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### **The effect of clozapine and olanzapine on the expression of genes encoding insulin signalling pathway and their epigenetic regulation molecules in human preadipocytes**

**Introduction:** clozapine and olanzapine are second generation antipsychotic drugs, frequently used in clinical practice, particularly in the pharmacotherapy of schizophrenia. It has been reported that these drugs can cause serious side effects, including the induction of diabetes and/or metabolic syndrome. Their mechanism is not sufficiently understood. Aim of the study: the aim of the study was to examine the effect of clozapine and olanzapine on the mRNA expression of genes encoding insulin pathway: IRS-1, PTEN, PIK3CG, PIK3R1 and microRNA: miR-152-3p, miR-214-3p, miR-15b-5p, miR-16-5p, miR-126-3p and lncRNA: XIST, H19, SNHG16, PVT1, in human visceral preadipocytes.

**Materials and methods:** The cell line of human visceral preadipocytes constituted the experimental model. Cell viability was assessed using the MTT assay. The mRNA expression of selected genes as well as microRNA and lncRNA was tested by real-time PCR.

**Results:** It was shown in human visceral preadipocytes that clozapine (concentrations of 5  $\mu\text{M}$  i 25  $\mu\text{M}$ ) decreased the expression of IRS-1 gene at the mRNA level after 24 and 48 hours of incubation. Olanzapine decreased the expression of IRS-1 gene at the mRNA level at concentrations of 5  $\mu\text{M}$  and 25  $\mu\text{M}$  after 24 hours and at concentration of 5  $\mu\text{M}$  after 48 hours. Moreover, at 24 hours, olanzapine at concentration of 25  $\mu\text{M}$  was shown to decrease the expression of PIK3CG, miR-152-3p, miR-214-3p, miR-15b-5p, miR-16-5p, and at a concentration of 5  $\mu\text{M}$  to increase the expression of miR-126-3p, while clozapine at that time point decreased the expression of miR-16-5p at a concentration of 25  $\mu\text{M}$  and increased the expression of SNHG16 lncRNA at a concentration of 5  $\mu\text{M}$ . After 48 hours of incubation of the cells, olanzapine at a concentration of 25  $\mu\text{M}$  increased the expression of PIK3R1 and decreased the expression of PIK3CG at a concentration of 5  $\mu\text{M}$ . Moreover, at that time point, both clozapine and 97 olanzapine at a concentration of 5  $\mu\text{M}$  increased the expression of miR-152-3p, miR-214-3p, miR-15b-5p, miR-16-5p. Additionally, clozapine at that concentration increased the expression of miR-126-3p.

**Conclusions:** Clozapine and olanzapine may affect the expression of key genes in the insulin signalling pathway and molecules that are involved in the epigenetic regulation of these genes. The results of this study could lead to a more detailed understanding of the mechanism by which these drugs induce insulin resistance in adipose tissue (and further on, diabetes and / or metabolic syndrome) and help in finding therapeutic targets for these disorders.