Effects of PCP on the prefrontal cortex metabolism in intact, anesthetized rats

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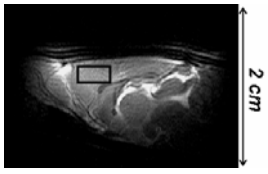
Objective. **A**cute administration of phencyclidine (PCP) in rats has been shown to mimic some features of schizophrenia, including behavioral disturbances, increased dopaminergic activity and prefrontal cortex dysfunction. PCP is a non-competitive antagonist of NMDA receptors, which are involved in glutamatergic neurotransmission. Therefore its use may be relevant to address the question of an altered glutamatergic transmission in schizophrenia (1). Prefrontal cortex is one of the main sites of action identified for PCP (2). Systemic acute administration of PCP has been shown to increase glutamate efflux in this brain region in rodents (3). The present study aims at assessing the global metabolism in the prefrontal cortex in intact anesthetized rats, before and after the injection of PCP using single-voxel ^{1}H MRS.

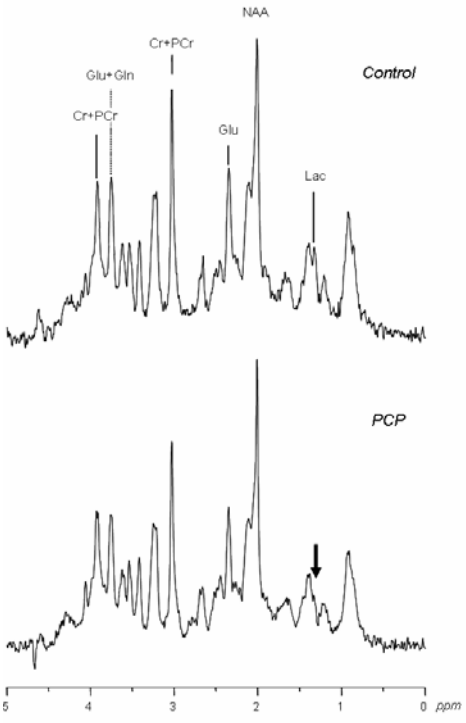
Methods. Male Sprague-Dawley rats were anesthetized with isoflurane (1.8 – 2.2 %) in O_2 / N_2O (0.4 / 0.6 $L.h^{-1}$). An intraperitoneal line was placed to deliver either saline (n = 6) or PCP (n = 6, 10 $mg.kg^{-1}$) in each animal. Experiments were conducted at 9.4 T. For spectra acquisition, a STEAM sequence with short echo time (TE = 2 ms, TR = 4.5 s) was used (4). Spectra were acquired in the prefrontal cortex (VOI = 32 µl) during 30 minutes before (baseline) and for 140 minutes after the PCP or saline bolus was given. Absolute concentrations for metabolites were assessed with LC-Model using water as an internal reference. Concentrations time courses were obtained for 8 to 10 metabolites with a temporal resolution of 10 minutes. Differences between PCP and control, post-injection vs. pre-, were tested using repeated measures ANOVA with adjustment for multiple comparisons.

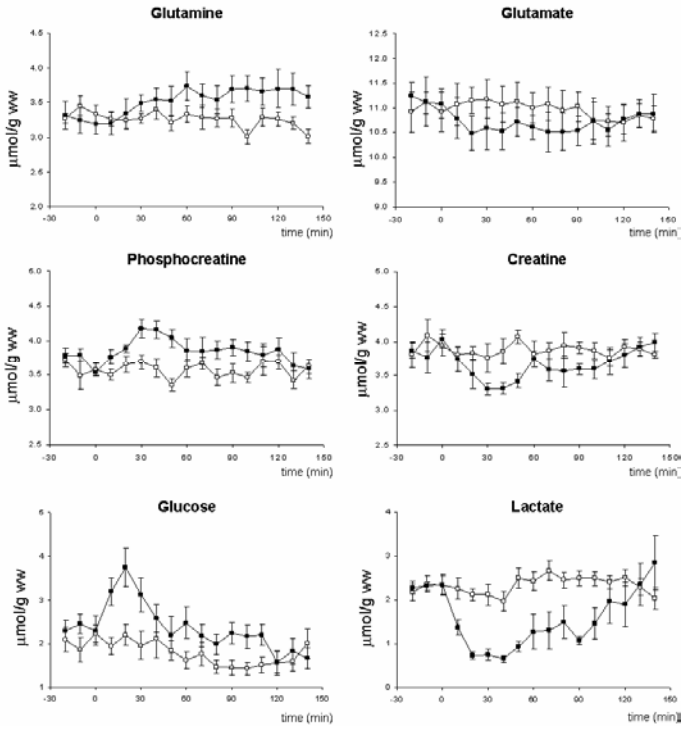
Results. The pool of glutamine (Gln, + 11 %) was significantly increased in the PCP rats compared to baseline ($p < 0.0001$). Glutamate (Glu, - 6 %), creatine (Cr, - 9 %) and lactate (Lac, – 70 %) were significantly decreased in PCP rats after the injection ($p < 0.0001$ for Glu and Lac, $p = 0.0052$ for Cr). Glucose (Glc, + 70 %) and phosphocreatine (PCr, + 11 %) were significantly increased in the PCP vs. the control group ($p < 0.05$). The total pool of Glu + Gln remained constant over time. For the PCP rats, Gln and Glc were significantly altered at 140 minutes compared to time of injection (time t = 0), but most metabolites returned to baseline levels.

Discussion. These results show a significant effect of PCP on energetic metabolism and neurotransmission in the prefrontal cortex. Increased glutamine and decreased glutamate levels likely reflect altered glutamatergic transmission following PCP administration. Interestingly, an elevated glutamine / glutamate ratio has been found in prefrontal cortex and cerebrospinal of never-treated schizophrenic patients (5,6). Energy metabolism was also affected. The initial increase in glucose (+ 70 %), and the equivalent decrease in lactate (- 70 %), suggest that glycolysis may be inhibited following PCP administration. PCr increase and concomitant Cr decrease likely reflect a decrease in energy utilization.

In conclusion, by using localized short-echo time ^{1}H MRS with quantitative LC Model analysis at 9.4 T, metabolic alterations caused by an acute dose of PCP were evidenced in the prefrontal cortex non invasively, over a relatively long experimental time period. This pharmacologic model of schizophrenia will be used in future studies to evaluate the effect of antipsychotic drugs on prefrontal cortex metabolism in intact animals.







Top left. Sagittal image of a rat brain. The box indicates the voxel in which spectra were acquired.
Middle. Spectra acquired 30 minutes after injection. Lactate is visibly reduced (arrow). NT=128.
Right. Time courses of metabolites. Mean ± SEM. Open squares, control rats, closed squares, PCP rats.

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