Neprilysin expression in pancreatic cells plays a protective role against pancreatic cell dysfunction

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Introduction

Neprilysin is also known as cluster of differentiation, enkephalinase, neutral endopeptidase, membrane metalloendopeptidase, and common antigen of acute lymphoblastic leukemia. NEP is a zinc inactivator of various peptide hormones including natriuretic peptide, bradykinin, oxytocin, neurotensin, substance P, enkephalin, angiotensin, endothelin, and glucagon-like peptide. It is a trans-membrane-dependent metalloproteinase. NEP is also involved in amyloid degradation and may be effective in preventing the development of Alzheimer's disease. NEP is widely expressed on the surface of endothelial cells, neutrophils, fibroblasts and various tissues including brain, kidney, lung, testis, gastrointestinal tract and heart. Soluble NEP is found in blood and reflects the concentration and activity of membrane-bound NEP. In fact, NEP is primarily involved in neuro-humoral activation and regulation of the sympathetic nervous system and the renin-angiotensin system 'RAS' various diseases, including heart failure.

Description

High expression of NEP is associated with poor prognosis in heart failure patients. However, in cohort and mixed cohort studies, NEP values had no clinical value for heart failure prognosis. NEP inhibitors such as sacubitril, RB-101, omapatrilate, ecadtril, and candoxatril are rarely used alone, but are Angiotensin Receptor Blockers (ARB). NEP inhibitors are also effective in treating type-2 diabetes by increasing circulating levels of GLP-1, which is degraded by NEP. However, the acute effects of NEP inhibitors have adverse effects by increasing blood glucose levels independently of GLP-1 increases. T2DM is a metabolic disorder characterized by hyperglycemia and insulin resistance due to pancreatic cell dysfunction and insulin insensitivity. T2DM is associated with cardiometabolic disorders such as obesity, hypertension, and dyslipidemia. Amyloid accumulation in pancreatic cells induces progressive pancreatic cell loss with pancreatic cell dysfunction and the development of overt T2DM. Progressive deposition of IAPP causes the development of pancreatic cytotoxicity. NEP blocks extracellular IAPP deposition in the pancreas and prevents pancreatic cell dysfunction. Thus, by regulating the IAPP and amyloid accumulation in the pancreas, NEP appears to prevent from developing type-2 diabetes. NEP has been reported to contribute to impaired glucose homeostasis through regulation of IR, pancreatic cell mass, and the development of pancreatic cell dysfunction seen in T2DM. Strikingly, NEP expression is increased in both T2DM and hyper-nutrition. Various experimental studies have shown that NEP activity is increased in mice fed a high-fat diet, correlating with reduced pancreatic cell mass and the development of IR experience better glycemic control due to increased activity. Genetic ablation of NEP improves glucose homeostasis through GLP-1-dependent signaling pathways. Similarly, bradykinin promotes glucose uptake and oxidation by activating the bradykinin-2 receptor. However, various studies have confirmed that NEP deficiency does not impair glycemic control and has no effect on glycemic abnormalities.

Conclusion

It is caused by high-fat diets, IR, glucose tolerance, and body/epidermal fat weight. The NEP enzyme inactivates various peptide hormones such as NP, bradykinin, oxytocin, neurotensin, substance P, enkephalins, ET-1 and GLP-1. NEP expression in pancreatic cells plays a protective role against pancreatic cell dysfunction and apoptosis by inhibiting pancreatic amyloid formation. Overexpression of the NEP enzyme is associated with the development of IR, impaired glucose homeostasis and cardiometabolic disorders by increasing DPP4 activity and decreasing circulating GLP-1. Therefore, NEP inhibitors improve glucose homeostasis by inhibiting DPP4 activity and increasing circulating GLP-1.

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Conflict of Interest

The author has nothing to disclose and also state no conflict of interest in the submission of this manuscript.

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