Proinsulin C-peptide and G-protein coupled receptor 146 (GPR146) – clinical investigation of the impact of their signalling network on molecular pathways involved in diabetes-induced complications

Proinsulin connecting peptide (C-peptide) is a short peptide that ensures proper assembly of insulin molecule during its production in the pancreas. For a long time, the function of C-peptide remained a mystery and researchers regarded this molecule as biologically inert by-product devoid of physiological activity. However, in recent years, it became evident that C-peptide is able to regulate a number of cellular pathways. Moreover, the results of many studies confirm that it may play a role in the onset and clinical course of long-term complications associated with diabetes such as damage of the blood vessels, peripheral nerves and loss of kidney function. The effects of C-peptide on diabetes-induced complications seem to depend on the type of diabetes. Data gathered by animal studies show that C-peptide supplementation in type 1 diabetes (T1DM), which is characterized by low to non-existent level of insulin and C-peptide secretion due to destruction of cells producing them in the process of autoimmunity, causes a beneficial effect on nerve and kidney function. On the other hand, persistently high levels of C-peptide that occur in type 2 diabetes (T2DM) – a disease caused by insulin resistance of the tissues – may promote development of atherosclerotic lesions. These results suggest that restoration of normal, physiological level of C-peptide in diabetes could be a reasonable therapeutical target to counteract the long-term sequelae of diabetes. However, C-peptide-based treatments have not been developed yet due to limited understanding of the molecule's mechanism of action and its downstream signalling in cells, as well as insufficient knowledge about the factors influencing its activity in the human organism.

While it is still unknown how C-peptide exerts its effects on cells, there is some evidence that a protein called G-protein coupled receptor 146 (GPR146) – interacts with C-peptide and transmits its signal to the cell. Interestingly, a recently published study showed that this protein may be involved in the process of cholesterol synthesis. The group of researchers found that stopping expression of the receptor in liver cells of a mice results in a decrease in the levels of low density lipoprotein (LDL) and triglycerides in the circulation and reduction of atherosclerotic lesions. The results of that investigation suggest that C-peptide may play a role in cholesterol metabolism, which would at least partially explain its association with atherosclerosis in T2DM. These recent findings provide a new insight into the role of C-peptide in T2DM and pave the way for a new approach to establish its precise mechanism of action in T2DM-related complications.

Given the increasing prevalence of T2DM it is surprising that there is still a lack of knowledge regarding the role of this persistently elevated peptide with the dynamics and nature of a hormone. Hence, the aim of this study is investigate the regulatory network of genes associated with GPR146 in a manner as accurate as possible and to explore the expression pattern of GPR146 across tissues affected by diabetic complications in patients undergoing cardiovascular surgeries. To achieve this aim we plan to recruit patients with T2DM and without diabetes. From these individuals biological samples will be collected during cardiosurgical operations which require the removal of vascular walls, incision of the cardiac wall and removal of the adipose tissue to provide access to the cardiac muscle. Thus, without endangering the patients we will be able, for the first time, to investigate the interplay between the C-peptide and its potential receptor in cells which are chiefly affected by T2DM. Although, scientists reportedly managed to identify a range of pathways regulated by this molecule the full picture of its cellular signalling is still unclear and the evidence is tenuous. Therefore, our investigation will explore cellular pathways regulated by C-peptide-GPR146 signalling by using techniques enabling large-scale gene expression studies. In addition, we will assess the association between the level of C-peptide and levels of zinc, albumin, cholesterol, LDL and triglycerides and GPR146 expression in human organism – factors associated with or speculated as important for C-peptide activity. We believe the results of this study will elucidate whether any and which of the diabetes complications-related processes are associated with signalling through the GPR146. This will lay the foundations for potential C-peptide-dependent pharmacological interventions and identify likely endpoints associated with this overlooked hormone.