POST-SYNAPTIC GLUTAMATE DYSFUNCTION INDUCED BY KETAMINE SELF-ADMINISTRATION

1)Caffino L. 2)Piva A. 3)Mottarlini F. 4)Giannotti G. 5)Di chio M. 6)Venniro M. 7)Yew DT. 8)Chiamulera C. 9)Fumagalli F.

University of Milan

Introduction. Ketamine is a noncompetitive antagonist of NMDA receptor and has been long used as an anesthetic agent in humans and veterinary medicine. Recently, ketamine abuse is becoming a major health problem worldwide due to its psychotomimetic and reinforcing properties. Despite recent data have identified a rapid antidepressant response following a single infusion of the compound in subjects with major depression, various lines of evidence have shown that repeated exposure to ketamine induces cognitive dysfunction and schizophrenia-like symptoms. Given that the non-medical use of ketamine has grown, therefore, it is imperative to understand the neuroplastic effects induced by repeated consumption.

Aims. Taking into account the crucial importance of unveiling the mechanism(s) through which ketamine mediates its multiple actions, the major aim of our work was to investigate in detail the contribution of the major components of the glutamatergic synapse following contingent chronic ketamine exposure, focusing our attention on medial prefrontal cortex (mPFC) and hippocampus (Hip), two brain regions involved in compulsive drug-seeking and drug-related cognitive disorders.

Methods. Adult male rats self-administered (S/A) ketamine (0.5 mg/kg/infusion) for 35-43 days and were sacrificed 24 hours after the last drug exposure, immediately before the daily ketamine S/A session. Molecular analyses were performed on the crude synaptosomal fraction of mPFC and Hip tissues by Western-blot analysis. Molecular data were collected in individual animals and were analyzed by an unpaired two-tailed Student's t test.

Results. Rats trained to self-administer ketamine (0.5 mg/kg/infusion) met the acquisition criteria at different session, maintained constant ketamine intake during 35-43 days of S/A. At the molecular level, our findings reveal an overall and region-dependent down-regulation of glutamate receptor expression. In particular, NMDA receptor subunits (the obligatory subunit GluN1 and the accessory subunits GluN2A and GluN2B) were reduced in the mPFC, whereas AMPA receptor protein levels (GluA1 and GluA2 subunits) were down-regulated in Hip. Interestingly, the scaffolding proteins specific for NMDA and AMPA receptors were reduced as well with the same region-dependent profile. Moreover, ketamine S/A down-regulated in both areas the metabotropic mGluR5 receptor.

Conclusion. These results reveal dynamic changes in the post-synaptic glutamatergic component of the mPFC and Hip delineating an impairment of glutamate homeostasis as a critical component of long-term ketamine S/A. While ketamine-induced changes in translation might alter the composition of NMDA and AMPA receptor complexes, an altered expression of the scaffolding protein may impair glutamate receptors cycling, a dynamic process that is pivotal for glutamate neurotransmission.

Further, this brain region-dependent decrement, similarly observed in humans and animal models of schizophrenia, may represent a specific feature of the human disease endophenotype.