

EDITORIAL

New and Emerging Approaches to Treatment of Schizophrenia

The dopamine hypothesis of schizophrenia has played a dominant role in driving both basic research and drug discovery efforts in the schizophrenia field for several decades, leading to several clinically useful treatments that alter dopamine neurotransmission. It is notable that blockade of the dopamine D2 receptor produces an antipsychotic effect in humans. However, these treatments are not typically effective against the full scope of symptoms found in this disease and D2 antagonists also induce a number of adverse effects that limit their use. However, recent years have seen major advances in our understanding of dopaminergic systems in the central nervous system as well as pathophysiological changes that may underlie different aspects of schizophrenia. These advances have led to a number of novel approaches that are currently being pursued in efforts to develop new treatments that have fewer adverse effects than and are effective in treatment of symptom clusters that are not effectively treated by current drugs.

Regulation of dopamine systems remains the most well validated approach to treatment of schizophrenia and recent advances suggest the possibility of using novel approaches to regulating dopaminergic function. Tamminga offers a review of studies that have led to interesting extension of the dopamine hypothesis of schizophrenia. In this review, the paradoxical idea of using dopamine agonists to reduce dopaminergic neurotransmission through activation of autoreceptors is considered. The history of this concept is outlined and the use of partial agonists both clinically and preclinically is discussed.

The glutamatergic or NMDA receptor hypofunction hypotheses of schizophrenia represent separate, albeit non-exclusive, alternatives to the dopamine hypothesis of schizophrenia. This hypothesis holds that pathological changes in circuits involving glutamatergic neurotransmission and/or decreased NMDA receptor function may account for the positive, negative and cognitive symptoms that occur in this disease. Accordingly, multiple approaches targeting relevant biological targets involved in regulating glutamatergic transmission are considered. Chavez-Noriega and Coauthors provide a comprehensive overview of the biological significance of metabotropic glutamate receptors on these systems. Recent progress in identifying pharmacological potentiators of mGlu2/3 and mGlu5 receptors is particularly encouraging. This review outlines preclinical studies suggesting that such potentiators may ultimately prove efficacious for schizophrenia by decreasing excessive prefrontal glutamate release (mGluR2/3) or via a modulatory potentiation of NMDA receptors (mGluR5). Kinney and Sur suggest additional approaches that could modulate NMDA receptors appropriately. In this review, modulation of the glycine_B site is discussed. Since activation of the glycine_B binding site is a necessary prerequisite for glutamatergic binding and activity, potentiation of this binding site has been considered as a possible approach towards the development of therapeutics. Several such approaches are discussed, including the use of direct activators and reuptake inhibitors. It is notable that these approaches both appear to have some clinical proof of concept.

Two additional reviews are offered by Volk and Lewis and separately by Sur and Kinney, which focus on approaches that may involve both dopaminergic and glutamatergic systems to differing extents. Volk and Lewis provide a compelling pathologically-based argument that implicates a subtype of inhibitory neuronal population in the control of prefrontal information flow. The identification of these chandelier neurons as potential mediators of the prominent working memory deficits found in schizophrenic patients suggest that enhancement of this inhibitory function may improve this symptom of schizophrenia. In this regard, drugs that specifically interact with $\alpha 2$ containing GABA_A receptors and/or CB1 receptors are contemplated to provide benefit. Sur and Kinney outline a complex role for muscarinic receptors in the

possible treatment of this disease. Subtype selective potentiators of muscarinic receptor subtypes have been lacking. Thus, the role of this highly homologous receptor family has not been fully elucidated. The present review considers the use of recently described murine knockout models and more selective pharmacological agents and suggests that M1 and M4 receptors may be particularly useful as novel drug targets for this disease. More preliminary evidence also suggests that M2 and M5 receptors could represent additionally interesting targets. Recent progress in developing selective pharmacological tools by targeting less-conserved ectopic binding sites is also discussed.

Finally, Aichhorn and Coauthors review gender based differences in the side-effect profile of newer atypical antipsychotic medications. This review outlines multiple differences that may contribute to male-female differences in disease presentation, therapeutic efficacy and side-effect profile.

The present edition of *Current Neuropharmacology* provides a comprehensive overview of the current state of the newest emerging targets contemplated for the treatment of schizophrenia. The high level of interest within academia and industry for each of the reviewed approaches suggests that there is a high likelihood that some of these approaches may be clinically tested with new pharmacological agents in the near future. The impetus for such research is high, as is the need for additional treatments. In that regard, it is rewarding to offer this edition of *Current Neuropharmacology* for all neuropharmacologists and neuroscientists with an interest in schizophrenia research and therapeutics.

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