Recently, diabetes mellitus type 2 (DMT2) represents one of the most important metabolic diseases according to its incidence and economic impacts. One of the main reasons of this diesease is loss of function and viability of pancreatic β-cells due to the effect of increased levels of saturated fatty acids (FAs). Unsaturated FAs are better tolerated by β-cells. They are even capable of inhibiting detrimental effects of saturated FAs. Molecular mechanisms of apoptosis induction in pancreatic β-cells by saturated FAs as well as mechanisms of inhibition of this induction by unsaturated FAs are not completely elucidated. The main aim of this study was to contribute to elucidation of these mechanisms.

Concerning human pancreatic β-cell line NES2Y we demonstarted: (1) Activation of caspase-2 by stearic acid (SA), in apoptosis inducing concentration (1 mM), is not crucial for the process of apoptosis induction. However, this caspase modulates SA-induced endoplasmic reticulum (ER) stress pathways. (2) SA (1 mM) activates the p38 MAPK signaling pathway and inhibits the ERK signaling pathway. Inhibition of the ERK signaling pathway is probably a consequance of the p38 MAPK pathway activation. However, p38 MAPK is not very likely crutial for the apoptosis induction by SA. Unsaturated oleic acid (OA, 0.2 mM) is able to inhibit the effects of SA on mentioned signalling pathways. OA itself has only minimal effect on these signaling pathways. (3) SA (1 mM) activates ER stress pathways, i.e. IRE1α, PERK and ATF6 pathways. OA (0.2 mM) is able to inhibit the effects of SA on IRE1α and PERK pathways and itself has only minimal effect on the activation of these pathways. Effect of OA on the ATF6 pathway was not tested. JNK kinase, similarly as caspase-2, is not crucial for the process of apoptosis induction by SA, but it modulates ER stress pathways activated by SA. (4) The point of induction of pro-apoptotic signaling by saturated FAs, as well as the point of inhibitory intervention of unsaturated FAs into mechanisms of apoptosis induction by saturated FAs, is located upstream of studied signaling pathways. It is probably located on the plasma membrane of cells. (5) Hypoxia potentiates pro-apoptotic effect of SA (1 mM), probably via increased ER stress signaling. Hypoxia also decreases protective effect of OA (0.2 mM) on pro-apoptotic effect of SA in such way that OA is not able to block the induction of apoptosis of β-cells due to SA effect anymore. Hypoxia alone has relatively weak detrimental effect on β-cells. Thus, hypoxia can represent a key factor which is decisive for survival/death of pancreatic β-cells in the presence of FAs and thus, as a consequence, also potentially decisive for the development of DMT2.

Our results contribute to understanding of mechanisms by which saturated FAs induce apoptosis of pancreatic β-cells and mechanisms of inhibition of this induction by unsaturated FAs. Results also contribute to eluciodation of the effect of hypoxia on apoptosis induction by

saturated FAs and on inhibition of this induction by unsaturated FAs in β-cells. These findings could be important in the search for new therapeutic approaches of DMT2 focused on maintaining function and viability of pancreatic β-cells.