Association of polymorphism in the dopamine receptors and transporter genes with hyperprolactinemia in patients with schizophrenia

Osmanova, D.; Boiko, A.S.; Fedorenko, O.Y.; Pozhidaev, I.V.; Freidin, M.B.; Kornetova, E.G.; Ivanova, S.A.; Wilffert, B.; Loonen, A.J.M.

Published in:
European Neuropsychopharmacology

Publication date:
2017

interact with CNS receptors known to cause adverse events, and the Ki of LB-102 against the 5-HT7 receptor was also similar to amisulpride. In vivo both LB-102 and LB-103 were as effective as amisulpride and risperidone in restoration of the ability to discriminate between novel and familiar objects in NOR. In the LMA study, 30 mg/kg doses of LB-102 attenuated the d-amphetamine-induced increase in LMA at lower doses than amisulpride ($P < 0.05$) while the 30 mg/kg dose was numerically more effective ($p = 0.07$). Plasma exposure following oral administration of LB-102 was similar to amisulpride and should be appropriate for oral administration. In a catalepsy bar test (an animal test of the=potential for extrapyramidal side effects) no difference was observed between LB-102 and LB-103 and vehicle control.

Conclusion: LB-102 and LB-103 have CNS receptor binding profiles similar to amisulpride. The efficacy of both compounds was similar to amisulpride in NOR and LB-102 was superior in the LMA study. Our initial preclinical evaluation suggests that both LB-102 and LB-103 have meaningful potential antipsychotic properties for the treatment of schizophrenia.

References

[1] Dos Santos Pereira, J.N, Tadjerpisheh, S., Abu Abed, M., Saadatmand, A.R, Weksler, B., Romero, I.A, Couraud, P.-O., Brockmöller, J., Tzvetkov, M. V., 2014. The Poorly Membrane Permeable Antipsychotic Drugs Amisulpride and Sulpride Are Substrates of the Organic Cation Transporters from the SLC22 Family'. The AAPS Journal 16, 1247–1258.

[2] Castelli, M.P, Mocci, I., Sanna, A.M, Gessa, G.L, Pani, L., 2001. (–)S Amisulpride Binds With High Affinity To Cloned Dopamine D3 And D2 Receptors. European J Pharmacol 432, 143–147.

Disclosure statement: VG, MB, MSH, ZP, and AV own shares of LB Pharmaceuticals. VG is on the Board of Directors of LB Pharmaceuticals, ZP and AV are employees of LB Pharmaceuticals, and MB and MH are consultants to LB Pharmaceuticals. JCN has received expenses to attend conferences and fees for lecturing and consultancy work (including attending advisory boards) from the manufacturers of various antipsychotic drugs. JCN, BG, GP and DC are employees of the University of Manchester. Acknowledgements: This research was supported by LB Pharmaceuticals Inc. (NY USA) and Rivopharm SA (Lugano, Switzerland).

P.3.c.006 Association of polymorphism in the dopamine receptors and transporter genes with hyperprolactinemia in patients with schizophrenia

D. Osmanova[1]*, A.S. Boiko[1], O.Y. Fedorenko[1], I.V. Pozhidaev[1], M.B. Freidin[2], E.G. Kornetova[3], S.A. Ivanova[1], B. Wilffert[4], A.J.M. Loonen[5] *[1]Mental Health Research Institute- Tomsk NRMC, Laboratory of Molecular Genetics and Biochemistry, Tomsk, Russia; [2]Research Institute of Medical Genetics, Tomsk NRMC, Laboratory of Population Genetics, Tomsk, Russia; [3]Mental Health Research Institute- Tomsk NRMC, Department of Clinical and Social Psychiatry and Addiction, Tomsk, Russia; [4]Groningen Research Institute of Pharmacy, Pharmacotherapy and Clinical Pharmacology, Groningen, The Netherlands; [5]Groningen Research Institute of Pharmacy, Pharmacotherapy in Psychiatric Patients, Groningen, The Netherlands*

Background: Long-term antipsychotic drug use remains the mainstay of treatment for patients with schizophrenia. However, pharmacotherapy with these drugs is complicated by several troublesome side effects, including hyperprolactinemia (HP). Prolactin secretion is persistently inhibited by dopamine, and antipsychotic drugs are believed to increase prolactin release by blocking dopamine receptors in the pituitary gland. Genetic factors play an important role in the development of antipsychotic induced HP [1,2]. Genes coding for dopamine receptors and transporters are considered to be responsible for HP in schizophrenia [3].

The present study aimed to investigate the role of polymorphisms of the dopamine receptors and transporters genes (DRD1, DRD2, SLC6A3) in the pathogenesis of antipsychotic-related HP in patients with schizophrenia.

Methods: 431 Russian patients with schizophrenia were examined. The average age of patients was 42.1 ± 1.4 years. Evaluation of serum prolactin level was performed by ELISA using reagents set PRL Test System (USA). Genotyping was carried out on 17 polymorphic variants of the dopamine receptors and transporters genes DRD1 (rs4532, rs936461), DRD2 (rs4245147, rs6279, rs2734842) and SLC6A3 (rs3756450, rs2550956, rs6347, rs2617605, rs3863145, rs250686, rs464049, rs4975646, rs1048953, rs11133767, rs27048, rs40184). The SPSS software was used for statistical analysis. The Hardy-Weinberg equilibrium (HWE) of genotypic frequencies was tested by the chi-square test.

Results: We studied the association between HP and a set of SNPs from DRD1, DRD2 receptor genes and neurotransmitter transporter SLC6A3 in patients from Siberia with a clinical diagnosis of schizophrenia who were treated with classical and/or atypical antipsychotic drugs. All patients with schizophrenia were divided into two groups: those with and without HP. Physiological normal results for the serum prolactin levels are less than 20 ng/ml in men, and less than 25 ng/ml in women. Statistically significant result was obtained for polymorphic variant rs2550956 of the gene SLC6A3 ($\chi 2 = 9.992$; $p = 0.007$), which suggests its involvement in the development of HP. The heterozygous genotype TC of rs2550956 was significantly less common in patients with elevated levels of prolactin and it presumably has protective properties (OR 0.54; 95% CI: 0.36–0.81). We did not find any statistically significant associations for other polymorphisms DRD1 (rs4532, rs936461), DRD2 (rs4245147, rs6279, rs2734842) and SLC6A3 (rs3756450, rs6347, rs2617605, rs3863145, rs250686, rs464049, rs4975646, rs1048953, rs11133767, rs27048, rs40184). The group of dopamine receptors is heterogeneous and only some of them participate in the formation of psychotic symptoms and, accordingly, in the antipsychotic action of neuroleptics. The effect of neuroleptics on other groups of dopamine receptors leads to the development of different side effects including extrapyramidal disorders [4], and their role is extremely low in the formation of the actual therapeutic response.

Conclusion: Our results indicate that genetic variants of SLC6A3 may have functional consequences on the modulation of prolactin secretion. Neurotransmitter systems are involved in the mechanisms of action of antipsychotic drugs; therefore, a further search for genetic markers associated with the development of antipsychotic-related hyperprolactinemia in schizophrenic patients is needed.

References

[1] Ivanova, S.A., Osmanova, D.Z., Boiko, A.S., Pozhidaev, I.V., Freidin, M.B., Fedorenko, O.Y., Semke, A.V., Bokhan, N.A., Kornetova, E.G., Rakhmazova, L.D., Wilffert, B., Loonen, A.J., 2016. Prolactin gene polymorphism (-1149G/T) is associated with hyperprolactinemia in patients with schizophrenia treated with

antipsychotics. Schizophrenia Research Oct 21, pii: S0920-9964 (16) 30473-X. doi: 10.1016/j.schres.2016.10.029.
[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 hyperprolactinaemia in antipsychotic drug-treated patients with schizophrenia. World J Biol Psychiatry 18 (3), 239–246.
[3] Miura, I., Zhang, J.P., Hagi, K., Lencz, T., Kane, J.M., Yabe, H., Malhotra, A.K., Correll, C.U., 2016. Variants in the DRD2 locus and antipsychotic-related prolactin levels: A meta-analysis. Psychoneuroendocrinology 72, 1–10.
[4] Al Hadithy, A.F.Y., Ivanova, S.A., Pechlivanoglou, P., Semke, A., Fedorenko, O., Kornetova, E., Ryadovaya, L., Brouwers, J.R.B.J., Wilffert, B., Bruggeman, R., Loonen, A.J.M., 2009. Tardive dyskinesia and DRD3, HTR2A and HTR2C gene polymorphisms in Russian psychiatric inpatients from Siberia. Progress in NeuroPsychopharmacology and Biological Psychiatry 33, 475–481.

P.3.c.007 GPR52 agonists represent a novel approach to treat psychotic disorders and improve cognitive function

A.J. Grottick[1], N. Schülert[2], H. Rosenbrock[2], M. Von Heimendahl[2], R. Arban[2], S. Hobson[2]* [1]*Beacon Discovery Inc., CNS Drug Discovery, San Diego, USA;* [2]*Boehringer Ingelheim Pharma GmbH & Co KG, Department of CNS Discovery Research, Biberach a.d. Riss, Germany*

Background: There is increasing awareness that key symptom domains within defined psychiatric and neurological diseases are under-treated. For example, cognitive impairments associated with schizophrenia (CIAS) are key predictors of functional outcome but antipsychotic drugs are ineffective. Similarly, in neurodegenerative diseases such as Alzheimer's and Parkinson's disease, psychotic symptoms occur frequently and are associated with poorer functional outcomes, but antipsychotics are not indicated for dementia-related psychosis and are contra-indicated for long-term use due to increased risk of death. Therefore, novel mechanisms to address these undertreated symptom domains are in need, and are currently under investigation.

Based largely on its expression pattern and functional coupling, the Gs-coupled orphan g-protein coupled receptor GPR52 is currently being investigated as a potential drug target for both CIAS and psychosis in AD. GPR52 is selectively expressed in brain, most strikingly in the striatum where it co-localizes almost exclusively with D2-expressing dopamine (DA) receptors, but additionally in cortex where it co-localizes with DA D1 receptors on glutamatergic neurons. Based on GPR52's g-protein coupling, agonists would be predicted to functionally resemble D2 receptor antagonists in the striatum, and to resemble D1 agonists in cortical areas, thus holding the promise to be efficacious and provide a novel treatment for both psychosis as well as cognitive dysfunction.

Methods: GPR52 agonists were tested in three separate assays. 1. Cortical electrophysiology: Rat medial prefrontal cortical slices (n = 4–6) were stimulated in layer II and excitatory postsynaptic potentials recorded in layer V in the presence or absence of a GPR52 agonist. To demonstrate the GPR52 specificity of any effect on synaptic potentials, slices were pre-treated with a GPR52 antagonist. 2. Social recognition task: A GPR52 agonist was administered to rats prior to interaction with a juvenile conspecific. 24h later, the same two rats were paired and interaction times at the first and second intervals compared. 3. Blockade of amphetamine-stimulated locomotor activity: Rats were treated with a GPR52 agonist prior to administration of amphetamine and subsequent locomotor activity recorded. Statistical significance for each of these measurements was ascertained by one or two-way ANOVA.

Results: GPR52 agonists produced a robust, long-lasting and concentration-dependent increase in synaptic potentiation which was prevented by pre-treatment with an antagonist ($p = 0.0017$ and $p < 0.0001$, respectively). In vivo, GPR52 agonists significantly reduced interaction time in the rat social recognition task after a 24h intertrial interval ($p = 0.008$ and 0.034), and reduced amphetamine stimulated locomotor activity in the absence of any appreciable effect on baseline activity when dosed alone ($p = 0.0007$).

Conclusions: Increased memory of a social interaction and potentiation of cortical synaptic transmission suggest enhanced cognitive function, whereas the ability to block amphetamine-induced locomotion is indicative of antipsychotic activity. These data underscore the potential of GPR52 agonists to treat both cognitive and psychotic symptoms associated with certain CNS disorders.

P.3.c.008 Long-term antipsychotic treatment and corpus callosum volume: an MRI study in patients with schizophrenia

M. Trehout[1,2]*, E. Leroux[2], N. Delcroix[3], S. Dollfus[1,2] [1]*Service de psychiatrie adulte- Centre Esquirol, Centre Hospitalier Universitaire, Caen, France;* [2]*Normandie Univ- UNICAEN- ISTS, GIP Cyceron, Caen, France;* [3]*Normandie Univ, UNICAEN, CNRS, UMS, GIP Cyceron, Caen, France*

Background: White matter volume changes have been evidenced in patients with schizophrenia (SZ) [1]. Nevertheless, studies on the corpus callosum, which is the main interhemispheric commissure of white matter, remain divergent [2,3]. One issue concerns the reasons of these changes and the question is to know if these changes are specific of the disease or are due to long-term antipsychotic treatment. Indeed, it has been revealed that chronic exposure to antipsychotic medication could significantly contribute to white matter volume change in SZ [4]. Therefore, the objective of the present study was to determinate CC volume changes in SZ compared to healthy controls (HC) and to evaluate the potential contribution of long-term exposure to antipsychotics on these changes.

Methods: The study included 19 SZ and 40 HC, all right-handed which did not differ significantly on education level, age and gender. All patients were stabilized outpatients with no change in their treatment over the last month. For each participant, the volumes of total CC and three sub-regions (anterior CC; middle CC; posterior CC) were extracted (in cm3) using an automated in-house segmentation method. The callosal volume was defined on ten sagittal slices (1mm thick). To test group differences, three ANCOVAs were run with the CC volumes as dependent variables and group as independent variable. Gender and brain volume were used as covariates. In SZ, ANCOVAs were conducted to evaluate the relationships between CC volumes and antipsychotic doses in chlorpromazine equivalents (mg/day) controlled by illness duration.

Results: ANCOVAs did not reveal any differences between SZ and HC for all CC volumes (anterior CC: $p = 0.59$; middle CC: $p = 0.92$; posterior CC: $p = 0.29$; total CC: $p = 0.43$). However, there were significant, negative correlations between antipsychotic