Human Obesity: Its Hormonal Basis and the Role of Gastric Inhibitory Polypeptide

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Key Words

Obesity • Gastric inhibitory polypeptide • Gastric inhibitory polypeptide-receptor • Fat feeding • Entero-insular axis • Incretins • Hormones

Abstract

Obesity is an abnormal expansion of the adipose organ and is a pathophysiological response to an imbalance between energy intake and energy expenditure. It is the result of a large number of diverse factors involving heritable and environmental characteristics. A simple definition of obesity is difficult and unsatisfactory and its age dependency has largely been ignored. Differentiation between healthy, age-related plumpness and obesity is often blurred and responsible for overdiagnosis of obesity in the developed world. In the past, epidemiological studies have often ignored the different prognostic significance of the two major phenotypes of human obesity making their conclusions of limited value. The role of heritable factors in determining both the propensity to develop obesity under favourable environmental conditions, including inactivity and unlimited access to fat-rich foods, and the phenotype it assumes received an enormous fillip from experiments involving genetically modified animals. The most important of these have demonstrated the key role played by a number of newly discovered or recently resurrected polypeptide hormones that are released from the intestine in response to food. Molecular manipula-

tion of these hormones, especially of glucose-dependent insulin-stimulatory polypeptide offers a new therapeutic approach.

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Introduction

Cells containing fat globules are found throughout the animal kingdom but recognisable adipose tissue is a comparatively late evolutionary development that occurs only in warm blooded, homoeothermic species [1]. Fish, for example, store fat either in cells dispersed throughout their body or in their livers where it can account for up to a third of their weight. Adipose tissue can be considered to constitute an adipose organ analogous to other diffuse organs of the body, such as muscle, with variable physiological functions depending on their location. Until about the 1950s, adipose tissue was considered to be a comparatively inert tissue with mainly mechanical insulation and long-term energy storage functions [1–3]. In migratory birds for example, in a spate of overeating, sufficient fat may be laid down within the space of a few weeks to double their weight but which will be dissipated in just a few days as heat and muscular work during a flight of many thousands of miles [4]. An analogous situation occurs in hibernating mammals.

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Obesity results from pathological enlargement of the adipose organ and is an exaggeration of the normal physiological response to energy intake exceeding what is sufficient to maintain body weight. Ordinarily, over an extended period – though not necessarily on a day-to-day basis – energy intake in the fully mature person balances energy expenditure. Imbalances are generally of short duration thus ensuring that adult weight, once achieved, is maintained more or less constant with only a marginal, progressive and beneficial increase with increasing age [5].

In view of the enormous number of variables determining energy intake – and to a much lesser extent energy expenditure – the maintenance of weight within comparatively narrow limits over a lifetime is extraordinary. To achieve this remarkable feat of homeostasis, it is necessary to postulate the existence of a ponderostat, or more correctly an adipostat, to ensure that the adipose organ never becomes too large or too small. Where it is situated and how it works has been the subject of intense speculation for almost a century.

Early clinical observation pointed to its location within the hypothalamus leading either to obesity or cachexia depending on the exact site and nature of the lesion. The importance of the hypothalamus in regulating body adiposity has been confirmed experimentally, too often, to need repeating and has served to emphasise the complexity of the mechanism which is beyond the scope of this review.

Bergmann and Stroebe [6] suggested that despite the central role played by the nervous system, and whilst endocrinology was still in its infancy, the primary cause of obesity is the greater capacity of certain individuals to store excessive amounts of fat in their adipose tissue and that this is under both neurological and hormonal control. Their suggestion has received ample support, but whilst the role of the nervous system has received a lot of attention, especially from sociologists and the psychologists, the role of the endocrine system received comparatively little until quite recently. This review will address that neglect.

Obesity

Definitions and Phenotypes

There is no satisfactory all-inclusive definition of obesity – especially in humans [7]. This is scarcely surprising as obesity is no more a single pathophysiological entity than is fever, blindness or lameness.

Obesity was uncommon, but far from unknown, before the modern era and confined to the rich and powerful in whom it was a status symbol and probably had important survival value when food was scarce. Nowadays in the developed world, where access to food is virtually unlimited and available to all but the destitute, it is, with a few notable exceptions, an affliction of the lower financial and educational strata of society and in them it is a health hazard.

Although often spoken of as assuming epidemic proportions, most people in long-established affluent communities appear to be immune to becoming obese and suffering disadvantage from it. They are however on average ‘plumper’ than their forbears almost certainly because of the change in lifestyle. Exactly how extensive adipose tissue enlargement must be to qualify as a health risk is still hotly disputed. This is partly because of the difficulty in determining a meaningful definition based on an identifiable end point and partly because of the enormous aetiological and morphological heterogeneity of ‘overweight’ or obesity [7].

Definitions and Epidemiology of Obesity

The definition most commonly used to define adiposity in adults nowadays is based on the Quetelet formula expressed as weight in kilograms/height in metres squared. Though formulated more than a century ago, the Quetelet index has only become popular with clinicians and epidemiologists within the past 2 decades. It is most commonly referred to as the body mass index (BMI). Despite its advantages as a tool for classifying people in epidemiological studies, one of its major failing is its inability to distinguish between heaviness due to (excessive) muscular development and that due to (pathological) enlargement of the adipose organ (obesity). A more important failing, and one that is still not fully appreciated, is the inability of the BMI to distinguish between the two major phenotypes of obesity, which carry very different prognoses [8].

Most investigators of obesity and reviewers have accepted a BMI of between 20 and 25 as the optimum, regardless of age. They describe those with BMIs between 25 and 30 as overweight, and those with a BMI of greater than 30 as obese. People with BMIs of over 35 are often described as ‘morbidly obese’. Most investigators have uncritically accepted that overweight, i.e. a BMI >25, is a health risk. It undoubtedly is when associated with various illnesses, such as hypertension and diabetes, but there is little evidence that plumpness, i.e. ‘overweight’, is a serious health risk in its own right [9], especially in the

middle-aged and elderly. A recent and extensive long-term follow-up study of persons enrolled in three massive National Health and Nutritional Examination Survey (NHANES) prospective studies in the USA showed that 'overweight' is not associated with premature death nor does it carry a longevity penalty compared to 'normal' weight subjects [9, 10]. Moreover, and contrary to expectations, slimness, defined as a BMI of less than 18.5, does contribute to premature death and constitutes a health risk [10].

Andres [5] reached a similar conclusion from a re-analysis of survival data on over a million life assurance policies some 20 years ago. His analysis showed, what every perceptive person has always known, that body weight expressed as BMI gradually increases with age. Not only is this normal, and seen in most domestic animals, but it is associated with improved expectation of life so that, by the age of 70 years, optimum survival for both men and women is linked to a BMI of about 27 plus whereas at age 30 it is associated with a BMI of 21 or 22. These crude survival figures do not take into account, however, either the cause or nature of the individual's adiposity [7]. We now know that this is crucial.

Though many attempts have been made to differentiate between types of obesity, none is wholly satisfactory for reasons already given. Jean Vague [11], a French diabetologist, was the first to identify, in the 1950s, two obesity phenotypes with different etiologically and prognostic significance [12]. The importance of this observation went largely unrecognised until comparatively recently when it was rediscovered and given the name of the metabolic syndrome. Vague [11] called the two types of obesity android and gynaecoid because of their greater, but far from exclusive, prevalence in men and women, respectively. People with these types of obesity are often referred to, in the lay-literature, as apples and pears because of a fanciful resemblance to these fruits, respectively.

Gynaecoid obesity is characterised by enlargement of the adipose organ in the subcutaneous tissues, especially below the waist, and is relatively benign. Android obesity, in which fat accumulates mainly above the waist, especially in the nape of the neck, subcutaneous tissues above the umbilicus and in the omentum, is more malign [12] and predisposes to a number of illnesses – most notably type 2 diabetes, hypertension and atherosclerosis [8, 11, 12]. It is obesity of this type that, when associated with some or all of the following conditions: hypertension, impaired glucose tolerance, insulin resistance, hypertriglyceridaemia, low high-density lipoprotein cholesterol

and hyperuricaemia, is known as the metabolic syndrome [13–15]. Though not a disease in its own right, the metabolic syndrome is a premorbid condition whose prevention or treatment can be expected to improve life expectancy.

What determines where excess adipose tissue is deposited within the body is still poorly understood except that it is influenced by sex and adrenal hormones [16, 17] and by genetics. That genetics play an important role in the pathogenesis of obesity has long been recognised in animal husbandry and by experimentalists using pure inbred strains of rodents with monogenic types of obesity. It is however only within the past few decades that the role of genetics in human obesity has been fully appreciated and that familial obesity owes less to 'greediness, overeating, inactivity and bad habits' than inheritance [18, 19] though they undoubtedly do play a part. The moralistic approach to obesity, so common in the past, is now recognised as unjustified in all but a minority of people. This is due to a much better, but still incomplete, understanding of the complex factors that control appetite, food intake and energy expenditure – and their propensity to disruption by both heritable and environmental influences.

Control of Energy Expenditure

With the growth of nutritional science during the last decade of the nineteenth and first half of the twentieth century, it was appreciated that in mammals and birds energy is expended partly on maintaining vital body functions, including body temperature, and partly on performing physical work. In human beings living in the developed world today, the former is responsible for most of the food-derived energy used each day. The amount of energy used to maintain body temperature remains more or less constant but is increased by exposure to the cold. Energy used to perform muscular work can vary enormously. It is however only when the increase in work is substantial that it makes a material difference to energy balance. Even quite vigorous training has little effect upon body weight though it may improve some surrogate markers of good health [20] through other mechanisms.

Most discussions about the impact of environment on the pathogenesis of obesity concentrate on the reduction in physical work (movement) undertaken by people living in modern society, but pay little or no attention to a possible role of the year-round warmer environment in which people now live due to central heating and which was formerly available only to the rich.

Discussion of the many features that control energy expenditure, such as resting metabolic rate – the main determinant of energy expenditure in all but the most physically active individuals – the thermogenic effect of nutrients and of exercise are beyond the scope of this review save to point out that the undoubted health benefits of mild to moderate exercise owe more to the physiological changes it produces in the body than to the amount of energy expended in performing it [20].

It is important to recognise that energy expenditure is controlled through its linkage to oxidative phosphorylation and that when this linkage is broken ‘futile cycling’ of metabolites is possible [21]. This generates heat over and above that required to maintain body temperature, which is dissipated through the skin and probably involves the autonomic nervous system [16].

The possibility that controlled uncoupling of oxidative phosphorylation, through recently discovered genetically determined uncoupling proteins [21], plays a role in maintaining constant body weight in the face of wildly different energy intakes and physical work requires serious consideration. It has for example long been known that pair-fed hyperphagic hyperinsulinaemic ob/ob mice gain weight faster than their heterozygotic littermates [22]. The opposite effect is observed in genetically engineered gastric inhibitory polypeptide-receptor (GIP-R) knockout mice suggesting that energy (calorie) intake is not the only determinant of obesity [23]. The ability of thyroxine given in excess to uncouple oxidative phosphorylation has long been recognised and led to its use and that of other uncouplers, such as dinitrophenol, as a treatment for obesity by unscrupulous practitioners. It was dangerous and thyroxine is now believed to have no role in the management of obesity except in proven cases of hypothyroidism.

The Appetite Centre(s)

Naturally occurring and experimental lesions of the brain can produce marked changes in appetite ranging from such profound anorexia as to cause death from inanition to unremitting hyperphagia producing such excessive weight gain as to produce total immobility [24]. Both extremes are pathological but whereas avoidance of food to such an extent as to cause death can be achieved voluntarily, by hunger strikers for example, it is doubtful whether the latter ever can [25]. In the only major voluntary overeating experiment performed on volunteer prisoners, the greatly increased energy intake was eventually balanced by an equally great increase in resting energy expenditure [25].

There are at least two – and possibly more – centres that control feeding behaviour within the brain and which together constitute a hypothetical adipostat. One is concerned predominantly with the initiation and termination of (intermittent) feeding, the other with maintaining body weight within optimum physiological limits [26].

Leaving aside the taste buds and olfactory organ, hypoglycaemia was probably the first change in blood chemistry to be identified with the ability to stimulate or inhibit appetite. Jean Mayer [27] incorporated this into a glucostat theory of appetite control: hunger develops when glucose metabolism by the tissues is decreased as indicated by a reduction in the peripheral arteriovenous glucose difference such as occurs during fasting, or when hypoglycaemia is induced artificially. Conversely, feeding is brought to an end when peripheral glucose utilization increases such as occurs during the absorption of a meal in the presence of an adequate insulin response. Current evidence suggests that whilst iatrogenic hypoglycaemia does affect glucoreceptors in peripheral tissues, as well as in the brain, the normal diurnal excursions in blood glucose that occur under everyday living conditions play a little role in initiating feeding.

The glucostat theory is however heavily entrenched in folklore and frequently invoked to support the belief that diets rich in readily available carbohydrates, i.e. those with a high glycaemic index (GI), predispose to obesity by producing rebound or reactive hypoglycaemia whilst those with a low GI do not.

Although neurons do not require insulin to enable them to utilise glucose, the brain does contain insulin receptors and there is evidence that they do play a role in regulating appetite [28–30] though exactly how remains unclear.

Modern Endocrinology and Obesity

An epoch-making development in elucidation of the enormous complexity of appetite control occurred with the discovery, less than 20 years ago, of leptin [31]. This regulatory peptide is produced largely, but far from exclusively, by white adipose tissue. It acts predominantly upon hypothalamic neurons to inhibit food intake. Its lack of production, through lack of the appropriate gene, is responsible for the phenotype known as the hyperglycaemic obese (ob/ob) mouse [32]. Since leptin was discovered, many other hormones, some of them produced by endocrine cells in the gastro-intestinal tract and already well known, have been identified by pharmacological and by molecular biochemical methods as being involved in

adipose tissue control. Some stimulate and others inhibit fat deposition. Their physiological and more especially their pathophysiological relevance to the pathogenesis of human obesity has so far been demonstrated in only a tiny minority of cases [23, 24]. They do, however, offer the hope, for the first time, of a physiopathological approach to the treatment of human obesity. It is with just one of these approaches that the rest of this review is concerned.

The demonstration that leptin deficiency is the cause of the gross obesity observed in ob/ob mice led to hope that leptin replacement therapy might result in a cure for obesity in humans, analogous to that of type 1 diabetes by insulin. This hope was shattered when it emerged that plasma leptin levels are high rather than low in most obese patients. In other words, obese subjects are at least partially resistant to leptin action in this respect resembling mice homozygous for the db/db gene. This gene is associated with an abnormality of the leptin receptor and produces a mouse phenotype of obesity very similar to that of the ob/ob mouse but in which plasma leptin levels are high instead of low.

The occurrence, through natural mutation, of receptor deletion has been mimicked experimentally by the creation of animals in which specific receptors to hormones thought to be involved in the pathogenesis of obesity have been created by molecular genetic techniques [23].

The rest of this review will concentrate on current knowledge of the role of certain gastro-intestinal hormones in the pathogenesis of obesity.

Hormonal Control of Adipose Tissue

Insulin and Obesity

Prior to 1921, patients with type 1 diabetes died either from diabetic ketoacidosis or from emaciation, the result of semistarvation – the only therapy then available to them. Emaciation was attributable to the combination of loss of glucose from the body in the urine and restricted intake of food. The restoration of weight to diabetic patients treated with insulin was one of the first of its properties to be identified and it soon became apparent that it produced obesity when administered experimentally to animals or supratherapeutically to humans [33]. Reports of obesity due to hypoglycaemia from endogenous hyperinsulinism resulting from insulinomas soon followed. Indeed insulinoma can – though rarely – present as apparently simple obesity [34]. These facts established a

link between insulin action and obesity long before it was possible to measure insulin in blood. The importance of insulin in the pathogenesis of obesity was confirmed by studies on adipocytes in vitro as well as in vivo [2, 3], which established a central role of insulin in the synthesis and storage of lipids within adipocytes.

With the invention of radio-immunoassay, it was soon established that hyperinsulinaemia is the single most characteristic clinical biochemical finding in all types of obesity, regardless of their primary aetiology. Obese subjects not only have high fasting plasma insulin levels but also show exaggerated insulinaemic responses to the majority of insulin-secretory stimuli [35] especially, though not exclusively, when administered orally as food. The hyperinsulinaemia of obesity differs from that of exogenous insulin or endogenous hyperinsulinism due to a primary defect of B cell function – such as occurs with insulinoma and nesidioblastosis – however in that it is never inappropriate, that is, it does not cause spontaneous hypoglycaemia, nor does it fail to suppress when the subject fasts or is rendered hypoglycaemic by exogenous insulin.

Apart from its effect on blood glucose, one of insulin's most important functions is to promote fatty acid synthesis from carbohydrates and turn them into triglycerides. It also prevents triglyceride breakdown by hormone-dependent lipase once they are deposited within adipocytes. Insulin activates adipose tissue lipoprotein lipase, a property it shares with GIP, to make fatty acids liberated from chylomicrons, following a meal, or very-low-density lipoproteins under other conditions, available for storage as intra-adipocyte triglycerides (fig. 1).

The question therefore arises as to whether hyperinsulinaemia is the cause or consequence of obesity. The latter now appears to be the case in all but an infinitesimal number of cases of endogenous hyperinsulinism. Abstention from food or reduction in caloric intake reduces or abolishes the exaggerated islet B cell response to insulinotrophic stimuli in obese people and lowers the high basal insulin levels before body weight loss becomes anything more than minimal [35]. Food intake rather than body mass alone is therefore the determining factor in the hyperinsulinaemia of obesity although acquired insulin resistance also plays a part.

Glucagon, the other pancreatic hormone intimately involved in glucose homeostasis, appears not to be closely involved in the pathogenesis of obesity. Indeed its ability in humans to induce lipolysis – which is an important feature of its actions in birds and in which family it is more potent than insulin in promoting lipogenesis – is

Fig. 1. Schematic representation of the effect of mixed food on gastro-intestinal hormones affecting appetite and deposition of triglycerides in adipose tissue. Four of the identified hormones have an inhibitory effect and one a stimulatory effect on appetite. Triglycerides are conveyed in the thoracic duct to the systemic circulation from which they are removed by adiposities. Adipose tissue lipoprotein lipase is activated by insulin and GIP to liberate fatty acids. These are resynthesised to triglycerides within the adipocytes in the presence of glucose, insulin and GIP. In the absence of these hormones or nonresponsiveness to them, triglyceride deposition is impaired. CHO = Carbohydrate; TAG = triacylglycerides (triglycerides); -ve = negative feedback or inhibition; +ve = stimulation; PYY = peptide YY.

difficult to demonstrate except under conditions of insulin deficiency.

Insulin and glucagon secretion exhibit a reciprocal relationship: glucagon is a potent stimulus to insulin secretion and is easily demonstrated; the inhibitory effect of insulin on glucagon secretion less readily so [36]. C-peptide, usually dismissed as an inert by-product of insulin secretion, has a similar action to insulin on glucagon secretion [37].

The anatomy of healthy human islets ensures that blood ordinarily flows from the centre of the islet through the core of B cells, the source of insulin, to a mantle of A and D cells, the sources of glucagon and somatostatin, respectively. Capillary blood on its way from the insular artery to a subsidiary of the portal vein picks up insulin on its passage through the B cell core depositing some of it on the surface of the A cells and D cells before entering the pancreatic vein. The net result is that insulin secretion increases after a meal and glucagon secretion either rises

very little or not at all under the inhibitory influence of insulin. As this inhibitory influence declines, at the conclusion of intestinal absorption of insulin-stimulatory nutrients, glucagon secretion begins to rise mobilising glycogen release from the liver and possibly fatty acids from adipocytes. The exact role of somatostatin in this autoregulatory endocrine-mediated process is still unclear as are any paracrine relationships that exist between the various islet cell types [36].

The anatomical relationships within the islets and the direction of blood flow are clearly very important in determining and preserving integrated islet endocrine function but are not necessarily retained in disease associated with changes in islet morphology. This may explain some of the disturbances in glucose homeostasis that occur with pathology of the exocrine pancreas and other conditions affecting islet morphology, such as the islet hyperplasia seen in some cases of morbid obesity.

Gastro-Intestinal Hormones and Obesity

In spite of its early links to endocrinology – it is exactly 100 years since the word ‘hormone’ was coined to describe a substance isolated from the intestine that stimulated pancreatic exocrine secretion – generations of endocrinologists have grown up and practised without any interest in or knowledge of the gastro-intestinal tract as an endocrine organ. It is only in the last half-century that its possible role in the pathogenesis of obesity and type 2 diabetes has been taken seriously [38]. The renewed interest is in large part due to the invention of immunoassay and its application to the measurement of hormones in blood under physiological and pathological conditions and, latterly, to the application of genetic engineering.

It is impossible in the space available to mention, let alone deal with, all of the 42 or more regulatory peptides that originate largely or exclusively within the gastro-intestinal tract [39] and which provide a link between the nature and quantity of food ingested and its disposition within the body [40]. Here I will deal only with those currently thought to have a major bearing on obesity.

Intestinal Glucagon-Like Immunoreactivity

A substance with properties similar to glucagon was identified by pharmacological and immunological methods in extracts of gut mucosa not very long after the isolation and chemical characterisation of glucagon [41]. It attracted little attention at the time apart from a few dedicated workers – possibly because it was not immediately linked to an overt clinical syndrome.

McIntyre et al. [42] in 1964 established that (arterial) hyperglycaemia produced by oral glucose was far more effective in stimulating insulin secretion than comparable hyperglycaemia produced by intravenous glucose. The phenomenon was called the incretin effect and attributed to a humoral factor released in response to food, and it was capable of stimulating insulin secretion only in the presence of mild to moderate hyperglycaemia.

Shortly after the paper of McIntyre et al. [42] appeared, Samols et al. [43] demonstrated that glucagon was the most potent stimulus to insulin secretion then known. They suggested that gut glucagon immunoreactivity, whose concentration in plasma had recently been shown to rise in response to the ingestion of dietary carbohydrates, could explain the incretin effect. However, it was not until some 30 years later, with the identification and characterisation of glucagon-like peptide 1 (GLP-1), that this was established as a fact [44–46].

GLP-1 and GIP, another member of the glucagon super-family [45] are now firmly entrenched as the two

most important, if not exclusive, hormonal contributors to the incretin effect. Other humoral factors [38, 44] that have been invoked from time to time as having an incretin function include secretin, pancreaticozym, bombesin, and oxyntomodulin. All are released into the circulation in response to the ingestion of food and can, under certain conditions, stimulate insulin secretion in the presence of hyperglycaemia but not at the concentration at which they occur in blood.

GLP-1 and GIP share many physiological functions but differ from one another in several other important respects. Both stimulate insulin secretion, but only in the presence of modest hyperglycaemia, are released into the circulation in response to foods, are rapidly degraded in the circulation to inactive (or antagonistic) metabolites by the ubiquitous circulating enzyme DPP IV which, by removing the two N-terminal amino acids, renders the native hormone inactive or even antagonistic [46, 47].

GLP-1 inhibits gastric emptying, reduces appetite and improves glucose homeostasis in patients with type 2 diabetes when administered parenterally. It also suppresses pancreatic glucagon secretion in contrast to GIP, which stimulates it. GIP inhibits gastric acid production, from which it derived its original name of ‘gastric inhibitory peptide’, but has no significant effect upon gastric emptying which GLP-1 does. GIP is reported as failing to improve glucose homeostasis when administered parenterally to patients with type 2 diabetes. This is in contrast to GLP-1, an analogue of which is currently in use as an antidiabetic agent.

The main difference between GLP-1 and GIP, however, is in their effects on fat metabolism. This is so pronounced that it led me in 1988 to describe GIP as ‘the obesity hormone’ [40].

Gastric Inhibitory Polypeptide

GIP was first isolated by Dr. John Brown working in the laboratories of Prof. Victor Mutt in Stockholm and was named for its potent inhibitory effect upon gastric acid secretion [48]. Some 3 years or so later, its potent insulin-stimulatory properties, which are seen only in the presence of mild to moderate hyperglycaemia, were discovered independently by Dupre et al. [49] in Montreal, Canada, and by Turner et al. [50] in Guildford, UK. Its insulin-secretory property soon became the centre of interest for groups investigating a physiological role for GIP and it is now commonly known as glucose-dependent insulin-stimulatory peptide. More recently, the key role of GIP in the pathogenesis of obesity has finally been recognised [23, 46, 51].

GIP is a 42-amino-acid, single-chain polypeptide secreted by K cells located mainly in the duodenal and jejunal mucosa. Small interspecies differences between GIPs do not necessarily affect their pharmacological properties, but porcine GIP, which differs from human GIP by a single amino acid, is sufficiently different immunologically to produce assay problems when incompletely cross-reacting antisera are used. This difficulty was responsible for much of the confusion that surrounded the potency and physiological functions of endogenous (human) GIP when compared to exogenous (porcine) GIP in the 1980s. It was also responsible for the almost complete eclipse of GIP as a subject for serious investigation until interest has recently revived [23, 46, 47, 51].

GIP secretion is stimulated by the ingestion of actively absorbed monosaccharides, such as glucose and galactose, but not by other carbohydrates, such as di- and polysaccharides, until they have been hydrolysed, or by passively absorbed sugars, such as fructose [52]. Long-chain fatty acids are equal or more powerful stimuli to GIP secretion compared to equimolar amounts of carbohydrates, as are triglycerides made from them; but only after hydrolysis into fatty acids and monoglycerides in the bowel [53]. Glucose-stimulated GIP secretion is abolished by blocking its active absorption, with phloridzin for example [52], and fat-stimulated GIP secretion is linked to its active absorption and conversion into chylomicrons, which enter the circulation through the thoracic duct. Short- and medium-chain fatty acids that are not packaged by mucosal cells into chylomicrons and do not take the lymphatic route into the circulation but enter it directly straight through the portal venous circulation do not stimulate GIP secretion [53]. Other nutrients such as proteins and amino acids are poor stimuli to GIP secretion and alcohol is completely without effect.

Insulin exerts negative feedback control on fat-stimulated GIP secretion and there is some evidence from rat studies that the C-peptide of pro-insulin exerts a similar inhibitory effect [37]. There appears to be no negative feedback control by insulin on glucose-induced GIP secretion serving to distinguish between the two major classes of stimuli to GIP secretion.

The inhibitory effect of insulin on fat-stimulated GIP secretion is attenuated experimentally by high-fat feeding, both in human beings and laboratory animals, and naturally in people consuming a high-fat diet [54]. A similar attenuation of insulin feedback control of fat-stimulated GIP secretion occurs in most obese subjects, wheth-

er diabetic or not. Indeed diabetes seems to be largely irrelevant to the control of GIP secretion except indirectly through insulin availability.

Pharmacophysiological Properties of GIP

GIP released from the gut in response to a meal consisting exclusively of fat does not stimulate insulin secretion. When, however, a complex meal providing both carbohydrate and fat is eaten, the effect upon insulin secretion is much greater than can be accounted for solely by the rise in arterial blood glucose concentration. This situation can be mimicked experimentally, during the course of an intravenous glucose infusion, by the ingestion of either fat or galactose – both of which stimulate GIP and insulin secretion under these circumstances but which have very little or no insulin-stimulatory properties in their own right [54].

GIP activates lipoprotein lipase in adipose tissue thereby hastening chylomicron clearance from the circulation and making the fatty acids available for assimilation by adipocytes [55, 56]. It also modulates insulin action on both the liver [57] and adipose tissue [58] by encouraging hepatocyte and adipocyte glucose uptake, respectively.

The first definitive link between GIP and obesity came with the observations that hereditary obesity (ob/ob) mice have much larger amounts of GIP in their gut mucosa than do their thin littermates [22, 59]. Later it was shown that oral glucose and fat produce an exaggerated plasma GIP response in obese people, whether they are diabetic or not, and that the inhibitory effect of insulin upon fat-stimulated GIP secretion is attenuated or lost. This insensitivity to negative feedback control by insulin on GIP secretion can be induced in healthy, normal-weight subjects by feeding them a high-fat diet for a month or so [54, 60, 61] before they become obese. The anomalies of GIP secretion are therefore not specifically caused by adiposity but by the diet that obese people eat.

Experimentally, animals fed various 'confectionery style' diets, differing in composition but not in total energy, show induction of GIP production and secretion in response to diets that are high in fat but not to diets that are high in sugar content [22]. Weight gain is significantly greater in animals [22, 62], and experimentally in humans [25], fed a high-fat diet than in those fed an equicaloric carbohydrate diet. Weight loss, on the other hand, is no different in obese people fed equicaloric high-fat or high-carbohydrate diets in clinical trials [63], which is not altogether surprising since weight gain (fat deposi-

tion) and weight loss (fat mobilisation and utilisation) are not the opposite of one another and do not involve the same processes.

There have been comparatively few attempts to produce obesity (as opposed to weight gain) experimentally in human volunteers [25]. Despite large increases in dietary energy intake, volunteers appear to reach a plateau when the maximum intake of energy they are able to achieve is balanced by energy expenditure, which is not associated with excessive exercise. The numbers involved in the only major study so far reported was small and therefore too much should not be read into the results. Nevertheless, the data support the suggestion that energy derived from dietary fat is more adipogenic than that derived from carbohydrates or proteins (or alcohol).

Experiments on healthy normal-weight human volunteers showed that after consumption of a fat-supplemented diet for 1 month plasma GIP responses to standard oral carbohydrate and fat loads are exaggerated and the normal inhibitory effect of exogenous insulin upon fat-stimulated GIP release is attenuated. Thus, amongst energy-providing foods, long-chain triglycerides currently seem uniquely able to induce non-insulin suppressible hyperGIPaemia. This may play a role in the hyperinsulinaemia observed in such conditions as spontaneous obesity where normal feedback control by insulin upon fat-induced GIP secretion is deranged.

A bizarre and totally unexpected property of GIP is its ability, under certain circumstances, to interact with GIP receptors on adrenocortical cells to stimulate cortisol production and produce a condition known as food-induced Cushing's syndromes [64]. Whether this role of GIP is only and purely a pathological phenomenon or has physiological significance has yet to be ascertained. It may be relevant to the type of obesity referred to as the metabolic syndrome, which, as Vague [11] and others pointed out many years ago, has many features resembling those of Cushing's syndrome [11, 17].

Bray et al. [16] have discussed the adrenal dependence of obesity. The possible involvement of cortisol in the preferential deposition of adipose tissue in the omentum and genesis of insulin resistance through activation of a specific isoform of the enzyme 11 β -hydroxysteroid dehydrogenase that converts inactive cortisone into active cortisol has also been raised. It is however still unresolved.

The postulated role for GIP in the genesis of obesity received an enormous fillip from the ground-breaking work by Miyawaki et al. [23, 58] with GIP-R knockout mice (Gipr $-/-$). These animals exhibit remarkably few, if

any, adverse effects when fed a normal (mouse) diet. But when fed an obesity-producing high-fat diet [65, 66], they do not become obese whereas their control wild-type mice fed the same diet in the same amounts do. A similar though not as complete inhibition of fat deposition in adipose tissue is observed in hyperphagic genetically obese mice (formerly referred to as ob/ob but now more appropriately as lep^{ob}/lep^{ob}) that have been rendered GIP-R deficient by selective crossbreeding [23, 67] with GIP-R knockout mice.

The inability of Gipr $-/-$ mice to become obese in response to a high-fat diet was shown not to be due to a reduction in food intake – indeed this was virtually identical to that of the Gipr $+/+$ controls – but to an increase in resting energy expenditure that was not reflected in any of the other metabolic parameters, such as body temperature, that were measured. Put differently, GIP action permits more efficient use and storage of energy intake. It is admirably suited, therefore, to fulfil the role of an agent that enables energy to be stored efficiently, as fat in adipose tissue, when food is plentiful and to release it as fatty acids when food is in short supply [40]. The alternative is to oxidise fatty acids and carbohydrates that are surplus for immediate requirements through the wasteful processes of thermogenesis and futile cycling of metabolites. GIP's lipogenic effect appears to be exerted minimally, if at all, through its ability to stimulate insulin secretion but mainly through a direct effect upon adipocytes [58].

Other Gastro-Intestinal Hormones Involved in Energy Balance

Whilst the key role played by GIP in the pathogenesis of obesity can now be considered as virtually established, offering new possibilities for its prevention and treatment [23, 46, 51, 68, 69], the role of other more recently discovered gastro-intestinal hormones cannot be ignored. Three – ghrelin, GLP-1 and peptide YY – must be mentioned in particular (fig. 2).

Ghrelin is certainly one of the most important hormones involved in appetite control to originate within the gastro-intestinal tract. It is a 28AA residue polypeptide produced by endocrine cells situated mainly by the oxyntic glands within the gastric mucosa. It was discovered as the natural ligand of the receptor for a synthetic growth hormone-stimulating agent. Its administration to laboratory rodents had – in view of its growth hormone stimulatory effects – the totally unexpected effect of making them obese [70]. Its concentration in blood rises during fasting and falls after the ingestion of food. It is cur-

Fig. 2. Simplified schematic representation of factors leading to obesity in humans (adapted and modified from Marks [40]). PYY = Peptide YY.

rently attracting most attention through its ability to influence appetite and the feeding centre [71, 72]. Its role in stimulating appetite and feeding behaviour is well established and thought to be one of the ways in which gastric bypass surgery serves to reduce obesity.

Peptide YY, another hormone produced in the gastrointestinal tract – as well as in the hypothalamus and certain other organs – has the opposite effect to ghrelin on appetite and feeding behaviour. When injected directly into the hypothalamus in experimental animals, or parenterally into humans [73], it reduces appetite and food intake from a cafeteria buffet. Its blood concentration rises in response to the ingestion of food and falls during fasting.

GLP-1 has displaced glucagon as the most potent insulin secretagogue known – but only in the presence of mild to moderate hyperglycaemia. It has, like GIP with which it shares incretin properties, attracted attention as a major player in the entero-insular axis [45, 46]. Its secretion is stimulated by the ingestion of food but does not require their active absorption [74] and occurs before the ingested food has reached the site of its production in the lower jejunum and ileum. Unlike GIP, the basal concentration of GLP-1 is not raised in obese subjects in whom – in absolute contrast to GIP – it is said to show a diminished response to food [75]. GLP-1 does however have an appetite-suppressant effect when injected direct-

ly into the hypothalamus of experimental animals. It has been suggested that the reduced GLP-1 response to nutrients shown by many obese subjects may, through failure to inhibit the appetite centre, contribute to their obesity. It is, however, still uncertain whether GLP-1 does contribute to appetite control when released from the intestine or injected parenterally in humans, except through its effect on delaying gastric emptying. If it does, the greater stimulatory effect of slowly digested over rapidly digested carbohydrates on GLP-1 secretion [74] could explain the beneficial effect claimed for low GI diets on obesity and type 2 diabetes. However, this benefit has not been established and must therefore be considered no more than speculation.

For a fuller discussion of modern views on the regulation of the appetite centre and feeding behaviour, readers are referred to the review by Dagogo-Jack [76].

Potential Therapeutic Applications of the New Knowledge of Gastro-Intestinal Endocrinology

The composition of the modern energy-dense, high-fat, high readily available carbohydrate diet – the so-called ‘western-style’ diet – is ideally suited to produce obesity in people with the appropriate genetic make-up. Its palatability is another important consideration. The almost uniform failure of enforced dietary changes to produce lasting [77], as opposed to temporary, benefit in the avoidance and treatment of obesity is equalled by a similar failure of most drug treatments. Currently some success is being claimed for rimonabant, a ligand for cannabinoid receptors in the brain [78], and for orlistat, an intestinal (pancreatic) lipase inhibitor. This produces up to a 9% weight loss that is sustained for as long as the drug is taken – but which is generally limited by its cost or other reasons [79]. Orlistat might reasonably be expected to reduce GIP secretion in response to dietary fat since active absorption is necessary for this effect to be manifest; however, this was not established in the only study that has been published on this subject so far [79].

The forbidding first of one and then of another type of food – especially so-called fast foods – though currently politically correct, has been uniformly unsuccessful in achieving permanent weight loss. Genuine lifestyle changes involving an increase in physical activity and decrease in dietary energy intake offer the best prospect of prevention and treatment of obesity but not in those with a strong genetic propensity to develop it, in whom the compulsion to eat is overwhelming [24, 80].

Peptide YY has been shown experimentally to reduce food intake in humans under double-blind conditions – seemingly without adverse effects – and it, or its more stable analogues, are currently under active consideration for the treatment of intractable obesity [73]. Oxyntomodulin is another intestinal hormone that is released from the lower small intestine in response to food and is a member of the glucagon superfamily of peptides [45]. Though discovered many years ago, oxyntomodulin has had no major physiological function assigned to it [81]. Nevertheless, it has recently been shown experimentally to reduce appetite and facilitate weight loss in obese subjects [82]. The need to give it by injection immediately prior to each meal limits its potential use for this purpose.

GIP, of all the gastro-intestinal hormones, has the best claim to a role in the pathogenesis of obesity and offers the greatest hope of producing an effective therapy for it. Genetic manipulations such as those produced in rodents by Miyawaki et al. [23] are a long way, if ever, from being practicable in men [83]. More promising is the possibility of blocking the effect of or interfering with the release of GIP [47, 68, 69] whose properties make it an ideal tool for deriving the maximum benefit from the energy content of food in an environment with limited and intermittent access to food. They become a menace when food, especially food rich in fat and readily assimilable carbohydrate, is plentiful and readily available. Results in vitro and in laboratory rodents are encouraging, but no results have yet been obtained in human beings.

Conclusion and Summary

Obesity is an extremely complex and varied syndrome with a simple final common pathway – namely excessive energy intake over energy expenditure – and an equally simplistic solution that involves life-long voluntary reduction of food intake, but which is totally impractical in all but a tiny minority of people. The compulsion to eat is the most primitive of all behaviour patterns. In higher animal forms, it is driven by centres within the hypothalamus which are inhibited or stimulated by a variety of neuronal and humoral agents – the newest of which, obestatin, was isolated within the past 6 months [84].

Superimposed on this primary control mechanism is another that determines the disposition of the food energy ingested. GIP is one of these agents and appears to have an important role in conserving ingested food energy and storing it in adipose tissue. Its biological properties predispose to the development of obesity when food energy is plentiful and to conservation of energy when food is in short supply. By inhibiting the secretion or, more likely, its biological effects upon the tissues it may be possible to prevent or ameliorate obesity without affecting appetite as most treatments in the past have done.

The question of which comes first, overeating from overstimulation or under-inhibition of the appetite centres, leading to secondary induction of hyperinsulinism and hyperGIPaemia, or primary overproduction of these adipogenic hormones as occurs very rarely in insulinoma, awaits elucidation.

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