Renormalisation by antipsychotics of the amphetamine and phencyclidine induced changes in dialysate amino acid levels in the rat mediodorsal thalamus - relevance for schizophrenia

Leenaars CHC, O'Connor WT*, Duffy A*, Vollmer FF, De Lange ECM**, Glennon JC
Solvay Pharmaceuticals Research Laboratories, Weesp, *Dept of Human Anatomy and Physiology, Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin, Ireland, **LACDR, Division of Pharmacology, University of Leiden, Leiden

The mediodorsal thalamic nucleus (MDT) is the primary thalamic projection area to the medial prefrontal cortex (mPFC). Altered MDT activity may underlie clinical psychosis as increased thalamic activity is observed during psychotic episodes. In this study, microdialysis is employed to examine the effect of the psychomimetics amphetamine and phencyclidine (PCP) alone and in combination with haloperidol or clozapine on dialysate glutamate (Glu), aspartate (Asp) and GABA levels in the MDT of intact conscious rat brain. Data is shown as mean±SEM percentage change from basal values and statistically compared (two-way repeated measures ANOVA followed by post-hoc Students t-test) *vs* the control (vehicle alone) group. Amphetamine (3 mg/kg *i.p.*) has no effect on Glu or Asp but is associated with a sustained increase in GABA (+115±26%, 60 min, $p<0.05$) levels in the MDT. In contrast, PCP (10 mg/kg *i.p.*) is associated with sustained increases in Glu (+251±84%, 80 min, $p<0.05$), Asp (+201±66%, 80 min, $p<0.05$) and GABA (+161±46%, 100 min, $p<0.05$) levels in the MDT. Co-administration of amphetamine or PCP together with haloperidol (0.3 mg/kg *i.p.*) or clozapine (30 mg/kg *i.p.*) reverses the sustained increase in GABA levels in the MDT associated with both psychomimetics. In addition, co-administration of PCP together with haloperidol or clozapine reverses the sustained increase in Glu and Asp levels in the MDT associated with PCP alone. It is tempting to speculate that the positive symptoms of psychosis as induced by these drugs may be associated with increased extracellular GABA levels in the MDT while the negative and cognitive symptoms of psychosis may be associated with increased Glu and Asp levels in the MDT. Furthermore, modulation of amino acid transmission in the MDT may represent a novel therapeutic strategy for antipsychotic drug action.

Jeffrey C. Glennon, Dept. of Biological Lead Optimisation, Solvay Pharmaceuticals Research Laboratories, Weesp, t +31-294-47-9704, e-mail jeffrey.glennon@solvay.com

Poster session: Neuroscience 2.