Carlsson's hypothesis revisited: animal models of psychosis are associated with an imbalance between mediodorsal thalamic-medial prefrontal cortical feed-forward and feed-back transmission. A dual probe microdialysis study

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). According to Carlsson's hypothesis, lowered MDT neurotransmission to the mPFC may underlie clinical psychosis. In this study, microdialysis is employed to examine the effect of the psychomimetics amphetamine, phencyclidine (PCP) and quinpirole on dialysate glutamate (Glu) and aspartate (Asp) levels in the MDT and mPFC 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) *v's* the control (vehicle alone) group. Amphetamine (3 mg/kg *i.p.*) has no effect on MDT or mPFC dialysate Glu or Asp levels. In contrast, PCP (10 mg/kg *i.p.*) is associated with sustained increases in Glu (+251±84%, 80min, $p<0.05$) and Asp (+201±66%, 80min, $p<0.05$) dialysate levels in the MDT, but has no effect on Glu or Asp levels in the mPFC. Quinpirole (3 mg/kg *i.p.*) however is not associated with changes in Glu and Asp levels in the MDT, but is associated with decreases in mPFC Glu (-48±6%, 100 min, $p<0.01$) levels but not Asp levels. Comparison of the ratios between MDT and mPFC Glu levels reveals a value of 0.82, 0.76, 1.89 and 2.25 for the control, amphetamine-, PCP- and quinpirole-treated groups respectively. In addition, the ratios between MDT and mPFC Asp levels are 0.87, 0.67, 2.41 and 0.87 for the control, amphetamine-, PCP- and quinpirole-treated groups respectively. The data suggests that drug-induced psychosis is associated in part with lowered feed-forward MDT-mPFC glutamatergic transmission relative to glutamatergic transmission in the feedback thalamocortical pathway. Imbalance between these reciprocal pathways may underlie clinical psychosis rather than hypofunctionality of the feed-forward MDT-mPFC pathway alone. Modulation of glutamatergic transmission in the reciprocal MDT-mPFC 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

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