Modelling negative symptoms of schizophrenia: Combined neonatal PCP and social isolation causes social interaction deficits in rats

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Introduction
Schizophrenia affects around 1% of the population (1), although current antipsychotics are effective in treating the positive symptoms, cognitive and negative symptoms are still poorly managed. The development of novel, more effective therapeutics requires availability of predictive animal models but at present few adequately model the negative symptoms.

Social isolation (SI) of rat pups from a weaning is a widely used neurodevelopmental model of schizophrenia which produces behavioural and cognitive deficits with translational relevance to the disorder. Neonatal administration of the NMDA-receptor antagonist, phencyclidine, has also been used to model symptoms of schizophrenia (1).

The current study: i. investigates whether combining these early-life manipulations causes more robust cognitive changes and can also cause negative symptom deficits not seen after SI alone, and ii. whether these cognitive deficits can be reversed by antipsychotics, clozapine.

Methods

Neither isolation alone nor combined with neonatal PCP had any affect on locomotor activity, however, clozapine reduced activity in both cohorts.

Novel object recognition (NOR): In two 3 minute trials separated by a 2h inter-trial interval time spent exploring two identical objects (familiarisation trial) or one novel (staged) and one familiar object (choice trial) was recorded manually.

Social interaction (SI): Two unfamiliar, weight (<30g) and treatment matched rats were placed in an unfamiliar arena for a 10 minute trial. Individual interaction behaviours were manually scored post-test using Ethovision XT software.

Isolation Alone:
- Eighty-four rats were obtained on PND 23 then housed in groups of 3-4 (GH) or singly (SI) for 6 weeks.

Neonatal PCP combined with isolation:
- 48 rats were obtained on PND 3 and received saline or phencyclidine (PCP; 10mg/kg; s.c.) on PNDs 7, 9 & 11.

On PND 23 saline-treated rats were housed in groups of 3-4 (SAL-GH) and PCP-treated rats were housed in social isolation (PCP-SI) for 6 weeks.

Locomotor activity

Neither isolation alone nor combined with neonatal PCP had an effect on locomotor activity, however clozapine reduced activity in both cohorts.

Novel Object Recognition

Clozapine attenuated the novel object discrimination deficits induced either by isolation-rearing alone or combined neonatal PCP and isolation-rearing.

Conditioned Emotional Response

Isolation-rearing alone or combined with neonatal PCP produced deficits in cue- and context-mediated freezing, but clozapine only reversed the later deficit.

Social Interaction

Only isolation combined with neonatal PCP reduced social interaction but the deficit was unaffected by clozapine.

Conclusions

- Neither isolation alone nor combined with neonatal PCP had any affect on locomotor activity, whilst clozapine reduced activity in both cohorts.
- Both isolation alone and combined with PCP impaired novel object discrimination and acute clozapine treatment attenuated this visual learning and memory deficit in both manipulations.
- Both isolation alone and combined with neonatal PCP induced deficits in cue and contextual fear motivated memory, however clozapine was only effective in attenuating the deficit induced by combined PCP and isolation rearing.
- Isolation alone had no effect on social interaction, however combined with neonatal PCP it reduced both the total social interaction and individual behavioural components. Consistent with clinical observation clozapine had no effect on this deficit.

- The data suggest that this ‘dual-hit’ neurodevelopmental model may be a major improved paradigm over isolation rearing alone to also enable assessment of ‘negative-like’ symptoms of schizophrenia and the reversal of this by potential novel therapeutic agents. Consistent with clinical data the deficit was unresponsive to the typical antipsychotic, clozapine.

Acknowledgements
We thank Mr Ian Topham and Miss Stacey Knapp for technical assistance and F. Hoffmann-La Roche Ltd for financial support.

References