

Title

Monogenic obesity; using drugs to bypass the problem

Abstract

Safe and effective pharmacological treatments for severe obesity remain scarce. In this issue, Iepsen *et al.* show that obese patients with pathogenic melanocortin 4 receptor mutations, the most common form of monogenic obesity, lose weight with glucagon-like peptide 1 (GLP-1) receptor agonist therapy.

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Main body

Obesity, defined as an excessive storage of energy as fat, is a serious medical and socioeconomic problem. Any intervention, pharmacological or otherwise, aimed at tackling this problem is likely to be more effective when underpinned by a rational understanding of the processes at work that lead to the problem in the first place. The past 50 years have seen huge changes in how humans both consume and expend energy and, correctly, much effort is concentrated on reshaping our interactions with foodstuffs and our living and working environment. In addition, the last two decades have revealed a much deeper understanding of the biological processes that control our energy intake and expenditure. The central nervous system, in particular regions such as the hypothalamus, have a dominant role in sensing and integrating humoral and neuronal signals from the periphery and thence orchestrating homeostatic effector systems. Key to this has been the careful study of obese human subjects carrying single gene defects perturbing critical signalling pathways. Similarly, detailed characterisation of how peptide hormones derived from the enteroendocrine cells (EECs) of the gastrointestinal tract play an important role in appetitive and digestive biology has enabled an array of pharmacological interventions that target intrinsic pathways to enter the clinical arena.

In this issue, Iepsen *et al.* (Iepsen et al., 2018) successfully link dysfunctional hypothalamic signalling with an established drug (liraglutide) derived from the gut hormone Glucagon-like peptide 1 (GLP-1) to demonstrate an effective treatment for the most common form of monogenic obesity, melanocortin-4 receptor (MC4R) deficiency.

GLP1 is a gut hormone derived from the proglucagon precursor that has long been recognised to be a potent incretin hormone, augmenting glucose stimulated insulin secretion after a meal (Gribble and Reimann, 2017). GLP1 receptors are found in the pancreas, vagal afferent neurons and in brain nuclei including the hypothalamus and the brainstem. GLP1-R agonists such as liraglutide (where the addition of a fatty acid chain to the native GLP-1 molecule substantially increases its duration of action, Figure 1 B) are used widely in clinical practice to combat type 2 diabetes and obesity.

MC4Rs sit at the heart of the central melanocortin pathway (Figure 1A). Specifically, within the arcuate nucleus of the hypothalamus 2 populations of neurons- one expressing pro-opiomelanocortin (POMC), the other agouti-related peptide (AgRP) - project to the paraventricular

nucleus of the hypothalamus where they synapse with neurons expressing the MC4R to regulate food intake (Cone, 2006). Peptide ligands called melanocortins derived from the larger POMC precursor act as anorectic agonist ligands at MC4R, while AgRP is antagonist and has an orexigenic effect. Loss of function *MC4R* mutations cause hyperphagia, early onset obesity and increased linear growth (Farooqi et al., 2003).

The 14 individuals in this study all carried pathogenic mutations within *MC4R*, with a mean weight of 122kg and a mean BMI of 37.5 kg/m². The intervention was a simple one: 3.0 mg of liraglutide given subcutaneously once daily for 16 weeks, and the effects were compared to those seen in a second group of similarly obese adults from the same clinic who did not carry *MC4R* mutations. This intervention caused identical results in both groups, with just over a 6 kg weight loss seen in all those treated.

On the face of it then, perhaps not a surprising result. A drug proven to cause weight loss does just that when given to individuals with severe obesity. However, this may not have been wholly predictable. There are animal data to show that neuronal GLP1R mediates liraglutide's anorectic effects (Sisley et al., 2014) and that around 10% of POMC neurons express *Glpr1r* (Lam et al., 2017), so liraglutide weight loss effects could potentially be diminished if the melanocortin pathway were dysfunctional.

The work by lepsen and colleagues sets out clear "proof of concept" evidence that when one critical route is blocked, one should consider combatting the deficiency by trying to maximise signal transmission through another anorectic pathways. These data are also helpful in not feeding into despair that *MC4R* deficiency is somehow resistant to treatment and beyond intervention. Being a cell surface, G protein coupled receptor makes MC4R an attractive drug target, but initial studies with MC4R agonist therapies were stymied by unwanted effects, in particular issues with increased blood pressure (Greenfield et al., 2009).

Other emerging pharmacological therapies hint to being more successful. When given setmelanotide (a synthetic 8 amino-acid, cyclic peptide MC4r agonist) for a month, a small cohort carrying heterozygous *MC4R* mutations lost around 3.5 kg without adverse cardiovascular effects (Collet et al., 2017). Setmelanotide has also proven efficacious in other subjects affected by monogenic obesity. Two individuals with POMC deficiency had dramatic reduction in their hunger and substantial weight loss with this therapy (Kuhnen et al., 2016) and, more recently, setmelanotide has been reported to bring about sustainable reduction in hyperphagia and body weight in obese individuals with leptin-receptor deficiency (Clement et al., 2018).

Encouraging as all these studies are, there remain important questions around efficacy and safety in the longer term. For example, the weight loss with liraglutide in lepsen *et al*'s study looked to be plateauing off at 16 weeks and by any measure the patients were still significantly obese. How might weight change if therapy were continued for several years? Would prolonged exposure, potentially at a higher dose, run the risk of more side effects? Might a cash strapped health economy be better investing resources into bariatric surgery than chronic GLP1-RA therapy?

Prolonged setmelanotide therapy too needs close scrutiny. MC4R is part of a family of five closely related receptors and the melanocortin 1 receptor (MC1R) is a key signalling molecule on skin melanocytes responsible for eumelanin synthesis. In the POMC deficient patients (Kuhnen et al., 2016), skin nevi that were present before drug administration darkened considerably following suggesting that setmelanotide and it will be crucial to determine over time if this is more than just a cosmetic issue.

Nevertheless, this cluster of studies are welcomed reports and set the scene for longer and larger studies, both using single agents and combinatorial therapies, in patient groups significantly affected by severe obesity. Given the importance of the leptin-melanocortin pathway, dysfunction does pose a substantial barrier to maintaining a healthy weight, but as our understanding of the multi-layered complexity controlling mammalian energy homeostasis becomes ever more comprehensive, we can look forward to additional ways to circumvent the roadblocks and bring about clinically meaningful outcomes for even more patients.

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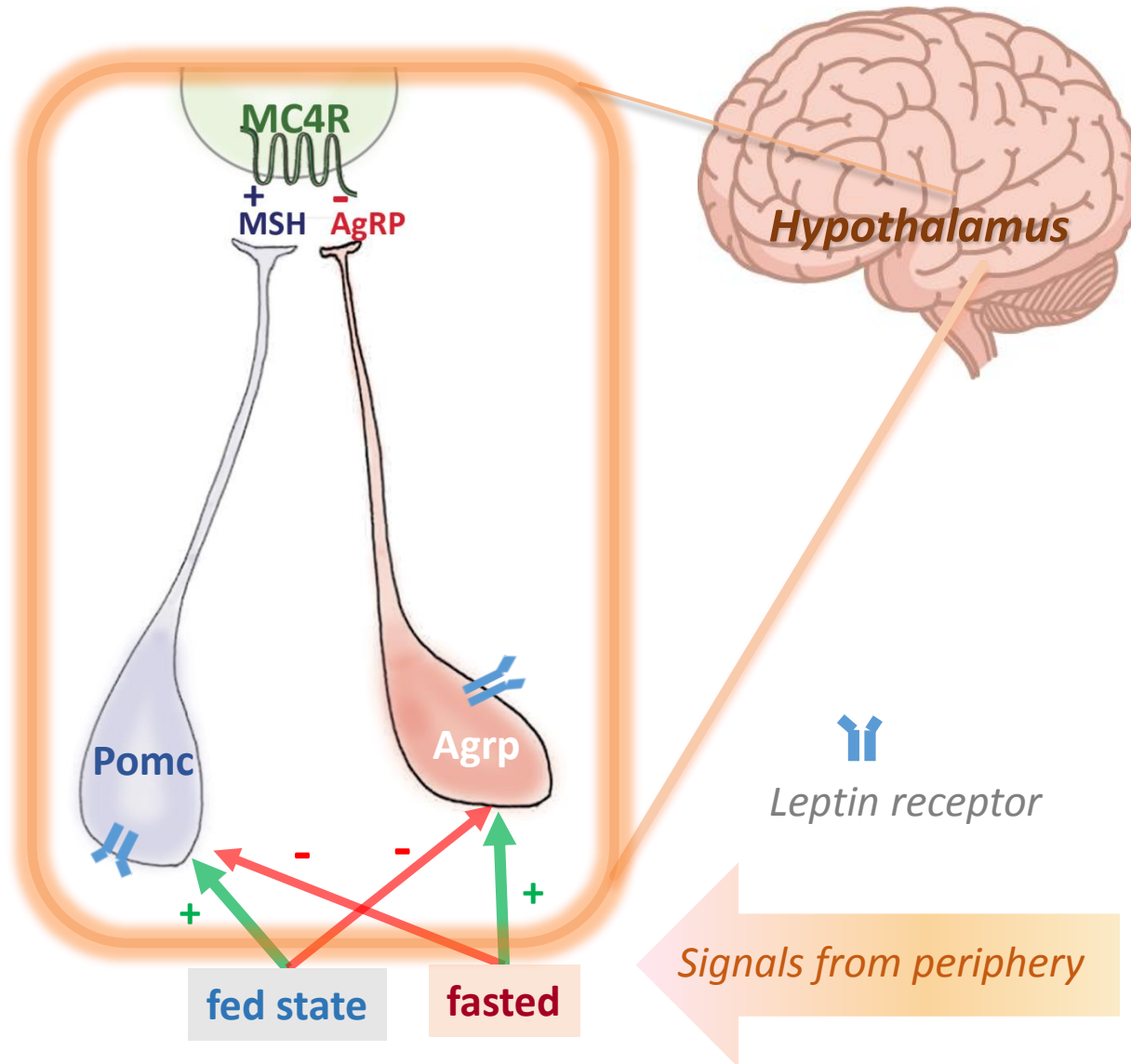
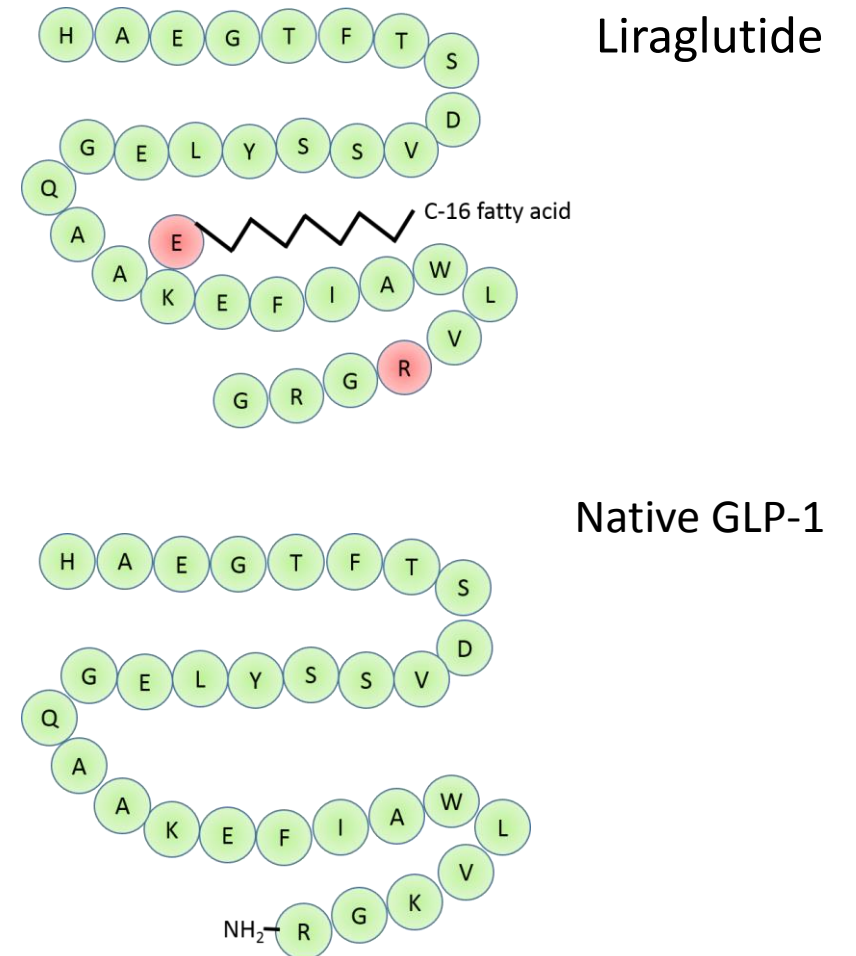
A**B**

Figure 1. A. The hypothalamus receives multiple inputs from the periphery to signal nutritional status. Within the arcuate nucleus of the hypothalamus two opposing neuronal populations (which have receptors for these peripheral signals) produce peptides which act either as agonist anorexigenic ligands (α - and β -melanocyte stimulating hormone, MSH) or antagonist orexigenic ligand (Agouti-related peptide, AgRP).

B. The Glucagon-like Peptide 1 receptor agonist Liraglutide is a modified version of endogenous GLP1, in which lysine at position 34 is replaced with arginine, and a palmitic acid chain is attached to lysine at position 26.