Risperidone: An Example of the Antipsychotic Treatment According to the Susceptibility Genes

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Editorial

Schizophrenia is a chronic psychiatric illness which affects about 1% of the population. In the prodromal phase, symptoms such as depression, social withdrawal and mutism occur during about 7 years, till an acute manifestation with symptoms as hallucinations, illusions and paranoia appears [1]. Since the proposal of the dopamine hypothesis, a multi-neurotransmitter system in different brain regions has been suggested. An increased dopamine release, via the dopaminergic D2 receptor, and an augmented serotonin release via the serotonergic 5-HT2A receptor occur in in the involved brain areas, e.g. ventral tegmental area. In preclinical studies, ketamine, an antagonist of the NMDA (N-methyl-D-aspartate) receptor can cause schizophrenia-like symptoms, which can be ameliorated with 5-HT2A antagonists, but not by first-generation antipsychotic drugs which block D2 receptors. The search for susceptibility genes has been developed, and some risk genes are known [2,3]. In most cases, schizophrenic patients are treated with first-generation antipsychotic drugs and more often with newer antipsychotic drugs which block, with different affinities, the dopaminergic D2 receptor and the serotonergic 5-HT2A receptor [4]. In schizophrenia, the current discovered susceptibility genes are the following: COMT (catechol-O-methyl-transferase), which is an enzyme that shows a decreased activity and catalyses the catabolism of dopamine; MAO (monoamine oxidase), which is also an enzyme with a reduced activity and catalyses the breakdown of dopamine; GAD 67 (glutamate decarboxylase), which indicates a diminished activity of GABAergic neurons, and the genes dysbindin and neuregulin, which refer to a declined activity of NMDA glutamatergic neurons [2].

In the mesolimbic system, the neural network is pointed out, as seen in Figure 1, dopaminergic neurons, which have a high activity according to genes (e.g., COMT, MAO), apply a postsynaptic excitatory potential via D2 receptor to GABAergic neurons, which according to the genes dysbindin-1 or neuregulin-1 exert a weak presynaptic inhibitory potential, via NMDA receptors, upon serotonergic neurons. The serotonergic neurons exert a strong activating potential via 5-HT2A receptors upon GABAergic neurons, which apply a weak presynaptic inhibitory potential upon dopaminergic neurons, which is encoded in the GAD 67 gene [2,3,5]. In the VTA, dopaminergic neurons transmit a postsynaptic excitatory potential to other dopaminergic neurons (A10 cell group) and serotonergic neurons apply an activating potential to other serotonergic neurons. Both neurons send an activating potential to each other and thus they increase dopamine and 5-HT release [5].

Figure 1: Neural network in the brain areas involved in schizophrenia. 5-HT: serotonin; DA: dopamine; GABA: gamma-aminobutyric acid; Glu: glutamate. 5-HT2A: 5-HT2A receptor of the serotonin (5-HT) receptor; D2: D2 receptor of the dopamine (DA) receptor; GABA2: GABA2 receptor of the GABA receptor; NMDA: N-methyl-D-aspartate receptor.
between the schizophrenia related genes and the improvement of positive and negative schizophrenic total score scale. A single nucleotide polymorphism referring to the COMT enzyme was related with a significantly better improvement of positive and negative symptoms in schizophrenia [6].

Does efficacy of the different antipsychotic drugs depend on the risk genes in schizophrenic patients?

References


