INVESTIGATION INTO THE EFFECTS OF ACUTE AND SUB-CHRONIC PHENCYCLIDINE TREATMENT ON BRAIN TISSUE N-ACETYLASPARTATE LEVELS IN THE RAT

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Previously, we showed that acute and sub-chronic phencyclidine (PCP) could induce a cognitive deficit in rats, in a reversal learning paradigm, a model with potential relevance for the pathology of schizophrenia (Abdul-Monim *et al.* 2003, Reynolds *et al*. 2004a). Recently our data demonstrate that PCP can induce changes in excitatory and inhibitory amino acid levels in selected regions of the rat brain (Idris *et al*. 2004). N-acetylaspartate (NAA) has a high concentration in the brain and is located in neurons. Alterations in NAA have been used a marker of neuronal function and NAA deficits may reflect cellular dysfunction and neuronal loss. Indeed, magnetic resonance spectroscopy studies have shown reductions of cortical and hippocampal NAA in schizophrenia. A regionally selective NAA deficit has been observed in the temporal cortex of schizophrenics in a recent post-mortem study (Nudmamud *et al*. 2003) and in rats administered PCP for 28 days (Reynolds *et al*. 2004b). In order to understand neurochemical changes that may underlie PCP-induced cognitive impairment, we have investigated brain tissue NAA levels following acute and sub-chronic administration of PCP at doses that were effective in our behavioural paradigm. We have measured NAA in the frontopolar cortex (acute study only), prefrontal cortex, cingulate cortex, and dorsal and ventral hippocampus from brain tissue of adult female hooded-Lister rats (Harlan, UK) housed under standard laboratory conditions. Experiment I: PCP (1.5mg/kg) or saline was administered i.p 30 min prior to decapitation (n=10). Experiment II: Saline or PCP (2.0 & 5.0mg/kg) was administered i.p twice daily for 7 days (n=6). Following a 7-day drug free period, animals were decapitated. Brains were frozen on CO_2 ice and then dissected using a rat brain matrix. The NAA content was measured using isocratic HPLC with UV detection (Reynolds *et al* 2004b). Data (mean ±SEM of nmoles/mg) were analysed by one way ANOVA using SPSSv11.

Acute PCP at 1.5mg/kg reduced NAA levels in the frontopolar cortex from 6.30±0.21 (vehicle) to 5.24±0.5 (PCP 1.5mg/kg, P=0.057) and prefrontal cortex from 6.43±0.5 (vehicle) to 5.34±0.3 (PCP 1.5mg/kg, P=0.063). No changes in NAA were observed in the cingulate cortex and the dorsal and ventral hippocampus. Sub-chronic PCP at 2mg/kg and 5mg/kg significantly reduced NAA levels in the prefrontal cortex from 5.99±0.3 (vehicle) to 5.11±0.2 (2mg/kg, P<.05) and 4.82±0.1 (5mg/kg, P<0.01), but again no significant effect was seen in the cingulate cortex, dorsal and ventral hippocampus. These regional effects of PCP on NAA levels are consistent with our previous finding that acute PCP can induce area-specific changes in tissue amino acid levels (Idris *et* al 2004), though further studies will be required to examine the effects of sub-chronic PCP on amino acid levels. In conclusion, treatment with PCP leads to a reduction in NAA levels in selected brain regions, an effect that is most marked following sub-chronic treatment. These changes may contribute to the impairments induced by PCP in the reversal learning paradigm in rats.

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