPA:</td>
<td>Alpha amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid</td>
</tr>
<tr>
<td>AOB:</td>
<td>Accessory olfactory bulb</td>
</tr>
<tr>
<td>ANOVA:</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>BDNF:</td>
<td>Brain-derived neurotrophic factor</td>
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<tr>
<td>cAMP:</td>
<td>Cyclic adenosine monophosphate</td>
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<tr>
<td>CGP39551:</td>
<td>(E)-(±)-2-Amino-4-methyl-5-phosphono-3-pentenoic acid ethyl ester</td>
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<td>CNS:</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>COMT:</td>
<td>Catechol-O-methyl transferase</td>
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<tr>
<td>CPu:</td>
<td>Caudate putamen</td>
</tr>
<tr>
<td>CT:</td>
<td>Computed tomography</td>
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<td>DAO:</td>
<td>D-amino acid oxidase</td>
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<tr>
<td>DI:</td>
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<td>DISC:</td>
<td>Disrupted in schizophrenia</td>
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<td>EDS:</td>
<td>Extra-dimensional shift</td>
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<td>Frontal cortex</td>
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<td>Guanine nucleotide binding proteins</td>
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<td>IEG:</td>
<td>Immediate early genes</td>
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<td>ITI:</td>
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<td>LSD:</td>
<td>Lysergic acid diethylamide</td>
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<td>LTP:</td>
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<td>MAM:</td>
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<td>MATRICS:</td>
<td>Measurement and Treatment Research to Improve Cognition in schizophrenia.</td>
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<tr>
<td>MeA:</td>
<td>Medial Nucleus of the amygdala</td>
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<tr>
<td>MeApd:</td>
<td>posterodorsal subnucleus of the medial amygdala</td>
</tr>
<tr>
<td>mGLuR:</td>
<td>Metabotropic glutamate receptor</td>
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MK-801: (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-monooimine Maleate (or) Dizocilpine
MRI: Magnetic resonance imaging
mRNA: Messenger ribonucleic acid
NAA: N-acetylaspartate
NAAG: N-acetylaspartylglutamate
NDMC: N-desmethylclozapine
NGF: Nerve growth factor
NMDA: N-methyl-D-aspartate
NMDAR: N-methyl-D-aspartate receptor
NOR: Novel object recognition
NR1-4: NMDA receptor subunits 1-4
NRG: Neuregulin
NRHypo: NMDA receptor hypofunction
NS: Not significant
NVHL: Neonatal ventral hippocampus lesion
PCP: Phencyclidine
PET: Positron emission tomography
PFC: Prefrontal cortex
PND: Postnatal day
PPI: Prepulse inhibition
Prh: Perirhinal cortex
RELN: Reelin
RGS4: Regulator of G protein signalling
Schizophrenia
SEM: Standard error of mean
SI: Social interaction
SMT: Spatial memory task
TH-Mrna: Tyrosine hydroxylase mRNA
TURNS: Treatment Units for Research in Neurocognition in Schizophrenia
VTA: Ventral tegmental area
WCST: Wisconsin Card Sorting Test