Abstract

Local production of reactive oxygen species (ROS) and changes in the redox environment influence the metabolism and function of β cells of the Langerhans islets (LO). Changing the ratio between NAD(P)H / $NAD(P)^+$ redox partners significantly affects sensitive proteins and ROS production. ROS are able to reversibly modify some amino acid residues (eg Cys, Met) of antioxidant enzymes and their interaction partners. Such a signaling cascade allows the transmission of a signal over longer distances and can also interfere with the influence of gene expression. The unique enzyme NADPH oxidase 4 (NOX4) is present on membranes within β cells and constitutively produces H_2O_2 depending on the presence of NAD(P)H. After glucose stimulation, both NAD(P)H and *Nox4* mRNA levels increase. As previously observed in our laboratory, C57BL/6J mice with a specific *Nox4* deletion in β cells have a disrupted biphasic insulin release and exhibit insulin resistance in fat and muscle tissue. We found that the absence of NOX4 in C57BL/6J mice affects LO architecture. Wildtype (WT) mice on a normal, predominantly carbohydrate diet (ND) have the majority of small LO with an area of up to 5 000 μm^2 (measured on histological sections). High-fat diet (HFD) feeding of WT for 8 weeks leads to the development of diabetic phenotype and an increase in LO hypertrophy (LO > 5 000 μm^2). The specific deletion of *Nox4* in β cells in mice causes LO hypertrophy already on ND. At the same time, it prevents the negative effect of HFD on the further amplification of LO hypertrophy. The same results were seen in both adult and young four-week-old mice. Reduction of *Nox4* gene expression in INS-1E β cells by siRNA resulted in increased basal proinsulin production already at low glucose levels (2.5 mM glucose /1 hour). Suppressed production of NOX4 by siRNA increases the mRNA level of the transcriptional factor pancreatic duodenal homeobox protein 1 (PDX1) in the INS-1E cells. There was no significant effect on the mRNA level of another transcription factor of insulin musculoaponeurotic fibrosarcoma oncogene homolog A (MAFA) and proinsulin to insulin splicing enzymes prohormone convertase 1 (PC1) and proprotein convertase 2 (PC2) and carboxypeptidase E (CPE). Based on our findings, ROS derived from active NOX4 have an important signaling role in the correct physiological function of β cells and whole islets of Langerhans. The reduction of NOX4 in β cells leads to disruption of GSIS at the cellular level, affects gene expression and its absence causes LO hypertrophy increase in rodents.