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THE POSSIBLE USE OF C-PEPTIDE IN TYPE I DIABETES

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Summary

The incidence of type I diabetes increases dramatically each year. This disease practically always causes severe complications in every system. The main complications are cardiovascular, neural and kidney pathologies. Complications occur even in case of aggressive treatment of hyperglycemia and proper diet. This leads to the conclusion that other factors are involved in the progression of the disease. Recent data indicates that C-peptide has an important role in different processes in human organism. In this article is presented a review of C-peptide studies regarding its beneficial role in type I diabetes.

Rezumat
Utilizarea posibila a peptidei C în diabetul zaharat de tip I

Incidenţa diabetului zaharat de tip I creşte dramatic în fiecare an. Ca regulă, această maladie determină complicaţii severe la nivelul tuturor sistemelor. Principalele complicaţii sunt patologiile cardiovasculare, neuronale şi renale. Complicaţiile apar chiar şi în cazul unui tratament intens al hiperglicemiei şi al unei diete adecvate. Acest fapt permite de a presupune că

şi alţi factori sunt implicaţi în progresia bolii. Recent a fost presupus că peptida C ar avea un rol important în diferite procese din organism. În acest articol este prezentată o analiză a studiilor referitoare la rolul benefic al peptidei C în diabetul zaharat de tip I.

Introduction

The incidence of type I diabetes (T1D) rises 3-5% each year. This disease is linked to severe complications which to some extend are managed with insulin injection and correct diet. Still T1D is a disease with high rate of morbidity and mortality due to its complications. Practically every system is affected by the disease among which are nervous, cardiovascular, excretory etc. The highest mortality rate in diabetic patients is associated with end stage of kidney disease. Other risk factors include obesity, insulin resistance and vascular problems.

One of the major problems of diabetes mellitus is micro and macroangiopathy. Clinical studies show that aggressive treatment of hyperglycemia is helpful but doesn't completely reduce the risk for vascular diseases. This leads to the conclusion that hyperglycemia or the absence of insulin is not the main problem in case of type I diabetes. Recent data indicates that C-peptide can have potential beneficial effects in T1D. It is important to understand that people with T1D unlike type II diabetes have not only reduced insulin synthesis but also C-peptide which is a part of proinsulin. Possibly C-peptide is one of the substances that should be administrated at the same level as insulin in case of T1D. For a long period of time C-peptide was considered biologically not relevant. Radioactive labeled C-peptide binds with the cells surface receptor, which means that our organism has a receptor complex for it and thus it has some role in it [1, 7, 8, 10].

C-peptide structure

C-peptide is a small 31-amino acid peptide. It is synthesized with insulin but later on cleaved from it. Proinsulin consists of 3 peptide chains: A, B and C. C-peptide is stored in secretory granules along with insulin and is secreted equimolar with it into the blood stream. Unlike insulin its half-live is 30 minutes. The molecular structure of C-peptide varies, but still it has several conservative regions found in different species. For example: N terminal acidic region, glycine-rich central segment, and C-terminal pentapeptide [10].

In mammals 8 residues in C-peptide are especially conservative. These are 1 (Glu), 3 (Glu), 6 (Gln), 11 (Glu), 12 (Leu), 26 (Leu), 27 (Glu) and 31 (Gln). C-peptide is a highly acidic peptide. It has 5 acidic residues in humans, with no counterbalance from the basic residues. The current data indicates that it has a G-protein coupled receptor [11].

Effects on cardiovascular system

With time almost all T1D patients develop angiopathy. One of the major beneficial roles of C-peptide is its effect on cardiovascular system.

C-peptide increases intracellular Ca^{2+}, which can affect nitric oxide (NO) production through nitric oxide synthase. This causes NO-dependent vasodilatation, which is important as vaso and cardioprotective effect [8].

C-peptide decreases smooth muscle proliferation through inhibition of platelet-derived growth factor receptor (PDGFr) and increases phosporylation of mitogen-activating protein kinase (MAPK). This effect decreases the risk for atherosclerosis [8].

Bo-Lennart Johansson et al., 2004 showed a significant improvement of left ventricular function in diabetic patients. Another problem in diabetic patients is red cell deformities. This results in high risk of thrombosis and decreased oxygen transport to the peripheral tissues. The possible explanation is activation of Na^+,K^+-ATPase on erythrocyte surface [6].

C-peptide decreases the expression of endothelial cell adhesion molecules. Can reduce leukocyte adhesion to endothelium preventing inflammation. In some experimental models promotes angiogenesis. This is both useful against ischemia and atherosclerosis [8].

Effects on central and peripheral nervous tissue

Neuropathy is another major problem in T1D which affects most of patients to some extent. It affects both central and peripheral nervous system.

In patient with neuropathies due to diabetes administration of C-peptide resulted in 80% correction of system conduction velocity with major improvement of sensory and motor functions as well as vibration sensation. But cold and warm sensation remains at the same level [3].

C-peptide prevents neuronal apoptosis in T1D. Promotes cell growth of neuroblastoma cell line in vitro. It protects neurons against swelling and degeneration [8].

Several cognitive impairments were associated with hippocampal apoptotic neuronal loss in diabetic patients. Diabetic mice with c-peptide administration showed significant spatial learning and memory improvements. C-peptide prevents oxidative stress and inhibits apoptosis, increases NF-κB production. NF-κB plays a role in neuron plasticity, learning, and memory [9].

Effects on kidney function

End stage kidney disease is considered to be the main cause of mortality among T1D patients.

C-peptide prevents tumor necrotic factor-mediated (TNF) apoptosis in proximal tubular cells, thus decreasing the progression of diabetes-related kidney disease [8].

One of the major problems in diabetic nephropathies is the epithelial-mesenchymal transformation due to the effect of transforming grow factor-b1 (TGF-b1). C-peptide prevents TGF-b1 signaling pathway [4].

C-peptide affects Na^+,K^+-ATPase increasing its activity. This is useful to increase kidney filtration and reassertion. Mouse models also show reducing glomerular hyperfiltration, hypertrophy and proteinuria. This can prove to be useful in case of first signs of kidney disease until transplantation can be performed.

Effects on lungs and possible use in critical care

C-peptide administration can be beneficial in diabetic as well as non-diabetic patients after trauma during systemic inflammation response and other critical conditions. It reduces the level of IL-1, IL-6, macrophage inflammatory protein-1a and cytokine-induced neutrophil chemoattractant-1. This decreases neutrophil infiltration and ameliorates inflammatory processes. Additionally C-peptide improves blood flow in lung tissue [2].

Due to its effect on neutrophils C-peptide can be a useful treatment for several syndromes such as: acute respiratory distress syndrome, acute lung injury and several other diseases that are encountered in the field of emergency medicine.

Metabolic effects

Several authors describe insulinomimetic effects in some tissues. C-peptide activates insulin receptor tyrosine kinase, insulin receptor substrate, phosphoinositol 3-kinase and MAPK phosphorylation, increases amino acid uptake. At the same time other researchers indicate glucose transport not using any insulin-like mechanism but with a separate molecular method [11].

C-peptide can disaggregate insulin, this increases its bioavailability because of monomerization [6].

It is important to mention that the use of C-peptide in non-diabetic patients still doesn't show any significant improvement. It is explained by the fact that increased C-peptide circulation presumably doesn't increase the expression of its receptor. [5]

Disscusion

C-peptide has several important functions in our organism. Presumably this can be one of the possible reasons of multiple diabetes-associated complications even in case of aggressive glucose control and diet.

C-peptide affects multiple cells and systems in the body which can be summarized in Table 1. Using molecular methods several authors indicate that C-peptide binds in great amounts to renal convoluted tubular cells, skin fibroblasts, and saphenous vein endothelial cells, erythrocytes etc. C-peptide affects Na^+,K^+-ATPase increasing its activity. The main cells affected by this mechanism are renal and nervous tissues [11].

It is important to note that some authors indicate C-peptide self-association. This can cause aggregation of peptides which can lead to amyloid-like formations [6]. Thus injection of C-peptide should be carefully measured.

Table 1

C-peptide's physiological and chemical beneficial effects in different tissues

Tissue	Cells	Effect	Result
Blood	Erythrocytes	Improves diabetes-induced erythrocyte deformability	Improves oxygen availability and uptake
Nervous tissue	Neurons	Improvements of endoneural blood flow, prevents axonal swelling and decreases oxidative stress	Decreases the risk for neuropathies, improves sensory and motor neuron function
		Antiapoptotic effect, increases NF-κB production	Neuronal development, regeneration and cell survival
		Increases Na^+,K^+-ATPase activity	Affects neuronal conduction ability
Kidney tissue	Kidney glomeruli	Reducing glomerular hyperfiltration, hypertrophy and proteinuria	Prevents renal damage
	Proximal tubular cells	Prevents apoptosis	Prevents diabetes-related kidney disease progression
	Renal tubular cells	Increases Na^+,K^+-ATPase activity	Facilitates reabsorbtion and filtration
Muscle tissue	Skeletal muscle	Increases blood flow and metabolic rate	Facilitates muscle activity, prevents ischemia
Cardiac tissue	Endothelial cells	Increases NO production	Cardioprotective effect, increases capillary blood flow
	Cardiomyocytes	Increases blood flow metabolic rate and contractility	Inotropic effect on left ventricular systolic function
Vascular tissue	Endothelial cells	Decreased the expression of endothelial cell adhesion molecules	Prevents inflammation, atherosclerosis
	Smooth muscle cells	Antiproliferative effects	Can delay atherosclerosis.
Lung tissue	Smooth muscle cells	Improves oxygenation and blood flow	Metabolic compensation, increased oxygenation rate.

Conclusion

C-peptide was considered biologically inert. Latest data indicates that this assumption was wrong indicating multiple effects in the body. It can be proved useful to make additional injections of C-peptide or to create a drug with a combination of two peptides: insulin and C-peptide. The use of C-peptide is still experimental in different other diseases but in case of T1D it can help to reduce morbidity, mortality and increase life expectancy rate.

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