Neuroendocrinology of obesity

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Accepted 2 January 2014

Abstract

Background: Recent advances in physiological understanding of obesity have provided a new perspective on its origins and potential treatments.

Sources of data: This review is based on published literature in the fields of gut hormone physiology and the neuroendocrinology of obesity.

Areas of agreement: The gut releases several hormones in response to changes in nutritional status. Changes in plasma concentration of these hormones are responded to by central nervous system circuits controlling appetite and energy expenditure. Modified gut hormone secretion is responsible, at least in part, for weight loss after certain forms of bariatric surgery.

Areas of controversy: The extent to which modified gut hormone secretion is also responsible for remission of diabetes after bariatric surgery is contested, as severe calorie restriction alone can restore insulin secretion.

Growing points: Many gut hormone-based drugs are being developed for obesity.

Areas timely for developing research: If suitable drugs receive marketing authorization, it will be important to discover whether their combined use, mimicking the hormonal milieu after bariatric surgery, can safely cause weight loss and metabolic benefits of similar magnitude to those resulting from bariatric surgery.

Key words: obesity, gut hormone, therapy

Over the last three decades, the prevalence of obesity in the UK population has increased exponentially. One-third of adults may now be classified as obese, according to World Health Organization criteria, with another third in the pre-obese, overweight range. Those affected are at increased risk of developing type
2 diabetes mellitus, hypertension, stroke, myocardial infarction, peripheral vascular disease, respiratory failure, non-alcoholic steatohepatitis, osteoarthritis, depression and several common cancers, as well as complications in pregnancy and labour. Increased awareness of these human and financial costs has brought the pathophysiology, treatment and prevention of obesity into the political arena, as well as onto undergraduate and postgraduate medical curricula.

It is a truism that obesity results from excess food intake, while the quantity of food required to maintain a stable body weight varies according to energy expenditure. The homeostatic system that controls this balance is complex, with a multitude of inputs and outputs (Fig. 1). Both inputs and outputs may broadly be grouped as hedonic (varying the pleasure derived from food intake), appetitive (varying the extent to which the requirement for food intake is perceived and desired) and satiating (varying the sense of fullness derived from food intake). To this homeostatic system is added the effect of higher cognitive function, which may take into account social circumstances and other environmental factors. This review outlines the physiological control of food intake and energy expenditure and describes potential avenues for drug discovery in the treatment of obesity.

**Discovery of leptin**

For much of the 20th century, it was thought that the ventromedial (VMH) and lateral hypothalamic areas (LHA) together constituted the ‘appetite centre’ of the brain. The ventromedial nucleus of the hypothalamus is considered to be the primary orexigenic (appetite-stimulating) area, while the lateral hypothalamic area is considered to be the primary anorexigenic (appetite-suppressing) area. These areas are interconnected by a network of neurons that communicate signals about food intake and energy expenditure. However, research has shown that additional factors, such as stimulation of the vagus nerve and input from the gut, also play a role in appetite regulation.

**Regulation of food intake**

The regulation of food intake is controlled by a complex network of neurons that communicate signals about food intake and energy expenditure. This network includes:  

- **Leptin**
  - Produced by adipose tissue, leptin is a hormone that signals to the brain about the body’s energy stores. A decrease in leptin levels is associated with increased hunger and food intake.
  - Leptin receptors are located in the arcuate nucleus of the hypothalamus, where they interact with other hormones and neurotransmitters to control appetite.

- **Ghrelin**
  - Produced by the stomach, ghrelin stimulates appetite and is involved in the control of food intake.

- **CCK and GLP-1**
  - Produced in the gut, CCK and GLP-1 are involved in the regulation of appetite and energy expenditure.

- **Neuropeptide Y (NPY)**
  - Produced by neurons in the brain, NPY is involved in the regulation of appetite and energy expenditure.

**Neural control of food intake**

The neural control of food intake is complex and involves a variety of regions in the brain, including the hypothalamus, cortex, and brainstem. The hypothalamus is a key region involved in the regulation of appetite and energy expenditure. It contains a network of neurons that communicate signals about food intake and energy expenditure, and is involved in the regulation of body temperature, circadian rhythms, and metabolism.

**Vagal and gut input**

Vagal and gut input are important factors in the regulation of appetite and energy expenditure. The vagus nerve, which is a major nerve that connects the brain to the gut, provides input to the hypothalamus and other brain regions involved in the regulation of appetite and energy expenditure. This input helps to coordinate the body’s responses to food intake and energy expenditure.

**Endocrine and humoral inputs**

Endocrine and humoral inputs, such as changes in blood glucose levels and insulin concentrations, also play a role in the regulation of appetite and energy expenditure. These inputs help to provide information about the body’s nutritional status and energy requirements, which can influence appetite and food intake.

**Conclusion**

The regulation of food intake and energy expenditure is a complex process that involves a variety of factors, including hormones, neurotransmitters, neural circuits, and environmental inputs. Understanding the role of these factors in the regulation of appetite and energy expenditure is crucial for developing effective strategies to prevent and treat obesity.

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**References**

central nervous system (CNS). Experimental damage to the VMH had been found to cause hyperphagia, while LHA lesions caused anorexia. When hypothalamic injury was combined with parabiosis, in which the circulations of two rodents were joined surgically, it was realized that one or more circulating factors must act as signals of nutritional status.

Publication of the sequence of the *obese* gene was followed swiftly by reports from several labs that obesity in *ob/ob* mice could be prevented by administration of the gene’s product, a hormone for which the name ‘leptin’ was coined. For a short time, it seemed as if a cure for obesity would soon be available. This proved to be true for a very few individuals who, as a result of a human equivalent of an *ob/ob* genotype, are genetically deficient in leptin. However, plasma leptin concentrations in the vast majority of obese people were found to be elevated, indicative instead of relative insensitivity to leptin.

Despite this disappointment, the discovery of leptin and of its receptor, encoded by the *diabetes* gene, has facilitated a revolution in understanding of the mechanisms controlling appetite and energy expenditure. Using molecular biology techniques, individual leptin-responsive neurones have been identified and a vast and complex neural network has thus been revealed, centred on the hypothalamus and brainstem but with projections throughout the CNS.

A miscellany of drug discovery programmes has come about, targeting many of the neurotransmitters expressed within this neural network. However, as neurotransmitters typically have several different, unrelated roles in the CNS, troublesome off-target effects have occurred. Other discovery programmes have failed through lack of efficacy, reflecting the fact that multiple layers of redundancy exist within the homeostatic network. Nevertheless, several drug targets continue to show promise, many of them based on gut hormones. These hormones are described in further detail below.

**Gut hormones: pancreatic**

**Pancreatic polypeptide**

Pancreatic polypeptide (PP) is secreted by PP cells in the islets of Langerhans. Plasma concentrations are maximal after meals in proportion to the quantity of energy consumed. PP is a high-affinity ligand for the Y4 receptor, which is expressed in the area postrema and median eminence, as well as on peripheral vagus nerve terminals. Its physiological role is uncertain, while the pharmacological effects differ between...
experimental species. There is no evidence that it has an anorectic effect in rats whereas, in mice, peripheral administration of PP reduces food intake and increases energy expenditure, resulting in weight loss during chronic treatment.\(^8\)

The effect of PP infusion in humans was first studied in children with Prader-Willi syndrome, after an observation that endogenous hormone release after meals was attenuated in comparison with healthy volunteers. The original study did not detect evidence of a difference in food intake but the investigators were told by parents of the children involved that appetite had been reduced at home after the study visits. A second study was performed, with a longer infusion protocol, and a 12% reduction in food intake was measured.\(^9\) In healthy lean volunteers, food intake is reduced significantly during the 24 h after a 90 min intravenous infusion of PP.\(^10\) There are as yet no reports of either acute or chronic effects of PP on human energy expenditure, nor on body weight during chronic treatment. Nevertheless, on the strength of the potential anorectic effect, analogues of PP are currently in development as treatments for obesity.\(^11\)

**Amylin**

Amylin, also known as islet amyloid polypeptide, is co-secreted with insulin by pancreatic beta-cells in the islets of Langerhans. Its release is thus glucose dependent but its physiological role is unclear. The native hormone is implicated in the development of type 2 diabetes mellitus as a result of amyloid deposition in the islets. However, a stable analogue of amylin, named pramlintide, lacking the propensity for toxic amyloid fibril formation, is licensed in the USA as an adjunct to insulin for treating type 1 and 2 diabetes mellitus. Pramlintide treatment suppresses glucagon release and retards gastric emptying. In long-term use this typically results in modest weight loss and a reduction in exogenous insulin requirement but is also associated with nausea and increased frequency of hypoglycaemia.\(^12\) Weight loss with pramlintide is potentiated by co-administration with human recombinant leptin.\(^13\) However, clinical trials of a combination preparation were suspended after antibodies were detected against endogenous leptin.

**Glucagon**

Glucagon is derived from proglucagon, an important endocrine precursor peptide, which is expressed in pancreatic islet alpha-cells, enteroendocrine L-cells and several areas of the CNS. Tissue-specific expression of proteolytic enzymes (Fig. 3) in pancreatic alpha-cells results in glucagon secretion, whereas other biologically active cleavage products are released from other sites.

Physiological glucagon secretion is greatest during severe stress. However, the most extensively characterized role for glucagon is, through promotion of glycogenolysis, gluconeogenesis and lipolysis, to prevent hypoglycaemia during fasting.\(^14\) Glucagon also has inotropic and chronotropic effects that are of therapeutic use in the treatment of beta-adrenergic receptor antagonist overdose. Acute administration of glucagon causes nausea, mediated via the brainstem, while repeated treatment results in weight loss,\(^15\) probably as a result of both reduced food intake and increased energy expenditure.

For many years, knowledge of the acute hyperglycaemic effect of glucagon has discouraged investigation of its potential for treating obesity. Indeed, glucagon antagonists are in development for the treatment of diabetes mellitus. However, evidence is emerging from animal models that, during continuous chronic treatment, glucagon agonists may have a neutral or even beneficial net effect on blood glucose concentration.\(^16\) Whether this is true for humans remains to be discovered.

**Gut hormones: upper bowel**

**Ghrelin**

Ghrelin is a 28-amino acid peptide hormone that is synthesized in endocrine cells in the mucosa of the gastric fundus. Its serine-3 residue is acylated by ghrelin \(O\)-acyltransferase (GOAT) to produce the bioactive form, which is the endogenous ligand for the growth hormone secretagogue receptor
Secretion predominantly occurs prior to meals\textsuperscript{17} and, in contrast to every other gut hormone discussed in this review, appetite is stimulated by an increase in plasma concentration of ghrelin.\textsuperscript{18} Proof in principle of the therapeutic potential of this effect is emerging from small-scale clinical trials in patients suffering weight loss secondary to chronic diseases such as cystic fibrosis and end-stage renal failure. However, whether short-term increases in food intake and body weight could translate into a meaningful survival benefit has yet to be discovered.

In addition to its effect on appetite, ghrelin stimulates release of growth hormone from the anterior pituitary gland. The possibility that this effect might ameliorate frailty in the elderly was tested in a placebo-controlled study of an orally available GHS-R1a agonist. Although lean body mass and muscle strength were enhanced, the mean blood glucose also increased, leading to a greater incidence of diabetes mellitus in volunteers on active treatment.\textsuperscript{19}

The orexigenic effect of ghrelin has encouraged numerous groups to investigate the possibility of targeting it to treat obesity. Inhibitors of GOAT are in development, as are GHS-R1a antagonists, while RNA interference has been used to show that down-regulation of hormone expression can reduce body weight in animal models of obesity.\textsuperscript{20,21} However, no drugs have yet been licensed.

**Cholecystokinin**

Cholecystokinin (CCK) is secreted by endocrine I-cells in the upper intestinal mucosa during meals. It circulates as a hormone and also acts in a paracrine fashion at CCK receptors on vagus and enteric neurons. As well as stimulating gallbladder contraction, CCK induces early satiety. Its satiating effect seems to be independent of long-term appetite, as illustrated by the fact that rodents treated repeatedly with CCK increase their meal frequency to compensate for reduced meal size.\textsuperscript{22} This may explain why weight loss was not observed in a Phase 3 clinical trial of an oral CCK receptor agonist.\textsuperscript{23} However, there have been several reports of synergy between CCK and other gut hormones in reducing food intake and body weight in rodents, suggesting that a role in combination treatment for this class of drug may be found in due course.
Glucose-dependent insulinotropic polypeptide

Glucose-dependent insulinotropic polypeptide (GIP, also known as gastric inhibitory polypeptide) is released after meals by endocrine K-cells in the upper intestinal mucosa. In healthy individuals, it acts as an incretin, i.e. it stimulates insulin secretion from pancreatic islets in a glucose-dependent fashion. However, the incretin response to GIP is reduced or absent in patients with type 2 diabetes mellitus, meaning that GIP-based treatments are unlikely to be of benefit for diabetes. Although GIP does not appear to have any effect on appetite, it has a direct lipogenic effect on adipocytes, independent of insulin-induced lipogenesis. As a result, GIP antagonists have been developed as potential treatments for obesity. The possibility that such drugs might have a deleterious effect on insulin secretion makes their potential role in obesity treatment unclear at present.

Gut hormones: lower bowel

Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is a cleavage product of proglucagon that is released after meals, in proportion to energy intake, by endocrine L-cells in the intestinal mucosa. It is best known for its incretin effect, which was in humans originally demonstrated along with that of GIP in the same study. However, whereas resistance to GIP develops in patients with type 2 diabetes mellitus, there is continued sensitivity to, and a relative deficiency of, GLP-1.

The effect of GLP-1 on blood glucose is complex, involving inhibition of glucagon release and gastric emptying, as well as stimulation of insulin release. In addition, GLP-1 is anorectic, an effect first demonstrated in rodents. This combination of effects is responsible for weight loss, as well as improved glycaemic control, when GLP-1 is administered by continuous subcutaneous infusion to patients with type 2 diabetes mellitus.

Endogenous GLP-1 exists in two equivalently bioactive forms, GLP-1(7–37) and GLP-1(7–36) NH₂, both of which are inactivated rapidly in the circulation by dipeptidyl peptidase-4. As a result, several pharmacological approaches have been used to harness the action of GLP-1 as a therapeutic target. First, peptide agonists for the GLP-1 receptor have been developed with sequences resistant to degradation by dipeptidyl peptidase-4, and/or with modifications to the peptide backbone that promote binding to albumin in the circulation. Secondly, slow-release formulations have been used to prolong drug absorption from subcutaneously injected depots. Small molecule, orally available GLP-1 receptor agonists have also been developed, although none has yet been licensed for use in humans. Another successful approach has been to develop orally available inhibitors of dipeptidyl peptidase-4 that increase the plasma concentration of endogenously secreted GLP-1. Interestingly, these lack the weight-reducing properties of GLP-1 receptor agonists, probably because dipeptidyl peptidase-4 is involved in the degradation of a wide variety of peptides with a multitude of functions. Lastly, a number of laboratories, pharmaceutical companies and food producers are investigating methods of enhancing endogenous release of GLP-1 from L-cells within the bowel.

The anorectic effect of peripherally administered GLP-1 is thought to be mediated by binding to GLP-1 receptors on peripheral vagus nerve terminals and in the brainstem. In addition, GLP-1 receptors and proglucagon are both expressed within the CNS, suggesting that GLP-1 functions physiologically as a neurotransmitter. Enhanced secretion of GLP-1 is likely to be one of the major factors that determine the extent of weight loss after Roux-en-Y gastric bypass surgery. Indeed, pharmacological blockade of GLP-1 release overcomes the weight-reducing effect of surgery through disinhibition of hyperphagia.

Peptide YY

Peptide YY (PYY) is co-secreted with GLP-1 from intestinal L-cells after meals in proportion to energy intake. It exists in two bioactive forms, PYY₁₋₃₆ and PYY₃₋₃₆, which have dichotomous effects on appetite. PYY₁₋₃₆ is an agonist for several Y family receptors, including the Y1 and Y5 receptors. As a result,
it is potently orexigenic when administered by intracerebroventricular injection to rodents. However, the predominant post-prandial circulating form is PYY$_{3-36}$, formed when dipeptidyl peptidase-4 cleaves the first two amino acids from the amino-terminal of PYY$_{1-36}$. In contrast to the full-length peptide, PYY$_{3-36}$ is a selective Y2-receptor agonist. This receptor, which is coupled to the G-inhibitory second messenger system, is expressed presynaptically on orexigenic neuropeptide Y-releasing neurones in the arcuate nucleus of the hypothalamus. Binding of PYY$_{3-36}$ to the Y2-receptor thus inhibits activity in these neurones, resulting in a reduction in appetite.

Reduction of food intake after administration of PYY$_{3-36}$ has been demonstrated acutely in both lean and obese humans. However, while chronic administration causes weight loss in animal models of obesity, efforts to harness this effect to treat human obesity have so far proven fruitless. In the first Phase 2 trial of intranasally administered native sequence PYY$_{1-36}$, weight loss in obese subjects receiving the lower of two doses was not significantly different from that of the group receiving placebo. In the higher dose group, the majority of subjects withdrew after experiencing nausea and/or vomiting. It thus appears that the potentially therapeutic window between the lowest anorectic plasma PYY$_{3-36}$ concentration and the lowest nauseating concentration, is narrow.

There are two reasons to think that PYY$_{1-36}$ may yet prove to be worth pursuing as a therapeutic target for treating obesity and diabetes. First, combined administration of a minimally anorectic dose of PYY$_{3-36}$ with a similarly efficacious dose of a GLP-1 receptor agonist or dual glucagon/GLP-1 receptor agonist appears to result in an additive anorectic effect. Secondly, prolongation of half-life may allow a stable plasma concentration, beneath the threshold that causes nausea, to be achieved during repeated dosing.

Whether nausea occurs during administration of PYY$_{3-36}$ simply as an expression of excess satiety, or as an independent effect, is unclear. This reflects the limited nature of our understanding of the hormone’s physiological role. However, nausea occurring during infective gastroenteritis is associated with a high plasma PYY$_{3-36}$ concentration. While this observation does not provide sufficient explanation for the physiological release of PYY$_{3-36}$ that occurs after every meal, it is nevertheless consistent with the hypothesis that PYY-induced nausea may constitute part of the gut’s physiological defence mechanism against infection.

**Oxyntomodulin**

Like GLP-1 and PYY, oxyntomodulin is secreted after meals by intestinal L-cells in proportion to energy intake. It is a cleavage product of proglucagon, curiously comprising the entire peptide sequence of glucagon but extended at the carboxy-terminal by the next eight peptides of the proglucagon sequence. This extension allows oxyntomodulin to act as an agonist for both the GLP-1 and glucagon receptors.

Oxyntomodulin was originally named for its ability to inhibit release of acid from gastric fundus parietal cells. It is also a potent inhibitor of gastric emptying. More recently, it has been shown to cause weight loss in obese volunteers during repeated treatment, both by reducing appetite and by increasing physical activity-related energy expenditure. This has led to pharmaceutical interest in oxyntomodulin as a drug target for obesity.

Despite its agonist activity at the glucagon receptor, oxyntomodulin seems to have little or no net effect acutely on blood glucose concentration. Nevertheless, blood insulin concentration rises, suggesting that oxyntomodulin may stimulate metabolic cycling of glucose. This may contribute to the effect of oxyntomodulin on energy expenditure, with cardiac inotropy and chronotropy possibly becoming relatively more important at higher plasma concentrations. Whether these effects are responsible for inducing physical activity-related energy expenditure has yet to be discovered.

Interest in oxyntomodulin has encouraged study of the therapeutic importance of the ratio of agonist activity at the glucagon and GLP-1 receptors. In animal models of obesity and diabetes, administration of a co-agonist can cause more weight loss than a hormone analogue with activity at just one receptor. Indeed, it has been suggested that, if the ratio of agonist activity is optimized, a co-agonist could.
combine enhanced weight loss efficacy with a glucose-lowering effect. It is likely, however, that such a combination of effects would be as dependent on pharmacokinetic profile as on the ratio of receptor agonism.

Summary

Obesity results from an imbalance between energy intake and energy expenditure. Within this context, the neuroendocrine role of gut hormones as regulators of appetite has become apparent through investigation of the effects on food intake and body weight of hormone and hormone analogue administration. Further evidence has accrued from studies demonstrating that hormone receptor antagonists abolish the effects of endogenously released hormones. However, the gastrointestinal endocrine system represents only one part of the homeostatic mechanism controlling appetite. As illustrated by the response of leptin-deficient obese individuals to leptin replacement therapy, adipose tissue has a fundamental role that extends beyond body weight to encompass interactions with the classical hypothalamo-pituitary endocrine axes and the immune system. In addition, it seems likely that, as the endocrine functions of bone, muscle and other metabolically active organs are uncovered, further novel appetite-regulating factors will be discovered.

This review has tried to describe the major components of the gut–brain endocrine axis and to give a flavour of the complexity of neural circuits involved in energy homeostasis. The field of obesity research

Table 1 Summary of gut hormone effects on human food intake and body weight and notes on pharmaceutical development

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Receptor</th>
<th>Short-term effect on human food intake</th>
<th>Long-term effect on human body weight</th>
<th>Stage of pharmaceutical development</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP</td>
<td>Y4R</td>
<td>↓</td>
<td>Unknown</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Amylin (IAPP)</td>
<td>Complexes of CTR and RAMP-1 or RAMP-3</td>
<td>↓</td>
<td>↓</td>
<td>Pramlintide licensed in the USA for T1DM and T2DM</td>
</tr>
<tr>
<td>Glucagon</td>
<td>GcgR</td>
<td>↓</td>
<td>↓</td>
<td>Licensed for treatment of hypoglycaemia</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>GHS-R1a</td>
<td>↑</td>
<td>↑</td>
<td>Preclinical and early phase clinical trials using several approaches to prevent endogenous ghrelin release or action</td>
</tr>
<tr>
<td>CCK</td>
<td>CCKAR</td>
<td>↓</td>
<td>Unknown</td>
<td>Stalled after Phase 3 clinical trial did not demonstrate superiority over placebo; combination use a possibility</td>
</tr>
<tr>
<td>GIP</td>
<td>GIPR</td>
<td>No effect</td>
<td>Unknown</td>
<td>Agonists and antagonists in preclinical development</td>
</tr>
<tr>
<td>GLP-1</td>
<td>GLP-1R</td>
<td>↓</td>
<td>↓</td>
<td>Several drugs licensed for treatment of T2DM; obesity indication a possibility for some members of the class</td>
</tr>
<tr>
<td>PYY3–36</td>
<td>Y2R</td>
<td>↓</td>
<td>Unknown</td>
<td>Native hormone stalled at Phase 2; long-acting analogues in phase 1; long-acting analogues in Phase 2</td>
</tr>
<tr>
<td>Oxyntomodulin</td>
<td>GcgR and GLP-1R</td>
<td>↓</td>
<td>↓</td>
<td></td>
</tr>
</tbody>
</table>

PP, pancreatic polypeptide; Y4R, Y4 receptor; IAPP, islet-associated polypeptide; CTR, calcitonin receptor; RAMP, receptor activity-modifying protein; GcgR, glucagon receptor; GHS-R1a, growth hormone secretagogue receptor type 1; CCK, cholecystokinin; CCKAR, cholecystokinin receptor type A; GIP, glucose-dependent insulinotropic polypeptide; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; PYY3–36, peptide YY3–36; Y2R, Y2 receptor; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.
has moved a long way in the last 20 years and it remains a highly active area, with a particular focus on drug discovery (Table 1). Nevertheless, despite numerous demonstrations of the acute effects of gut hormones on human food intake, the only drug development target currently to have yielded a drug that seems likely to be licensed for weight reduction is GLP-1.

With so many hormones involved in appetite regulation, it remains to be seen whether targeting several different hormone receptors simultaneously will be useful or will merely increase the incidence of adverse effects. Nevertheless, as short-term studies of food intake in humans are for the most part supportive, it seems appropriate that the efficacy and safety of combination treatment should be investigated as new drugs become available. One may speculate that use of drug combinations might allow medical therapy to rival bariatric surgery in terms of extent of weight loss. For now, this must remain a matter for conjecture.

Funding

B.C.T.F. is the recipient of a Medical Research Council (MRC) Clinical Research Training Fellowship and a National Institute for Health Research (NIHR) Clinical Lectureship.

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