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Mini Review

Developing New Antipsychotic Agents: The Need to Understand Potential Targets

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Abstract

Present clinical available antipsychotics are mainly effective to treat positive symptoms of psychosis whereas their efficacy is partial for negative symptoms deficits which limit their use. Researchers are constantly making their efforts to explore new possible therapeutic strategies for the treatment of psychosis to manage symptoms at different stage of disease pathologies. In order to develop new treatments and prognostic outcomes, it is very much critical and essential to understand the disease pathophysiology that contributes to its effective management. Thus, in the present article efforts have been made to address novel molecular targets beyond the dopamine hypothesis, including GABA, glutamate, serotonin, inflammatory cytokines, oxidative stress and matrix metalloproteinase. Moreover, these targets may be probably incorporated with new treatment strategies at various phases of the disorder.

Keywords: *Antipsychotics; Dopamine; NMDA Receptors; Psychosis; Pathophysiological Targets*

Introduction

Psychosis is a multifactorial brain disorder that affects approximately 1% of the total population worldwide [1]. It is categorized into positive symptoms (delusions, hallucinations), negative symptoms (lack of emotional expression, social withdraw, suicidal thoughts) and cognitive decline. Pathophysiologically, it is associates with the alteration of neurotransmitters system including dopaminergic dysfunction, GABAergic hypoactivity, glutamatergic hypofunction, disturbances in the extracellular matrix, neuroinflammation and oxidative stress [2]. NMDA receptors (NMDAR) have inhibitory control on neurotransmission of dopaminergic neurons therefore hypofunctioning of NMDA receptors loss the control on dopaminergic functioning [3]. In many preclinical studies, it has been observed that NMDA receptors antagonists such as ketamine, phencyclidine etc. appeared to disrupt the NMDA neurotransmission which leads to increased dopaminergic transmission alike to that seen in psychotic brain [4,5]. Declined NMDA transmission can lead to reduce prefrontal activity by decreasing the mesocortical-dopaminergic transmission associated with cognitive symptoms of psychosis [6]. NMDA receptors antagonists are found to escalate glutamate release at certain synapses that abnormally raised the glutamate transmission on non-NMDAR in AMPA receptors [7]. Moreover, the fundamental pathological role also appears to be instigated by NMDAR hypofunction on GABAergic interneurons followed by the disinhibition of glutamatergic transmission and hyperactivation of non-NMDARs on pyramidal neurons [8]. While the involvement of serotonin is still not clear completely in psychosis. But, increased 5-HT1A receptor density and reduced cortical 5-HT2A receptor density have been observed in psychosis. Some psychedelic agents like dimethyltryptamine, lysergic acid diethylamide and psilocybin cause alterations in perception, and cognition similar to psychotic symptoms. Chronic nitrosative and oxidative stress in-

duces during embryogenesis or mitochondrial dysfunctioning and chronic inflammation also seems to contribute in the pathophysiology of psychosis by reacting with cell components like lipids, proteins, DNA and mitochondria leads to neuronal degradation and abnormal neurogenesis [9]. Additionally, microglial activation is showed to trigger the pro-inflammatory cytokines such as IL-6, TNF-α and IFN-γ in order to control the synaptic maturation, neuronal migration and GABAergic and dopaminergic neuronal differentiation [10]. If there is an imbalance of these pro-inflammatory chemicals can produce neuronal inflammation and degeneration of neurons, thus associating with various neuropsychiatric disorders including psychosis. NMDA receptors antagonists offer a suitable animal model of psychosis by activating microglial cells. Interestingly, matrix metalloproteinase (MMPs) are also contributes to the pathophysiology of psychosis by degrading extracellular matrix (ECM). Biologically ECM composition can affect fundamental parts of glutamatergic transmission by encouraging integrin signaling and AMPAR overstimulation which in turn produce excitotoxic damage to glutamatergic neurons [11]. Brain ECM is composed of chondroitin sulfate proteoglycans (CSPGs), hyaluronic acid and glycoproteins. CSPGs are the controllers of brain ECM and hyaluronan exemplifies the backbone of ECM. CSPGs are important elements of ECM, mainly expressed by astrocytes in amygdala are reported in psychotic brain. MMPs are entailed in the degradation of CSPGs and reduced levels CSPGs have been seen in the psychotic patients [12]. Moreover, CSPGs also interacts with dopaminergic, GABAergic and glutamatergic neurotransmitter systems. Hyaluronan component of ECM controls lateral mobility of various neurotransmitter receptors. Lateral distribution of AMPARs is enhanced after subtraction of hyaluronan-based ECM and this process enhances the AMPARs ultimately their hyperactivation. First-generation (typical) and second-generation (atypical) antipsychotics are commonly prescribed to treat the psychotic symptoms. Typical antipsychotics are effective to treat positive symptoms of psychosis by reducing dopamine receptor activity. Whereas, atypical antipsychotic agents are potential to treat positive, negative and cognitive symptoms of psychosis as they suppress the activity of dopamine D2 and 5-HT2A receptor [1]. Typical antipsychotics are effective to treat positive symptoms of psychosis by reducing dopamine receptor activity. Whereas, atypical antipsychotic agents are potential to treat positive, negative and cognitive symptoms of psychosis as they suppress the activity of dopamine and 5-HT receptor. Although these drugs have been prescribed for several decades, most of them are not successful to stop the progression of the disorder and also unwanted side-effects (diabetes, dyslipidemia, hypertension, extra-pyramidal syndromes), non-compliance, incomplete efficacy and high risk of psychotic relapse [13]. The atypical drugs are chosen over typical because of the lesser risk of side effects. Consequently, with the partial improvement associated with atypical antipsychotics, different interventions approaching new targets are the leading focus of researchers. But, it is very important for a drug developer to have a thorough understanding of emerging targets of psychosis. The present paper discussed the emerging targets of psychosis which can encourage researchers to explore and develop effective therapeutic molecules with negligible side effects.

Conclusion

Despite disease pathogenic complexity researchers have elucidated very few antipsychotics, most of them act by inhibiting dopamine D2 receptors but side effects associated with them have provoked the scientists to introduce novel antipsychotic drug would work via non dopaminergic mechanisms. Owing to a significant improvement in the field of neuropharmacology, new therapeutic targets has been identified that would reduce the underlying process. Moreover, multi-targeted approach is new therapeutic strategy to treat this complex disorder. Present article highlights the different aspects of pathophysiological targets that can potentially provide therapeutic opportunities to treat the disorder effectively. Future investigations are necessary in order to evaluate the pathophysiological contributions of these mechanisms responsible for the development of psychotic symptoms and most favorable treatment approaches.

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Conflict of Interest

The authors declare no conflict of interest.

Bibliography

1. Yadav M., *et al*. "Potential effect of spermidine on GABA dopamine acetylcholinesterase oxidative stress and proinflammatory cytokines to diminish ketamine induced psychotic symptoms in rats". *Biomedicine Pharmacotherapy* 98 (2018): 207-213.

2. Yadav M., *et al*. "Brain targeted oral delivery of doxycycline hydrochloride encapsulated Tween coated chitosan nanoparticles against ketamine induced psychosis behavioral biochemical neurochemical and histological alterations in mice". *Drug Delivery* 24.1 (2017): 14429-1440.

3. Spear N., *et al*. "Preclinical profile of a novel metabotropic glutamate receptor 5 positive allosteric modulator". *European Journal of Pharmacology* 659.2-3 (2011): 146-154.

4. Chatterjee M., *et al*. "Effect of 'chronic' versus 'acute' ketamine administration and its 'withdrawal' effect on behavioural alterations in mice: implications for experimental psychosis". *Behavioural Brain Research* 216.1 (216): 247-254.

5. Langen B., *et al*. "Effect of PDE10A inhibitors on MK-801-induced immobility in the forced swim test". *Psychopharmacology* 221.2 (2012): 249-259.

6. Keshavan MS., *et al*. "New drug developments in psychosis: challenges, opportunities and strategies". *Progress in Neurobiology* 152 (2017): 3-20.

7. Chatterjee M., *et al*. "Neurochemical and molecular characterization of ketamine-induced experimental psychosis model in mice". *Neuropharmacology* 63.6 (2012): 1161-1171.

8. Cohen SM., *et al*. "The impact of NMDA receptor hypofunction on GABAergic neurons in the pathophysiology of schizophrenia". *Schizophrenia Research* 167.1-3 (2015): 98-107.

9. Snyder MA and Gao WJ. "NMDA hypofunction as a convergence point for progression and symptoms of schizophrenia". *Frontiers in Cellular Neuroscience* 7 (2013): 31.

10. Davis J., *et al*. "Neuroprogression in schizophrenia: Pathways underpinning clinical staging and therapeutic corollaries". *Australian and New Zealand Journal of Psychiatry* 48.6 (2014): 512-529.

11. Kroken RA., *et al*. "A critical review of pro-cognitive drug targets in psychosis: convergence on myelination and inflammation". *Frontiers in Psychiatry* 5.11 (2014): 1-13.

12. Haylock-Jacobs S., *et al*. "Chondroitin sulphate proteoglycans: extracellular matrix proteins that regulate immunity of the central nervous system". *Autoimmunity Review* 10.12 (2011): 766-772.

13. Chopra K., *et al*. "MMPs: a novel drug target for schizophrenia". *Expert Opinion on Therapeutic Targets* 19.1 (2015): 77-85.

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