THE RESEARCH OF INFLUENCE 1-(4-CHLORPHENYL)-N,N-DEMETHYLE-ALPHA-(2-METHYLEPROPYLE) CYCLOBUTANEMETHANEAMINE (SIBUTRAMINE) ON THE EXPERIMENTAL INSULIN-RESISTANCE COURSE AND ENDOTHELIAL DYSFUNCTION DEVELOPMENT IN RATS

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Introduction. Insulin resistance (IR) – is a pathological syndrome, which is accompanied by a decrease in the sensitivity of cells to insulin. It is associated with the development of a number of diseases: type 2 diabetes, obesity, metabolic syndrome, atherosclerosis, cardiovascular and some others. These diseases are widespread in the population and are characterized by high mortality rates. This point explains the urgency of finding ways of pharmacological correction of the disease developing on the background of IR. One of the promising methods of the pharmacotherapy is the use of 1-(4-Chlorphenyl)-N,N-demethyle-alpha-(2-methylepropyle) cyclobutanemethaneamine (Sibutramine) – anorectics means of central action, pharmacodynamics of which is due to the inhibition of the reuptake of serotonin and norepinephrine (normalization of eating behavior), as well as activating an effect on β3-adrenergic receptors of brown adipose tissue (the increase of thermogenesis). In a number of studies we have proved the marked therapeutic efficacy of the substance in IR's presence, but there has been a significant increase in the number of cardiovascular events (heart attacks and strokes). One possible reason for the development of cardiovascular disease is the development of endothelial dysfunction (ED).

The aim of this work has been to study the effect of sibutramine on individual rates of lipid and carbohydrate metabolism, the state of NO-synthase system during the experimental IR in rats.

Materials and methods. The researches has been performed on Wistar male rats of the line. The IR has been simulated by intraperitoneal injection of low doses of dexamethasone (Severino C. and co-author, 2002). The sibutramine that has been injected intraperitoneally at an effective therapeutic dose (assuming a ratio of specific resistance). The effect of the drug has been evaluated by the glucose content, immunoreactive insulin (IRI), triacylglycerol (TAG), free fatty acids (FFA),

cholesterol (CH), nitric oxide (NO), nitrate and nitrite (NO2 + NO3), arginine, citrulline.

Results and discussion. Intraperitoneal administration of dexamethasone has been accompanied by the IR syndrome development, which has been confirmed by a significant in glucose levels increase by 55.4%, IRI - by 44.12%, TAG - by 70.14%, FFA - by 91.11%, CH – by 25% compared to the intact animals. There has been the reduction of the blocking action of insulin on lipolysis, which has been accompanied by an increase in the content of free fatty acids, which has led to an increase in the concentration of TAG, cholesterol and aggravate IR. The sibutramine has generally normalized the studied parameters due to the correction of obesity as a trigger factor of IR. Moreover, the drug mediates the adiponectin level increase, which increases the sensitivity of tissues to insulin. The development of hyperglycemia and hyperinsulinemia has been associated with some significant pathological changes of the markers of NO-synthase system: NO content has increased by 1.22 times, NO_2 + NO_3^- by 1.2 times, citrulline – by 1.26 times, the concentration of arginine has decreased by 1.48 times compared with the indicators of the intact rats. Such dynamics of parameters is characterized to the state of the ED. Insulin is a powerful inducer of NO-synthase (NOS) of endothelial cells that stimulates arginine entrering to the cells, thereby reducing its content in the blood. This resulted in increased formation of NO and the second reaction product – citrulline. Hyperglycemia and also increase of the content of NO, by activating the expression of iNOS and generation of reactive oxygen species. Hyperglycemia and hyperinsulinemia cause the formation of peroxynitrite ($ONOO^-$), which is accompanied by the development and progression of ED. When administered with sibutramine we have observed similar, though less pronounced dynamics of NO-synthase marker system. This is probably due to the formation of active metabolites of the drug during its biotransformation, which has a negative impact on these indicators.

Conclusions. The administration of low doses of dexamethasone is the cause of the IR syndrome, which entails some pathological changes in lipid and carbohydrate metabolism types, as well as in the NO-synthase system. The administration of the sibutramine has led to the normalization of rates accompanying the formation of IR, however, the lack of positive dynamics with respect to the changes in the NO-synthase system can be considered as one of the mechanisms of cardiovascular complications during the use of the drug.