Role of Pancreatic Thyrotropin releasing Hormone in Directing Insulin Secretion to Regulatory Pathway

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Abstract

Thyrotropin releasing hormone (TRH; pGlu-His-ProNH2) is expressed also in pancreatic β cells where it is colocalized in secretory granules with insulin. High perinatal changes of the TRH gene expression and TRH concentrations in rat pancreatic islets coincide with the perinatal maturation of the adequate insulin secretory responsiveness to glucose and other nutrient secretagogues. TRH secretion from pancreatic islets is stimulated by glucose and inhibited by insulin. Disruption of the TRH gene in knockout mice results in hyperglycaemia accompanied by impaired insulin secretory response to glucose. Progress in understanding TRH - insulin relations may be substantial for improving knowledge of pathophysiological mechanisms included in changes of insulin secretion with possible clinical impact. Block of the last step of biosynthesis of α-amidated peptides, including TRH by disulfiram (DS) treatment of adult male rats subcutaneously with 200 mg/kg for five days in our experiments resulted in barely detectable levels of peptidyl-glycine α-amidating monooxygenase (PAM) in their pancreatic islets. TRH in physiological concentration (1 nM) does not affect basal insulin secretion from intact rat pancreatic islets. In contrast, basal insulin secretion from islets of DS-treated rats is four times higher compared to controls and could not be further stimulated by high-glucose. The addition of 1 nM TRH into medium decreased immediately basal insulin secretion in DS (TRH lacking) islets to control level and normalized also their response to glucose. Interestingly, absence of the secretory response to glucose in islets from TRH depleted rats was connected with their increase of insulin content during stimulation. Glucose stimulation together with 1 nM TRH normalized also insulin content in DS islets. Apparently, high insulin content in islets from TRH depleted animals is a result of block of regulatory secretion pathway redirected to constitutional secretion which was corrected by the addition of TRH.

Type 2 diabetes mellitus is a disease characterized by various range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance. These symptoms suggest a possible role of TRH dysregulation. In conclusion, presence of TRH in β cells ensures appropriate low basal (constitutive) insulin secretion. Release of TRH induced by glucose and possibly by other secretagogues has autocrine effect resulting in directing insulin secretion to regulatory pathway reacting to stimulation. If some defects of insulin secretion could be treated by TRH, various ways of applications (also oral and nasal) could be utilized. Moreover, positive side effects shown in animal experiments may accompany the treatment: TRH has the potential to prevent apoptosis and promotes insulin-producing cell proliferation and has also aging-reversing properties.

Biography

Vladimír Štrbák has worked at Institute of Experimental Endocrinology, Slovak Academy of Sciences. He was Organizer and Chairman of the five International Symposia on Hormones in Milk, resident of the International Symposium on Cell Volume and function 1997.

He was Organizer and Chairman Symposium Cell Volume, physiological and pathophysiological aspects, 5th International Congress of Pathophysiology, June 28-July 1, 2006, Beijing, China, published in *Chinese Journal of Pathophysiology*, June 2006, Volume 22, No 13, Supplement p. 167. Organizer and Chairman of the session Cell Volume Regulation and Cell Functions.

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