Introduction

- Schizophrenia is a complex, chronic neuropsychiatric disorder characterised by 3 symptom domains: positive symptoms, negative symptoms and cognitive deficits.
- GABAergic dysfunction has been strongly implicated in the symptomatology of schizophrenia (Harrison and Weinberger 2005, Beneyto et al 2011).
- Tonic GABAergic dysfunction is thought to contribute to cognitive deficits with GABA-containing receptors being the focus for recent research (Atack 2011).
- Our sub-chronic PCP rodent model has been consistently shown to induce long-lasting cognitive deficits in rats, similar to those shown in schizophrenia patients (Neill et al 2010).
- PCP administration has been shown to alter expression of a variety of genes in humans (Liu et al 2010) and in rats (Kaiser et al 2004).
- AIM: To investigate GABAergic gene expression in cortical, striatal, hippocampal and cerebellar brain regions in the sub-chronic PCP rodent model of schizophrenia symptomatology, with a focus on tonic GABAergic inhibition.

Materials & Methods

- Adult female Hooded-Lister rats received bi-daily injections of PCP (2mg/kg i.p.) or vehicle (0.9% saline i.p) for 7 days, n=5 per group followed by a 7 day washout period before killing by CO2 overdose and cervical dislocation.
- Brains were removed on ice and dissected into the following regions of interest:
  - Frontal Cortex (A) (Bregma = +4.7mm - +3.2mm)
  - Striatum (B) (Bregma = +1.6mm - 0.3mm)
  - Hippocampus (C) (Bregma = -2.5mm - 3.8mm)
  - Cerebellum (D) (Bregma = -10.3mm - 12.7mm)


- RNA was extracted using Trizol® reagent and Invitrogen miniprep columns and converted to cDNA using a Qiagen reverse transcription kit.
- Gene expression was measured with SYBR green qRT-PCR.
- Data were shown as mRNA molecules relative to GAPDH ±S.E.M and analysed using REST software.

Results

- These data show sub-chronic PCP causes significant down-regulation of α4 and α5 (p<0.001) and gamma-2 (p<0.01) GABA_A subunit genes in rat frontal cortex
- Significant down-regulation of other GABA-related genes including GAD1(GAD67) (p<0.01), GAT-1 (p<0.05) and GAT-3 (p<0.01) and calcium-binding proteins parvalbumin (p<0.01) and calretinin (p<0.001) was also observed in PCP-treated frontal cortex
- A reduction in GFAP transcription was also observed in PCP-treated frontal cortex (p<0.05)
- A reduction in GFAP transcription was observed in the striatum (p<0.05)
- An increase was observed in delta subunit transcription in the cerebellum (p<0.05)
- Frontal Cortex data are also shown as 2-ΔΔCt expression ratios relative to vehicle transcription

Conclusions

- These data show sub-chronic PCP causes significant down-regulation of multiple GABAergic genes in the frontal cortex with no significant change in transcription in other regions.
- These data suggest that dysfunction of tonic GABA_A receptor –mediated signalling in the frontal cortex could play a role in the behavioural and cognitive deficits shown in the sub-chronic PCP rat model summarised in Neill et al (2010).
- These data also show close similarity between the GABAergic deficits in the sub-chronic rodent model and human post-mortem studies into GABAergic deficits in schizophrenia. (Lewis et al 2008, Guidotti et al 2000, Hashimoto et al 2008)

References

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