Abstract

Background Effort has been made in the past decades to clarify the pathogenesis of schizophrenia and much of this progress has centered on the role of various neurotransmitters other than dopamine, with glutamate receptor dysfunction being one of the most attractive hypotheses. There were gaps in explaining the various aspects of schizophrenia solely by dopaminergic hyperstimulation. It has been suggested that the combined dysfunction of the dopamine and glutamate neurotransmitter systems could resolve the skepticisms in the pathogenesis of schizophrenia in a much more convincing way. The NMDA receptor hypofunction which centers this hypothesis plays a particularly important role. The fundamental concept of this hypothesis derives from the effects of NMDA receptor antagonists and post mortem findings in brain samples of schizophrenia patients. Accumulating evidence has been proving the efficacy of various glutamatergic agents in the treatment of schizophrenic symptoms in particular negative and cognitive symptoms. These likely render further research necessary and this could be a milestone in future improvement in pharmacotherapy in schizophrenia.

Aims In this article, I intend to conceptualize the pathophysiology of schizophrenia from the dopamine hypothesis in the past decades to a more comprehensive view of the illness based on recent researches and evidence for the postulated glutamatergic hypothesis.

Method The overview was developed through literature review with access to major electronic databases, using specific keywords and inclusion/exclusion criteria.

Results A broader review of evidence supports the glutamate hypothesis, encompassing the molecular aspects like receptor expression, synaptic abnormalities and the altered neural circuitry and impaired connectivity of the brain; the neurodevelopmental and neurodegenerative skepticisms seems better explained with the glutamatergic hypothesis. Modest effect was found with preliminary studies of glutamatergic agents in treatment of schizophrenia.

Conclusion Glutamate hypothesis is not to replace the dopamine's leading status, but to encompass the whole concept of neurotransmission dysfunction and altered connectivity. Future trend in development of antipsychotic agents would be essential to possess multi-site and multimodal properties. Environmental and/or genetic manipulation of the glutamate system may be the future target in the development of schizophrenia treatment.