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Unravelling novel actions of gut peptides-biological mechanisms and therapeutic implications

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Abstract:

The 20th century has witnessed a scientific transformation in our understanding and treatment of human disease, encompassing the birth and maturation of the science underlying endocrinology and metabolism. For most of the 20th century, hormone discovery was rooted in purification and characterization of extracts and substances with biological and endocrine activity. In many cases, newly discovered hormones (insulin, cortisol, thyroid hormone) were immediately used to treat corresponding hormone-deficient states in humans. The era of modern molecular biology later unveiled the sequences of hundreds of putative new hormones and their receptors, often without knowledge of their putative biological activity. In some instances, insights from mouse and human genetics provided substantial useful information supporting the functional relevance of newly discovered genes and proteins. In contrast, the putative roles of many newly discovered genes and proteins remained obscure, setting in motion the biological analysis of novel proteins and hormonal effectors. Here I discuss the discovery and characterization of two glucagon-like peptides, co-encoded within the proglucagon gene, highlighting key biological insights, and their subsequent therapeutic relevance. In particular, I discuss how modern day discovery of hormone action, exemplified by studies of GLP-2, remains anchored in multidisciplinary science spanning human and animal physiology, peptide biochemistry, and mouse genetics. The discovery and characterization of glucagon, followed by GLP-1, oxyntomodulin, and GLP-2, peptides co-encoded by a single gene, provides a compelling timely reminder that mechanism-based hormone discovery continues to play an essential role in the development of new therapies for the treatment of metabolic disorders.

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