University of Groningen

Apolipoprotein serum levels related to metabolic side effects in patients with schizophrenia

Ivanova, S.A.; Boiko, A.S.; Mednova, I.A.; Kornetova, E.G.; Loonen, A.J.M.

Published in:
European Neuropsychopharmacology

DOI:
[10.1016/j.euroneuro.2018.11.221](https://doi.org/10.1016/j.euroneuro.2018.11.221)

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:
2019

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

Citation for published version (APA):

Ivanova, S. A., Boiko, A. S., Mednova, I. A., Kornetova, E. G., & Loonen, A. J. M. (2019). Apolipoprotein serum levels related to metabolic side effects in patients with schizophrenia. *European Neuropsychopharmacology*, 29, S115-S116. <https://doi.org/10.1016/j.euroneuro.2018.11.221>

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.

docannabinoid systems have been discussed as potential causes of schizophrenia [2], but the difficulty in obtaining viable tissue samples for study has limited its exploration. Recently, due to its low invasiveness and high scalability, olfactory neuroepithelium-derived cell models are becoming a promising surrogate system to explore neuronal biomarkers in schizophrenia and other neuropsychiatric disorders [3], providing a unique opportunity to unveil novel, potentially relevant molecular targets for psychopharmacology research and to investigate its clinical significance.

Objectives: In this study we aimed to investigate the expression and functionality of CB1-5-HT2A receptor heteromers in the olfactory neuroepithelium of schizophrenia patients and to correlate these parameters with clinical and neuropsychological measures.

Methods: We recruited a group of schizophrenia patients (n = 12) and sex- and age-matched healthy controls (n = 16). Diagnoses were confirmed by the Structured Clinical Interview for DSM disorders. The expression of CB1-5-HT2A receptor heteromers in olfactory neuroepithelium-derived cells was quantified using proximity ligation assays and confocal microscopy. Potential correlates of clinical severity were assessed with the Positive and Negative Syndrome Scale (PANSS) and the Calgary Depression Scale for Schizophrenia (CDS). A complete neuropsychological assessment was conducted using the Cambridge Neuropsychological Test automated Battery (CANTAB). Statistical analysis was performed using JMP software version 14 [4].

Results: Schizophrenia patients and healthy controls did not differ significantly in age or gender. Olfactory neuroepithelium-derived cells were viable and expressed neuronal markers. CB1-5-HT2A heteromers were observed in olfactory neuroepithelium-derived cells from schizophrenia patients and healthy controls, but heteromer expression was significantly increased in schizophrenia patients compared to healthy controls ($p < 0.05$). Heteromer expression was not related to clinical severity as measured by the PANSS or CDS in the schizophrenia group. A significant negative correlation was observed in the entire population between heteromer expression and attention performance as measured by the Spatial Span Direct Recall test ($p < 0.05$).

Conclusion: The use of this novel methodology allowed the non-invasive study of CB1-5-HT2A heteromers in a model closely related to the central nervous system, as well as the exploration of its clinical significance in schizophrenia patients. In this study, heteromer expression appears to be related to cognitive deficits, particularly regarding attention performance, in line with previous studies conducted by our group in a sample of cannabis users [5]. Since all patients were treated with atypical antipsychotics, the influence of this type of treatment, as well as other treatments, remains to be characterized. More studies are needed to further explore the role of this heteromer and its clinical significance, as well as other potential biomarkers that could become promising molecular targets for future psychopharmacology research in schizophrenia and other neuropsychiatric disorders.

References

- [1] Kahn, R.S., Sommer, I.E., Murray, R.M., Meyer-Lindenberg, A., Weinberger, D.R., Cannon, T.D., O'Donovan, M., Correll, C.U., Kane, J.M., van Os, J., Insel, T.R., 2015. Schizophrenia. *Nature Reviews Disease Primers* Nov 12 1, 15067.
- [2] Bernardo, M., Bioque, M., Cabrera, B., Lobo, A., González-Pinto, A., Pina, L., Corripio, I., Sanjuán, J., Mané, A., Castro-Fornieles, J., Vieta, E., Arango, C., et al., 2017. Modelling gene-environment interaction in first episodes of psychosis. *Schizophr Res.* Nov 189, 181-189.
- [3] Lavoie, J., Sawa, A., Ishizuka, K., 2017. Application of olfactory tissue and its neural progenitors to schizophrenia and psychiatric research. *Curr Opin Psychiatry* 30 (3), 176-183.
- [4] JMP®, Version 14. SAS Institute Inc., Cary, NC, 1989-2007
- [5] Galindo, L., Moreno, E., Lopez, F., Guinart, D., Cuenca-Royo, A., Izquierdo, M., Xicota, L., Fernandez, C., Menoyo, E., Fernandez, J., Canela, E., Casado, V., Perez, V., de la Torre, R., Robledo, P., 2018. Cannabis Users show Enhanced Expression of CB1-5HT2A Receptor Heteromers in Olfactory Neuroepithelium Cells. *Mol Neurobiology*. <https://doi.org/10.1007/s12035-017-0833-7>.

doi: 10.1016/j.euroneuro.2018.11.220

P.108 Apolipoprotein serum levels related to metabolic side effects in patients with schizophrenia

S.A. Ivanova^{1,*}, A.S. Boiko¹, I.A. Mednova¹, E.G. Kornetova², A.J.M. Loonen³

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

²*Mental Health Research Institute Tomsk NRMC, Department of Endogenous Disorder, Tomsk, Russia*

³*University of Groningen, Groningen Research Institute of Pharmacy, Groningen, The Netherlands*

In the general population, metabolic syndrome (MetS) is associated with a 4 times relative risk of developing diabetes and approximately a 2-fold risk of coronary heart disease, stroke, and premature mortality [1]. In patients with schizophrenia the overall rate of MetS is 32.5% [1]. This contributes to having an average mortality rate that is 2-3 times higher than the general population, corresponding to a 10-25 year shortened life expectancy [2]. Antipsychotics are associated with an increased risk for several physical diseases, including obesity, dyslipidemia, diabetes mellitus [2,3]. Use both of classical conventional and modern atypical neuroleptics have been associated with metabolic disturbances; so drug-induced metabolic disturbances are observed in 39.0% of patients taking haloperidol, 44.0% - clozapine, 22.0% - aripiprazole, 33.3% - amisulpride, 34.0% - olanzapine, 35.0% - risperidone [4]. Therefore, an ongoing need exists for reliable predictors of metabolic risks in individual patients indicated for antipsychotic treatment.

Apolipoproteins and cholesterol play a critical role in synapse and myelin maintenance as well as integrity and may thus be both appealing candidates in the pathogenesis of schizophrenia and biomarkers of antipsychotic induce side metabolic effects [5].

The aim of this study is to investigate serum apolipoproteins concentration in schizophrenic patients with or without metabolic syndrome and healthy donors.

Methods: The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declara-

tion of Helsinki) for experiments involving humans. After obtaining approval of the study protocol by the local ethical committee, suitable participants were recruited from psychiatric hospitals. We included 53 patients with diagnosis of paranoid schizophrenia verified according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10: F20). Patients have been divided into two groups with and without MetS according to criteria the International Diabetes Federation (2005). All patients received antipsychotic treatment. The control group included 20 mentally and physically healthy subjects. Serum apolipoproteins A1, C3, E, A2 and C2 were measured using xMAP technology (Luminex). Statistical analysis was performed by SPSS version 20.0.

Results: We found a significant decrease in the concentration of apolipoprotein A1 in the serum of schizophrenic patients with a MetS ($p = 0.002$) and no side effects ($p = 0.013$) compared with the control group. The level of ApoC3 ($p = 0.001$) and ApoC2 ($p = 0.002$) were increased in patients with schizophrenia with MetS in comparison with the control group and patients without MetS. No other significant differences were established concerning the other assayed apolipoproteins.

Conclusions: Literature data and our results suggest that disturbances in level of Apo A1 play role in pathogenesis of schizophrenia while level of ApoC3 and ApoC2 can reflect the metabolic disbalance and could be a novel biomarker to predict metabolic side effects associated with antipsychotic treatment. Future studies with a larger sample size, a well-defined control group, a longer study time duration could be of great clinical utility, when these can predict antipsychotic-associated metabolic problems in patients that carry a higher cardiovascular risk.

Disclosure statement: This work is supported by RSF grant N 18-15-00011

References

- [1] Mitchell, A.J., Vancampfort, D., Sweers, K., van Winkel, R., Yu, W., De Hert, M., 2013. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders-a systematic review and meta-analysis. *Schizophr Bull* 39, 306-318.
- [2] Correll, C.U., Detraux, J., De Lepeleire, J., De Hert, M., 2015. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. *World Psychiatry* 14, 119-136.
- [3] Meye, J.M., Davis, V.G., Goff, D.C., McEvoy, J.P., Nasrallah, H.A., et al., 2008. Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE Schizophrenia Trial: prospective data from phase 1. *Schizophr Res* 101, 273-286.
- [4] Lee, J.S., Kwon, J.S., Kim, D., Kim, S.W., Kim, J.J., Kim, J.H., Nam, H.J., Ryu, S., 2017. Prevalence of metabolic syndrome in patients with schizophrenia in Korea: A multicenter nationwide cross-sectional study. *Psychiatry Investig* 14, 44-50.
- [5] Woods, A.G., Sokolowska, I., Taurines, R., Gerlach, M., Dudley, E., Thome, J., et al., 2012. Potential biomarkers in psychiatry: focus on the cholesterol system. *J Cell Mol Med* 16, 1184-1195.

doi: 10.1016/j.euroneuro.2018.11.221

P.109 Predictors of weight change after long-term treatment with brexpiprazole in schizophrenia

M.K. Josiassen^{1,*}, A.H. Tvistholm¹, C. Weiss², S.R. Meehan³, M. Hobart², R.A. Baker⁴

¹H. Lundbeck A/S, Biostatistics, Valby, Denmark

²Otsuka Pharmaceutical Development & Commercialization Inc., Global Medical Affairs, Princeton, USA

³H. Lundbeck A/S, Medical Affairs, Valby, Denmark

⁴Otsuka Pharmaceutical Development & Commercialization Inc., CNS Global Medical Affairs, Princeton, USA

Background: Increases in body weight, body mass index (BMI), and incidence of clinically significant ($>7\%$ increase) weight gain are a common side effect of most antipsychotics. Weight gain can have a negative impact on quality of life, treatment adherence, cause poor long-term functional outcomes and reduced likelihood of treatment response. Weight gain and aberrant metabolic parameters can result in diabetes and cardiovascular disease. The objective of the current analysis was to assess the contributing effects to weight gain with long-term treatment with brexpiprazole in schizophrenia.

Methods: Data from an open-label (OL), 52-week extension study [1] of brexpiprazole in schizophrenia was used. Patients included in the analysis had either completed one of the two short-term parent studies [2,3] and continued with OL treatment, or were *de novo* patients. The change in weight was assessed from the time of starting brexpiprazole, whether this being in the parent studies or the OL study.

A criterion of $>7\%$ weight increase at any time after starting treatment with brexpiprazole was used for this analysis and contributing factors were then assessed using a logistic regression with relevant variables. A point of interest was to assess the potential effect of regions, and a model including three regions (US and Canada, Europe, other) was used as a starting point. The "other" category comprised patients from Asia and Latin America.

A stepwise approach was used to assess potential other contributing factors. Since BMI at baseline is closely related with the regions, step 1 identified the best manner to include BMI in the model (as a continuous or categorical factor). Step 2 took the resulting model and introduced several other terms, one at a time, to assess whether the other terms were better at explaining the change in weight, than the region and BMI, based on the type 3 error from the logistic regression model. Terms investigated included: baseline weight (continuous), age (continuous, categorical), sex, baseline PANSS total score, region interaction with BMI.

Results: The analysis set comprised 815 patients receiving long-term treatment with brexpiprazole. The change in weight for this population depended on the region, and BMI was best included as a categorical variable (<25 ; ≥ 25 to <30 ; ≥ 30). No other variable tested contributed with an effect ($p < 0.05$) that explained more than region ($p = 0.0347$) and BMI category ($p < 0.0001$).

Regional differences were reflected in the Odds Ratios (OR) of patients with $>7\%$ weight gain: Europe versus US and Canada OR = 0.781, Other vs US and Canada OR = 1.422.