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Intracellular and peptide interactions of C-peptide

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Abstract

Proinsulin C-peptide is depleted together with insulin in type I diabetic patients. The supplement of insulin to these patients is necessary for their survival, but it is also likely that the loss of C-peptide may contribute to both short- and long-term complications. In this thesis, molecular effects of C-peptide have been investigated. In particular, nuclear effects of C-peptide and C-peptide involved in oligomerization have been studied, as well as method development to facilitate further protein interaction analysis.

C-peptide is a small peptide hormone with known membrane-binding properties that is thought to stimulate G-protein coupled receptor associated pathways. In this thesis we report that C-peptide not only acts extracellularly, but that it is internalized via specific mechanims and interacts with cytoskeletal proteins. We show that C-peptide is transferred to the nucleus, and specifically to the rRNA-synthesizing organelle nucleolus where it stimulates transcription of rDNA. Transcription of rDNA is related to a complex of proteins at the promoter region including histone 4 that gets acetylated upon interaction with C-peptide. We further link this transcriptional activity of C-peptide to proliferation in a model system relevant to the bone growth retardation observed in type I diabetic patients suffering from fractures. To understand more of C-peptide's effects on the basis of the transcriptional activity observed, a genome analysis of proximal tubular cells isolated from type I diabetic rats was performed. It revealed that C-peptide within 2 hrs exerts tight effects on transcription with ~500 genes affected and the majority of them being repressed. This observation suggests that C-peptide treatment corrects malfunctioning pathways, especially pathways of circulatory and inflammatory diseases. We have also studied oligomerization of C-peptide, and find that C-peptide oligomers are disrupted by insulin in addition to a previous study reporting that C-peptide disrupts insulin hexamers. The C-peptide oligomers are formed via electrostatic interactions, and can further lead to aggregates with a high content of ß-sheets.

In summary, this thesis provides data on C-peptide being an intracrine hormone with intracellular effects in addition to having extracellular activity via classical endocrinological pathways. We also discuss the implications of the C-peptide oligomers we observe, which provide evidence that C-peptide may act as an insulin chaperone. It is evident that a fine-balanced homestasis of C-peptide is necessary for optimal health in both type I and II diabetic patients.

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