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Application of single nucleotide polymorphisms of risk genes in schizophrenia in choosing the appropriate antipsychotic drug

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SUMMARY

Schizophrenia has a genetic etiology in about 80% of patients concerned. In recent years, some risk genes have been described. Table 1 summarizes some important risk genes, the functions of these risk genes in the neurotransmission in the brain areas involved in schizophrenia, the SNPs of the risk genes and an improved therapeutic effect or a lack of efficacy regarding a specific antipsychotic drug. The rs 165599 SNP of the COMT gene is connected with a higher therapeutic efficacy of risperidone, whereas the SNP of this risk gene is linked with a pharmacotherapy resistance. The SNP (rs 1799836) of the MAO B gene is correlated with schizophrenia and hyperprolactinemia. Both risk genes encode a reduced activity of enzymes catalyzing the dopamine degradation. Consequently, an increased dopamine release occurs via D2 receptors in the mesolimbic system and hippocampus. The GAD 67 gene is associated with a disturbed GABAergic neurotransmission, and in the hippocampus, GABAergic neurons which coexist with CCK weakly inhibt D2 dopaminergic neurons. The neuregulin-1 gene is linked with a glutamatergic dysfunction via NMDA receptors and an increased activation of the D2 receptor. In the hippocampus, glutamatergic neurons weakly activate GABAergic neurons which enable dopamine hyperactivity through a reduced presynaptic inhibition. The DAOA gene encodes as well a glutamatergic dysfunction via NMDA receptors. The SNPs of the D2 receptor (rs 1801028) and D3 receptor (rs 6280) genes are correlated with a better therapeutic efficacy of risperidone, whereas the SNPs (rs 4680 and rs 1800497) of the D2 receptor gene are more frequently found in patients with a pharmacotherapy resistance. In this review, the neural networks in the mesolimbic system, hippocampus and prefrontal cortex are updated according to the reviewed literature. In the future, it is of importance to examine the SNPs of schizophrenic patients in order to differentiate patients with a better response to a specific antipsychotic drug and patients with a pharmacotherapy resistance. The latter patients could be treated with the antipsychotic drug clozapine and an additional therapy with cariprazine, a partial D2 and D3 receptor agonist.

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INTRODUCTION

Schizophrenia is a chronic disabling mental disease that approximately 1% of the population suffers from. In this disease, positive (paranoia, illusions, and hallucinations), negative schizophrenic (social withdrawal, mutism, depression, and autism) and cognitive symptoms can be observed. Schizophrenia is manifested as an acute psychosis and shows remitted, residual and chronic forms in the course of the disease. Pharmacotherapy, that is, the administration of mostly second-generation antipsychotic drugs, can improve psychotic symptoms, but an accompanying sociotherapy and different forms of psychoeducation are also very essential to reach a good maintenance therapy [1].

Some genetic examinations have revealed that the onset/course of the disease and the therapeutic efficacy of a determined antipsychotic drug are associated with single nucleotide polymorphisms (SNPs) of risk genes [2]. Genetic research on the risk genes involved in schizophrenia has greatly been enlarged, and, till now, about 260 risk genes have been described. In schizophrenia, risk genes encoding, for example, alterations of dopaminergic, GABAergic, and glutamatergic neurotransmission have been found. Other factors, for example, stressful life-events, childhood trauma and drugs and substances abuse of substances such as cannabis, alcohol, nicotine or amphetamines, can deteriorate psychotic symptoms [3].

Besides, interactions between risk genes and environment play an important role in schizophrenia. Neural circuits, which describe the interaction between classical neurotransmitters and neuropeptides in a multi-neurotransmitter system, have been described in previous studies and updated [4]. In these neural circuits, the pharmacodynamic effect of antipsychotic drugs at dopaminergic and as well serotonergic and glutamatergic receptors has been considered. These neural circuits (including ventral tegmental area, hippocampus, and prefrontal cortex) are the neuroanatomical and pharmacological basis to choose an appropriate antipsychotic drug in clinical practice [5].

It is essential to further examine SNPs of risk genes in schizophrenia and to establish a correlation between the clinical efficacy of specific antipsychotic drugs and the reduced therapeutic effect of these drugs, i.e. a pharmacotherapy resistance [2]. An updating of the neural circuits serves to further understand the cellular function of the recently discovered risk genes in schizophrenia [6].

A literature search was performed at the PubMed database

using the following keywords: first-episode schizophrenia, risk genes in schizophrenia, then the neurotransmitters dopamine, serotonin, acetylcholine, GABA and glutamate, and later the risk genes described in previous reviews: catechol-O-methyl transferase (COMT), monoamine oxidase (MAO), glutamic acid decarboxylase 67 (GAD 67), neuregulin-1 and dysbindin-1 [3].

Risk genes in schizophrenia

In schizophrenia, some risk genes have been described and among them, it is important to mention the catechol-O-methyl transferase and monoamine oxidase genes, which are connected with dopamine degradation and hence a genetically encoded deficiency in these enzymes leads to dopamine hyperactivity; the glutamic acid decarboxylase (GAD) 67 gene that encodes a reduced activity of GAD and hence it causes a deficiency in the presynaptic inhibitory neurotransmitter gamma-aminobutyric acid (GABA), and the dysbindin-1 and neuregulin-1 genes which are linked with a reduced glutamatergic neurotransmission via the N-methyl-D-aspartate (NMDA) receptor [3].

The cellular functions of these risk genes and a possible association between them and the therapeutic efficacy or decreased therapeutic effect of specific antipsychotic drugs will be mentioned. For example, Han et al. [2] examined the COMT and the D1, D2 and D3 dopaminergic receptors risk genes and correlated the results of SNPs of these risk genes with the clinical efficacy of risperidone as a maintenance therapy in schizophrenia. Other risk genes related to the serotonergic, GABAergic or glutamatergic pathways in the brain centers involved in schizophrenia will also be mentioned [6].

Catechol-O-Methyl Transferase (COMT)

SNPs of the COMT gene were examined in a cohort of 55 schizophrenic patients and 53 healthy volunteers who also underwent magnetic resonance examinations. The first-episode schizophrenic patients who were Val homozygotes showed a correlation of the SNPs of the COMT gene with the severity of negative schizophrenic symptoms, i.e. social withdrawal, a decreased drive and mutism; in the MRI imaging showed an altered resting-state functional connectivity of the neural circuits which originate in the dorsolateral prefrontal cortex [7]. In a clinical study performed in Iran, 100 schizophrenic patients, 100 patients with bipolar disorder I and 127 healthy subjects were genotyped; for the risk genes, SNPs of the COMT and D-amino acid oxidase activator (DAOA) genes were determined. The DAOA gene was related to a glutamate dysfunction via NMDA receptors. SNPs (rs156699 and rs4680) of the COMT risk gene and rs946737 and rs3918342 of the DAOA risk gene were both correlated with schizophrenia and bipolar disorder I [8]. In a cohort of Mexican schizophrenic patients, SNPs of the COMT and D2/D3 receptor risk genes were examined, and a continuous maintenance therapy or a pharmacoresistance was correlated to the SNPs of these risk genes. SNPs of the COMT/Val158Met (rs4680) and D3 receptor/Ser9 Gly (rs6280) risk genes were found in patients with a good response to an antipsychotic treatment and also in patients with pharmacoresistance. The SNP: rs1799978 of the D2 receptor gene was found in non-responders to an antipsychotic treatment [9]. In another study, 690 schizophrenic patients and 430 healthy subjects were studied for the COMT, D1, D2 and D3 receptors risk genes. SNPs of the COMT (rs165599) and D2 receptor (rs1801028) genes were correlated with an increased responder rate to an antipsychotic treatment with risperidone [2].

Monoamine oxidase A and B (MAO A and B)

Monoamine oxidases A and B are mitochondrial enzymes that encode dopamine degradation and other amines such as serotonin and noradrenaline. SNPs of the MAO A and B genes can be detected in schizophrenic patients with hyperprolactinemia, caused by antipsychotic drugs such as risperidone and palliperidone which show a D2 antagonistic effect and a high affinity for the D2 receptor. In a cohort of schizophrenic patients in West Siberia, SNPs of MAO B, D1, D2, D3 and D4 receptor and dopamine transporter SLC6A3 genes were examined. In schizophrenic men, the SNP: rs1799836 of the MAO B gene was related with hyperprolactinemia under a treatment with antipsychotic drugs. SNPs of the dopamine transporter SLC6A3 gene was correlated with hyperprolactinemia in schizophrenic patients treated with risperidone and palliperidone, but not with other antipsychotic drugs [10].

Glutamic Acid Decarboxylase 67 (GAD 67)

GAD 67 is the 67 kDA isoform of the GABA synthesizing enzyme; alterations of the GABAergic neurotransmission have been found in schizophrenia. In 10 paranoid schizophrenic subjects, 6 residual schizophrenic patients and 16 controls, a quantitative densitometric analysis of the GAD-immunoreactive neuropil in the hippocampus, superior temporal gyrus and laterodorsal thalamic nucleus was performed. Reduced GAD-immunoreactive neuropil in the hippocampus CA1 region and the superior temporal gyrus was found in the brains of paranoid schizophrenic patients in contrast to schizophrenic patients with a residual form; however, this decrease was less found when the dosage of the antipsychotic drugs was increased [11].

Dysbindin-1, Disrupted in Schizophrenia 1 (DISC 1) and Dystrobrevin Binding Protein 1 (DTNBP1)

In schizophrenic patients the dysbindin-1 activity, which regulates the copper metabolism, is reduced. In the serum of schizophrenic patients, the copper level is elevated; however, since the copper transport is altered in schizophrenia, normally copper-containig brain areas such as the substantia nigra contain less copper in schizophrenic patients than the controls. Reducing the copper level can induce schizophrenia-like behavior. Antipsychotic drugs can decrease the copper level [12]. In a meta-analysis including 21 studies, SNPs of the COMT (rs165599), DISC (rs3737597) and DTNBP1 (rs1047631) genes were found in schizophrenic patients [13].

Neuregulin-1

321 schizophrenic patients and 309 healthy volunteers were examined to know whether they were carriers of the m8nrg433E1006 SNP of the neuregulin-1 gene. 62 schizophrenic patients and 24 healthy subjects were found to bear this SNP. In these patients, the neuregulin-1 gene was found

to be overexpressed. The overexpression of this gene is connected with an increased activity of the enzyme tyrosine kinase, which is co-expressed with parvalbumin and cholecystokinin, and with a glutamatergic dysfunction via NMDA receptors. Consequently NMDA glutamatergic neurons less activate GABAergic neurons, which presynaptically inhibit pyramidal neurons [14].

Alterations of classical neurotransmitters in schizophrenia

Dopamine

Dopamine is a postsynaptic excitatory neurotransmitter, which acts at five receptors (D1, D2, D3, D4 and D5) and plays the major role in the pathophysiology of schizophrenia. In this disease, due to a decreased activity of the COMT and MAO A and B enzymes, the dopamine degradation is reduced. Consequently, hyperactivity of dopamine mostly via D2 receptors occurs in the ventral tegmental area, hippocampus and prefrontal cortex [6]. SNPs of the COMT and MAO A and B, as well of the D2 and D3 receptors genes can be associated with an increased therapeutic efficacy of antipsychotic drugs such as risperidone. The SNP: 165599 of the COMT gene is significantly correlated with a higher therapeutic efficacy of risperidone in the treatment of schizophrenia. However, the SNP: 4680 of the COMT gene occurs more frequently in patients who develop an antipsychotic-induced dopamine hypersensitivity psychosis and therefore a pharmacoresistance [2]. The SNP: 1799836 of the MAO B gene were found in patients with hyperprolactinemia [10].

Serotonin

Serotonin, a postsynaptic excitatory neurotransmitters, which acts at different 5-HT receptors is involved in the pathophysiology of schizophrenia. Due to an altered 5-HT transporter, serotonin shows hyperactivity in schizophrenia in the ventral tegmental area, hippocampus and prefrontal cortex. The 5-HT2 receptor gene has a dysfunction in schizophrenia. In animal experiments, NMDA receptor antagonists can cause schizophrenia-like behavior, which can be treated by risperidone, a D2 and 5-HT2 receptor antagonist, but not by haloperidol, a D2 receptor antagonist. In the brain areas involved in schizophrenia, NMDA glutamatergic neurons might, due to the risk genes, weakly presynaptically inhibit 5-HT2A serotonergic neurons and enhance serotonin hyperactivity [4, 15]

Gamma-Aminobutyric Acid (GABA)

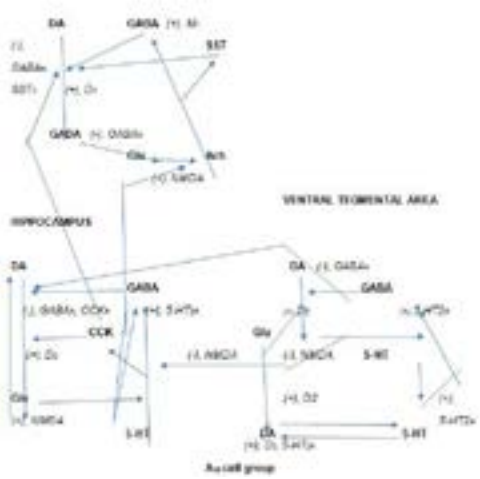
Gamma-aminobutyric acid is a presynaptic inhibitory neurotransmitter, which acts at three GABA receptors (GABAA, GABAB, GABAC). It exerts a protecting influence on dopaminergic and noradrenergic neurons in the whole central nervous system. In schizophrenia, the GAD 67 risk gene indicates that a GABAergic dysfunction is involved in the pathophysiology of the disease. Medium spiny neurons have been located in the extrapyramical system and prefrontal cortex; in these neurons, GABA is colocalized with the neuropeptides substance P, enkephalin and cholecystokinin [4, 11].

Glutamate

Glutamate is mostly a postsynaptic excitatory neurotransmitter, i.e. an excitotoxic neurtransmitter and partly a presynaptic inhibitory neurotransmitter that acts at ionotropic, i.e. NMDA, AMPA and metabotropic glutamatergic receptors. In two thirds of schizophrenic patients and one third of healthy subjects, the SNP: m8nrg433E1006 of the neuregulin-1 gene can be found. This SNP is associated with an activation of the D2 receptor and a glutamatergic dysfunction via NMDA receptors. Consequently, glutamatergic neurons weakly activate GABAergic neurons, which weakly presynaptically inhibit D2 dopaminergic neurons in the ventral tegmental area and hippocampus. The DAOA gene encodes a dysfunction of the glutamatergic neurotransmission via NMDA receptors. As indicated in the neural circuits, glutamatergic neurons might weakly inhibit 5-HT2A serotonergic neurons in the mesolimbic system and hippocampus [8, 14].

Neural circuits in the ventral tegmental area, hippocampus and prefrontal cortex under consideration of the neurotransmitter alterations due to risk genes

Neural networks involved in schizophrenia (ventral tegmental area, hippocampus, prefrontal cortex) have been updated from previous reviews [4]. In these neural networks, the neurotransmitter alterations due to the risk genes have been considered (Figure. 1).



In the vental tegmental area, D2 dopaminergic neurons show an increased release of dopamine due to the COMT and MAO A and B risk genes and activate glutamatergic neurons. Due to the D2 receptor risk gene, a dysfunction of the D2 receptor can be found. Glutamatergic neurons, due to the neuregulin-1 and DAOA risk genes, weakly inhibit 5-HT2A serotonergic neurons [8] which show hyperactivity due to the serotonin transporter risk gene. The serotonergic neurons activate GABAergic neurons, which due to the GAD 67 gene, weakly inhibit D2 dopaminergic neurons. In the ventral tegmental area, D2 dopaminergic neurons activate other D2 dopaminergic neurons, and 5-HT2A serotonergic neurons activate 5-HT2A serotonergic neurons in the A10 cell group. In this brain area, D2 dopaminergic neurons and 5-HT2A serotonergic neurons activate each other.

In the hippocampus, D2 dopaminergic neurons activate glutamatergic neurons which weakly presynaptically inhibit, via NMDA receptors, 5-HT2A serotonergic neurons and activate via NMDA receptors D2 dopaminergic and GABAergic neurons.

The serotonergic NEURONS activate GABAergic neurons, that also contain cholecystokinin (CCK). GABAergic neurons, due to the GAD 67 gene, weakly inhibit D2 dopaminergic neurons via GABAA and CCKA receptors. GABAergic neurons located in the ventral tegmental area inhibit hippocampal D2 dopaminergic neurons and glutamatergic neurons in the mesolimbic system inhibit 5-HT2A serotonergic neurons.

In the prefrontal cortex, D2 dopaminergic neurons activate GABAergic neurons, which via GABAA receptors inhibit NMDA glutamatergic neurons. The latter neurons activate M1 muscarinic cholinergic neurons which activate medium spiny neurons, namely GABAergic and somatostatinergic neurons. The medium spiny neurons inhibit D2 dopaminergic neurons via GABAA and somatostatin 1 receptors. D2 dopaminergic neurons are inhibited by GABAergic neurons, located in the hippocampus [14].

Schizophrenia: Association between the snps of risk genes and the therapeutic efficacay of a specific antipsychotic drug

The results have been summarized in Table 1 [2, 4, 7-10, 13, 14].

Table 1: Risk genes in schizophrenia: functions, SNPs and the depending therapeutic effect of a specific antipsychotic drug or a pharmacotherapy resistance.

Risk genes in schizophrenia	Function of the risk gene	Altered function of neurotransmitters in the brain areas involved in schizophrenia	SNP	Therapeutic effect of a specific antipsychotic drug or pharmaco-therapy resistance
COMT	Decreased dopamine degradation	Dopamine hyperactivity via D2 receptors in the mesolimbic system and hippocampus	rs 169774	Increased therapeutic efficacy of risperidone
COMT	Decreased dopamine degradation	Dopamine hyperactivity via D2 receptors in the mesolimbic system and hippocampus	rs 4680	Antipsychotic-induced dopamine hypersensitivity psychosis and pharmacotherapy resistance
MAO	Decreased dopamine degradation	Dopamine hyperactivity via D2 receptors in the mesolimbic system and hippocampus	rs 1799836	Schizophrenia with hyper-prolactinemia
D2 receptor	Altered dopamine activity	Dopamine hyperactivity via D2 receptors in the mesolimbic system and hippocampus	rs 1801028	Inc-eased therapeutic efficacy of risperidone
D3 receptor	Altered dopamine activity	Dopamine hyperactivity via D2 and D3 receptors in the mesolimbic system and hippocampus	rs 4680	Pharmacotherapy resistance in the treatment with risperidone
DAOA	Altered glutamatergic function via NMDA receptors	Glutamatergic dysfunction via NMDA receptors allows serotonin hyperactivity through a reduced presynaptic inhibition		Risk gene associated with bipolar disorder I and schizophrenia
GAD 67	Glutamatergic dysfunction via GABAA receptors	GABAergic neurons weakly inhibit D2 dopaminergic neurons		Associated with paranoid schizophrenia

Conclusion

Schizophrenia has a genetic etiology in about 80% of patients concerned. In recent years, some risk genes have been described. Table 1 summarizes some important risk genes, the functions of these risk genes in the neurotransmission in the brain areas involved in schizophrenia, the SNPs of the risk genes and an improved therapeutic effect or a lack of efficacy regarding a specific antipsychotic drug. The rs 165599 SNP of the COMT gene is connected with a higher therapeutic efficacy of risperidone, whereas the SNP of this risk gene is linked with a pharmacotherapy resistance. The SNP (rs 1799836) of the MAO B gene is correlated with schizophrenia and hyperprolactinemia. Both risk genes encode a reduced activity of enzymes catalyzing the dopamine degradation. Consequently, an increased dopamine release occurs via D2 receptors in the mesolimbic system and hippocampus. The GAD 67 gene is associated with a disturbed GABAergic neurotransmission, and in the hippocampus, GABAergic neurons which coexist with CCK weakly inhibt D2 dopaminergic neurons. The neuregulin-1 gene is linked with a glutamatergic dysfunction via NMDA receptors and an increased activation of the D2 receptor. In the hippocampus, glutamatergic neurons weakly activate GABAergic neurons which enable dopamine hyperactivity through a reduced presynaptic inhibition. The DAOA gene encodes as well a glutamatergic dysfunction via NMDA receptors. The SNPs of the D2 receptor (rs 1801028) and D3 receptor (rs 6280) genes are correlated with a better therapeutic efficacy of risperidone, whereas the SNPs (rs 4680 and rs 1800497) of the D2 receptor gene are more frequently found in patients with a pharmacotherapy resistance. In this review, the neural networks in the mesolimbic system, hippocampus and prefrontal cortex are updated according to the reviewed literature. In the future, it is of importance to examine the SNPs of schizophrenic patients in order to differentiate patients with a better response to a specific antipsychotic drug and patients with a pharmacotherapy resistance. The latter patients could be treated with the antipsychotic drug clozapine and an additional therapy with cariprazine, a partial D2 and D3 receptor agonist.

REFERENCES

1. Werner FM, Coveñas R (2014) Safety of antipsychotic drugs: focus on therapeutic and adverse effects. Expert Opin Drug Saf 13(8): 1031-42. PMID: 24975932
2. Han J, Li Y, Wang X (2017) Potential link between genetic polymorphisms of catechol-O-methyltransferase and dopamine receptors and treatment efficacy of risperidone on schizophrenia. Neuropsychiatr Dis Treat 13: 2935-43. PMID: 29255361
3. Collier DA, Li T (2003) The genetics of schizophrenia: glutamate not dopamine? Eur J Pharmacol 480(1-3): 177-84. PMID: 14623361
4. Werner FM, Coveñas R (2016) Classical neurotransmitters and neuropeptides involved in schizoaffective disorder: focus on prophylactic medication. Sharjah: Bentham Science Publishers.
5. Haller CS, Padmanabhan JL, Lizano P, Torous J, Keshavan M (2014) Recent advances in understanding schizophrenia. F1000Prime Rep 6: 57. PMID: 25184047
6. Werner FM, Coveñas R (2021) Risk genes in schizophrenia and their importance in choosing the appropriate antipsychotic treatment. Curr Pharm Design 27(30): 3281-92.
7. Kang Y, Huang K, Lv Y, Zhang W, Cai W et al (2019) Genetic contribution of catechol-O-methyltransferase in dorsolateral prefrontal cortex functional changes in the first-episode schizophrenia. Behav Brain Res 364: 225-32. PMID: 30738913
8. Ahmadi L, Kazemi Nezhad SR, Behbahani P, Khajeddin N, Pourmehdi-Boroujeni M (2018) Genetic variations of DAOA (rs946737 and rs3918342) and COMT genes (rs156699 and rs 4680) in schizophrenia and bipolar disorder I. Basic Clin Neurosci 9(6): 429-38. PMID: 30719257.
9. Escamilla R, Camarena B, Saracco-Alvarez R, Fresán A, Hernández S et al (2018) Association study between COMT, DRD2, and DRD3 gene variants and antipsychotic treatment response in Mexican patients with schizophrenia. Neuropsychiatr Dis Treat 14: 2981-7. PMID: 30464483.
10. Osmanova DZ, Freidin MB, Fedorenko OY, Pozhidaev IA, Boiko AS NA et al (2019) A pharmacogenetic study of patients with schizophrenia from West Siberia gets insight into dopaminergic mechanisms of antipsychotic-induced hyperprolactinemia. BMC Med Genet 20(Suppl. 1): 47. PMID: 30967134
11. Steiner J, Brisch R, Schiltz K, Dobrowolny M, Mawrin H et al (2016) GABAergic system impairment in the hippocampus and superior temporal gyrus of patients with paranoid schizophrenia: A post-mortem study. Schizophr Res 177(1-3): 10-7. PMID: 26922657
12. Schoonover KE, Queern SL, Lapi SE, Roberts RC (2020) Impaired copper transport in schizophrenia results in a copper-deficient brain state: A new side to the dysbindin story. World J Biol Psychiatry 21(1): 13-28. PMID: 30230404
13. Mohamed ZI, Tee SF, Tang PY (2018) Association of functional polymorphisms in 3′-untranslated regions of COMT, DISC1, and DTNBP1 with schizophrenia: a meta-analysis. Psychiatr Genet 28(6): 110-9. PMID: 30252773
14. Kotzadimitriou D, Nissen W, Paizs M, Newton N, Harrison NP, Paulsen (2018) Neuregulin-1 type I overexpression is associated with reduced NMDA receptor-mediated synaptic signaling in hippocampal interneurons expressing PF or CCK. eNeuro 5(2).
15. Nilsson M, Waters S, Waters N, Carlsson A, Carlsson ML (2001) A behavioural pattern analysis of hypoglutamatergic mice-effects of four different antipsychotic agents. J Neural Transm (Vienna) 108 (10): 1181-96. PMID: 11725821