

Research Progress of C-Peptide and Its Physiological Function

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How to cite this paper: Zeng, R., Huang, S.Y. and Liao, S.B. (2020) Research Progress of C-Peptide and Its Physiological Function. *International Journal of Clinical Medicine*, 11, 207-215.

<https://doi.org/10.4236/ijcm.2020.115021>

Received: April 15, 2020

Accepted: April 27, 2020

Published: April 30, 2020

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Abstract

As a product in the process of insulin synthesis, C-peptide's physiological function is still not very clear. Recent studies have shown that C-peptide has many potential cell targets and has biological effects on a variety of tissue systems in humans and other animals. In this paper, the effects of C-peptide on diabetic complications, reproductive endocrine system, blood system, tissue repair, and neoplastic diseases were reviewed to provide references for further clarification of c-peptide related problems.

Keywords

C-Peptide, Physiological Functions, Review

1. Introduction

C-peptide is a polypeptide composed of 31 amino acids; it is a key substance connecting proinsulin alpha chain and beta chain, and plays an important role in the correct folding of proinsulin and the formation of disulfide bonds. Endogenous or exogenous substances such as glucose, amino acids, glucagon, etc. stimulate β cells to release equal amounts of insulin and C-peptide from their secretory vesicles. The regulation of insulin on blood glucose, fat and protein metabolism has been very clear, and has long been used clinically as a hypoglycemic drug. As a homologous active substance secreted by insulin, C-peptide has not been paid enough attention for a long time, and its physiological function is still not very clear. C-peptide was previously considered to be inert, but now more and more studies have shown that C-peptide is a physiologically active molecule with many potential cellular targets [1]; it can play an important role in diabetic complications, reproductive endocrine system, blood system, tissue re-

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pair, tumor diseases and other aspects.

2. The Role of C-Peptide in Diabetic Complications

2.1. Effect of C-Peptide on Kidney

Diabetic nephropathy (DN) is a serious diabetic microvascular complication; it is the main cause of end-stage renal disease and the leading cause of death in T1DM patients. The appearance of urinary protein and the gradual decline of renal function are the signs of the development of DN.

Studies have shown that C-peptide has the effect of improving DN, and its protective effect on the kidney is reflected in two aspects of structure and function. A study in rats showed that physiological dose of C-peptide treatment can reduce urinary protein, improve glomerular sclerosis and podocyte morphology, reduce the thickness of glomerular basement membrane, and inhibit the synthesis of glomerular mesangin [2]. Another Meta analysis showed that C-peptide can reduce glomerular hyperfiltration and reduce urine protein in T1DM patients with normal renal function or early renal disease; C-peptide can reduce urine protein, diminish glomerular volume and mesangial matrix area in diabetic animals [3]. However, research by Nakamoto *et al.* showed that C-peptide did not improve the glomerular filtration membrane structure of early T1DM rats, and believed that the protective effect of C-peptide on reducing glomerular filtration rate was functional, not Structural [4]; but the duration of this study is short (only 1 day of C-peptide injection), and its long-term effect is unknown, so the conclusion is open to question. Evaluation of the effect of pancreatic transplantation surgery further supports the beneficial effect of C-peptide on DN, because renal function in patients with T1DM can be partially improved after transplantation, which is considered to be due to the supplementation of C-peptide [5].

Research by Li *et al.* showed that C-peptide hardly enters glomerular cells when blood glucose levels are normal, but C-peptide can be dynamically localized in the nucleus after high glucose stimulation, which provides a basis for elucidating the mechanism of C-peptide on DN [6]. The protective mechanism of C-peptide on DN is as follows: a) C-peptide stimulates eNOS gene transcription, inhibits iNOS expression, down-regulates RAGE and up-regulates PKA, and prevents and delays microangiopathy in the kidney [2] [6]. b) Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases, which can degrade many types of extracellular matrix components. C-peptides may reduce the accumulation of DN extracellular matrix by delaying MMP-9 expression, thus reversing DN [7]. c) C-peptide may be used as a natural antioxidant to protect the function of islet β cells and delay DN [8]. d) C-peptide can play a protective role in the kidney by reducing the inflammatory response [9].

2.2. Effect of C-Peptide on Retina

Diabetic retinopathy (DR) is the most common microvascular complication of

diabetes and one of the main causes of blindness in adults, which greatly reduces the quality of life of diabetic patients. 45% of T2DM patients with a disease course of more than 10 years are associated with varying degrees of DR [10].

A large number of studies have shown that C-peptide can reduce the occurrence of DR. A retrospective analysis of the Diabetes Control and Complications Test showed that the residual secretion of serum C-peptide reduced the incidence of DR in T1DM patients. Studies have shown that serum C-peptide levels are negatively correlated with the prevalence of DR in patients with T2DM; DR patients show lower levels of fasting C-peptide, 2 h postprandial C-peptide, and Δ C-peptide (2h postprandial C-peptide minus fasting C-peptide) [11]. Retinal pigment epithelium (RPE) is a layer of epithelial cells containing pigment between the neural retina and the choroid; RPE cells have the potential to differentiate into photoreceptors and ganglion cells. The main cause of DR is damage to RPE, which leads to the destruction of the blood-retinal barrier and macular edema [12]. An animal experiment (STZ-induced T1DM mouse model) showed that C-peptide can improve retinal vascular permeability and prevent vascular leakage [13].

The mechanism by which C-peptide protects the retina is as follows: a) C-peptide improves retinal vascular permeability and prevents retinal neovascularization by affecting various effector proteins and transcription factors of RPE [13]. b) C-peptide normalizes $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity [14], on the one hand prevents RPE into fibroblasts and myofibroblasts [15], on the other hand inhibits the activity of retinal vascular endothelial growth factor dependent signaling pathway recovery [13], thereby preventing retinal detachment.

2.3. Effect of C-Peptide on Nervous System

Diabetic peripheral neuropathy (DPN) is the most common neurological complication of diabetic patients. DPN greatly increases the risk of diabetic patients suffering from foot ulcers, ankle fractures and lower limb amputations, leading to a significant decline in the quality of life of patients. It also causes a huge socio-economic burden.

C-peptide may have a potential inhibitory effect on the occurrence of DPN. A study of Chinese people showed that serum C-peptide was negatively correlated with the prevalence of DPN in T2DM patients; the serum concentration of fasting C-peptide, 2 h postprandial C-peptide and Δ C-peptide in the non-DPN group was significantly higher than that in the clinical DPN group and the confirmed DPN group [16]. Jolivalt *et al.* research showed that exogenous C-peptide can delay and prevent STZ-induced T1DM mice from experiencing movement, pain, temperature, and tactile dysfunction [17]. Clinical studies have shown that exogenous C-peptide can improve the ability of lower limb vibration perception in T1DM patients [18].

The mechanism by which C-peptide delays the occurrence of DPN is that C-peptide stimulates eNOS gene expression, enhances $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity,

and increases the secretion of neurotrophic factors, thereby protecting nerve cells and nerve fibers from high glucose toxicity damage [19].

2.4. Effect of C-Peptide on Macrovascular Disease

Diabetic macroangiopathy mainly includes coronary arteriosclerosis, cervical vascular and cerebral vascular sclerosis, renal arteriosclerosis, extremity arteriosclerosis, etc., which is the main cause of death in T2DM patients.

Studies have shown that serum C-peptide can promote arteriosclerosis. Pikkemaat *et al.* showed that increased baseline serum C-peptide concentration was associated with increased risk of all-cause death and cardiovascular death in newly diagnosed T2DM patients [20]. Further research shows that for all T2DM patients (regardless of whether they are newly diagnosed or not, regardless of whether they have atherosclerotic disease), C-peptide is positively correlated with cardiovascular mortality risk [21] [22].

The mechanism by which C-peptide promotes the occurrence of macrovascular complications is that C-peptide increases the lipid deposition on the vascular wall by increasing triglycerides or reducing high-density lipoprotein cholesterol levels; Increased risk of cardiovascular disease by promoting proliferation of vascular wall macrophages and vascular smooth muscle cells [23] [24].

3. The Role of C-Peptide in Other Aspects

3.1. Effect of C-Peptide on Reproductive Endocrine System

Non-alcoholic fatty liver disease (NAFLD) refers to a wide range and varying degrees of liver damage, from steatosis to steatohepatitis, advanced liver fibrosis and cirrhosis. C-peptide may promote the development of NAFLD. Data from the National Health and Nutrition Examination Survey show that fasting C-peptide is a risk factor for NAFLD in the general population of the United States [25]. Studies have shown that C-peptide is independently associated with liver fibrosis in T2DM patients [26]. The mechanism by which C-peptide promotes NAFLD is that C-peptide increases leptin by activating PI3K or PKB pathway [27], and the increase of leptin promotes hepatic steatosis [28].

C-peptide has a positive effect on the increase of bone mineral density (BMD). Studies have shown that C-peptide levels are positively correlated with lumbar BMD in postmenopausal women [29]. A study of postmenopausal women with diabetes has similar conclusions [30]. The mechanism by which C-peptide increases BMD may be through the ERK 1/2 pathway acting on osteoblasts, increasing collagen biosynthesis, and inhibiting osteoclasts by reducing RANKL expression [30].

C-peptide can maintain the reproductive system function of diabetic animals. Studies have shown that C-peptide can be combined with insulin (or even replace insulin) to prevent or delay mouse testicular dysfunction caused by diabetes [31]. The mechanism is as follows: a) The antioxidant effect of C-peptide reduces DNA breakage and apoptosis [32]; b) C-peptide can activate protein ki-

nase α , inhibit the generation of reactive oxygen species by mitochondrial NADPH oxidase, thereby preventing the apoptosis of endothelial cells [33].

3.2. C-Peptide Levels Are Associated with Hematological Diseases

C-peptide has a positive effect on the increase of hemoglobin. A cross-sectional study of T2DM patients showed that the concentrations of fasting C peptide, 2 h postprandial C-peptide, and Δ C-peptide in anemia patients were lower than those without anemia, indicating that the degree of anemia was negatively correlated with serum C-peptide concentrations in T2DM patients (fasting C peptide: $r = -0.057$, $p = 0.032$; 2 h postprandial C-peptide: $r = -0.098$, $p < 0.001$; Δ C-peptide: $r = -0.095$, $p < 0.001$) [34]. Hemoglobin is used as an indicator to evaluate the degree of anemia. The lower the hemoglobin, the more severe the anemia. At present, the mechanism of C-peptide on hemoglobin is not clear; it is considered that C-peptide may have the effect of anti-oxidation and maintenance of Na^+ - k^+ -ATPase activity, so as to prolong the life of red blood cells.

3.3. Effect of C-Peptide on Tissue Repair

C-peptide may have a potential role in promoting the repair of tissue damage. Studies have shown that C-peptide can significantly promote skin wound healing in diabetic mice [35]. A study of T1DM mice showed that when simvastatin induces skeletal muscle apoptosis, C-peptide can effectively inhibit apoptosis [36]. Tauber *et al.* study has shown that angiogenesis and granulation tissue formation in the early healing stage of non-diabetic rabbit skeletal muscle tissue samples are positively correlated with the level of C-peptide in peripheral blood [37], so it is believed that C-peptide can also be used to monitor the healing process of tissues without diabetes. The mechanism of C-peptide to promote tissue healing is as follows: a) C-peptide inhibits apoptosis through pertussis toxin sensitive pathway [36]. b) C-peptide induces endothelial cell migration and mediates neovascularization by activating extracellular signal-related kinases and inducing nitric oxide production [35].

3.4. The Role of C-Peptide in Neoplastic Diseases

C-peptide plays an important role in a variety of neoplastic diseases. C-peptide may have different effects on tumors in different parts. C-peptide can promote the occurrence and development of various tumors. A large prospective study showed that high levels of C-peptide increased the risk of developing cancer in the colon (OR = 1.73), liver (3.23), kidney, renal pelvis, and ureteral cancer (2.47) [38]. Another study showed that high levels of C-peptide may be associated with high-risk prostate cancer. The mechanism by which C-peptide promotes the occurrence of these tumors is not clear [39].

C-peptide may have an inhibitory effect on tumor formation and metastasis in certain parts. Studies have shown that C-peptide can prevent vascular leakage and metastasis of melanoma cells in the lungs of diabetic mice caused by hyper-

glycemia [40]. The mechanism may be that C-peptide reduces the damage of adhesion molecules to the vascular endothelium by inhibiting the induced intracellular events of vascular endothelial growth factor (including the increase of intracellular reactive oxygen levels, TGase2 activation, etc.), thereby preventing vascular leakage [40]. Research by Nogueira *et al.* Showed that C-peptide levels are inversely related to pancreatic duct adenocarcinoma in current smoking patients [41].

4. Outlook

In summary, C-peptide can play an active role in multiple systems, including chronic microvascular complications of diabetes, bone mineral density, reproductive system, anemia, tissue repair, and the occurrence of some tumors; however, it has adverse effects on diabetic macrovascular complications, fatty liver, and other tumors. At present, the many mechanisms of C-peptide are still unclear. At present, many mechanisms of action of C-peptide are still unclear; as a small molecule peptide, it is unclear whether it can cooperate with other substances to exert physiological and biochemical functions. With the deepening of research, C-peptide may be used as a breakthrough in diabetes treatment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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