

GLP-1 and the Hypothalamic-Pituitary-Gonadal Axis

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1. Introduction

The knowledge that nutrition can have profound effects on reproduction has been long understood with philosophers as early as Aristotle observing that poor nutrition is associated with poor reproductive success. However, relatively little is known about how signalling occurs between the two axes of metabolism and reproduction. Understanding the physiology underpinning this relationship not only allows for better management of nutrition during periods of stress (e.g., starvation or obesity), but also provides insight into the unintended effects of manipulating one of these two axes.

2. Nutrition and reproduction

One obvious reason that a relationship exists between reproduction and energy balance is that the former comes at a cost to the latter (Clarke, 2014). Energy used for reproduction – the synthesis of hormones, gamete production, and reproductive behaviour- cannot be used for storage or other metabolic activities. Similarly, in times of nutritional stress, reproduction may fail due to a lack of substrate availability. However, indirect effects also exist; the hypothalamic-pituitary- gonadal axis can respond to changes in feeding behaviour before any appreciable change in energy stores has occurred.

There are many hormones, neurons, neurotransmitters and peptides that could act to mediate the relationship between these two axes. Generally, these can be classed as either anorexigens, which are typically released in response to

nutrient intake and suppress appetite, or orexigens, which stimulate feeding behaviour when a nutrient deficit exists. Because anorexigens are released in response to feeding, they are well placed to signal that nutritional conditions are suitable for pro-creation. This seems to hold true, with anorexigens such as POMC/CART neurons, leptin, insulin and GLP-1 having a stimulatory effect whilst orexigens such as NPY/AgRP, orexin and RFRP3 neurons and ghrelin inhibit the reproductive axis.

3. Glucagon-like peptide 1

Glucagon-like peptide 1 is a post-translational product of the preproglucagon gene and is released primarily from the distal intestine. Centrally, it is produced in the brainstem and hypothalamus¹. It is released in response to feeding and nutrient arrival in the gastro-intestinal tract. It is a potent anorexigen with insulinotropic activity¹. These actions have led to increasing use of GLP-1 receptor agonists in the treatment of type II diabetes mellitus and obesity in humans eg semaglutide (Ozempic[®]).

It has been hypothesized that GLP-1 may be, at least in part, responsible for the rapid response of the reproductive axis to improved feeding condition and there is considerable supporting evidence for this².

The GLP-1 receptor is expressed in the hypothalamus, pituitary, ovaries, testes and endometrium³. Neuroanatomical studies show there is communication between GLP-1 producing neurons and Kisspeptin and GnRH neurons^{4,5}. Exposure of a GnRH cell line to GLP-1 resulted in GnRH release. Similarly, exposure of kisspeptin neurons to a GLP-1 agonist stimulated kisspeptin secretion⁵.

Intracerebroventricular injection of GLP-1 in rats, and micro-injection into the hypothalamus of sheep stimulates LH release^{6,7}. Infusion of a GLP-1 agonist into the jugular vein in ewes likewise resulted in increased LH secretion⁸, suggesting that both peripherally- and centrally-produced GLP-1 can affect gonadotrope release, with a very short time between administration and effect.

4. Conclusion

There is a growing body of evidence that GLP-1 is likely to upregulate the

hypothalamic-pituitary-gonadal axis, with a relatively rapid effect.

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