STRUCTURAL BRAIN ABNORMALITIES AND ALTERED SENSITIVITY TO PSYCHOTOMIMETIC DRUGS IN NEUREGULIN-1 KNOCKOUT MICE

O'Tuathaigh C[1], O'Sullivan G[1], O'Leary C[1], Tighe O[1], Desbonnet L[1], Lai D[2], Harvey R[2], Croke DT[1], Waddington JL[1]. [1] Molecular & Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland, [2] Victor Chang Cardiac Research Institute, Darlinghurst, New South Wales, Australia.

INTRODUCTION

• Molecular genetic studies have identified several genes conferring risk for schizophrenia, many of which play some role in glutamatergic neurotransmission.

• Mice containing heterozygous deletion of neuregulin-1 (NRG1) display several behavioural features relevant to schizophrenia including hyperactivity (clozapine sensitive), disrupted prepulse inhibition and abnormalities in social interaction.

• Heterozygous NRG1 knockout mice demonstrate a reduction in NMDA receptor (NMDAR) expression, and there is biochemical evidence to suggest that reduced NRG1 signaling may contribute to the pathophysiology of schizophrenia via disruption of NMDAR function.

• Studies comparing brain structure in patients with schizophrenia *vs*. controls have found structural abnormalities in specific brain regions implicated in schizophrenia.

• In the present study, we examined whether acute or subchronic administration of the NMDAR antagonists MK-801 (0.1-0.2 mg/kg) or phencyclidine (PCP; 2.0 mg/kg) would impact upon the schizophrenia-related behavioural phenotype seen in the NRG1 mutant. Locomotor responsivity to acute or repeated cocaine (10 mg/kg) was also assessed in female NRG1 KO *vs.* WT mice.

• NRG1 knockout (KO) and wildtype (WT) controls mice were also examined by magnetic resonance (MR) volumetry using high-resolution T2-weighted imaging at 7 T in order to examine effects of NRG1 genotype on presence of schizophrenia-relevant structural endophenotypes.

AIMS

• Modulation of hyperactivity and disrupted social functioning was assessed following acute or subchronic PCP or MK-801 in male and female NRG1 KO and WT mice.

• Volumetric changes across several brain structures were assessed in NRG1 KO mice *vs.* controls using structural MRI.

METHODS

- ***Drugs*** – All drugs were administered in a volume of 4 ml/kg, subcutaneously. Drugs used were: phencyclidine hydrochloride (2 mg/kg; Sigma, UK), MK-801 (0.1, 0.2 mg/kg), cocaine (10 mg/kg), vehicle (distilled water).
- ***Subchronic Treatment Protocol*** – Male and female WT and heterozygous (HET) were given PCP, MK-801 (0.1 or 0.2 mg/kg) or vehicle subchronically - twice daily / 7 days. Assessments began following a 1 week washout period.
- ***Activity Monitoring –*** General horizontal and vertical activity was assessed using an automated photobeam interruption based activity monitoring system.
- ***Social Interaction in a Novel Environment*** – Social and approach and agonistic behaviours towards an unfamiliar mouse in a novel environment were assessed during the 10 min observation session.
- ***Sociability and Social Novelty Preference*** – Assessment of social approach behaviour in a three chambered apparatus (O'Tuathaigh et al., 2007).
- ***MRI*** **-** Female NRG1 and WT mice were examined by 7T MRI (Bruker Avance Biospec 70/30 USR, Karlsruhe, Germany).

RESULTS

(a) Reversal of hyperactivity phenotype in NRG1 KO mice following subchronic PCP [Fig. **A**] or MK-801 [Fig. **B**].

(b) Acute challenge with PCP or MK-801 in mice pre-treated with subchronic PCP or MK-801 respectively, indicated reduced responsivity to acute PCP in vehicle-treated NRG1 KO mice, but increased sensitised response in PCP pre-treated mice [Fig. **C**].

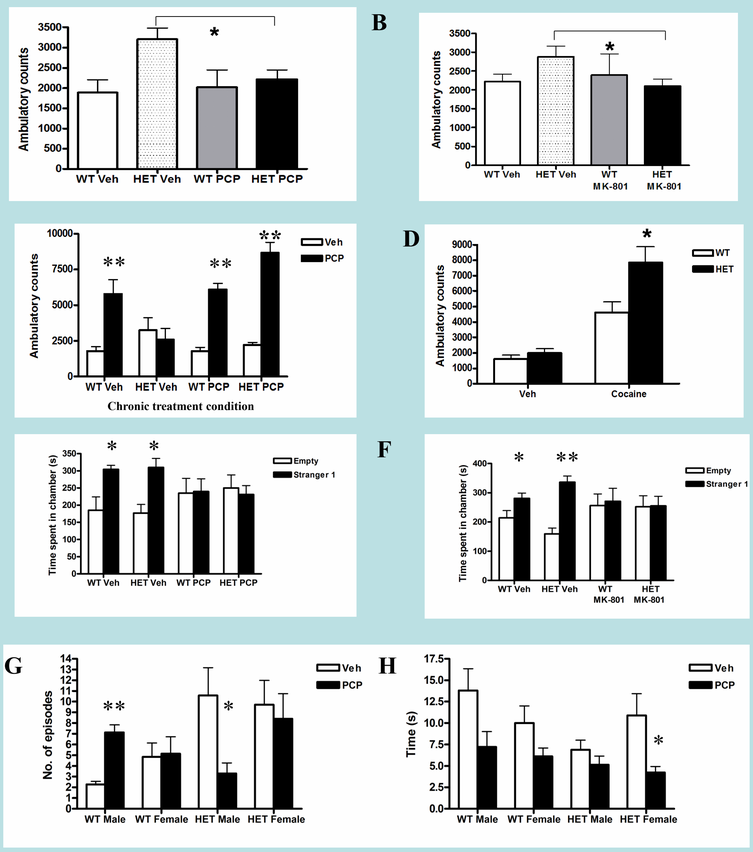
(c) Increased locomotor activatory response to acute cocaine in female NRG1 KO [Fig. **D**]; NRG1 females also evidenced an increased sensitised behavioural response to a second dose administered 24 hr later ($P < 0.05$).

(d) Disruption of sociability in WT and NRG1 KO mice following subchronic PCP [Fig. **E**] or MK-801 [Fig. **F**]; social novelty preference was also disrupted in the same treatment groups.

RESULTS

(e) Altered pattern of phenotypic social behaviours in NRG1 KO including reduction in number of walkover behaviours and a sex-specific reduction in time spent engaged in social sniffing following subchronic PCP [Fig. **G** & **H**]; subchronic MK-801 reduced all social behaviours in a genotype-independent manner.

(f) Volumetric changes in specific brain areas in NRG1 KO *vs.* WT: reduction in total ventricular and olfactory bulb volume [both $P < 0.05$].



* $P < 0.05$; ** $P < 0.01$

DISCUSSION

- These data suggest that functional modulation of the NMDA receptor may underlie NRG1-mediated changes in social and exploratory behaviour, thereby supporting the prevailing glutamatergic hypothesis of schizophrenia.

- Volumetric analysis of brain areas implicated in schizophrenia would suggest that developmental loss of NRG1 function in our mutant model produces structural changes in the brain relevant to those observed in schizophrenia.

ACKNOWLEDGMENTS

This work was supported by the Health Research Board of Ireland and Science Foundation Ireland