Molecular mechanisms underlying glutamatergic dysfunction in schizophrenia: Therapeutic implications

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Early models for the etiology of schizophrenia focused on dopamine neurotransmission because of the powerful anti-psychotic action of dopamine antagonists. Nevertheless, recent evidence increasingly supports a primarily glutamatergic dysfunction in this condition, where dopaminergic disbalance is a secondary effect. A current model for the pathophysiology of schizophrenia involves a dysfunctional mechanism by which the NMDA receptor (NMDAR) hypofunction leads to a dysregulation of GABA fast- spiking interneurons, consequently disinhibiting pyramidal glutamatergic output and disturbing the signal-to-noise ratio. This mechanism might explain better than other models some cognitive deficits observed in this disease, as well as the dopaminergic alterations and therapeutic effect of anti-psychotics. Although the modulation of glutamate activity has, in principle, great therapeutic potential, a side effect of NMDAR overactivation is neurotoxicity, which accelerates neuropathological alterati