

## Clinical Efficacy of Antipsychotic Drugs in the Treatment of Schizophrenia

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### Abstract

We describe in schizophrenia the alterations of classical neurotransmitters and neuropeptides in the mesolimbic system, the hippocampus and the prefrontal cortex. The susceptibility genes, which encode dopamine hyperactivity and glutamate and GABA hyperactivity, are described. Using a neural network in the mesolimbic system, the coherence between the risk genes and the cellular mechanisms is derived. The therapeutic and adverse effects of the commonly prescribed second-generation antipsychotic drugs are pointed out. We suggest examining the risk genes in a large cohort of schizophrenic patients in order to have a tool to choose the appropriate antipsychotic drug. We recommend psychoeducation in the therapy of schizophrenic patients so that they can better deal with the schizophrenic symptoms and the adverse effects.

**Keywords:** Schizophrenia; Susceptibility gene; Antipsychotic drug; Dopamine; Serotonin; Psychoeducation

### Introduction

Schizophrenia is a chronic mental illness which becomes manifest as an acute psychosis with positive schizophrenic symptoms such as paranoia, hallucinations and illusions after a prodromal phase with negative symptoms [1]. We mostly focus on the paranoid and hallucinatory form of schizophrenia. In this disease, some susceptibility genes have been discovered [2]. In the mesolimbic system and the hippocampus, dopamine hyperactivity via D2 receptors and serotonin hyperactivity via 5-HT<sub>2A</sub> receptors occurs. In animal models of schizophrenia, schizophrenia-like behavior can be induced after administration of NMDA (N-methyl-D-aspartate) antagonists, which can be relieved by 5-HT<sub>2A</sub> antagonists, but not by D2 antagonists [3]. In this short communication, some susceptibility genes and the coherence between the genetic localization and the cellular mechanisms are pointed out [2,3]. Schizophrenia is treated by administering second-generation antipsychotic drugs which exert a D2 and 5-HT<sub>2A</sub> antagonistic effect. The therapeutic and adverse effects of the commonly administered antipsychotic drugs are discussed [4].

### Alterations of Classical Neurotransmitters and Neuropeptides in Schizophrenia

In schizophrenia, in the mesolimbic system and the hippocampus dopamine and serotonin hyperactivity and hypoactivity of presynaptic inhibitory neurotransmitters (GABA and glutamate) have been reported [5]. In the prefrontal cortex, D1 dopamine hyperactivity and M4 acetylcholine hypoactivity was found [5]. An antagonistic interaction between D1 dopaminergic and M4 muscarinic cholinergic neurons has also been described. The alterations of some neuropeptides, such as neurotensin, cholecystokinin and tachykinins will be also mentioned [5].

### Dopamine

Dopamine hyperactivity, via D2 receptors, can be found in the mesolimbic system and the hippocampus and D1 dopamine hyperactivity in the prefrontal cortex [5]. Dopamine hyperactivity can be associated with the susceptibility genes, for example the catechol-O-methyl transferase (COMT) and the monoamine oxidase (MAO) genes, which encode reduced dopamine degradation and thus lead to increased dopamine levels [6].

### Serotonin

In schizophrenia, serotonin hyperactivity via 5-HT<sub>2A</sub> receptors is partly encoded in polymorphisms of the serotonin transporter gene [7]. Since in animal experiments schizophrenic-like behavior can be induced by NMDA antagonists, the following neural combination could be possible: a reduced presynaptic inhibition of 5-HT<sub>2A</sub> serotonergic neurons through glutaminergic neurons, via NMDA receptors, could as well contribute to serotonin hyperactivity [8].

### Gamma-aminobutyric Acid (GABA)

A GABA hypofunction, via GABA<sub>A</sub> receptors, has been reported in the mesolimbic system and the hippocampus and it has been correlated with cognitive dysfunction [9]. In the above-mentioned brain areas, GABA hypoactivity is encoded in the glutamic acid decarboxylase (GAD) 67 gene [2,10].

### Glutamate

Glutamate, a mainly excitatory (postsynaptic excitatory) and partly presynaptic inhibitory neurotransmitter exerts its effect on NMDA receptors and on metabotropic glutaminergic receptors. Glutamate hypofunction, via NMDA receptors, is encoded in the dysregulin-1 and neuregulin-1 susceptibility genes [2]. In the mesolimbic system and the hippocampus, a reduced presynaptic inhibition via NMDA

receptors of 5-HT<sub>2A</sub> serotonergic neurons could cause serotonin hyperactivity [5].

## Acetylcholine

Acetylcholine is a postsynaptic excitatory neurotransmitter that exerts its function at muscarinic cholinergic and nicotinic cholinergic receptors. Agonists of both receptors could be of therapeutic value in the antipsychotic treatment. In schizophrenia, alpha7 and alpha4beta2 nicotinic cholinergic agonists improve cognitive functions [11]. M4 agonists could have antipsychotic properties. In schizophrenia, there is an antagonistic interaction between M4 muscarinic cholinergic and D1 dopaminergic neurons in the prefrontal cortex [12].

## Alterations of Neuropeptides in Schizophrenia

Among the altered neuropeptides in schizophrenia, cholecystokinin, neurotensin and tachykinins will be mentioned.

Cholecystokinin (CCK) levels were found to be decreased in the striatum, the nucleus accumbens and in the frontal and temporal cortices [13]. The CCKA gene is associated with persistent auditory hallucinations in schizophrenia. It should be examined whether CCKA receptor agonists could be used as an additional therapy to improve these symptoms [14]. In schizophrenic patients, neurotensin levels were reduced in the mesolimbic system and the prefrontal cortex. Neurotensin agonists, which activate the NTS1 receptor and the neurotensin NT69L analogue, have been proved to show an antipsychotic effect [15]. Neurokinin A and B are of importance in the pathophysiology of schizophrenia. Neurokinin-3 receptor antagonists could have antipsychotic properties, because in the mesolimbic system they reduce the activity of D2 dopaminergic neurons [16].

## Susceptibility Genes in Schizophrenia and the Depending Pathophysiology

The neuregulin-1, dysbindin-1, COMT, MAO and GAD 67 susceptibility genes will be described, and the coherence of these genes to the cellular mechanisms will be derived [3]. In the mesolimbic system, the neuregulin-1 and dysbindin-1 risk genes are linked to glutamate hypoactivity (2). Fatjó-Vilas et al. [17] examined ten dysbindin-1 single nucleotide polymorphisms (SNP) in 894 Caucasian individuals, namely 268 patients with a functional psychosis, 483 parents and 143 siblings and correlated the found SNP's with the patient's age at onset, the risk for psychosis and the familiar neurocognitive performance. These authors found different haplotypes of the dysbindin-1 gene, an haplotype (a 5-marker haplotype encompassing exons 2-4) was associated with an early onset of psychosis and other haplotypes were correlated with an adult-onset of schizophrenia [17]. The authors conclude from their findings that the haplotype of the dysbindin-1 gene is correlated with the form and severeness of schizophrenia [17]. The susceptibility genes COMT and monamine oxidase are linked with a decreased activity of these enzymes, catalyzing the breakdown of dopamine. Hence, in the mesolimbic system and the hippocampus dopamine hyperactivity occurs [5]. The GAD 67 gene is associated with a hypofunction of the presynaptic neurotransmitter GABA (3). In the mesolimbic system, the neural networks can be described as follows [18]: due to the neuregulin-1 and dysbindin-1 genes, glutaminergic neurons weakly inhibit presynaptically 5-HT<sub>2A</sub> serotonergic neurons which therefore have a high activity. The serotonergic neurons are connected to GABAergic neurons. Due to the GAD 67 gene, GABAergic neurons

weakly inhibit presynaptically D2 dopaminergic neurons which exert a high activity. Dopamine hyperactivity is enhanced through the decreased activity of the COMT and MAO-B enzymes, which degrade dopamine. Tachykinin neurons, via NK3 receptors, strongly activate D2 dopaminergic neurons. In the ventral tegmental area, the dopaminergic neurons are connected to glutaminergic neurons. Dopamine and serotonin hyperactivity is still strengthened, because in the A10 cell group D2 dopaminergic and 5-HT<sub>2A</sub> serotonergic neurons activate each other [5]. GABAergic neurons in the mesolimbic system inhibit neurotensin neurons in the prefrontal cortex which weakly activate glutaminergic neurons via NTS1 receptors. GABAergic neurons in the ventral tegmental area also inhibit cholecystokinin neurons in the prefrontal cortex which weakly activate glutaminergic neurons via CCKA receptors. The glutaminergic neurons weakly inhibit serotonergic neurons in the VTA (ventral tegmental area) via NMDA receptors. Cannbinoid neurons strongly inhibit CCK neurons in the prefrontal cortex via CB1 receptors and have a hallucinogenic effect.

In the mesolimbic system, GABAergic neurons weakly inhibit, via GABAA receptors, D1 dopaminergic neurons in the prefrontal cortex (PFC), which strongly activate glutaminergic neurons. The latter neurons strongly inhibit via NMDA receptors M4 muscarinic cholinergic neurons, which weakly activate GABAergic neurons. These neurons weakly inhibit D1 dopaminergic neurons. The glutaminergic neurons in the PFC weakly inhibit via NMDA receptors serotonergic neurons in the mesolimbic system.

GABAergic neurons in the mesolimbic system weakly inhibit, via GABAA receptors, D2 dopaminergic neurons in the hippocampus which have a high activity. The D2 dopaminergic neurons are connected to glutaminergic neurons which weakly inhibit, via NMDA receptors, 5-HT<sub>2A</sub> serotonergic neurons which have a high activity. The serotonergic neurons are connected to GABAergic neurons. Alpha4beta2 nACh neurons weakly activate GABAergic neurons. 5-HT<sub>7</sub> serotonergic neurons strongly activate 5-HT<sub>2A</sub> serotonergic neurons. The glutaminergic neurons in the hippocampus, via NMDA receptors, weakly inhibit the serotonergic neurons located in the mesolimbic system [18].

## Therapeutic and Adverse Effects of the commonly used Second-Generation Antipsychotic Drugs

After schizophrenia is diagnosed, treatment with second-generation antipsychotic drugs (SGAs) is started. In this chapter, the therapeutic and adverse effects of the commonly used SGAs are described.

Risperidone is a D2 and 5-HT<sub>2A</sub> antagonist with a great affinity for the D2 receptor. Due to its mechanism of action, it induces extrapyramidal symptoms (EPS) more often than olanzapine, and hyperprolactinemia. It improves negative symptoms, for example social withdrawal, autism and depression, like other antipsychotic drugs such as ziprasidone. It causes metabolic side effects, but less often than olanzapine [4,19,20]. Olanzapine is a SGA with a greater affinity for the 5-HT<sub>2A</sub> receptor than risperidone. Olanzapine has a superior effect than other second-generation antipsychotic drugs to improve negative schizophrenic symptoms [19] and causes less often EPS than risperidone. In comparison to other SGAs, it causes metabolic side effects (glucose and cholesterol increases, weight gain) to a great extent [4,21]. Quetiapine is a SGA with a greater affinity for the 5-HT<sub>2A</sub> receptor than olanzapine; seldom causes EPS and it is a prolactin-sparing SGA. It has a therapeutic effect on positive and

negative symptoms like risperidone [4]. Ziprasidone is a SGA with an additional antidepressant effect through a 5-HT<sub>1A</sub> agonistic effect. It improves positive and negative schizophrenic effects and has side effects, which are comparable to those induced by olanzapine [21]. Clozapine has a D<sub>3</sub>, D<sub>4</sub> and 5-HT<sub>2A</sub> antagonistic effect and exerts the strongest antipsychotic effect. It seldom causes EPS and is a prolactin-sparing antipsychotic drug. The occurrence of neutropenia, which may occur in 3% of the patients, must be controlled by a weakly blood cell count [4]. Aripiprazole has a different mechanism of action. It has a D<sub>2</sub> partial agonism, a 5-HT<sub>2A</sub> antagonistic effect and a 5-HT<sub>1A</sub> agonistic effect. It has been shown to have a secure antipsychotic effect and seldom causes EPS and weight gain [19]. Up to now, there has not been chosen a way to select the appropriate antipsychotic drug [5].

## Conclusion

In schizophrenic patients, we have described the alterations of classical neurotransmitters and neuropeptides in the mesolimbic system, the hippocampus and the prefrontal cortex and we have also established the coherence between the susceptibility genes and the cellular mechanisms. Among the commonly prescribed second-generation antipsychotic drugs, risperidone has a greater affinity for the D<sub>2</sub> receptor, and olanzapine and quetiapine have a greater affinity for the 5-HT<sub>2A</sub> receptor. In a large cohort of schizophrenic patients, the risk genes for the disease should be examined. It should be also examined if a specific antipsychotic drug has a better therapeutic effect when a certain susceptibility gene has been found; for example, it should be studied whether risperidone which shows a great affinity for the D<sub>2</sub> receptor has a better therapeutic effect in patients with the COMT and MAO-B risk genes, i.e. the patients have an increased dopamine hyperactivity [5]. The combination of two antipsychotic drugs, for example risperidone and quetiapine can better treat schizophrenic symptoms; however the side effects must be considered [4]. After psychotic symptoms have improved, the dosage of the antipsychotic drug can be reduced, but a basic dose must be maintained, and the occurrence of side effects may occur less often. The patients should have a psychoeducation in order to deal with positive and negative symptoms and to recognize a recurrence of psychotic symptoms [4]. In clinical trials, it was shown that newer antipsychotic drugs with a different mechanism of action like aripiprazole have a safe therapeutic effect. In clinical trials, it should be examined if recently developed antipsychotic drugs, like lurasidone and cariprazine, exert a long-lasting safe antipsychotic effect and if they can improve patients's quality of life [4].

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