Crucial roles of neuronatin in insulin secretion and high glucose-induced apoptosis in pancreatic beta-cells.

Joe MK, Lee HJ, Suh YH, Han KL, Lim JH, Song J, Seong JK, Jung MH.

Division of Metabolic Diseases, Center for Biomedical Sciences, National Institute of Health, 5 Nokbun-dong, Eunpyung-gu, Seoul, 122-701, Republic of Korea.

Abstract

Neuronatin (Nnat) was initially identified as a selectively-expressed gene in neonatal brains, but its expression has been also identified in pancreatic beta-cells. Therefore, to investigate the possible functions that Nnat may serve in pancreatic beta-cells, two Nnat isotypes (alpha and beta) were expressed using adenoviruses in murine MIN6N8 pancreatic beta-cells, and the cellular fates and the effects of Nnat on insulin secretion, high glucose-induced apoptosis, and functional impairment were examined. Nnatalpha and Nnatbeta were primarily localized in the endoplasmic reticulum (ER), and their expressions increased insulin secretion by increasing intracellular calcium levels. However, under chronic high glucose conditions, the Nnatbeta to Nnatalpha ratio gradually increased in proportion to the length of exposure to high glucose levels. Moreover, adenovirally-expressed Nnatbeta was inclined to form aggresome-like structures, and we found that Nnatbeta aggregation inhibited the function of the proteasome. Therefore, when glucose is elevated, the expression of Nnatbeta sensitizes MIN6N8 cells to high glucose stress, which in turn, causes ER stress. As a result, expression of Nnatbeta increased hyperglycemia-induced apoptosis. In addition, the expression of Nnatbeta under high glucose conditions decreased the expression of genes important for beta-cell function, such as glucokinase (GCK), pancreas duodenum homeobox-1 (PDX-1), and insulin. Collectively, Nnat may play a critical factor in normal beta-cell function, as well as in the pathogenesis of type 2 diabetes.

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