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REVIEW

Insights Into the Physiology of C-peptide

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Summary

Current knowledge suggests a complex role of C-peptide in human physiology, but its mechanism of action is only partially understood. The effects of C-peptide appear to be variable depending on the target tissue, physiological environment, its combination with other bioactive molecules such as insulin, or depending on its concentration. It is apparent that C-peptide has therapeutic potential for the treatment of vascular and nervous damage caused by type 1 or late type 2 diabetes mellitus. The question remains whether the effect is mediated by the receptor, the existence of which is still uncertain, or whether an alternative non-receptor-mediated mechanism is responsible. The Institute of Endocrinology in Prague has been paying much attention to the issue of C-peptide and its metabolic effect since the 1980s. The RIA methodology of human C-peptide determination was introduced here and transferred to commercial production. By long-term monitoring of C-peptide oGTT-derived indices, the Institute has contributed to elucidating the pathophysiology of glucose tolerance disorders. This review summarizes the current knowledge of C-peptide physiology and highlights the contributions of the Institute of Endocrinology to this issue.

Key words

C-peptide • Insulin • Diabetes mellitus • Therapy • Diabetes complications

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Basic framework

Connecting peptide (C-peptide), a cleavage product of proinsulin, is a small linear molecule composed of 31 aminoacids. In the Golgi complex of pancreatic beta cells, C-peptide is removed from proinsulin, forming the insulin molecule. Both insulin and C-peptide are then stored in an equimolar ratio in the secretory vesicles of the beta cells until stimulation by elevated glycemia. After their release to portal circulation, insulin and C-peptide differ in their kinetics: insulin has a half-life of about 3 min, C-peptide about 30 min. Its stability, along with the fact that C-peptide escapes first-pass metabolism by the liver, allows the use of C-peptide as a reliable marker of beta cell function in clinical practice.

The intrinsic biological activity of C-peptide and therapeutic potential

For decades, C-peptide was thought to be a biologically inert by-product of insulin processing. However, recent studies have shown that C-peptide is a bioactive molecule with remarkable effects on various cell types and tissues. Its action appears to be ambiguous depending on the target tissue, physiological environment, its combination with other bioactive molecules such as insulin (Richards *et al.* 2014), or depending on its concentration. Some trials have demonstrated that C-peptide is associated with macrovascular complications when its concentrations are high and with microvascular complications when its concentrations are low. For example, insulin resistant

patients with early type 2 diabetes mellitus (T2DM) have high serum levels of C-peptide. Elevated C-peptide contributes to the atherosclerotic process in these patients (Wang *et al.* 2015) and higher C-peptide has also been shown to be associated with cardiovascular morbidity in the insulin resistant non-diabetic population (Cabrera *et al.* 2015). On the other hand, in type 1 diabetes mellitus (T1DM) patients with serious defects in their own C-peptide production, its replacement exerts a beneficial influence on microvascular complications (Wahren 2017) and nerve function (Ekberg *et al.* 2007). Also, residual C-peptide production in T1DM patients correlates negatively with HbA_{1c} levels, daily insulin dose, the incidence of severe hypoglycemia and with the severity of microvascular dysfunction leading to neuropathy, suggesting C-peptide even at low picomolar levels may be essential for the long-term maintenance of endothelial function (Lachin *et al.* 2014). *In vitro*, C-peptide has been shown to reduce oxidative stress by inhibiting the formation of endothelial cell reactive oxygen species under hyperglycemic or stressful conditions (Bhatt *et al.* 2013a, Luppi and Drain 2017), contributing to anti-apoptotic and anti-inflammatory responses. C-peptide also inhibits the expression of hyperglycemia-induced adhesion molecules, thus reducing leukocyte adhesion to endothelial cell walls and preventing atherosclerotic plaque formation (Yosten *et al.* 2014). In addition, beta cell transplantation resulting in the restoration of endogenous insulin and C-peptide concentrations leads to the amelioration of structural and functional peripheral nerve and kidney damage induced by diabetes (Fiorina *et al.* 2003, Navarro *et al.* 1997).

Receptor or non-receptor-mediated signaling?

These findings suggest a complex role of C-peptide in human physiology, although the mechanism behind this role is only partially understood. The question remains whether the effect is mediated by the receptor, the existence of which is still uncertain, or whether alternative non-receptor-mediated mechanisms are responsible. Multiple studies have demonstrated that C-peptide binds specifically to many cell types such as fibroblasts, kidney tubules, and endothelial cells (Pramanik *et al.* 2001, Henriksson *et al.* 2001, Yosten and Kolar 2015). C-peptide has been shown to activate various intracellular signaling pathways, such as phospholipase C (PLC), mitogen-activated protein kinase (MAPK), phosphoinositide-3-kinase/protein kinase B (PI3K/AKT), AMP-activated protein kinase (AMPK), nuclear factor kappa B (NF-κB), protein kinase A (PKA) and protein kinase C (PKC). These pathways initiate endothelial nitric oxide synthase (eNOS) and the activity of Na^+ or K^+ ATPses and thus trigger the expression of many transcription factors (Kitamura 2001, Richards 2015, Bhatt *et al.* 2013b, Haidet *et al.* 2012, Zhong *et al.* 2004, Zhong *et al.* 2005). Involvement in the aforementioned signaling cascades, together with the high pertussis toxin-sensitivity of C-peptide action, would imply an interaction of C-peptide with a G-protein-coupled receptor (GPR) or receptor complex on the surface of cell membranes. Specifically, GPR146 has been identified as a putative receptor for C-peptide (Yosten *et al.* 2013), with the authors' suggestion that confirmatory experiments are especially important.

However, at the same time non-receptor-mediated mechanisms for C-peptide biological effect have been proposed. C-peptide has been reported to be internalized in the cytosol and in the nucleus of some cells types (Luppi *et al.* 2009, Li *et al.* 2013). Here, direct interaction with intracellular proteins and enzymes affects multiple processes including glycolysis and cell growth (Ishii *et al.* 2012, Jagerbrink *et al.* 2009).

C-peptide points to gender differences in glycoregulation throughout life

Several current approaches are available for the diagnosis of impaired beta cell function (Muniyappa *et al.* 2008). Among them, the oral glucose tolerance test (oGTT) and the derived equations (insulin sensitivity and insulin secretion indices) are being used in various clinical settings in which the performance of clamps or the minimal model would be impractical. Being relatively simple to implement and not very expensive, oGTT is the most suitable test for epidemiological studies (Stumvoll *et al.* 2000). Recently, significant influence of the hepatic extraction of insulin (Faerch 2010) and thus use of alternative C-peptide oGTT trajectories and C-peptide-derived indices has been discussed and gradually put into practice as more accurate markers of beta cell function compared to insulin trajectories and insulin-derived indices (Vrbikova *et al.* 2009, Tura *et al.* 2011, Tura *et al.* 2012, Včelák *et al.* 2012, Saisho *et al.* 2013, Vejrazkova *et al.* 2015, Lukášová *et al.* 2015, Vejrazkova *et al.* 2017, Wildová *et al.* 2017). Subsequently, several authors, including our research group (Bendlová *et al.* 2015), have reported sex differences in insulin and C-peptide

responses to oGTT, indicating that the pathogenesis of diabetes may differ between the genders (Kautzky-Willer *et al.* 2012, Vistisen *et al.* 2014, Tura *et al.* 2018). According to our data based on the long-term monitoring of large cohorts of volunteers with varying degrees of glucose tolerance, the volume of insulin metabolized during the first-pass elimination by the liver seems to decline more markedly in men compared to women, and it turns out that these differences deepen over the course of life (Bendlová *et al.* 2015, Bendlová *et al.* 2018).

The methodological contribution of the Institute of Endocrinology

The Institute of Endocrinology in Prague has been paying much attention to the issue of C-peptide and its metabolic effects since the 1980s. At that time, the diagnostic potential of C-peptide was already evident, but foreign commercial kits to measure its concentrations were unavailable in the then Czechoslovakia. Thanks to the support of the then management of the institute, Prof. Luboslav Stárka and Prof. Karel Vondra, and also thanks to the pragmatism of Dr. Pavel Štolba, a novel radioimmunoassay method (RIA) appropriate for C-peptide measurements began to evolve. As a relatively high amount of human C-peptide was required for its development, the chemical synthesis of a modified human C-peptide – one of the longest peptides synthesized at that time – was successfully implemented and subsequently patented by Dr. Běla Bendlová in cooperation with the Institute of Organic Chemistry and Biochemistry. The synthesized C-peptide was then used for the immunization of guinea pigs. The antiserum with the best association constant (K_a = 1.9x10^{10} l/mol) was selected for the RIA determination of human C-peptide. This methodology has been transferred to commercial production and has been widely used since 1988 (Bendlová *et al.* 1988, Bendlová 1994a).

Monoclonal antibodies produced using the synthesized C-peptide (Hilgert *et al.* 1991) have been further used to determine or extract molecules containing C-peptide fragments, i.e. human proinsulin and split proinsulins. The application area here was the diagnosis of pancreatic beta cell tumors, familial hyperproinsulinemia, or studies of insulin and proinsulin secretion under other pathological conditions.

The Institute has also contributed to elucidating the contradictory biological functions of C-peptide. In an effort to identify specific binding sites for C-peptide, membranes of human placenta and erythrocytes were isolated, on which fully functional insulin receptors were detected. However, under the same experimental conditions, no specific C-peptide binding sites were demonstrated on these cell membranes. It is thus possible to assume that the binding of C-peptide to receptors requires completely different conditions or that C-peptide acts in tissues by another mechanism (Bendlová 1994a, Bendlová 1994b).

The scientific team of the Institute of Endocrinology was also behind the observation that the increase of 24-h urine excretion of C-peptide was predictive for remission of newly diagnosed T1DM after the therapy with somatostatin (Vondra *et al.* 2004). Attention deserves also finding of coexistence and tight association between thyroid and Langerhans islets autoimmunity, which was described in young adults with T1DM. During long-term follow-up, faster cessation of endogenous C-peptide secretion was associated with thyroid peroxidase and thyroglobulin antibodies positivity (Vondra *et al.* 2005).

Conclusion and perspectives

In summary, there is much evidence that C-peptide is a biologically active molecule that serves as an endogenous antioxidant, preventing, in adjunction with insulin, hyperglycemia-induced microvascular dysfunction. It is also apparent that C-peptide has therapeutic potential for the treatment of vascular and nervous damage caused by T1DM or late T2DM (Yosten *et al.* 2014). Thus far, its replacement in T1DM patients has yielded positive results (Johansson *et al.* 2000, Wahren *et al.* 2012), though the short half-life of C-peptide has proven to be a limiting complication in the conduction of large human trials. However, chemically modified long-acting C-peptide molecules have already been developed (Wahren *et al.* 2016, Zashikhina *et al.* 2019). If they show long-term safety and their effects translate to improved outcomes for diabetic patients, the introduction of C-peptide into clinical practice in the therapy of T1DM and late T2DM-associated complications would be a very important and desirable achievement.

Once C-peptide was shown to be a biologically active molecule, the search for its receptor has led to significant progress in ascertaining the physiological relevance of the peptide. Most intracellular signaling cascades observed following exposure to C-peptide have

been associated with the activation of a GPR, although the binding dynamics indicates that the peptide may bind to a complex of proteins rather than to a single receptor (Pramanik *et al.* 2001). Furthermore, some studies have suggested that C-peptide exerts its action through alternative non-receptor-mediated mechanisms.

As C-peptide, unlike insulin, escapes hepatic extraction and has a much longer half-life in the circulation, it has widely been used as a measure of insulin secretion to assess beta cell function. Bypassing clearance by the liver also allows a much wider use of C-peptide in human physiology research, such as evaluations of hepatic insulin extraction changes throughout life or during the development of some pathological condition. The diagnostic potential of C-peptide and especially C-peptide oGTT-derived indices may provide a deeper understanding of the pathophysiology of not only type 1 and type 2 diabetes mellitus, but also possibly other diabetes-associated pathological conditions such as non-alcoholic fatty liver disease.

Conflict of Interest

There is no conflict of interest.

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