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Extrapyramidal Symptoms in Patients Treated with Antipsychotic Drugs

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Abstract

Extrapyramidal symptoms are adverse effects of second-generation antipsychotic drugs which are generally used to treat schizophrenia and schizoaffective disorder. These adverse effects are due to the D2 receptor blockade. Neurotransmitter and neuropeptide alterations in the mesolimbic system and in the extrapyramidal system and the derived neural networks are described. M4 antagonists, GABAA agonists or NMDA antagonists can be used to treat the extrapyramidal symptoms because they improve the dopaminergic-cholinergic neurotransmitter imbalance in this neural system. Recently developed antipsychotic drugs such as aripiprazole and cariprazine cause less often and, to a lesser extent, extrapyramidal symptoms because they exert a partial agonism at the D2 receptor.

Keywords: Antipsychotic drug; Dopamine; Extrapyramidal symptom; Glutamate; Neural network; Schizophrenia; Antipsychotic drug; Serotonin

Introduction

Schizophrenia is a chronic psychiatric disease with positive, negative and cognitive symptoms. The heritability of schizophrenia is not yet clarified, however some susceptibility genes that encode dopamine hyperactivity and glutamate and GABA (Gamma-Aminobutyric Acid) hypoactivity in the hippocampus, mesolimbic system and prefrontal cortex, have been reported [1,2]. Schizophrenic patients are treated with Second-Generation Antipsychotic Drugs (SGAs) such as risperidone, olanzapine, quetiapine and aripiprazole and, in some cases, with First-Generation Antipsychotic Drugs (FGAs) such as haloperidol [3]. Adverse effects of the FGAs and to a lesser extent of the SGAs are Extrapyramidal Symptoms (EPS), for example Parkinsonism, dystonia, dyskinesia or oculogyric crises [4]. These adverse effects are due to the blockade of D2 dopaminergic receptors in the extrapyramidal system. It has been reported that recent developed antipsychotic drugs exert a mechanism of action different from the blockade of the D2 receptor and cause less often EPS [4].

Treatment of Schizophrenia with Antipsychotic Drugs

Schizophrenic patients are treated generally by SGAs. Risperidone is a SGA with a D2 and 5-HT2A antagonistic effect and a high affinity for the D2 receptor. It therefore often causes EPS. Olanzapine is a SGA with a D2 and 5-HT2A antagonistic effect and a lower affinity for the D2 receptor than risperidone. It consequently causes EPS to a lesser extent. Quetiapine is a SGA with a D2 and 5-HT2A antagonistic effect and a higher affinity for the 5-HT2A receptor and therefore seldom causes EPS [3]. Aripiprazole has a different mechanism of action: It has a partial agonism at the D2 receptor and an antagonistic effect at the 5-HT2A receptor. It causes EPS to a lesser extent. The FGA haloperidol often causes EPS, for example Parkinsonism, because its main mechanism of action is the D2 receptor blockade; haloperidol shows a high affinity for this receptor [5].

Schizophrenia: Neurotransmitter Alterations in the Mesolimbic System

In schizophrenia, the mentioned neurotransmitter alterations occur in the hippocampus, mesolimbic system and prefrontal cortex. Dopamine hyperactivity is encoded by the susceptibility genes Monoamine Oxidase A/B (MAO) and Catechol-O-Methyltransferase (COMT), which encode the hypoactivity of both enzymes. These enzymes catalyse in a reduced activity the degradation of dopamine and induce dopamine hyperactivity in the hippocampus, mesolimbic system and prefrontal cortex [1]. GABAergic neurons might weakly presynaptically inhibit D2 dopaminergic neurons, via GABAA receptors, in the hippocampus and mesolimbic system and thus enhance dopamine hyperactivity [1]. Serotonin hyperactivity is partly due to the alteration of the serotonin transporter gene [6]. Glutamatergic neurons might weakly presynaptically inhibit 5-HT2A serotonergic neurons in the hippocampus and mesolimbic system, via NMDA (N-methyl-D-aspartate) receptors and thus enhance serotonin hyperactivity. NMDA receptor antagonists can induce schizophrenic-like behaviour in animal experiments, which can be only relieved by antipsychotic drugs showing a 5-HT2A antagonistic effect [7]. GABA dysfunction is encoded by the GAD 67 gene and the glutamate dysfunction by the dysbindin-1 and neuregulin-1 genes [1].

Neurotransmitters and Neuropeptides Involved in the Extrapyramidal System

In Parkinsonism induced by antipsychotic drugs, a neurotransmitter imbalance between D2 dopaminergic neurons with a hypoactivity and M4 muscarinic cholinergic neurons with hyperactivity occurs. The neurotransmitter alterations in Parkinson's disease have been described as follows: dopamine and GABA hypoactivity and acetylcholine and glutamate hyperactivity [8].

Dopamine hypoactivity occurs after treatment with FGAs and SGAs. Dopaminergic neurons in the substantia nigra activate D1 and D2 dopaminergic neurons located in the caudate nucleus. In this nucleus, D1 dopaminergic neurons weakly activate dynorphin neurons, which inhibit via mu receptors substance P neurons [9,10].

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The latter neurons activate GABAergic neurons in the internal globus pallidus. D2 dopaminergic neurons activate GABAergic neurons in the external globus pallidus [5]. When extrapyramidal symptoms occur, a dopaminergic-cholinergic neurotransmitter imbalance appears due to the blockade of the D2 receptor in the extrapyramidal system. In the internal globus pallidus, GABAergic neurons weakly inhibit, via GABAA receptors, M4 muscarinic cholinergic neurons located in the putamen and enhance acetylcholine hyperactivity. Consequently, M4 receptor antagonists can counteract the dopaminergic-cholinergic neurotransmitter imbalance in the extrapyramidal system [11].

In the putamen exists an antagonistic interaction between D2 dopaminergic and 5-HT2A serotonergic neurons through presynaptic inhibitory NMDA glutamatergic neurons. Therefore, SGAs with a 5-HT2A antagonistic effect and a high affinity for the 5-HT2A receptor less often and to a lesser extent cause EPS [12].

GABAergic neurons in the internal globus pallidus inhibit, when EPS occur, M4 muscarinic cholinergic neurons located in the putamen, via GABAA receptors. Therefore, GABAA agonists stabilize the dopaminergic-cholinergic neurotransmitter balance in the extrapyramidal system and enhance the antipsychotic effect of SGAs and FGAs by presynaptically inhibiting D2 dopaminergic neurons in the mesolimbic system and hippocampus [13].

NMDA antagonists reduce glutamate hyperactivity and inhibit presynaptically D2 dopaminergic neurons in the putamen. These drugs can also be used to reduce EPS; however they have a psychotomimetic effect, because the reduced presynaptic inhibition of 5-HT2A serotonergic neurons, via NMDA receptors, increases serotonin levels [11].

Neural Networks in the Extrapyramidal System

The neural networks in the extrapyramidal system can be described as shown in Figure 1: Dopaminergic neurons in the substantia nigra activate, via D1 and D2 receptors, other dopaminergic neurons located in the caudate nucleus. In this nucleus, D1 dopaminergic neurons transmit an activating impulse to dynorphin neurons, which inhibit substance P neurons via mu receptors. Substance P neurons activate GABAergic neurons in the internal globus pallidus, via NK1 receptors. D2 dopaminergic neurons located in the caudate nucleus transmit a postsynaptic excitatory impulse to GABAergic neurons placed in the external globus pallidus, which presynaptically inhibit via GABAA receptors NMDA glutamatergic neurons placed in the Subthalamic nucleus. The latter neurons presynaptically inhibit D2 dopaminergic neurons in the substantia nigra and GABAergic neurons in the internal globus pallidus. The striato-thalamo-cortial pathway is described in Figure 1. GABAergic neurons in the internal globus pallidus presynaptically inhibit, via GABAA receptors, NTS1 neurotensin, 5-HT2A serotonergic and M4 muscarinic cholinergic neurons placed in the putamen. These three types of neurons activate glutamatergic neurons in the putamen, which presynaptically inhibit D2 dopaminergic neurons. D2 dopaminergic neurons in the putamen have an antagonistic interaction with A2A adenosine neurons via presynaptic m5Glu (subtype 5 of metabotropic glutamatergic) receptors and GABAA receptors. Besides, they are activated by nicotinic cholinergic neurons via ß2 nach (ß2 nicotinic cholinergic) receptors. D2 dopaminergic neurons in the putamen are connected to other dopaminergic neurons in the caudate nucleus [13].

Treatment of Extrapyramidal Symptoms

Extrapyramidal symptoms can occur after the treatment with FGAs and, to a lesser extent with SGAs. Due to the blockade of D2 receptors in the extrapyramidal system, dopaminergic hypoactivity (via D2 receptors) and hyperactivity of M4 muscarinic cholinergic neurons occur. Some additional drugs can be administered to improve these movement disorders. M4 antagonists, GABAA agonists and NMDA antagonists can improve EPS [14].

M4 receptor antagonists, for example biperiden, can be used to treat EPS. These drugs reduce the hyperactivity of muscarinic cholinergic neurons and raise dopamine levels by reducing the glutamatergic presynaptic inhibition of D2 dopaminergic neurons via NMDA receptors. Adverse effects of M4 antagonists are those that can worsen psychotic symptoms and cognitive functions. Moreover, they can cause tachycardia and constipation [15].

GABAA agonists can as well be administered to improve EPS. These drugs reduce acetylcholine hyperactivity and raise dopamine levels. Besides, they decrease dopamine hyperactivity in the mesolimbic system. Adverse effects of GABAA agonists, for example benzodiazepines are sedation, addiction and amnesia [16].

Finally, NMDA receptor antagonists, for example amantadine can improve EPS for a short period of time. These drugs reduce acetylcholine hyperactivity and raise dopamine levels in the extrapyramidal system through a reduced glutamatergic presynaptic inhibition. However, they might have a psychotomimetic effect, because in the mesolimbic system, a reduced glutamatergic presynaptic inhibition via NMDA receptors of 5-HT2A serotonergic neurons can cause serotonin hyperactivity [14,17].

Extrapyramidal Systems in Patients Treated with Recently Developed Antipsychotic Drugs

Most SGAs, which cause EPS less often than FGAs, have a D2 and 5-HT2A antagonistic effect. Quetiapine with a higher affinity for the 5-HT2A receptor than the D2 receptor seldom causes EPS in comparison to risperidone, which often induces EPS, because it has a high affinity for the D2 receptor. Two recently developed antipsychotic drugs, namely aripiprazole and cariprazine, have a different mechanism of action. Aripiprazole exerts a partial D2 agonistic effect, a 5-HT2A antagonistic effect and a 5-HT1A agonistic effect. It shows good antipsychotic properties and seldom causes EPS [18]. Cariprazine is a new SGA with a partial agonistic effect at the D2 and D3 receptors. It shows antipsychotic and antimanic effects. Due to the different mechanism of action, it seldom causes EPS. Akathisia occurs in 11% of patients treated with cariprazine [19]. SGAs such as risperidone, olanzapine and quetiapine cause cognitive impairment, because they inhibit dopamine/serotonin release, above all in the prefrontal cortex [20]. Recently developed SGAs such as aripiprazole and cariparzine have a different mechanism of action; they act as partial agonist at the D2 receptor. In clinical studies, it has been found that cariprazine, which is a partial agonist at the D2 and D3 receptors, improved cognitive functions [21].

Conclusion

Schizophrenia and schizoaffective disorder is generally treated with second-generation antipsychotic drugs. Antipsychotic drugs are D2 and 5-HT2A antagonists and decrease dopamine and serotonin hyperactivity in the mesolimbic system, hippocampus and prefrontal cortex. Because of the D2 receptor blockade, EPS can occur. Neurotransmitter and neuropeptide alterations and the neural networks in the mesolimbic system and extrapyramidal system are described in detail. EPS can be treated with M4 receptor antagonists, which reduce acetylcholine

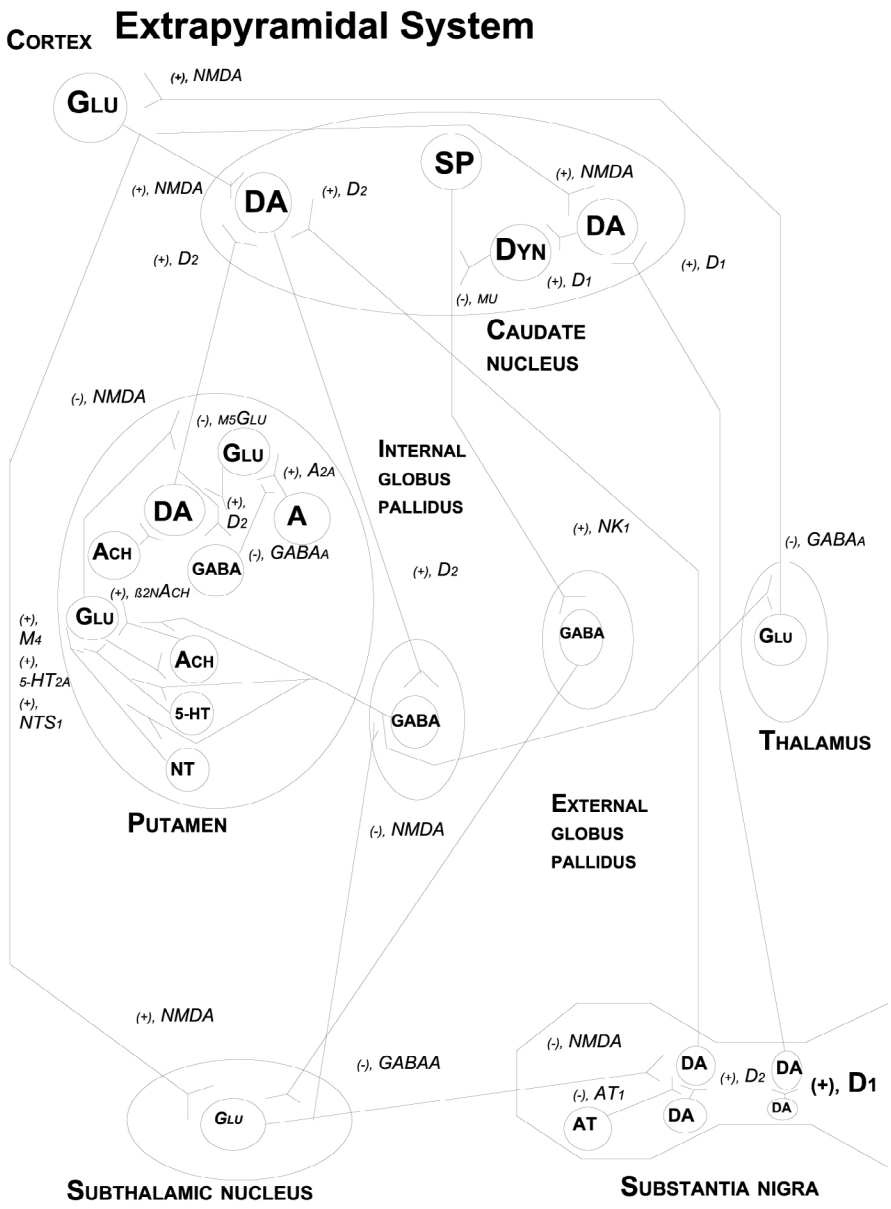

Figure 1: Neuronal pathways, classical neurotransmitters and neuropeptides involved in the extrapyramidal system. 5-HT: serotonin; A: adenosine; Ach: acetylcholine; DA: dopamine; Dyn: dynorphin; GABA: gamma-aminobutyric acid; Glu: glutamate; NT: neurotensin; SP: substance P. The following subreceptors are indicated: A2A: A2A receptor, subreceptor of the adenosine receptor; ß2nAch: ß2nAch receptor: a subreceptor of the nicotinic cholinergic receptor; GABAA: GABAA receptor, a subreceptor of the GABA receptor; 5-HT2A: 5-HT2A receptor, a subreceptor of the serotoninergic receptor; D1: D1 receptor, a subreceptor of the dopaminergic receptor; D2: D2 receptor, a subreceptor of the dopaminergic receptor; kappa: kappa receptor: a subreceptor of the opioid receptor; M4: M4 receptor: a subreceptor of the muscarinic cholinergic receptor; m5Glu: m5Glu receptor, a subreceptor of the metabotropic glutamatergic receptor; NK1: NK1 receptor: a subreceptor of the substance P receptor; NMDA: NMDA (N-methyl-D-aspartate) receptor, a subreceptor of the ionotropic glutamatergic receptor; NTS1: NTS1 receptor: a subreceptor of the neurotensin receptor. A plus mark indicates a postsynaptic excitatory impulse; a minus mark indicates a presynaptic inhibitory impulse.

hyperactivity in the extrapyramidal system, with GABAA agonists, which inhibit muscarinic cholinergic neurons and with NMDA antagonists, which raise dopamine levels in the extrapyramidal system. Some recently developed antipsychotic drugs, for example aripiprazole and cariprazine, exert a reduced occurrence of EPS. They have a different mechanism of action: a partial agonism at the D2 receptor.

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