Extended Abstract

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The Role of ABC Efflux Transporter in Treatment of Pharmaco-Resistant Schizophrenia: A Review Article

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Abstract

A large percentage of schizophrenic patients respond poorly to antipsychotic treatment. This could be explained by inefficient drug transport across the blood-brain barrier due to ABC efflux transporter, in particular, P-glycoprotein, mediated efflux. P-glycoprotein (P-gp) activity and expression in the blood-brain barrier can be affected by genetics (polymorphism), inflammation and pharmacotherapy. The level of expression of P-gp at BBB is thought to be one of the factors contributing for pharmaco-resistant schizophrenia. Despite the differences in the experimental set-up that partly explain the controversies regarding the interaction between P-gp and antipsychotics, it is feasible to say that the majority of the antipsychotics have shown (mostly weak) affinity as a P-gp substrate and that most have a weak inhibitory effect on P-gp in vitro. The three major Single Nucleotide Polymorphisms (SNPs) in protein coding region at C3435T, G2677T, and C1236T of ABCB1 at BBB have been associated with efflux pump efficiency and with predicting changes in the function of P-gp that determines the inter-cerebral concentration and therapeutic response in human studies to anti-psychotics unlike serum concentration of these agents. The effects of ABCB1 polymorphisms and their significance remain unclear due to contradictory and inconsistent study results, and so far they have not been able to incontestably explain differences in the pharmacokinetics of substrate drugs. P-gp modulators/inhibitors/chemosensitizers are seemed to have low potency, weak effectiveness, and poor selectivity, and would have to be given chronically at high doses to block transporter function effectively in human which bears an increased risk of severe side effects. Owing to these complications, no transporter inhibitors are currently in clinical use to improve brain delivery of anti-psychotic for treatment-resistant schizophrenia. In general, the functional significance of P-gp efflux transporters as drug carriers are constantly increasing in current medical practice and as they represent a key factor in clinical outcome.However, direct evidence for a major role of P-gp in pharmacokinetics has been lacking, and thus requires further standardized research in future in particular in tackling pharmaco-resistant schizophrenia.

Keywords:

ABC efflux transporter; Blood-brain barrier
Antipsychotic; Pharmaco-resistant

Introduction:

Schizophrenia is a chronic and disabling brain disease and serious mental disorder with an annual incidence of 0.23 per 1000 persons and a prevalence rate over life of around 1%.

The effectiveness of drug treatments for Central Nervous System disorders (epilepsy, depression, and schizophrenia) is limited by poor therapeutic outcomes or drug resistance might due insufficient drug enter brain . This makes up to 12.9%-50% of schizophrenic patients are pharmaco-resistant schizophrenia.

Even though the causes of pharmaco-resistant schizophrenia are likely to be multifactorial, the ABC drug efflux transporter Pglycoprotein expressed at the blood-brain barrier, in particular, might play an important role.

This current review focuses on the functional significance of membrane transporters as drug carriers: as their role is constantly increasing in current medical practice and as they represent a key factor in clinical outcome. It elaborately assesses the impact of efflux transporter, mainly P-gp, its polymorphism and its modulation on the drug therapy of schizophrenia, while the other ABC transporters were briefly reviewed. We used different searching terms like ABC transporters, efflux transporter, P-gp, MDR1 protein, ABCB1, Multi drug resistant associated proteins, MRP1, ABCC1, Breast cancer resistance proteins, BCRP, ABCG2, MRP2, ABCC2, Polymorphism of P-gp, P-gp substrate, anti-psychotic agents, pharmaco-resistant schizophrenia, P-gp modulator and P-gp inhibitor from searching engine like Medline, Pubmed and Google scholar.

Conclusion
Concluding remarks and future directions

Among those patients taking antipsychotic, several patients suffered from pharmaco-resistant schizophrenia. Among many factors that contribute to pharmaco-resistant, active efflux of these agents by ABC efflux transporter, in particular by P-gp, from brain into periphery takes pivotal consideration recently. Consequently, the promising applicability to the future therapy of pharmaco-resistant schizophrenia due to efflux transporter took greater concern.

Majority of clinically used antipsychotic drugs such as amisulpride, aripiprazole, dehydroaripiprazole, risperidone, paliperidone,

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quetiapine, clozapine, olanzapine, chlorpromazine etc., are substrates of P-gp at the BBB having weak to moderate degree of affinity for the P-gp efflux transporter. Most of them are weak inhibitors of P-gp including thioxanthene derivative. Moreover the three major Single Nucleotide Polymorphisms (SNPs) of ABCB1 at C3435T, G2677T, and C1236T have been associated with efflux pump efficiency and with predicting tolerability of antipsychotic drugs in addition to the disease and drugs itself. So that concomitant administration of agents, that modulate ABC efflux transporter at BBB, with antipsychotic will be one possible way to overcome the pharmaco-resistant schizophrenia.

However, taking all findings into consideration published observations, even when made with the same probe drug and in the same racial group, is controversial. There are multiple possible explanations for these discordant results include differential experimental conditions, such as probe drug used, applied dose, steady-state versus single dose pharmacokinetics, small sample sizes, sample selection, or genetically heterogeneity due to ethnical diverse populations.

In order to determine conclusive result and the actual impact of all ABC efflux transporter on the schizophrenia and its treatment; multicenter (i.e., multiethnic), large sample size, multi-dose, long term cohort and well standardized study should be conducted to optimize its usefulness in individualized pharmacotherapy of drug resistant schizophrenia. And also identification of genetic variants and the complex regulatory pathways involved in P-gp modulation should be well elucidated in future. P-gp transport screening and its polymorphism has to be incorporated into the drug discovery process as recently recommended by the FDA.

In general, the role of P-gp in pharmaco-resistant schizophrenia was under studied even though majority of antipsychotic drugs are substrate for this efflux transporter. As a result, great focus should be given to P-gp efflux transporter at BBB in future if it is necessary to tackle drug resistant schizophrenia.

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