The Peptide Paradox in Pharmacology of Obesity

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Abstract

Peptide biology is a fascinating subject, and peptide pharmacology even more so. Peptides have multiple bodily functions, including their work as hormones and metabolic modulators. However, certain pharmacodynamic and kinetic properties of peptides used in obesity result in paradoxical outcomes. It is helpful for the treating clinician to be aware of these peptide paradoxes, which not only help in understanding the rationale of using these drugs but also help to explain their differences in clinical actions.

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Introduction

Advances in basic and pharmaceutical sciences have lead to an increase in the way peptides can be harnessed for clinical use. While insulin remains the best-known example of a therapeutic polyprotein in endocrinology, other classes of drugs are increasingly being used.[1] Till recently, pharmaceutic innovations had been restricted to single peptide preparations (glucagon-like peptide receptor 1 agonist [GLP1RA] insulin and glucagon). Apart from GLP1RA, glucose-dependent insulinotropic polypeptide receptor agonists (GIPRA), as well as antagonists and glucagon agonists, are being used or are under development. Co-formulations based on these drug classes have now been developed for use in diabetes and obesity care.[2] Some comprise a GLP1RA plus insulin, and others are created by combining two (or three peptide) peptide receptor agonists.

There is a paradox in the rationale of these dual and triple receptor agonists, however (Figure-1). While the physiological properties of the peptides are different, their receptor agonists exhibit different pharmacological effects.

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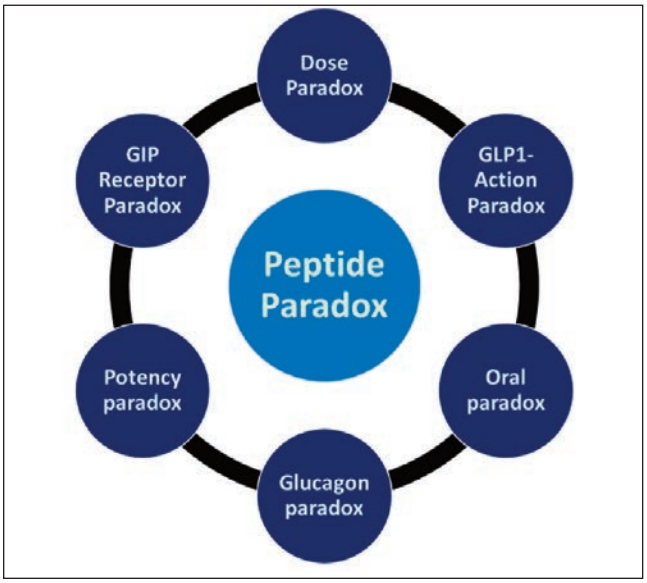

Figure-1: The peptide paradox in the management of Obesity.

Another issue is that both agonists and antagonists of the same peptide receptor are being used to manage the same disease. We discuss these challenges as the Peptide Paradox.

The Peptide Paradox may be defined as the differential effects that a peptide receptor ligand may have in physiological and pharmacological settings and concentrations, in isolation and in combination with other drugs and in different disease conditions.

The GLP1RA Action Paradox

GLP1RA are an integral part of the diabetes and obesity treatment landscape. The wide variety of drugs is matched by variation in their glucose-lowering, weight reduction, cardiovascular and renal protection. In general, longer-acting GLP1RA are shown to have more potent effects on weight and a greater degree of cardiovascular protection. The fact that not all GLP1RA exhibit a class effect of weight loss and cardiovascular benefit (though all help in achieving glucose control and offer cardiovascular safety may be termed a peptide paradox.[3,4] This may be explained by the duration and degree of GLP1 receptor binding of each pharmaceutical preparation or by factors unique to its structure and pharmacokinetics.

The Dose Paradox

Dual peptide agonists, which include GLP1RA and GIPRA,

such as tirzepatide, have been demonstrated to improve glucose and weight homeostasis. By doing so, this drug can break the KgA1c paradox, or the rise in Kg (weight) that is encountered while reducing A1c (glucose) with conventional therapy. Tirzepatide also bucks another KgA1c paradox, which is also noted with the higher doses of liraglutide and semaglutide. Both these medications are effective in lower doses for glucose control. Higher doses are needed to manage weight in non-diabetic or diabetic individuals. With tirzepatide, however, the same dosage strengths are used in both diabetes and obesity.[3]

GIP Receptor paradox

The use of tirzepatide does highlight another peptide paradox. Animal studies show that GIP receptor (GIPR) knockout mice are protected from diet-induced obesity. The GIPR locus is associated with body weight reduction in humans as well. It makes sense, therefore, that a GIPRA antagonist be used to manage obesity. Tirzepatide, on the other hand, is a GIPR agonist as well as a GLP1RA.[3]

This contrasts with a newer drug, maridebart cafraglutide, an optimized GIPR/GLP1R bispecific molecule that acts as an agonist of GLP1RA and antagonist to GIPR. This mixed peptide agonist/antagonist has been shown to be effective in preclinical and phase 1 trials.[5]

It may be that GIP has variable effects at different concentrations. It is also possible that GLP1 and GIP act as cofactors or co-promoters for each other, at particular concentrations, leading to a synergistic effect in certain, but not all, cases. Another possibility may be that GIPR modulation in any direction, leads to a change in the microbiome or bowel-brain axis, and influences weight homeostasis.

The Glucagon Paradox

Glucagon is a 29-amino acid polypeptide that serves as a counter regulatory hormone to insulin. In pharmacologic settings, glucagon agonists work as anti-obesogenic drugs despite their potential hyperglycaemic effect. They do so by reducing food intake and increasing energy expenditure through their action on hepatic vagal afferent nerves supplying the hypothalamus, as well as directly at the hypothalamic arcuate nucleus. This paradox of differential physiological and pharmacologic action has been utilized to develop long-acting glucagon receptor mono, dual, and triple agonists. Agonists can also be classified as partial. biased, and super agonists. Co-formulations of glucagon agonists with GLP1RA, or GLP1RA and GIPR, are being, are being studied in clinical trials. Examples include efinopegdutide, mazdutide, pemvidutide, and retatrutide.[6]

The Paradox of Potency and abundance

Of all drugs currently available for the management of diabetes and obesity, tirzepatide seems to have the most promising results. Amongst those in development, retatrutide has the maximum effect on weight loss. This is another peptide paradox: a combination of two or three peptide receptor agonists seems more potent than a GLP1R mono-agonist given along with insulin.[7] This is even though a GIPRA, administered alone, will not affect glycaemia, while insulin, even alone, is a very potent glucose-lowering agent.

This paradox can be explained by the beneficial effect of the involved peptides on weight. By reducing weight, tirzepatide improves insulin sensitivity and contributes to better glycaemic control.[8] The availability of multiple peptide agonist preparations, which can be used in varied permutations and combinations, creates a paradox of plenty. While these drugs hold the promise of better control, they must be used with rationale and responsibility. One should be aware of not only the indications but the caution and contraindications for use as well. Awareness about the benefits, limitations, adverse effects, cost, and knowledge required for administration is necessary to optimize outcomes and minimize risks.

The Oral Paradox

The same medication, when given through different routes of administration, has a very different impact on weight loss. Semaglutide, when given orally, leads to roughly 5 percent weight loss, while if given subcutaneously, it may have about 15 percent weight loss. This may be explained by the bio-availability of the drug in the hypothalamic region, which regulates satiety and weight balance, Hence, this would qualify for another type of peptide paradox. It must be noted that higher doses or oral semaglutide are being studied for their utility in obesity management.

Table-1: The different types of peptide paradox.

1.	The GLP1RA Action Paradox	Not all GLP1RA exhibit a class effect of weight loss and cardiovascular benefit (though all help in achieving glucose control and offer cardiovascular safety)
2.	The Dose Paradox	Lower doses of GLP analogues are effective in glycaemic control but higher doses manage glycaemic and weight control. However, with GIP and GLP1 dual receptor agonist (tirzepatide), weight control can be achieved at lower doses.
3.	GIP Receptor Paradox	Both GIP receptor agonists and antagonists help in weight loss despite having opposite action on the GIP receptor.
4.	The glucagon paradox	Glucagon agonists work as anti-obesogenic drugs and help in remission of diabetes, despite their potential hyperglycaemic effect.
5.	The Paradox of Potency	The combination of two or three peptide receptor agonists seems much more potent than the a GLP1R mono-agonist given along with insulin. This is in spite of the fact that a GIPR, administered alone, will have no effect on glycaemia.
6.	Oral paradox	The same medication, when given through different routes of administration, has differing impact on weight loss.

Conclusion

While several anti-obesity medications are now available in the market, the clinician must understand the different aspects regarding the differential action of these molecules when used across different doses and combinations. This is summarized in Table-1. It is helpful for the treating clinician to be aware of these peptide paradoxes, which not only help in understanding the rationale of using these drugs but also help to explain their differences in clinical actions.

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