University of Groningen

Polymorphisms in BDNF, AKT1, GSK3B genes: possible association with antipsychotic-induced hyperprolactinemia in schizophrenia patients

Ivanova (Svetlana Ivanova), S.A.; Paderina, Diana Z.; Boiko, Anastasiia S; Pozhidaev, Ivan V; Kornetova, E. G.; Wilffert, Bob; Loonen, Anton

Published in:
European Neuropsychopharmacology

DOI:
[10.1016/j.euroneuro.2020.09.427](https://doi.org/10.1016/j.euroneuro.2020.09.427)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Ivanova (Svetlana Ivanova), S. A., Paderina, D. Z., Boiko, A. S., Pozhidaev, I. V., Kornetova, E. G., Wilffert, B., & Loonen, A. (2020). Polymorphisms in BDNF, AKT1, GSK3B genes: possible association with antipsychotic-induced hyperprolactinemia in schizophrenia patients. *European Neuropsychopharmacology*, 40(Supplementum 1), S331-S332. <https://doi.org/10.1016/j.euroneuro.2020.09.427>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

receiving statins had higher HR for mortality [6.79 (95%CI 3.48-13.25), $p < 0.005$], compared to patients receiving appropriate prescriptions of statins. Similarly, patients diagnosed with diabetes mellitus not receiving hypoglycemic drugs had higher HR [7.95 (95%CI 3.49-18.15, $p < 0.005$) to die compared to patients who received appropriate treatment. Prescription of antihypertensive drugs for chronic hypertension had no significant effect on HR for death. No significant differences were found between the groups regarding medical service utilization in the community (e.g. general practitioner and specialist visits). However, patients who died were hospitalized more often and for longer periods than patients in the survivor group ($p < 0.005$).

Conclusions: Inadequate treatment for metabolic syndrome was found to be a mortality predictor under clozapine treatment. More appropriate rigorous regimen for detection and treatment of metabolic risk factors might prolong life expectancy among this population.

No conflict of interest

doi: [10.1016/j.euroneuro.2020.09.426](https://doi.org/10.1016/j.euroneuro.2020.09.426)

P.583

Polymorphisms in BDNF, AKT1, GSK3B genes: possible association with antipsychotic-induced hyperprolactinemia in schizophrenia patients

S.A. Ivanova¹, D.Z. Paderina¹, A.S. Boiko¹, I.V. Pozhidaev¹, E.G. Kornetova², B. Wilffert³, A.J.M. Loonen⁴

¹Mental Health Research Institute Tomsk NRMС, Molecular Genetics and Biochemistry Laboratory, Tomsk, Russia

²Mental Health Research Institute Tomsk NRMС, Department of Endogenous Disorders, Tomsk, Russia

³University of Groningen, Pharmacotherapy- Epidemiology & Economics- GRIP, Groningen, The Netherlands

⁴University of Groningen, Pharmacotherapy- Epidemiology & Economics- GRIP, Groningen, The Netherlands

Background: Antipsychotic drug therapy is the main method of schizophrenia treatment, which does not only improve the long-term prognosis and facilitates its transition to remission, but unfortunately also has a wide range of side effects including hyperprolactinemia (HPRL). HPRL is primarily attributed to blockade of dopamine D2 receptors. We have previously studied the possible association with *dopamine* and *serotonin receptor* genes, *P-glycoprotein* and *cytochrome P450* genes [1-3]. In theory, several other genes could also have functional significance and influence prolactin secretion. Brain-derived neurotrophic factor (BDNF) plays a major role in neurogenesis and neuroplasticity and modulates several neurotransmitter systems which are involved in pharmacological activity of antipsychotic treatment. Apart from the well-known G protein-dependent DRD2 signalling involving inhibition of cAMP, another pathway is G protein-independent and involves AKT serine/threonine kinase 1 (AKT1) and glycogen synthase kinase 3 β (GSK3B). We found evidence for an association with remission in depression, but not with the pathogenesis of another side effect (tardive dyskinesia) [4,5].

Aim: The present study aimed to investigate the association between polymorphisms of BDNF, AKT1, GSK3B genes and antipsychotic-related HPRL in patients with schizophrenia.

Methods: The protocol was approved by the local Ethics Committee and all patients gave informed consent. We included 446 patients with schizophrenia (age 42.1 ± 1.4 years) according to the diagnostic criteria of ICD-10 (F20) who were treated with classical and/or atypical antipsychotic drugs. Evaluation of serum prolactin level was performed by ELISA using reagents of PRL Test System (Monobind Inc., USA). Genotyping was carried out on polymorphic variants of the *BDNF* (rs6265, rs7124442, rs11030104), *GSK-3 β* (rs334558), *Akt1* (rs3730358, rs1130214) using the MassARRAY® Analyzer 4 by Agena Bioscience™ (the Genome Analysis Facility, University Medical Center Groningen) and the QuantStudio™ 3D Digital PCR System Life Technologies amplifier (the Core Facility "Medical Genomics", Tomsk NRMС). Patients were divided into individuals with and without HPRL in accordance with international criteria: more than 20 ng/ml in men, and 25 ng/ml in women [1-3]. Genotype and allele frequencies were compared between groups with the χ^2 test and were considered significant at $p < 0.05$ level.

Results: The frequency of HPRL according to predefined criteria was 51%. Statistically significant results were obtained for polymorphic variant rs7124442 of *BDNF* ($\chi^2 = 10.73$; $p = 0.005$), which suggests its involvement in the development of HPRL. The homozygous genotype CC was significantly less common in patients with HPRL which indicates protective properties (OR 0.38; 95% CI: 0.20 - 0.74). We did not find any statistically significant associations for other polymorphisms of *BDNF* (rs6265, rs11030104), *GSK-3 β* (rs334558), or *Akt1* (rs3730358, rs1130214) genes.

Conclusion: Our results indicate that rs7124442 of *BDNF* gene may have functional consequences for prolactin secretion. We found no association between *AKT1* and *GSK3B* and antipsychotic-induced HPRL in our population, despite the important role the two kinases play in the G protein-independent DRD2 signalling.

Disclosure statement: This work was supported by the Russian Foundation for Basic Research [Grant #17-29-06035].

References

- [1] Osmanova, D.Z., Freidin, M.B., Fedorenko, O.Y., Pozhidaev, I.V., Boiko, A.S., Vyalova, N.M., Tiguntsev, V.V., Kornetova, E.G., Loonen, A.J.M., Semke, A.V., Wilffert, B., Bokhan, N.A., Ivanova, S.A., 2019. A pharmacogenetic study of patients with schizophrenia from West Siberia gets insight into dopaminergic mechanisms of antipsychotic-induced hyperprolactinemia. *BMC Medical Genetics* 20. doi:[10.1186/s12881-019-0773-3](https://doi.org/10.1186/s12881-019-0773-3).
- [2] Ivanova, S.A., Osmanova, D.Z., Freidin, M.B., Fedorenko, O.Y., Boiko, A.S., Pozhidaev, I.V., Semke, A.V., Bokhan, N.A., Agarkov, A.A., Wilffert, B., Loonen, A.J., 2017. Identification of 5-hydroxytryptamine receptor gene polymorphisms modulating hyperprolactinemia in antipsychotic drug-treated patients with schizophrenia. *The World Journal of Biological Psychiatry* 18, 239-246. doi:[10.1080/15622975.2016.1224926](https://doi.org/10.1080/15622975.2016.1224926).
- [3] Geers, L.M., Pozhidaev, I.V., Ivanova, S.A., Freidin, M.B., Schmidt, A.F., Cohen, D., Boiko, A.S., Paderina, D.Z., Fedorenko, O.Y., Semke, A.V., Bokhan, N.A., Wilffert, B., Kosterink, J.G., Touw, D.J., Loonen, A.J., 2020. Association between eight P-glycoprotein (MDR1/ABCB1) gene polymorphisms

and antipsychotic drug-induced hyperprolactinemia. *British Journal of Clinical Pharmacology*. doi:10.1111/bcp.14288.

- [4] Levchenko, A., Losenkov, I.S., Vyalova, N.M., Simutkin, G.G., Bokhan, N.A., Wilffert, B., Loonen, A.J., Ivanova, S.A., 2018. The functional variant rs334558 of GSK3B is associated with remission in patients with depressive disorders. *Pharmacogenomics and Personalized Medicine* Volume 11, 121-126. doi:10.2147/pgpm.s171423.
- [5] Levchenko, A., Vyalova, N., Pozhidaev, I.V., Boiko, A.S., Osmanova, D.Z., Fedorenko, O.Y., Semke, A.V., Bokhan, N.A., Wilffert, B., Loonen, A.J., Ivanova, S.A., 2019. No evidence so far of a major role of AKT1 and GSK3B in the pathogenesis of antipsychotic-induced tardive dyskinesia. *Human Psychopharmacology: Clinical and Experimental* 34. doi:10.1002/hup.2685.

doi: 10.1016/j.euroneuro.2020.09.427

P.584

The actions of lumateperone and single nucleotide polymorphism (SNP) converge on the glutamate-NO-cGMP pathway

J. Titulaer^{1,2}, O. Radhe¹, A. Ström¹, L. Almer¹,
O. Yakimenko¹, Å. Konradsson-Geuken^{1,2}, R. Davis³,
S. Dutheil³, K. Vanover³, G. Snyder³, T.H. Svensson²

¹Uppsala University, Department of Pharmaceutical Biosciences, Uppsala, Sweden

²Karolinska Institutet, Department of Physiology and Pharmacology, Stockholm, Sweden

³Intra-Cellular Therapies, Inc., New York, USA

Introduction: Lumateperone is a novel first-in-class drug providing selective and simultaneous modulation of serotonin, dopamine and glutamate. The drug was recently approved by the FDA for the treatment of adult schizophrenia. Lumateperone is an antagonist with high-affinity for the 5-HT_{2A} receptor and it has a 60-fold higher affinity for these receptors compared to dopamine D₂ receptors. As the dose is increased, it acts as a partial agonist at D₂ receptors presynaptically and as a D₂ antagonist postsynaptically. Lumateperone also exhibits potent serotonin reuptake inhibition and increases phosphorylation of glutamatergic N-methyl-D-aspartate (NMDA) GluN2B receptors in a mesolimbic-specific manner [1]. A single injection of the antihypertensive nitric oxide donor sodium nitroprusside (SNP) has been found to induce a rapid (within 4 hours) and sustained (several weeks) antipsychotic effect in young treatment-resistant schizophrenic patients [2]. Moreover, we have recently shown that a low dose of SNP may significantly enhance the antipsychotic-like effect of a sub-effective dose of risperidone in rats in the conditioned avoidance response (CAR) test to a clinically relevant level [3].

Methods: Against this background, we have now studied the antipsychotic-like effect of lumateperone and the combination of lumateperone and SNP in rodents using the same behavioral assay. We used young male rats in the CAR test to determine the antipsychotic-like efficacy, since this behavioral test has shown a very high predictive validity to identify drugs with clinical antipsychotic activity. The experiments were analyzed with Friedman's analysis of variance

(ANOVA) followed by Wilcoxon matched-pairs signed-ranks tests. All experiments were approved by the local animal ethics committee, Uppsala and Uppsala University, Sweden. **Results:** Lumateperone caused a dose-dependent antipsychotic-like effect in the CAR test, where 10 mg/kg lumateperone significantly suppressed CAR by 77% to a clinically relevant level (≥ 70 -80%), 3 mg/kg and 7 mg/kg significantly suppressed CAR as well, but in a sub-effective manner (6% and 54%). SNP alone had no effect on CAR suppression (0%). However, when SNP (1.5 mg/kg) was added to lumateperone (3 and 7 mg/kg) the CAR suppression was enhanced to 27% and 86% respectively.

Conclusion: The present study shows that lumateperone dose-dependently suppresses CAR and that SNP can indeed enhance the antipsychotic-like effect of a sub-effective dose of lumateperone to a clinically relevant level. Whereas Hallak and colleagues found that additional SNP treatment significantly improved positive, negative and depressive symptoms of schizophrenia, a more recent clinical study could not replicate these findings, as SNP had no significant effect compared to placebo [4]. However, significantly older patients were used, and the authors argue that SNP may be more effective in patients with recent-onset psychosis [4]. Lumateperone has already shown to be safe and well-tolerated with a safety profile similar to placebo for motor disturbances, prolactin changes, weight gain, cardiovascular and metabolic side effects in several phase 3 clinical trials. Our current data propose that the combination of lumateperone and SNP may allow for a lower dosage of lumateperone and a potentially long lasting reduced risk of adverse side effects in young schizophrenic patients.

No conflict of interest

References

- [1] Snyder, G.L., Vanover, K.E., Zhu, H., Miller, D.B., O'Callaghan, J.P., Tomesch, J., Mates, S., 2015. Functional profile of a novel modulator of serotonin, dopamine, and glutamate neurotransmission. *Psychopharmacology* 605-621.
- [2] Hallak, J.E.C., Maia-de-Oliveira, J.P., Abreu, J., Evora, P.R., Zuardi, A.W., Crippa, J.A.S., Dursun, S.M., 2013. Rapid Improvement of Acute Schizophrenia Symptoms After Intravenous Sodium Nitroprusside: A Randomized, Double-blind, Placebo-Controlled Trial. *JAMA Psychiatry* 70 (7), 668-676.
- [3] Titulaer, J., Malmerfelt, A., Marcus, M., Svensson, T.H., 2019. Enhancement of the antipsychotic effect of risperidone by sodium nitroprusside in rats. *European Journal of Neuropsychopharmacology* submitted manuscript.
- [4] Brown, H.E., Freudenreich, O., Fan, X., Heard, S.O., Goff, D., Petrides, G., Perlis, R.H., 2019. Efficacy and Tolerability of Adjunctive Intravenous Sodium Nitroprusside Treatment for Outpatients With Schizophrenia. *JAMA Psychiatry* 02118, 1-9.

doi: 10.1016/j.euroneuro.2020.09.428

P.587

Prohibitin 2 study in postmortem prefrontal cortex in schizophrenia

È. Vila¹, R. Pinacho², R. Prades³, T. Tarragó³, I. Ferrer⁴,
A. Escanilla⁵, B. Ramos¹