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Review

An overview on biological functions and emerging therapeutic roles of apelin in diabetes mellitus

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ABSTRACT

Type 2 diabetes mellitus is a common type of diabetes and considered as multifactorial disease. Apelin is an adipokine which secreted from white adipose tissue and involved in various functions such as insulin sensitivity and food intake. Many studies showed that apelin has a crucial role in diabetes and its concentration will change in relation with insulin resistance. In this review, we will discuss the roles of apelin in energy metabolism and pathogenesis of diabetes and explain why apelin can be a good candidate adipokine to promoting insulin sensitivity.

Contents

Abbreviations: T2DM, Type 2 diabetes mellitus; WAT, White adipose tissue; APJ, angiotensin II protein J receptor; GPCRs, G-protein couple receptors; DN, diabetic nephropathy; WHO, World Health Organization; T2DM, type 2 diabetes mellitus; CVD, cardiovascular disease; BMI, body mass index; BAT, brown adipose tissue; WAT, white adipose tissue; PAI-1, adiponectin plasminogen activator inhibitor; RBP-4, retinol binding protein; [pyr^1] apelin-13, pyroglutamated apelin-13; AT1, angiotensin II receptor; DR, diabetic retinopathy; PDR, proliferative diabetic retinopathy; VEGF, vascular endothelial growth factor; RPE, retinal pigment epithelium; DN, Diabetic nephropathy; GDM, Gestational diabetes mellitus; AMPK, MP-activated protein kinase; eNOS, endothelial NO-synthase; IRE1α, inositol-requiring enzyme 1α; PERKPKR, like eukaryotic initiation factor 2α kinase; PLCβ, phospholipaseβ; DAG, diacylglycerol.

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1. Introduction

In the recent century, obesity is one of the most issue in health. According to WHO, 2.5 and 3.7 million people die each year due to global obesity and T2DM, respectively. Obesity result in poor quality of life through many diseases such as T2DM, hypertension, stroke, CVD, cancer, and early death [37]. Obesity is determined by BMI, expressed as Kg/m^2, which more than 25 kg/m^2 and 30 kg/m^2 indicated obesity and overweight, respectively [24].

There are two kinds of adipose tissues in human, including BAT and WAT, which has different origins. BAT is predominant in the

birth but after growing up it will be replace by WAT [14]. Also, with due attention to WATs location it categorized to two types: subcutaneous and intrabdominal [27]. Insulin sensitivity and secretory function are two significant properties of WAT. In fact, adipose tissue acts as an endocrine organ like pancreas and take part in pathogenesis of obesity and T2DM [27]. WAT not only stores excess energy in form of triglycerides, but also acts as endocrine organ which secrets the adipocytokines. So, nowadays scientists consider adipose tissue as an important endocrine organ which cause major effect on being health [17,30].

WAT could secret kind of cytokines which named adipocytokines or adipokines. The greatest importance of adipokines is their effects on health by different ways such as vascular inflammation, hepatic lipoprotein, immune system, endocrine, metabolic and cardiovascular systems. Changes in adipokines levels, which may occur in obesity, can take part in pathogenesis of obesity and related complication [8]. There are various adipokines including leptin, resistin, SAA, IL-6, adiponectin, PAI-1, angiotensinogen, visfatin, vaspin, omentin, RBP-4, FGF21, BMP-4 and 7, DPP-4, TNF α, IL-1β and apelin [18,29]. However, apelin is the newest finding among these adipokines, it has drawn much attention and extended studies have been done on possible biological and molecular functions. In this review, we will discuss how. Increased level of apelin in insulin resistance condition cause to insulin sensitivity Furthermore, the mechanisms which apelin act via them will be summarized. Due to possible changes of apelin concentration in diabetes, we focused on new findings about apelin in diabetes. Newest findings revealed that apelin will be a novel potential marker for diabetes and also as therapeutic agent in obesity-related disease.

2. Apelin

In 1998, Tatemoto et al. could succeed to discover the apelin when they investigated about APJ receptor, and suggested apelin as an endogenous ligand for the angiotensin II protein J (APJ) receptor [22]. Apelin located on Xq25-q26.3 chromosome and synthesis as preproapelin which contains 77 amino acids [48]. Apelin revealed as various isoforms, which are result in different cleavage sites by proteasome, including apelin-36, apelin-17, and apelin-13, apelin-12 and pyroglutamated apelin-13 [pyr^1] apelin-13. Shorter isoforms, like apelin-13, have higher affinity to APJ receptors [6,32]. The presence of at least 12 amino acids in C-terminal region is necessary for function [2]. The concentration of apelin isoforms are different in various organs. For example, apelin-17 and [pyr^1] apelin-13 are predominant in plasma [6]

In healthy subjects, the level of apelin depends on nutritional state. It was reduced in fasting, and became rescued by refeeding [47], while in both impaired glucose tolerance and diabetic subjects, fasting apelin levels and also 2-houres post glucose load were increased. Most scientists are believed, that some criteria such as insulin resistance, fasting plasma glucose, insulin level and TNF-alpha has positive relationship with apelin level, but its relationship with BMI is controversial [44,47].Yu shan et al. showed that BMI is not one of the main factor which influence on apelin [44], while Xu S et al. succeed to demonstrated that following reduction of weight, apelin will be reduced too [42].

3. Apelin receptor

In 1993, before apelin isolation, O'Dowd et al. could succeeded to clone apelin receptor but until discovery of apelin, in 1998, it considered as an orphan GPCR. He named it APJ, and it belongs to (GPCRs) family [20]. Apelin receptor (APLNR) or APJ has 54% homology with angiotensin II receptor (AT1), however angiotensin II couldn't bind to it [26] Scientists estimated that hypotensive features of apelin is related to this homology. APJ gene is located on chromosome 11 (11q12) and has not any intron in coding region [20,25]. It encoded 380-amino acids [33]. All isoforms of apelin could bind to APJ, although their biological potency are different [35]. C-terminal regions of preproapelin and N-terminal of APJ is required for specific binding and receptor function, respectively. Also, Glu20 and Asp23 in APJ, positive charged residue in N-terminal, take a part in apelin binding [20,26]. Comparison of human, rat and mouse sequence indicated that sequences were conserved among evolution (Table 1).

4. Apelin, insulin and diabetes mellitus

The level of apelin in obese patients with T2DM are significantly increased in comparison with healthy peoples [10,44]. Similarly, the level of apelin in patients with T1DM is more than normal subjects. In the other word, lack of insulin secretion cause increase of apelin concentration [10]. In fact, apelin could affected by insulin [45]. Conditions such as diabetes or obesity which associated with hyperinsulinemia could cause increase of apelin levels. In such situation apelin could upregulated by insulin. So whether obesity cause increase apelin levels depended on its stage [42]. Scientists believed that hyperapelinemia is a compensatory mechanism in which not only inhibited the pancreatic secretion, but also led to insulin sensitivity [42] and induced uptake of glucose in muscular tissues of mice independent of insulin (Fig. 1) [44]. In support of this idea, it should notice that weight loss cause decreased the level of apelin [45] On the other hand, lack of insulin in T1DM cause hyperapelinemia (26).

The effect of apelin on glucose depends on the level of digestion. In the beginning of digestion, apelin has stimulatory effect on intestinal glucose absorption via action on GluT2 translocation, while at the end, it increases muscle glucose utilization [19].

5. Apelin, angiogenesis and diabetic retinopathy

Patients with diabetes mellitus are expose to impair vision condition which named diabetic retinopathy (DR). DR is associated with vascular dysfunction and occlusion, retinal edema, hemorrhage and inappropriate growth of new blood vessels [1]. Atsushi Kasai et al. explored on the role of apelin in angiogenesis. They believe that apelin trigger maturation by proliferation phase. In detail, they showed that excess expression of apelin from tip cells in mice with oxygen-induced retinopathy model, and its binding to APJ of stalk cells in endothelial could induced proliferation. Latter,

Table 1
The comparison of apelin in human, mouse and rat species.

Species	The number of amino acids which encoded by gene	Location of chromosome	The name of apelin receptor[a]	The percentage of APJ amino acid homology with human
Human	380	11q12	APLNR	
Mouse	377	2E	*Aplnr*	92
Rat	377	3q24	*Aplnr*	90

[a] Extracted from gene bank.