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Role of Amylin in Thyroid Cancer

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Abstract

The prevalence of thyroid nodules and cancers were shown to be associated with type II diabetes mellitus (T2DM), obesity especially central obesity, and metabolic diseases. Recent studies reported that amylin, an amyloidogenic pancreatic peptide deposited in the pancreas in T2DM, theses aggregates enter the circulation and recently reported to be deposited in the brain and involved in the development of Alzheimer's disease. These circulatory amyloid aggregates may also deposit in the thyroid gland and causes activation of some pathogenic pathways that may result in the development of thyroid nodules and cancers. This review presents some of the available data about the role of amylin in type 2 diabetes mellitus (T2DM), the association between T2DM with thyroid carcinoma, and the possible role of amylin in the pathogenies of thyroid nodules and cancers.

Keywords: Cancer, Amylin, Insulin, Diabetes, Obesity, Neurodegenerative Diseases

Introduction

Amylin and its Physiological Functions

Amylin is a 37-amino acid peptide that is co-secreted with insulin from β cells of the pancreas in response to nutrients intake, such as glucose, amino acids and lipids [1]. It is also called as islet amyloid polypeptide (IAPP) as it is found in the form of myeloid aggregates in the pancreatic islets [2]. Amylin plays a role in glucose homeostasis, reducing blood glucose level, inhibiting food intake, an action that can be mediated by the effect of amylin on leptin expression and signalling in the ventromedial nucleus of the hypothalamus [3]. The effect of amylin on food intake can be also due to the central action of amylin on the area postrema as ablation of this area abolished the inhibitory effect of amylin on food intake [4]. Amylin decreases gastric motility and delay gastric emptying, an effect that helps in delaying the entry of nutrients into the small intestine, delaying intestinal absorption and subsequently decreasing the serum levels of different nutrients especially glucose. All those effects of amylin can explain athe effectiveness of using amylin agonists in the treatment of diabetes and the potential use of amylin obesity [5]. In addition to the centrally-mediated effect of amylin in delaying gastric empting and food intake, it has been also reported that amylin mRNA and its receptors are expressed in the stomach, suggesting a direct effect of amylin on gastric emptying [6].

Amylin is a member of the calcitonin family, which includes, αcalcitonin-gene related peptides (αCGRP), βCGRP, adrenomedullin (AM) and intermedin (AM2). The effects of the calcitonin family members are mediated by calcitonin receptors (CTR) and CTR-like receptors (CLR). The specificity of those receptors for the members of calcitonin family depends on certain receptor-associated proteins called receptor-activity-modifying proteins (RAMPs) [7]. The receptors for amylin include, AMY1, AMY2, and AMY3, each consists of a combination of CTR with RAMP1, RAMP2, and RAMP3 respectively [8]. Amylin is metabolised via renal excretion and by proteolysis into less active and inactive metabolites [5]. Amylin (1-37) is the major molecular form of human amylin revealed by radioimmunoassay of the pancreatic tissue. There are two forms of circulating human amylin, the non-glycosylated form which is the biologically active form and the glycosylated form [9].

Dysregulation of Amylin with Diabetes Mellitus

Although amylin works to decrease blood glucose level, it is reported that amylin can be cytotoxic due to the formation of amylin aggregates; amyloids that associated conditions of T2DM [10]. Amylin aggregation in the pancreatic β cells induces endoplasmic reticulum stress and damage of mitochondrial membrane resulting in death of the β cells of the pancreas [8]. Normally, these aggregates once, formed, an autophagy process with be stimulated and degrade the aggregates protecting the cells from their cytotoxic effects as evidenced by the appearance of amyloids in the pancreatic β cells of mice lacking ATG-7, ATG the autophagy-related proteins [11].

Diabetes Mellitus and Thyroid Cancer

Studies over decades confirmed the association of different types of cancer with diabetes especially T2DM. Worldwide, thyroid cancer is the most common endocrine malignancy among women [12]. The increasing prevalence of thyroid carcinoma as well as diabetes suggesting a link between them [13]. In 2017, Li et al. [14] published a met-analysis of 16 cohort studies that included 10,725,884 individuals, with a total of 8032 cases of thyroid cancer reported a positive association between the diabetes mellitus and increased risk of thyroid cancer mainly among women. In addition, a recent study reported a decrease in survival among patients with thyroid carcinoma who suffer from T2DM as compared with thyroid cancer patients who are not diabetics [13]. A more recent study reported an association between the increased risk of thyroid nodules with obesity, central obesity, insulin resistance and disturbed lipid profile [15]. Based on these studies, amylin may play a role in the pathogenesis of thyroid carcinoma. Understanding the regulation of amylin can help in enhancing its uses as a treatment or even as prophylactic.

Conclusion

Amylin is physiologically important in glucose homeostasis. However, if it forms aggregates, it causes cellular stress resulting in diseases such as diabetes mellitus. Increased association between T2DM with thyroid nodules and cancers suggests a possible role of amylin in the pathogenesis of thyroid carcinoma mediated by deposition of amyloids.

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