

Allosteric Modulators: Potential Treatment for Schizophrenia

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As an Honours Life Science student, Ritesh Daya worked in the department of Psychiatry and Behavioural Neuroscience. Following a presentation of his work at the Ontario Undergraduate NeuroXchange conference, Ritesh was given an award for best poster presentation by a group of delegates from The Meducator. Under the supervision of Dr. Ram Mishra, Ritesh has been investigating the pathophysiological mechanisms that underlie schizophrenia, a severe and debilitating mental illness. The focus of his research involves testing a novel allosteric modulator to potentially treat schizophrenia and other dopamine-related disorders.

Schizophrenia is a debilitating mental illness, affecting approximately seven in every 1000 Canadians.¹ Symptoms include the inability to distinguish reality from illusion, as well as deficiencies in social interaction, logical thinking, and emotional response.² While the etiology of schizophrenia remains unclear, it is thought to involve environmental, genetic, and developmental factors.¹ Schizophrenia affects not only the lives of the patients themselves, but also that of their families and friends.¹ Although it is relatively rare in the population, the disorder also puts an enormous burden on the health care system in Canada. In 2004 for example, the total economic cost associated with schizophrenia was 6.85 billion USD.⁴

Much of the complexity surrounding schizophrenia results from the fact that it is not one simple illness, but rather a combination of multiple psychological conditions. Schizophrenia commonly manifests itself between the ages of 16 and 30 and is typically diagnosed through three categories of symptoms: positive, negative and cognitive.³ Positive symptoms include hallucinations, delusions, and disorganized speech and behaviour, while negative symptoms consist of social withdrawal, anhedonia and avolition.³ Cognitive symptoms involve deficits in thinking, memory, and learning.³ In many cases, various symptoms of schizophrenia can be alleviated by drug treatment. However, there is no single cure for this severe mental illness to date.³

Schizophrenic patients commonly exhibit an aberrant dopamine system. The first traditional drug treatments for schizophrenia involved targeting the dopaminergic system using antagonists (blockers) to the dopamine receptor family. Second generation antipsychotic drugs targeted the serotonergic and glutamatergic systems. However, these antipsychotic drug treatments often prove to be inadequate, as they fail to manage all the symptoms of schizophrenia while causing debilitating side effects.^{4,5} Of these, extrapyramidal (movement) and metabolic side effects are the most common, critically limiting the therapeutic value of antipsychotic treatment.⁵⁻⁷ Patients who respond positively to treatment can often maintain functional lives. However, those who do not respond well often experience a lower quality of life and may be hospitalized as a result.⁵

Dysregulation of the dopaminergic system in animals has been shown to lead to various symptoms typical of schizophrenia.^{12,13} Thus, the dopamine receptor has become the focus of many studies investigating schizophrenia and other related psychoses.^{8-11,14} The dopamine receptor contains both an orthosteric site and an allosteric site. The former is the main active site of the receptor, while the latter is an additional binding site on the receptor that modulates activity of the active site. When the allosteric site is occupied, the conformation of the orthosteric site is altered to either increase or decrease orthosteric binding. Conventional antipsychotic drugs bind the orthosteric site of the dopamine receptor, usually with antagonistic effects.¹⁵

However, recent developments have led to a new generation of anti-psychotic drugs—called *allosteric modulators*, which can be used in the treatment of various central nervous system (CNS) diseases and disorders.⁶ As their name suggests, these drugs bind to and modulate the allosteric site of specific receptors in the CNS. This provides these drugs with the unique ability to control the intensity of a response, which is in sharp contrast to the rudimentary “on/off” control of conventional antipsychotic drugs that bind to the active site of the receptor.¹⁶ Allosteric modulators also possess several other advantages over traditional antipsychotic drugs. Firstly, they are generally more specific for the target receptor. Secondly, they require the presence of an agonist to elicit an effect and thus cannot cause abnormal activation of the receptor. Lastly, they do not compete with endogenous ligands for the orthosteric site, which increases their potency.⁶ These novel characteristics open up the potential for a reduced side effect profile—a critical shortcoming of traditional antipsychotic drugs.

As an undergraduate student under the supervision of Dr. Ram Mishra, my efforts focused on developing new therapeutic compounds that effectively regulate dopamine and other neurotransmitter systems. It is hoped that this research will generate effective therapies for the treatment of schizophrenia and other dopamine-related disorders.

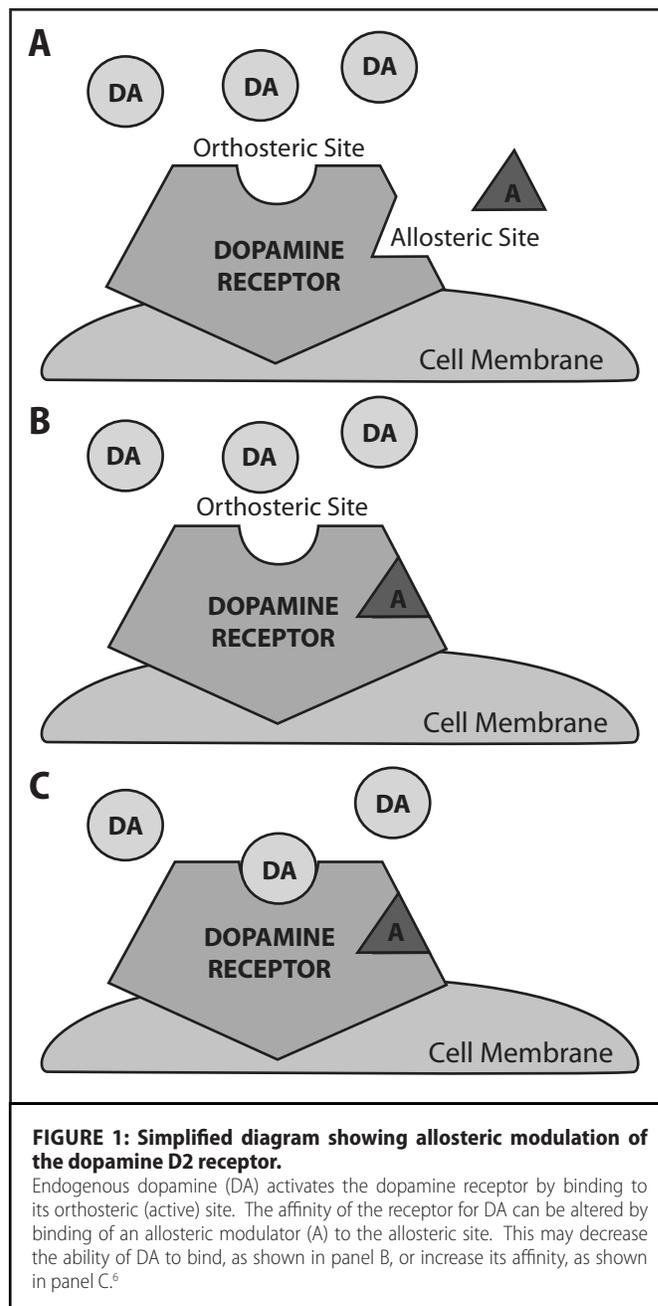
NOVEL COMPOUND FOR THE TREATMENT OF SCHIZOPHRENIA: VALIDATION IN RECEPTOR BINDING ASSAYS AND IN A PRECLINICAL ANIMAL MODEL OF SCHIZOPHRENIA

Our laboratory, in collaboration with the University of Minnesota, has designed several allosteric modulators for the dopamine receptor. These novel compounds are structurally based on the endogenous brain peptide L-prolyl-L-leucyl-glycinamide, itself an allosteric modulator of the dopamine receptor. Radiolabeled ligand binding assays were performed to evaluate these species in bovine striatal tissues. Our primary interest was to assess one of such allosteric modulators that had previously been shown to positively modulate the dopamine D2 receptor. This receptor, a subtype of the dopamine family of receptors, is specifically implicated in schizophrenia.¹⁷ Our compound of interest was capable of significantly increasing binding of [³H]N-propylnorapomorphine, a dopamine D2/D3 radiolabeled agonist, in bovine striatal samples. The increase in [³H]N-propylnorapomorphine binding under specific conditions represents significant positive modulatory activity of the compound. The success of this compound in receptor binding assays provided a basis for its assessment in a pre-clinical animal model of schizophrenia.

The observation that chronic amphetamine users often exhibit psychotic-like symptoms that closely resemble paranoid schizophrenia led to the development of a pre-clinical animal model of schizophrenia.²¹ In this model, rats are challenged with repeated doses of amphetamine, which results in the development of schizophrenia-like behaviors such as defects in movement and social interaction.^{18-20,22,23} Interestingly, low doses of our drug reversed schizophrenic defects in this animal model.

Biochemical changes were subsequently measured in postmortem brain tissue with high performance liquid chromatography. In the striatum—an area of the brain highly implicated in schizophrenia—we observed an increase in striatal dopamine in amphetamine-sensitized rats.⁵ This change was also prevented in rats concurrently treated with amphetamine and our allosteric compound. These results have significant implications for treating schizophrenia during early diagnosis and once symptoms have fully developed.

Further validation of our findings is required prior to offering this compound as a treatment for schizophrenia. Our future goals include evaluating this compound in other well-established models of schizophrenia, developing the drug further and testing in human clinical trials. To date, our laboratory has completed assessing the drug's toxicological profile and verified its safety at various concentrations. Gross examination of organs showed no toxic effects on the liver, kidney, and brain at five times the effective dose. We have recently filed for an international patent after obtaining a provisional patent for this novel compound.



CONCLUSION

Allosteric modulators hold significant potential for the treatment of neurological disorders. Unlike drugs that bind to the orthosteric site, allosteric modulators have the advantage of increased selectivity, modulatory control, and non-competitive binding in the presence of endogenous ligands. Specifically, our lab's allosteric compound was successful in preventing and treating the development of schizophrenic-like symptoms in an animal model of schizophrenia. Of particular importance is its ability to do so with few extrapyramidal or metabolic side effects, a significant shortcoming of current antipsychotic medications. Our findings warrant further research in the development of compounds that may successfully treat schizophrenia and potentially other mental illnesses. ■

Reviewed by Dipa Basu, PhD Candidate

Dipa Basu is a PhD candidate under the supervision of Dr. Ram Mishra at McMaster University in the Department of Medical Sciences. She is currently studying drug receptor interactions and their implications in neurological disorders such as schizophrenia and Parkinson's disease.

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