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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

Lakshmi Rajagopal

School of Pharmacy

University of Bradford

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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

1. **Rajagopal L,** Neill JC, Harte MK (2009) Evaluation of neonatal phencyclidine treatment in male and female rats: a neurodevelopmental model of schizophrenia. European Neuropsychopharmacology 19: S49. ECNP conference, Nice, France.

2. **Rajagopal L,** Neill JC, Harte MK (2009) Neonatal phencyclidine treatment induces object recognition and spatial memory deficits in both male and female rats: a neurodevelopmental model of schizophrenia. The British Association for Psychopharmacology (BAP).

3. **Rajagopal L,** Neill JC, Harte MK (2009) Neonatal phencyclidine treatment induces sex specific deficits in social interaction in adult rats. TheBritish Association for Psychopharmacology (BAP).

4. **Rajagopal L,** Neill JC, Harte MK (2010) Neonatal phencyclidine induces long-term object memory deficits in male and female rats: reversal by risperidone, but not haloperidol". Schizophrenia Research 117: 319-20 SIRS, Florence, Italy.

5. **Rajagopal L,** Neill JC, Harte MK (2010) Risperidone, but not haloperidol reverses the object memory deficits induced by neonatal phencyclidine in adult rats. The British Association for Psychopharmacology (BAP).

6. Neill JC, Barnes S, Cook S, Grayson B Idris NF, McLean S, Snigdha S, **Rajagopal L**, Harte MK (2010) Animal models of cognitive dysfunction and negative symptoms of schizophrenia: focus on NMDA receptor antagonism. Pharmacology and Therapeutics 18: 419-32.

7. **Rajagopal L,** Neill JC, Harte MK (2011) Neonatal phencyclidine treatment induces object recognition and spatial memory deficits in both male and female rats: A neurodevelopmental model of schizophrenia *(In Preparation).*

8. **Rajagopal L,** Neill JC, Harte MK (2011) Sexual dimorphic effects of neonatal PCP on negative symptoms of schizophrenia in adolescent and adult rats using social interaction paradigm *(In Preparation).*

9. **Rajagopal L,** Neill JC, Harte MK (2011) Long-term effects of neonatal phencyclidine administration on novel object and spatial memory task in male and female rats *(In Preparation).*

Table of content

Chapter 3
To investigate the sexually dimorphic effects of neonatal PCP on negative symptoms of schizophrenia in adolescent and adult rats using the social interaction paradigm

Chapter 4
Investigating the effects of antipsychotic agents on cognitive and negative symptomotology using NOR and social interaction paradigms in neonatal PCP model.

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List of Abbreviations

Acronym	Definition
5-HT:	5-hydroxytrytamine or serotonin
$5\text{-HT}_{1\text{-}7}$:	5-hydroxytryptamine receptor subtypes 1-7
Acb:	Nucleus accumbens
AMPA:	Alpha amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AOB:	Accessory olfactory bulb
ANOVA:	Analysis of variance
BDNF:	Brain-derived neurotrophic factor
cAMP:	Cyclic adenosine monophosphate
CGP39551:	(*E*)-(±)-2-Amino-4-methyl-5-phosphono-3-pentenoic acid ethyl ester
CNS:	Central nervous system
COMT:	Catechol-O-methyl transferase
CPu:	Caudate putamen
CT:	Computed tomography
D1:	Dopamine receptor subtype 1
D2:	Dopamine receptor subtype 2
D3:	Dopamine receptor subtype 3
D4:	Dopamine receptor subtype 4
D5:	Dopamine receptor subtype 5
DA:	Dopamine
DAO:	D-amino acid oxidase
DAT:	Dopamine transporter
DI:	Discrimination index
DISC:	Disrupted in schizophrenia
EDS:	Extra-dimensional shift
FC:	Frontal cortex
G Proteins:	Guanine nucleotide binding proteins
GABA:	Gamma-aminobutyric acid
GluR1-4:	Glutamate receptor subunits 1-4
HPA:	Hypothalamus-pituitary- adrenal axis
IEG:	Immediate early genes
ITI:	Intertrial interval
LC:	Line crossings
L-DOPA:	L-3,4Dihydroxyphenylalanine
LMA:	Locomotor activity
LSD:	Lysergic acid diethylamide
LTP:	Long-term potentiation
M1-4:	Muscarinic receptor subtypes 1-4
MAM:	Methylmethazoxymethyl
MATRICS:	Measurement and Treatment Research to Improve Cognition in schizophrenia.
MeA:	Medial Nucleus of the amygdala
MeApd:	posterodorsal subnucleus of the medial amygdala
mGLuR:	Metabotropic glutamate receptor

MK-801:	(+)-5-methyl-10,11- dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-monaimine 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