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Kynurenine aminotransferases and the prospects of inhibitors for the treatment of Schizophrenia

Schizophrenia is a complex neuropsychiatric disorder with limited treatment options and highly debilitating symptoms, leading to poor personal, social, and occupational outcomes for an afflicted individual. Our current understanding of schizophrenia suggests that dopaminergic and glutamatergic systems have a significant role in the pathogenesis of the disease. Kynurenic acid, an endogenous glutamate antagonist, is found in elevated concentrations in the prefrontal cortex and cerebrospinal fluid of patients with schizophrenia, and this affects neurotransmitter release in a similar manner to previously observed psychotomimetic agents, such as phencyclidine, underlining the molecular basis to its link in schizophrenia pathophysiology. Kynurenic acid is a breakdown product of tryptophan degradation, through a transamination process mediated by kynurenine aminotransferase (KAT) enzymes. There are four KAT homologues reported, all of which are pyridoxal 5'-phosphate-dependent enzymes. All four KAT isoforms have been analysed structurally and biochemically, however the most extensive research is on KAT-I and KAT-II. These two enzymes have been targeted in structure-based drug design as a means of normalising raised kynurenic acid levels. The most potent KAT-I inhibitors and KAT-II inhibitors include phenylhydrazine hexanoic acid derivatives and a pyrazole series of compounds, respectively. KAT inhibitors have been shown to be effective in reducing kynurenic acid production, with accompanying changes in neurotransmitter release and pro-cognitive effects seen in animal studies. This review will discuss the characteristics pertaining to the different KAT isoforms, and will highlight the development of significant KAT inhibitors. KAT inhibitors have great potential for therapeutic application and represent a novel way in treating schizophrenia.

Biography

Richard Sadig has completed an honours degree in Pharmacy from the University of Sydney focusing on drug inhibitors for the treatment of schizophrenia. He came first in his cohort for Drug Discovery and Design and received the Dean's award for Academic Excellence. Since then he has completed a Postdoctorate degree in Medicine and Surgery at the University of Notre Dame, Sydney. He was recently appointed as Security and Advisory Committee Member for the medico-legal indemnity company AVANT in 2017 and is currently working as a Clinical Doctor in St. George Public Hospital. His goal is to one day procure a molecule that can manage the negative symptoms of schizophrenia which contributes to the overall morbidity of the patient. His position in both the Pharmacy sector and the Medicine field has helped him significantly in these goals.

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