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Pharmacogenetic and Epigenetic Mechanisms of Antipsychotic Drugs

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INTRODUCTION

In the last decades accumulating evidence suggested the influence of genetic factors on antipsychotic treatment. It has been shown that drug dosage, treatment response, and occurrence of adverse effects are associated with large interindividual variability. According to statistical data, most drugs are effective for about 30% to 60% of patients and nearly 10% receive serious adverse effects after treatment with psychotropic drugs.

It is well established that disease severity, diet, age, other diseases and concurrent medication therapies contribute to the variability in response to drug therapy. In addition, pharmacogenetic studies have demonstrated that individual differences may be due to a combination of factors linked to drug metabolism (pharmacokinetics) and drug action at their target sites (pharmacodynamics).

Lots of studies have demonstrated a clear genetic contribution to the inconsistent response to psychotropic treatment. Unwanted effects profile has also revealed apparent genetic component. Epigenetic aberrations in the mechanisms of psychoactive drugs have been shown to have a key role in determining dysfunctional genes in neuroplasticity, in enhancing drug efficacy and in foreseeing adverse effects of drugs in the therapy of neuropsychiatric diseases.

PHARMACOGENETIC CHARACTERISTICS IN THE METABOLIZING SYSTEMS OF ANTIPSYCHOTIC DRUGS

Most antipsychotic medications are known to undergo intense first-pass metabolism and thus, drug-metabolizing systems have an important role in psychiatric treatment.

The microzomal cytochrome P450 (**CYP**) monooxygenase system is a family of enzymes that catalyze oxidative reactions of phase I biotransformation of drugs. The most common chemical reactions catalyzed by CYP enzymes are aliphatic hydroxylation, aromatic hydroxylation, N-dealkylation, and O-dealkylation. For drug metabolism major role play three CYP isozymes named CYP1, CYP2 and CYP3.

Many classical and atypical antipsychotic drugs (neuroleptics) are metabolized by 5 important enzymes: CYP1A2, CYP2D6, CYP2C9, CYP2C19, and CYP3A4. Genetic variability (polymorphism) in cytochrome enzymes may influence biotransformation of antipsychotic drugs.

Clinical and experimental evidence have shown that the genes encoding CYP enzymes are polymorphic and their variation leads to differences in catalytic activity. Combinations of CYP genotypes that affect catalytic activity are classified as "star (*****) alleles". An individual's phenotype for a particular CYP enzyme is commonly referred to as "Poor Metabolizer" (**PM**, two inactive star alleles), "Intermediate Metabolizer" (**IM**, one inactive star allele + one active or decreased activity star allele, or two decreased activity star alleles), "Extensive/normal Metabolizer" (**EM**, two active star alleles), or "Ultra-Rapid Metabolizer" (**UM**, gene duplication of active star alleles).

CYP2D6

This enzyme metabolizes many neuroleptics such as haloperidol, perphenazine, chlorpromazine, zuclopentixol, thioridazine, risperidone, aripiprazole, clozapine, olanzapine, quetiapine, and iloperidone. Eichelbaum et al. (1987) found that the encoding gene of CYP2D6 enzyme is localized on chromosome 22q13.1 [1]. It has been shown that this gene is highly variable, with more than 100 variations described which have determined variable enzymatic activity [2]. There have been identified poor metabolizers with low enzyme activity (2 nonfunctional alleles), intermediate metabolizers with intermediate enzyme activity (2 partly defective alleles or 1 nonfunctional allele), extensive metabolizers with normal enzyme activity (2 functional alleles), and ultra-rapid metabolizers (> 2 functional alleles) [3]. Vetti et al. (2010) have reported that 5-10% of the population in Europe is poor metabolizers, and 1-2% is ultra-rapid metabolizers; 1% of the population of North Africa are poor metabolizers, and 30-40% are

ultra-rapid metabolizers; 1-2% of the population of Asia are poor metabolizers [4]. Experimental studies have shown four polymorphism causing defective alleles in Caucasians: CYP2D6 *3, *4, *5 and *6 [5]. It is documented that some variations in CYP2D6 gene are associated with ultra-rapid metabolizers phenotype. For example, de Leon (2006) have demonstrated that CYP2D6*1XN, *2XN and *35XN duplications might be linked with ultra-rapid metabolizers phenotype [6].

Psychiatric patients who are poor metabolizers have higher plasma levels of antipsychotics and increased risk of adverse drug effects in comparison with extensive metabolizers. Biotransformation of haloperidol is reduced in poor metabolizers [7]. Studies of Kakihara et al. (2005) and Riedel et al. (2005) showed that poor metabolizers had higher blood levels of risperidone [8,9]. Other clinical studies demonstrated that CYP2D6 polymorphism was associated with neuroleptic-induced tardive dyskinesia [10-12] and antipsychotic-induced extrapyramidal syndromes [13-16] in schizophrenic patients. Some studies reported for relationship between CYP2D6 polymorphism and atypical antipsychotic-induced weight gain [17,18].

CYP2D6 extensively metabolizes risperidone to 9-hydroxirisperidone (equi-effective with risperidone). A correlation between CYP2D6 polymorphisms and higher plasma risperidone to 9-hydroxirisperidone ratio has been reported [8,9]. CYP2D6*10 polymorphism and co-medication with CYP2D6-dependent drugs exerted significant influences on the biotransformation of risperidone [19].

CYP1A2

Substrates for a CYP1A2 are several antipsychotics including chlorpromazine, fluphenazine, perphenazine, clozapine and olanzapine [2,20,21]. CYP1A2 gene is located on chromosome 15q24.1 [2]. Polymorphism in the CYP1A2 include variants *1C, *1K and *11 showing enzyme decreased activity [22,23]. Cigarette smoking among schizophrenic patients affects the enzyme activity of CYP1A2. Polyaromatic hydrocarbons in cigarette smoke may induce CYP1A2 and reduce plasma concentrations of drugs metabolized by this enzyme. van der Weide et al. (2003) reported that serum concentration of clozapine in smokers was lower compared with those in non-smokers [24].

CYP1A2 polymorphisms have not been associated with considerable differences in clozapine elimination [25]. However, patients with ultra-rapid CYP1A2 activity demonstrated slow response to clozapine [26,27]. Clinical study of Laika et al. (2010) showed that CYP1A2*1F polymorphism in psychiatric patients influenced serum concentration and treatment response to olanzapine [28].

In addition, Basile et al. (2000) reported for association between functional polymorphism in the CYP1A2 gene and tardive dyskinesia in patients with schizophrenia [29].

CYP3A4

Human CYP3A locus is localized on chromosome 7q21.1 and contains four genes: CYP3A4, CYP3A5, CYP3A7, and CYP3A43 [30]. CYP3A4 is involved in the metabolism of most atipycal

antipsychotics including clozapine, quetiapine, ziprasidone, sertindole, aripiprazole, zotepine, risperidone, bifeprunox, and iloperidone.

Substantial data have demonstrated the important role of CYP3A4 genetic variations in elimination and efficacy of antipsychotics. Dai et al. (2001) reported for two polymorphisms of CYP3A4 (CYP3A4*17 and CYP3A4*18) which affected metabolism of testosterone and chlorpyrifos [31]. A clinical study of Du et al. (2010) described a connection between CYP3A4 polymorphisms and response to risperidone in schizophrenia patients [32]. Also, Bigos et al. (2011) identified a single-nucleotide polymorphism in the cytochrome P450 3A43 (CYP3A43; rs472660) that had influenced olanzapine clearance and clinical response [33]. Another study has demonstrated that genetic variation in CYP3A43 (rs472660 and rs680055 single nucleotide polymorphisms) was associated with treatment response to antipsychotics from second generation [34].

Furthermore, a polymorphism of CYP3A4*22 increased serum level of quetiapine in psychiatric patients [35]. Interestingly, heterozygous presence of CYP3A4*22 did not increase plasma concentration of aripiprazole, haloperidol, pimozide, and risperidone [36].

CYP2C19

This enzyme is involved in the biotransformation of clozapine, thioridazine, perphenazine and many antidepressants. Recent studies have identified subjects as: extensive metabolizers (genotype *1/*1); intermediate metabolizers (heterozygous carrier of one inactive CYP2C19 allele) and poor metabolizers (homozygous combination of two deficient CYP2C19 alleles) [7]. Jaquenoud-Sirot et al. (2009) found that poor metabolizers of CYP2C19 had substantially higher clozapine concentrations than extensive metabolizers [37]. Other experimental results have described a novel allele CYP2C19*17 with increased transcriptional activity [38].

CYP2C9

CYP2C19 gene variations are also associated with altered enzymatic activity. Clozapine and bifeprunox, a partial dopamine-receptor agonist, are known as substrates of CYP2C9 enzyme. Examination of bifeprunox metabolism in adults with reduced activity of CYP2C9 showed increased maximum plasma concentration of the drug [39].

Taken together, the abovementioned data demonstrate the considerable importance of genetic variants in metabolizing systems for effective treatment response and/or drug safety. Although further understanding is needed, it is now clear that pharmacogenetic studies of drug metabolism have offered the most important novel contributions for enhancing the response to psychotropic therapy.

EPIGENETIC CHARACTERISTICS OF ANTIPSYCHOTIC DRUGS

The typical and atypical antipsychotics (first and second generation drugs) are the main pharmacological groups in the treatment of SZ and other neuropsychiatric disorders. Antipsychotic drugs or their active metabolites have several molecular targets in the Central Nervous System

(**CNS**). A progress in the treatment of SZ is the individualized drug therapy which uses molecular genetic approaches [40,41]. Experience with the individualized treatment of SZ based on genome and DNA studies has generated a large amount of data [42,43]. The studies on pharmacogenomics of antipsychotic drugs also proposed the important role of genes in the pharmacotherapy of psychoses. Experimental and clinical trials have led to a progress in the pharmacogenomics of antipsychotic therapy: 1) the dopamine receptor studies; 2) the serotonin receptor studies and 3) studies on novel genes as targets for pharmacotherapy and pharmacogenomics of antypsychotic drugs. For example: DRD2 gene was found to influence the short-term response to DRD2 receptor antagonist haloperidol and risperidone [44]. The influence of 5-HT_{2A} gene on clozapine response suggests a clear link between the gene polymorphism and the clozapine response [45,46]. In addition, it is demonstrated that new target genes as the Dopamine Receptor Interacting Protein **(DRIP)** gene or NEF3 from the DRIP gene family are responsible for the early reaction to antipsychotic drugs [47].

Typical antipsychotics such as chlorpromazine, fluphenazine, haloperidol, loxapine, pimozide, thioridazine, thiothixene, trifluoperazine, have been used for many years in psychiatry. Unfortunately, they caused various side effects, so a new generation of drugs named atypical antipsychotics such as amisulpride, aripiprazole, clotiapine, clozapine, lurasidone, olanzapine are now considered to be the first line treatment for SZ [48-50]. Research data illustrate genetic and epigenetic profiles determining variations in the receptor binding characteristics and side effects of atypical antipsychotics [51-53]. Serotoninergic system in the epigenetic characteristics of both typical and atypical antipsychotics has also been a subject of various studies [54,55]. The link between clozapine response and allelic variation in 5-HT2A receptor gene was documented [45]. Furthermore the 5-HT2A receptor blockade has been suggested as a promising method for treating of SZ.

The incomplete understanding of the etiopathogenesis underlying the symptomatology of psychiatric disorders and the strong hereditary component that is established for Schizophrenic **(SZ)** and Bipolar Disorder **(BPD)** have demonstrated the important role of epigenetics as a target mechanism for drug discoveries.

Epigenetic modulations are associated with processes of DNA methylation, histone modifications and RNA alterations. Lots of studies have indicated that epigenetic processes may function as transcriptional regulators in response to various signals in neurons [56,57]. DNA methylation has been shown to contribute to gene expression, and processes involved in neuroplasticity and pathogenesis of neuropsychiatric disorders [58,59].

Alterations in DNA-methylation as well as histone modifications in GABAergic and glutamatergic promoters are linked to neuronal dysfunction in schizophrenic and bipolar patients. Epigenetically induced down-regulation in markers such as Reelin **(RELN)** and glutamic acid decarboxylase 67 (GAD 67) has been identified in the pathogenesis of psychoses and has recently served as a target mechanism in investigation of the effectiveness of antipsychotic treatment.

Antipsychotic drugs promote DNA demethylation and reverse the hypermethylation of genes involved in GABAergic transmission [60]. Aoyama et al, have demonstrated that clozapine decreases epigenetic and behavioral abnormalities induced by phencyclidine through activation of DA D1 receptors in mice [61]. Furthermore, Melka et al reported that olanzapine caused methylation changes in genes linked to DA neurotransmission [62]. Additionally, in studies of genomic DNA methylation and promoter methylation of *RELN* and *SOX10* in twins suffering from SZ, it was documented that global DNA methylation was considerably and this reduction was higher in nonmedicated patients. However, in discordant twins, there was a relative hypermethylation of the *SOX10* promoter [63]. Experimental investigations demonstrate that the demethylation of DNA in neurons is mediated by the conversion of 5-methylcytosine into Thymine **(T)** through deamination, and then by T removal by means of a Guanine **(G)**/T mismatch DNA-glycosylase [64]. The coupling between 5-methylcytosine deaminase and G/T mismatch DNA glycosylase is facilitated by Gadd45-*α* (growth arrest and DNA-damage-inducible protein 45 alpha), which plays an important role in the development of hippocampal neurons [65]. Recently, it was reported that electroconvulsive treatment induced Gadd45 expression, increased Gadd 45 binding to cytosine deaminase or G/T mismatch glycosylase and induced DNA demethylation at specific promoters (*Bdnf, Fgf1*). These processes were not observed in Gadd45 KO mice [66]. On the other hand clozapine, in doses that induce promoter demethylation, increased Gadd45 expression [67].

Histones are target for epigenetic modulations and haloperidol, neuroleptic fails to modify histones or induce DNA demethylation [60,68]. Additional studies also demonstrate changes of histones after haloperidol administration [69]. Haloperidol increases histone H3 phosphorylation selectively in striatopallidal neurons [70].

Li J et al, 2004 show that treatment with D_2-like antagonists induces phosphorylation of histone H3 at serine 10 and acetylation of H3-lysine 14 in striatal neurons [69]. In addition, epigenetic changes were detected in mice after treatment with D_2-like agonist quinpirole, D_2-like antagonist S(-)-raclopride tartrate, haloperidol lactate and the atypical antipsychotic risperidone hydrochloride. Other results also support the abovementioned data for the role of haloperidol in histone modulation due to increase of H3 phospho-acetylation in bulk chromatin. Also, the H3 epitope defined by the dual modification, phospho-serine 10 in conjunction with acetyl-lysine 14 (H3pS10-acK14), was consistently and on average 2.2-fold increased by haloperidol in haloperidol-treated animals compared to controls. Other studies also demonstrate that typical and atypical antipsychotic drugs may promote epigenetic changes via acting on D2 receptors. For example, it is reported that the increase in H3pS10-acK14 in bulk chromatin of striatum is specific for drugs acting as D_2-like antagonists and is not present after treatment with quinpirole. Studies demonstrated that D_2-like antagonists induce striatal H3 phospho-acetylation by activating cAMP-dependent protein kinase. Results suggest that D_2-like blockade may change histone modification patterns in nuclei of striatal neurons. Additionally, Bertran-Gonzalez et al, 2009 [71] demonstrated that the mutation of cAMP-dependent phosphorylation site (Thr34) of the 32-kDa

dopamine- and cAMP-regulated phosphoprotein (DARPP-32) decreased haloperidol-induced H3 phosphorylation. They found that haloperidol induced a rapid and sustained increase in the phosphorylation of histone H3 in the striatopallidal Medium Spinal Neurons **(MSNs)** of the dorsal striatum, with no change in its acetylation. Taken together these data propose the role of cAMP in haloperidol-modulated H3 phosphorylation. The involvement of Extracellular Signal-Regulated Kinase **(ERK)** phosphorylation in striatopallidal MSNs in epigenetic effects of haloperidol was demonstrated as well. Haloperidol induces ERK without implication on H3 phosphorylation in Mitogen- and Stress-Activated Kinase 1 (MSK1)-KO mice. In addition, recent data illustrated that that the histone H3 phosphorylation is under the opposite tonic control of dopamine D2 and adenosine A2A receptors in striatopallidal neurons. Results suggest that haloperidol as well as other antipsychotic D2 antagonists may modulate histone H3 phosphorylation via cAMP system and chromatin alteration is a molecular mechanism of drug-induced changes in development and differentiation of striatal neurons.

Epigenetic changes were associated with the action of various atypical antipsychotics (e.g., clozapine, quetiapine, etc). Experimental studies revealed chromatin remodelling by histone modifications and DNA demethylation in GABAergic or glutamatergic neurons [60,68] due to antipsychotic treatment. Clozapine and sulpiride but not haloperidol or olanzapine have been shown to activate nuclear DNA-demethylation in the brain [68]. Clozapine induced histone hyperacetylation and activated DNA demethylation [60].

VPA (a mood stabilizer and anticonvulsant drug) has been co-administered for over a decade with atypical antipsychotics to medicate BPD and SZ patients. It is reported that VPA, like clozapine, may correct the *RELN* and *GAD67* promoter hypermethylation and the decrease in GAD67 and RELN expression associated with social interaction deficits induced by methionine treatment [68,72]. Also, the combined treatment with VPA and clozapine but not that of VPA and haloperidol, has been shown to induce Histone 3 (H3) hyperacetylation at RELN or GAD67 promoters in frontal cortex of mice.

Taken together, these data suggest that the activation of DNA demethylation may reverse a repressed nuclear epigenetic function expressed in postmitotic cortical GABAergic neurons of SZ or BPD patients.

Dysregulation of the serotonin receptor type-2 (HTR2A) gene also plays a role in pathogenesis of psychosis (SZ and BP disorder), as well as in the pharmacotherapy with atypical antipsychotic drugs via targeting HTR2A receptors [73,74]. Strong correlation between the DNA Methylation **(DNAM)** and the monoallelic expression of HTR2A was demonstrated. Experimental data for a strong linear relationship between HTR2A and RELN expressions and an inverse correlation between HTR2A expression and RELN promoter DNAM suggest the involvement of epigenetic changes of HTR2A gene in both psychosis and effects of antipsychotic drugs [75]. Having in mind that the methylation of histone tails and DNA-promoter methylation or covalent acetylation are

detected in SZ and BP disorders [60,76] and antipsychotic drugs may modulate DNA by epigenetic mechanism, further understanding of mechanism involved in epigenetic alterations due to antipsychotic treatment pave a way for new strategies in psychiatric pharmacotherapy. Moreover, a detailed knowledge for the effects of antipsychotic drugs on neuroepigenetic mechanisms is not only promising the development of novel more effective and safer pharmacological agents in non-responding patients with SZ and BPD, but will also provide insights for the etiopathogenesis of neuropsychiatric disorders.

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