Modulation of DDAH/ADMA/NOS pathway in pancreatic β -cells under diabetic condition

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Nitric oxide (NO) regulates various physiological and pathophysiological processes. We have previously demonstrated that a small amount of NO, which is produced by constitutive NO synthase (cNOS), has a dual effect on insulin secretion, depending on its concentration. Furthermore, we have previously shown that low-concentration NO, which is assumed to be produced by cNOS, exhibits an anti-apoptotic effect in β -cells. Thus, the deterioration of cNOS-derived NO production is likely to be involved in the dysfunction of pancreatic β -cells. Asymmetric N^G,N^G-dimethyl-L-arginine (ADMA) is an endogenous methylated amino acid that inhibits NOS. ADMA is formed when arginine residues in proteins are methylated by protein arginine methyltransferase (PRMT), and is metabolized to L-citrulline by dimethylarginine dimethylhydrolase (DDAH). The present study investigated the involvement of the DDAH/ADMA/NOS pathway in the regulation of NO production in pancreatic β -cells under diabetic conditions. The mRNA expression of DDAH and PRMT was determined in the pancreatic β -cell line INS-1. In endothelial cells, the expression of DDAH2 has been shown to be decreased by 5-day culture in the presence of high glucose. We thus investigated the effect of high glucose on the expression of DDAH mRNA in INS-1 cells using quantitative PCR. INS-1 cells were cultured in the medium containing 10 or 20 mmol/l glucose for 3 days. We found no significant differences in the expression of DDAH1 mRNA between the different glucose conditions. In contrast, DDAH2 mRNA expression was strongly reduced in the cells treated with 20 mmol/l glucose. Moreover, the protein expression of DDAH1 was also unchanged, whereas that of DDAH2 was significantly suppressed in the cells treated with 20 mmol/l glucose. Finally, we measured ADMA contents in INS-1 cells treated with high glucose by HPLC, and found that the ADMA formation was increased in the presence of 20 mmol/l glucose. These results suggest that the DDAH/ADMA/NOS pathway is working in β -cells and might contribute to modulate NO production in pancreatic β -cells under diabetic conditions, possibly by changing the balance between production and metabolism of ADMA.