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tytuł pracy: **„Wpływ obniżenia ekspresji PGC-1α na rozwój insulinooporności w linii komórkowej mięśni szkieletowych L6”**

Summary

Nowadays obesity is a predominant metabolic condition and an important risk factor for the development of other diseases, including type 2 diabetes mellitus (T2DM). Importantly, many authors indicate skeletal muscles insulin resistance (IR) as a key link between both the aforementioned pathological conditions. Moreover, it seems that the increased intramyocellular long chain fatty acids (LCFA) uptake play a dominant causative role in the IR development. In the case of prolonged positive body energy balance the aforementioned influx surpasses cellular oxidative capacity eventually contributing to lipids accumulation. At first lipids are stored in a relatively safe triacylglycerol (TAG) fraction, and subsequently also in biologically active fractions of ceramides (CER) and diacylglycerols (DAG). The latter two groups interfere with the cellular insulin signal transduction pathway, thus directly contributing to myocellular insulin resistance (IR). Therefore, given constantly increasing prevalence of IR the researchers concentrate their interests on examination of its pathomechanism and identification of potential therapeutic targets for its prevention. PGC-1α is an important protein coregulator vitally involved in the regulation of mitochondria number and function, and hence an important regulator of cellular energy metabolism. Moreover, some of the previous research has indicated its role in the regulation of transporter mediated fatty acid uptake and lipid biosynthesis. The aim of the current investigation was to assess the effects of PGC-1α gene silencing on myocellular lipid metabolism in the light of this tissue insulin resistance.

In the present study we have shown, presumably for the first time, that the reduction of the protein level of PGC-1α (-24%) resulted in a decreased mitochondrial activity in general (reduced Cyt C content) and FAs oxidation in particular (diminished β-HAD expression). The aforementioned changes were not accompanied by an increased fatty acid

uptake [no changes in the expression of the investigated FA transport proteins (FAT/CD36, FATP-1, 4) nor palmitate uptake]. PGC-1α gene silencing contributed to an increased cellular accumulation of triacylglycerol (TAG, +75%), but not ceramide (CER), nor diacylglycerol (DAG). This was most likely the effect of a decreased cellular lipid oxidation (the aforementioned reduction in β-HAD expression) and/or increased lipids biosynthesis (increased expression of FASN). Interestingly, we observed only a small trend (-15%, $p > 0.05$) towards decreased insulin stimulated glucose uptake, as well as a reduced activity of some enzymes (-58%, pAkt/Akt, $p < 0.05$) linked to insulin signalling pathway. Some of the observed phenomena seem to be the first symptoms of myocyte insulin resistance development.