The aim of the study was to create a new animal model of schizophrenia based on a neurodevelopmental hypothesis. The central idea of the project has been that a transient insult at early postnatal age will reveal itself in the form of delayed distinct behavioral changes that can be related to schizophrenia. The experimental design used intracerebroventricular (icv) infusion of N-acetyl-L-aspartyl-L-glutamate (NAAG) to rats at postnatal day 12, followed by combination of histology and quantitative morphology in brain tissue obtained within 24 and 96 hours of the NAAG administration and used to investigate possible neurodegeneration. Finally, a battery of behavioural tests was performed several weeks later (late adolescence/early adulthood). NAAG is the most abundant neuropeptide and interacts with the active site of metabotropic glutamate receptors (mGluR II), however, it is also an agonist at NMDA receptors.

Neonatal icv infusion of NAAG resulted in detectable damaged neurones in gyrus dentatus. The damage appeared greater at 24 hours, as compared to 96 hours, after the infusion. The presence of damaged neurons was easily demonstrated by Nissl stain, Fluoro Jade B staining combined with Hoechst 33342 and by TUNEL technique.

Neonatal administration of NAAG resulted in the appearance of specific, potentially abnormal, behavioural traits in young adult rats as indicated by open field. Thus, there was an increased spontaneous grooming and a decrease in immobility and grooming after administration of GBR 12909 (inhibitor of dopamine transporter). The lesioned rats were, however, less susceptible to the effects of the NMDA antagonist MK-801, both in the open field behaviour (immobility) and in the tests of prepulse inhibition of acoustic startle response. Interestingly, the early postnatal administration of NAAG resulted in reduced specific binding of [3H]glutamate in entorhinal cortex and in the reduced specific binding of [35S]TBPS in hippocampus of adult rats.

The neonatal NAAG model of schizophrenia was compared with another known neurodevelopmental animal model of schizophrenia based on neonatally-induced lesions using quinolinic acid (QUIN). Following QUIN infusion, the damage to hippocampus and cortex was greater than that caused by NAAG. Early postnatal QUIN dramatically reduced specific binding of [3H]glutamate in striatum, hippocampus and entorhinal cortex and in addition, decreased high-affinity uptake of [3H]choline, particularly in the left hippocampus. All these changes have been observed in postnatally lesioned rats allowed to reach early adulthood. It is possible that QUIN-induced changes in the cholinergic system may have been linked to the memory deficit as detected in the QU1Nlesioned
rats using Morris water maze. No similar changes have been, however, detected in NAAG-infused rats. Furthermore, the QUIN-lesioned rats, unlike those infused with NAAG, showed a deficit in play behavior on postnatal day 22 and a decrease in immobility in young adult rats. In addition, when compared to NAAG-infused rats, the QUIN-lesioned animals showed higher locomotory and exploratory activity following a challenge with GBR 12909.

It is concluded that the early postnatal administration of both substances NAAG and QUIN to rats represents a potentially useful neurodevelopmental model of schizophrenialike behaviour and shows constructive and face validity.