The prodigal peptides

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Abstract

The identification and isolation of newer hormones and transmitters has helped establish and expand the field of gastrointestinal endocrinology.[1] Our understanding of these molecules, and their receptors, has allowed us to unlock their therapeutic potential as well. Agonists of these peptides are now used as treatment for type 2 diabetes and obesity, as well as prophylaxis to reduce adverse cardiovascular and metabolic outcomes.[2] Their development has enhanced the relevance of peptide pharmacology from an insulin-centric industry to a dynamic multipeptidic discipline.

Various peptides, discovered over the past few decades, are now being evaluated for their diagnostic and therapeutic potential. We term these the prodigal peptides. Based upon the Biblical parable of the prodigal son, we use this description to highlight the "coming of age" of these hormones.

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Insulin

The power of insulin has been harnessed for over a century now. Advances in pharmaceutical engineering have facilitated the production of novel preparations with protracted duration of action (once-weekly insulin icodec) or non-conventional routes of administration (inhaled insulin).[3,4] Its counter-regulatory hormone, glucagon, has for long been used as an antidote to hypoglcaemia. Newer delivery devices (prefilled pens), routes of use (nasal glucagon) and analogues (dasiglucagon) are now being used.[5]

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GLP1

The prodigality of peptide pharmacotherapeutics extends beyond pancreatic hormones. Glucagon like peptide 1 receptor agonists (GLP1RA) such as the first generation exenatide, lixisenatide and liraglutide, and current generation oral and injectable semaglutide, have revolutionized the treatment of diabetes and obesity. Their use has been so ubiquitous that GLP1 is now considered a 'conventional' target of metabolic therapy.[2]

Oral route of administration is always considered person-friendly. Oral semaglutide has been studied uptil a daily dose of 50 mg, in the management of obesity. Orforglipron, a non-peptide oral GLP1RA, has cleared phase 2 and phase 3 trials in obesity and diabetes. This, too, is a biased or asymmetric agonist, which favours G-protein activation over β-arrestin recruitment.

Dual Peptide Agonists

Prodigal peptide agonists are now being studied in combination with GLP1RA. This represents a development over earlier monopeptide formulation (pramlintide) and dual insulin-based coformulations (IGlarLixi, IDegLira). Tirzepatide, a dual GLP1RA and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist, is already in use across the world. This unique drug offers asymmetric agonism at GLP1 and GIP receptor, in a 1: 5 ratio. This allow for greater efficacy, along with lower side effects and better tolerability. Other coformulations being developed explore and elucidate the power of various prodigal peptides for metabolic modulation.[6]

CagriSema is a coformulation which combines the amylin agonist cagrilintide with the GLP1RA semaglutide. The drug has been found it have a synergistic effect on appetite reduction and weight loss, through its effects on the GLP-1 and amylin/calcitonin receptors. Results of the phase 3 REDEFINE trial have been released.

Triple Peptide Agonists

Retatrutide is a triple peptide agonist, which acts upon the GLP1 GIP and glucagon receptor. Found to have excellent results in phase 2 trials the drug is being evaluated in the TRIUMPH phase 3 clinical trial programme.[6]

Newer Horizons

Amylin, one of our prodigal peptides, is the foundation of amycretin, a unimolecular oral and subcutaneous GLP1/amylin dual agonist, as well as petrelintide, a long acting amylin analogue. Other drugs in development include survolutide and pemvidutide, dual GLP1 and glucagon receptor agonists; and mazdutide, an oxyntomodulin analogue; Survodutide and pemvidutide have ongoing research focussed on the management of metabolic associated steatotic liver disease (MASLD). A newer GLP1/GIP receptor agonist is VK2735, which is being studied both as oral and subcutaneous formulations.[7]

Twists In The Tale

MariTide (maridebart cafraglutide), a monthly subcutaneous preparation, takes a somewhat antipodal approach to metabolic modulation. This is a GLP1RA conjugated to a GIP receptor antagonist antibody.[8]

Other prodigal peptides are coming to the fore. Though not directly related to the gastrointestinal tract, they represent the pluri-potential power of peptide biology. These include growth differentiation factor (GDF)-15 agonists and activin type II receptor antibodies (bimagrumab).

Summary

Further developments are exciting, as well as exhilarating. As we work towards better health for our compatriots, the evolution of peptide-based pharmaceuticals for metabolic care provides cause for cheer.

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