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# Pancreatic signals controlling food intake; insulin, glucagon and amylin

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The control of food intake and body weight by the brain relies upon the detection and integration of signals reflecting energy stores and fluxes, and their interaction with many different inputs related to food palatability and gastrointestinal handling as well as social, emotional, circadian, habitual and other situational factors. This review focuses upon the role of hormones secreted by the endocrine pancreas: hormones, which individually and collectively influence food intake, with an emphasis upon insulin, glucagon and amylin. Insulin and amylin are co-secreted by B-cells and provide a signal that reflects both circulating energy in the form of glucose and stored energy in the form of visceral adipose tissue. Insulin acts directly at the liver to suppress the synthesis and secretion of glucose, and some plasma insulin is transported into the brain and especially the mediobasal hypothalamus where it elicits a net catabolic response, particularly reduced food intake and loss of body weight. Amylin reduces meal size by stimulating neurons in the hindbrain, and there is evidence that amylin additionally functions as an adiposity signal controlling body weight as well as meal size. Glucagon is secreted from A-cells and increases glucose secretion from the liver. Glucagon acts in the liver to reduce meal size, the signal being relayed to the brain via the vagus nerves. To summarize, hormones of the endocrine pancreas are collectively at the crossroads of many aspects of energy homeostasis. Glucagon and amylin act in the short term to reduce meal size, and insulin sensitizes the brain to short-term meal-generated satiety signals; and insulin and perhaps amylin as well act over longer intervals to modulate the amount of fat maintained and defended by the brain. Hormones of the endocrine pancreas interact with receptors at many points along the gut–brain axis, from the liver to the sensory vagus nerve to the hindbrain to the hypothalamus; and their signals are conveyed both neurally and humorally. Finally, their actions include gastrointestinal and metabolic as well as behavioural effects.

**Keywords:** glucose; meals; satiety; pancreatic polypeptide; somatostatin

## 1. INTRODUCTION

The normal control of food intake and body weight by the brain relies upon the detection and integration of signals reflecting energy stores and fluxes and their interaction with myriad inputs related to food palatability and gastrointestinal handling as well as social, emotional, circadian, habitual and other situational factors. This review focuses upon the role of hormones secreted by endocrine cells in the islets of Langerhans in the pancreas, hormones which individually and collectively influence food intake, with an emphasis upon insulin, glucagon and amylin.

There are several categories of peripherally arising signals that influence food intake (Woods *et al.* 1998; Schwartz *et al.* 2000). One category includes the signals generated during meals that influence satiation (i.e. signals that contribute to the perception of fullness and the termination of an ongoing meal) and satiety (i.e. signals that function to prolong the interval until hunger or the onset of the next meal). These acutely acting signals are collectively called 'satiety signals' in this review, and the prototypical example is cholecystonin (CCK). Satiety signals are either relayed to the hindbrain by sensory nerves or else stimulate the hindbrain directly. A second category includes hormones whose secretion is proportional to the amount of fat in the body, and it includes insulin from the pancreatic islets and leptin from adipose tissue, stomach and elsewhere. These adiposity signals are transported from the circulation into the hypothalamus in the forebrain. Satiety signals and adiposity signals arising from the endocrine pancreas, as well as their interactions with other controls of food intake, are the topic of this review. Other peripherally arising signals include steroid hormones from the gonads and adrenal cortex, cytokines and nutrients and they are the topics of other articles in this volume.

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## 2. OVERVIEW OF THE CONTROLS OVER FOOD INTAKE

For body weight (body fat, actually) to remain stable over time, energy intake (food intake) must match energy expenditure (the sum of excreted energy, heat loss and physical work). Any deviation from this equilibrium will result in weight gain or loss. Humans and most mammals take in energy in discrete episodes or meals. For most of us, the impetus to begin a meal is rarely if ever based on a biological deficit or need such as insufficient glucose or other energy source in some critical tissue. Rather, the timing of when specific meals are initiated is based on any of several psychological factors such as habit, time of day, the social situation, convenience and others (Woods 1991; Woods & Strubbe 1994; Strubbe & Woods 2004). Because meal initiation relies on psychological as opposed to more purely physiological factors, if body weight is indeed regulated via a linking of energy intake to energy expenditure, the regulatory process must logically be manifest as a control over how many calories are consumed once a meal begins; i.e. on meal size. Consistent with this, many signals generated during meals are proportional to the number of calories consumed, and some of these secretions function as satiety signals to the central nervous system to help limit meal size (see reviews in (Kaplan & Moran 2004; Moran & Kinzig 2004; Woods 2004; Strader & Woods 2005)). Pancreatic islet hormones in this category include glucagon and amylin and possibly insulin as well.

In contrast to satiety signals that are secreted mainly during meals, adiposity signals are tonically active, providing an ongoing message to the brain proportional to total body fat. When an individual's weight changes, the amount of insulin and leptin secreted into the blood changes in parallel, and this is reflected as an altered adiposity signal reaching the brain. As discussed in detail below in §5*a* the net effect is a change of the brain's sensitivity to satiety signals. For example, when an individual is food restricted or voluntarily diets sufficiently to lose weight, the consequent reduction of leptin and insulin renders brain circuits that control meal size less sensitive to meal-generated satiety signals. This means that more calories than normal must be consumed before a sufficient signal is generated to stop a meal. This situation persists until body weight returns to normal. Conversely, if an individual gains excess weight, the increased insulin and leptin signal in the brain results in increased sensitivity to satiety signals. Smaller meals are consumed until the excess weight is lost.

## 3. THE ENDOCRINE PANCREAS

The endocrine pancreas comprises of isolated islets containing endocrine cells that are dispersed within the exocrine pancreas. In humans, there are around one million islets, totalling one gram of tissue. Most islets contain at least three types of cells, A-cells that secrete glucagon, B-cells that secrete insulin and amylin and D-cells that secrete somatostatin. Other, distinct, islets contain mainly F-cells that secrete pancreatic polypeptide (PP). Although these individual hormones have numerous functions, the generalization can be made that a major function of the pancreatic islets is the control of glucose homeostasis. Insulin and glucagon are perhaps most important in this regard, with insulin being the primary determinant of glucose removal from the blood and the suppression of glucose secretion by the liver. Glucagon on the other hand is a primary stimulant of glucose production and secretion by the liver. Amylin is co-secreted with insulin, and its best known functions are reducing food intake and gastric emptying, and inhibiting pancreatic glucagon secretion and pancreatic and gastric enzyme secretion.

Like the other endocrine pancreatic hormones, PP exerts a variety of regulatory functions, including modulation of gastric motility, pancreatic exocrine secretion and eating, and many of these effects appear to be related to a modulation of cholinergic output. The primary function of pancreatic somatostatin (which is also made in the gastrointestinal tract and hypothalamus) appears to be to provide a local modulatory influence, mainly inhibition, of the secretion and/or activity of most metabolic processes, including the secretion of insulin, amylin and glucagon (Krantic *et al.* 2004; Guillemin 2005).

## 4. SOMATOSTATIN, PANCREATIC POLYPEPTIDE AND INGESTIVE BEHAVIOUR

Acute administration of somatostatin to animals either systemically (Lotter *et al.* 1981; Levine & Morley 1982) or directly into the brain (Vijayan & McCann 1977; Lotter *et al.* 1981) reduces food intake. As is the case with several other satiety signals, the ability of systemic somatostatin to reduce food intake requires an intact vagus nerve (Levine & Morley 1982). Chronic infusion of somatostatin, on the other hand, is without effect on food intake, body weight or other parameters (Lins *et al.* 1980).

The secretion of PP during meals requires an intact vagus nerve and plasma PP levels are directly proportional to the caloric load consumed. Systemic administration of PP to normal and obese mice reduces food intake (Malaisse-Lagae *et al.* 1977; Asakawa *et al.* 2003) and body weight (Malaisse-Lagae *et al.* 1977), and this is thought to be due to stimulation of Y4 receptors in the dorsal vagal complex, including the area postrema (AP), the nucleus of the solitary tract (NTS) and the dorsal motor nucleus of the vagus (DMV) (Whitcomb *et al.* 1997). PP presumably modulates gastrointestinal function via the actions of these receptors on vagovagal reflexes because the NTS and DMV are the primary sensory nucleus and the site of vagal lower motor neurons, respectively.

Transgenic mice that over-express PP are hypophagic and lean (Ueno *et al.* 1999). Their plasma PP levels are 20-fold higher and increase twice as much in response to a meal as in normal wild-type mice. The food intake suppression of PP-overexpressing mice is accompanied by a decrease in gastric emptying and both can be counteracted by systemic administration of PP antibodies. Systemic PP administration also reduces food intake in humans (Berntson *et al.* 1993; Batterham *et al.* 2003). In contrast to its peripheral action, when PP is administered directly into the brain, it increases food intake (Clark *et al.* 1984; Flynn *et al.*

1999) and stimulates rather than inhibits gastric emptying. It is presently unclear which central Y receptors mediate the orexigenic action of PP. Interestingly, however, Y4-receptor immunoreactivity is abundant on orexin neurons in the lateral hypothalamus (Campbell *et al.* 2003).

## 5. INSULIN AND INGESTIVE BEHAVIOUR

Historically, insulin was considered to act entirely in the periphery since it is too large a peptide to cross the blood–brain barrier and since neurons do not require insulin in order to take up and oxidize glucose for energy (Seaquist *et al.* 2003). The best-known action of insulin is to increase glucose uptake in most peripheral tissues, consequently lowering the level of glucose in the blood. Diabetic patients take insulin to reduce their hyperglycemia, and a not uncommon side effect of this routine practice is to lower blood glucose to the point of hypoglycemia. However, because hypoglycemia *per se* can elicit hunger and induce eating (MacKay *et al.* 1940; Lotter & Woods 1977), the best-characterized behavioural effect of insulin administration is increased food intake resulting from insufficient glucose reaching the brain. This is not a direct effect of insulin since administering glucose along with insulin does not result in eating (Booth 1968), and since reducing the ability of the brain to utilize glucose for energy by administering non-metabolizable glucose analogues also increases eating (Smith & Epstein 1969; Langhans 1996). The view that the brain *per se* is insensitive to insulin was dispelled by the findings that insulin does in fact enter the brain, that it reacts with specific insulin receptors on neurons, and that it triggers diverse events including reducing food intake and body weight (see reviews in Plum *et al.* 2005; Porte *et al.* 2005).

### (a) *Insulin decreases feeding behaviour*

Plasma insulin is low during fasting (basal condition) and increases mainly during and immediately after meals (prandial condition) or glucose administration (stimulated condition). Basal, prandial and stimulated insulin levels are all direct functions of the amount of white adipose tissue in the body, leaner individuals having lower levels and more obese individuals having higher levels (Bagdade *et al.* 1967; Woods *et al.* 1974; Polonsky *et al.* 1988). The amount of insulin in the plasma (along with the amount of leptin in the plasma since its secretion is also directly proportional to white fat (Considine *et al.* 1996)) may therefore convey an important signal indicating the degree of adiposity to any insulin-sensitive tissue. Indeed, it is now generally accepted that some insulin enters the brain from the circulation, thereby providing a key negative feedback signal in the regulation of body fat (figure 1). When an individual loses weight, less insulin is secreted and less insulin consequently reaches insulin receptors in the hypothalamus and elsewhere in the brain. Because insulin in the brain reduces food intake, food intake consequently increases until body weight (and the insulin signal) is restored. Conversely, when an individual overindulges to the point of gaining body weight, the insulin signal increases, reducing food intake until the weight is lost. Insulin (like leptin) is

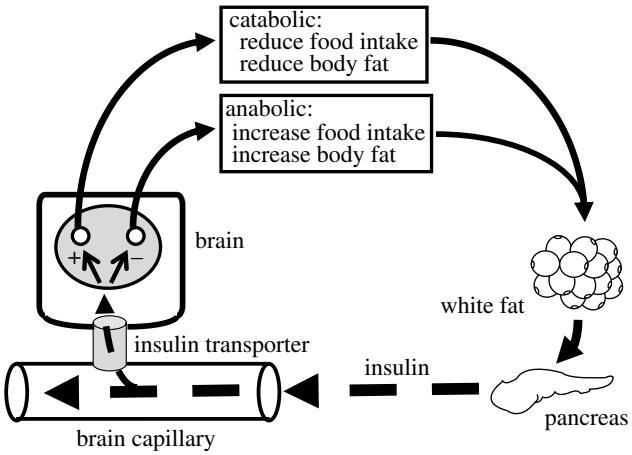


Figure 1. Insulin is secreted into the blood from the pancreas in direct proportion to the amount of fat stored in white adipose tissue. As it circulates through brain capillaries, a small amount of insulin is transported into the brain where it acts on insulin receptors on neurons with either net catabolic or anabolic activity, for example in the arcuate nucleus of the hypothalamus. These neurons in turn influence energy homeostasis (food intake and energy expenditure) and ultimately the amount of fat stored in the body by exerting a net catabolic action.

therefore an important adiposity signal whose activity is integrated with diverse other information to determine food intake; and both hormones fit reasonably well with the concept of a fat-related lipostatic signal to the brain as proposed by Kennedy more than a half a century ago (Kennedy 1953).

When exogenous insulin is administered directly into the brain, near or directly within the mediobasal hypothalamus, animals behave as if they have excess fat in the body; i.e. they reduce their food intake and lose weight (see reviews in (Schwartz *et al.* 1992; Woods *et al.* 1995; Woods 1996; Woods & Seeley 2001)). The response is dose-dependent (Woods *et al.* 1979; Riedy *et al.* 1995), has been documented in numerous species including non-human primates, and is not secondary to illness or incapacitation (Chavez *et al.* 1995*b*). Conversely, when insulin antibodies are administered in or near the mediobasal hypothalamus, animals overeat and gain weight (Strubbe & Mein 1977; McGowan *et al.* 1992). When insulin levels in the brain are held constant for long intervals by means of slow, steady local infusions, body weight is maintained and defended at a level determined by the dose of insulin administered (Woods *et al.* 1979; Chavez *et al.* 1995*a*). Although insulin has not been administered directly into the brains of humans, certain formulations of insulin have been administered intranasally to humans with a consequent increase of cerebrospinal fluid but not plasma insulin (Born *et al.* 2002). Humans receiving insulin in this way eat less food and lose body fat (Hallschmid *et al.* 2004*a*,*b*).

Although there are suggestions that the brain is able to synthesize insulin (Gerozissis 2004), the bulk of evidence implies the opposite and it is generally acknowledged that most if not all insulin influencing the brain reaches it via the circulation (Schwartz *et al.* 1994; Woods *et al.* 2003*b*; Banks 2004). Insulin enters the brain via insulin receptor-facilitated transport

through capillary endothelial cells (Baura *et al.* 1993; Banks *et al.* 1997). The process is saturable and selective for insulin. The transport of insulin into the brain is reduced in fasted animals (Strubbe *et al.* 1988), in animals maintained on a high-fat diet (Woods *et al.* 2004; Gotoh *et al.* 2003) and in genetic (Stein *et al.* 1983) and dietary-induced obesity (Israel *et al.* 1993; Kaiyala *et al.* 2000).

Since insulin in the brain ultimately derives from plasma insulin, it should be the case that experimentally induced increases of plasma insulin enter the brain and result in reduced food intake and body weight. The problem, as discussed above, is that experimentally or therapeutically induced increases of plasma insulin typically result in hypoglycemia and a consequent increased tendency to eat. However, when insulin is administered systemically at very low doses that do not elicit hypoglycemia, animals do in fact reduce their food intake (Anika *et al.* 1980; Vanderweele *et al.* 1982). Alternatively, when sufficient glucose is administered simultaneously with systemic insulin to circumvent hypoglycemia, animals also eat less (Nicolaidis & Rowland 1976; Woods *et al.* 1984). In these experiments it cannot be determined whether the insulin is acting in the brain or the periphery to reduce food intake. For whereas increases of plasma insulin are manifest within a few minutes in the brain during meals or following an intravenous insulin infusion (Steffens *et al.* 1988; Strubbe *et al.* 1988), centrally administered exogenous insulin usually reduces food intake with a longer latency (Plata-Salaman & Oomura 1986). There is also evidence that insulin acts in the liver to reduce food intake (Surina-Baumgartner *et al.* 1995), perhaps interacting with glucose (Langhans *et al.* 2001). Intrameal hepatic portal infusions of insulin antibodies increase meal size, implying that the normal prandial increase in insulinemia is a necessary part of meal termination (Surina-Baumgartner *et al.* 1995). Although these studies did not disclose the site of origin of the anti-satiating effect of insulin antibodies, the rapid onset of action coupled with the finding that subdiaphragmatic vagotomy eliminates the inhibition of food intake elicited by a low dose of systemic insulin (Vanderweele 1993) is consistent with an abdominal site of action of insulin in satiety. Despite the consistent increase in meal size in response to hepatic portal insulin antagonism, insulin infusions failed to reduce meal size consistently under the same conditions (Surina-Baumgartner *et al.* 1995). When appropriate doses of insulin and glucose were administered together, however, meal size was reliably reduced (Langhans *et al.* 2001), consistent with the hypothesis that the acute satiating effect of systemic insulin depends on the presence of glucose.

Insulin receptors are expressed in many areas of the brain (Figlewicz *et al.* 1985; Corp *et al.* 1986), with high concentrations in the mediobasal hypothalamus, especially the arcuate nucleus (Plum *et al.* 2005), which also expresses the most active form of the leptin receptor (Baskin *et al.* 1999). This region is thought to mediate most of insulin's catabolic action.

Insulin and leptin act in part by increasing the sensitivity of the brain to meal-generated satiety signals. As discussed above, these signals, including amylin and

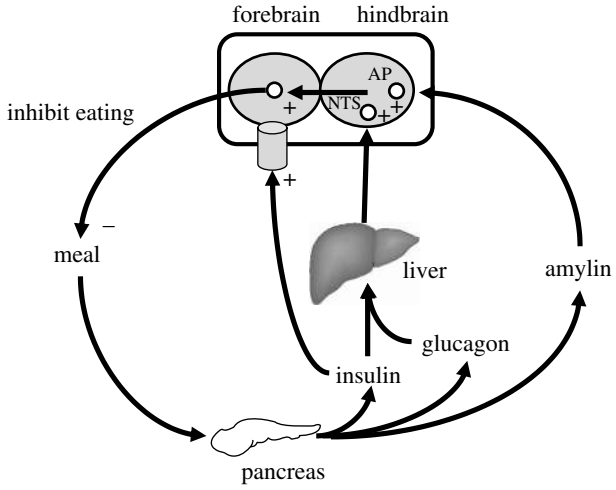


Figure 2. Insulin, glucagon and amylin are all secreted from the endocrine pancreas, and all participate in the regulation of energy homeostasis. Insulin acts at both the liver and the forebrain to reduce energy intake as well as to suppress hepatic glucose production. Glucagon acts mainly at the liver where it increases glucose production while generating a signal to reduce energy intake that is relayed to the hindbrain. Amylin acts directly at the hindbrain to reduce energy intake. NTS, nucleus of the solitary tract; AP, area postrema; + indicates stimulation.

glucagon (figure 2) as well as CCK, are secreted during meals from endocrine cells in both the pancreas and the gastrointestinal tract (Moran 2004; Woods 2004; Strader & Woods 2005). Their cumulated message is integrated within the brain, where it interacts with many other factors (including the signal provided by adiposity signals) to terminate the meal and contribute to the sensation of satiety. When the insulin (Figlewicz *et al.* 1986; Riedy *et al.* 1995) or leptin (Matson *et al.* 1997; Emond *et al.* 1999, 2001; Matson & Ritter 1999; Ladenheim *et al.* 2005; Morton *et al.* 2005) signal is experimentally increased locally within the brain, the ability of CCK and other satiety signals to reduce meal size is increased. Likewise, when the adiposity signal is lowered, the ability of satiety signals to reduce meal size is decreased (McMinn *et al.* 2000). Thus, adiposity signals contribute to the regulation of body weight by influencing the amount of food eaten during individual meals. When an individual is underweight, the reduced adiposity signal allows larger meals to be consumed until weight is restored and vice versa.

To summarize, increased insulin in the mediobasal hypothalamus provides a signal that ample or excess energy is available in the body, and one consequence is a reduction of the amount of energy subsequently ingested. Simultaneously, the increased hypothalamic insulin signal also elicits a vagal reflex to the liver to suppress the production of glucose (Obici *et al.* 2002*c*). Increased insulin (and probably leptin) is therefore analogous to other signals indicating a surfeit of energy, such as an increase of certain lipids (Davis *et al.* 1981; Obici *et al.* 2002*b*) or glucose (Levin *et al.* 2004) locally within the hypothalamus; and there is evidence that overlapping intracellular signalling pathways mediate the overall catabolic response to these diverse metabolic signals (Levin *et al.* 2002; Niswender & Schwartz 2003; Lam *et al.* 2005*a*,*c*; Porte *et al.* 2005; Seeley & York 2005).

### (b) *Disruptions of central insulin signalling*

Individuals with insulin-dependent diabetes mellitus (IDDM) are hyperphagic. They are not obese because insulin is required for adipocytes to store fat, such that the excess calories consumed are wasted via inefficient utilization as well as via excretion in the urine. When insulin is administered locally into the brain of animals lacking insulin, their hyperphagia is attenuated with no change in other diabetic symptoms (Sipols *et al.* 1995). Mice lacking insulin receptors selectively in neurons (Brüning *et al.* 2000), and rats with reduced insulin signalling locally in the hypothalamus (Obici *et al.* 2002*a*), have increased food intake and an obese phenotype. Thus, accurate sensing of insulin by hypothalamic receptors is necessary for effective control of food intake, and this is also true of normal control of hepatic glucose output (Lam *et al.* 2005*b*). Mice lacking insulin receptors are hyperglycemic and have a short life span (Okamoto & Accili 2003). Genetic rescue of insulin receptors in the pancreas and liver ameliorates but does not normalize the syndrome (Okamoto *et al.* 2004), and when the insulin receptor is additionally rescued in the brain, the mice are normoglycemic (Okamoto *et al.* 2004). The important point is that insulin signalling in the hypothalamus is necessary for normal energy homeostasis.

Analogous to insulin receptors in other tissues, hypothalamic insulin receptors are linked to an intracellular signalling cascade utilizing insulin receptor substrate-phosphatidylinositol 3-OH kinase (IRS-PI3K), and when these enzymes are stimulated directly by an insulin mimetic that bypasses the extracellular portion of the insulin receptor, animals eat less and lose weight (Air *et al.* 2002) and have reduced hepatic glucose production (Obici *et al.* 2002*c*). Administering drugs that block the IRS-PI3K pathway locally in the arcuate nucleus prevents insulin from exerting its catabolic effect (Niswender *et al.* 2003). Although most tissues, including many brain cells, use IRS-1, arcuate neurons and pancreatic B-cells use IRS-2 (Torsoni *et al.* 2003). Mice lacking IRS-2 have severe obesity and hyperglycemia, and this can be reversed by inserting the *IRS-2* gene uniquely into the brain (Burks *et al.* 2000; Kubota *et al.* 2004; Lin *et al.* 2004). The implication from all of these experiments is that the insulin signalling system in the hypothalamus controls many aspects of energy homeostasis and that disruptions of the signalling cascade at any point can lead to overeating, obesity and glucose dysregulation.

As discussed above, plasma insulin is low during weight loss or fasting, and the entry of insulin into the brain is disproportionately decreased even further in such individuals (Owen *et al.* 1974; Strubbe *et al.* 1988). This is adaptive since when available energy is low, circulating insulin has less access to key receptors in the hypothalamus thereby allowing larger meals to be consumed once food becomes available; and when available energy is high, insulin more readily enters the brain and limits food intake.

Rats fed a high-fat diet have central insulin resistance (Arase *et al.* 1988; Chavez *et al.* 1996; Woods *et al.* 2004; Gotoh *et al.* 2003), perhaps contributing to the obesity that often develops. When rats are allowed to select their own mix of macronutrients (protein, carbohydrate and fat), most select a high-fat blend. When insulin is administered into the brain of such rats, food intake and body weight are decreased. However, the intake of dietary carbohydrate and protein is protected as there is a selective reduction of dietary fat (Chavez *et al.* 1996; van Dijk *et al.* 1997). This may occur because when insulin is high, carbohydrate is the preferred source of energy by most tissues such that maintaining carbohydrate intake would make teleological sense. Conversely, when insulin is low, fat is the preferred fuel for most tissues. Consistent with this, animals deficient in insulin become hyperphagic on low-fat diets, spilling off the excess consumed carbohydrate as they obtain enough fat for utilizable energy, but normophagic when offered a diet high in fat (Friedman *et al.* 1983; Chavez *et al.* 1998).

An important point from this literature is that the ability of insulin to exert its central catabolic action interacts with body fat and its metabolism. It also interacts with the location of fat in the body. Fat distribution differs between males and females. On average, men carry more visceral and less subcutaneous fat, whereas the converse is true of women (Wajchenberg 2000). Body fat distribution in turn is related to the risk for developing the metabolic syndrome, with visceral obesity having a substantially higher risk than subcutaneous obesity. Hence, the metabolic co-morbidities of obesity are more frequent in men (Bjorntorp 1997; Wajchenberg *et al.* 2002). The relative secretion of leptin and insulin also correlates with fat distribution. Insulin directly correlates with visceral fat and is therefore a risk factor for the metabolic syndrome, whereas leptin correlates better with subcutaneous fat and does not carry the same metabolic risk (Woods *et al.* 2003*a*). Insulin is therefore a more relevant adiposity signal in males and leptin a more relevant adiposity signal in females. Consistent with this, the male brain is relatively more sensitive to the catabolic action of insulin than the female brain (Clegg *et al.* 2003; Hallschmid *et al.* 2004*b*), whereas the female brain is relatively more sensitive to leptin (Clegg *et al.* 2003; Woods *et al.* 2003*a*).

### (c) *Central neural networks influenced by insulin*

There are many excellent reviews of the central pathways influenced by insulin and leptin (Woods *et al.* 1998; Elmquist *et al.* 1999; Ahima *et al.* 2000; Schwartz *et al.* 2000; Cone *et al.* 2001; Havel 2002; Porte *et al.* 2002, 2005; Seeley & Woods 2003; Flier 2004; Schwartz & Porte 2005) and they need not be reiterated here. The important features are that the critical receptors are in the mediobasal hypothalamus and especially the arcuate nucleus, and that parallel anabolic and catabolic circuits are both tonically active and both influenced by adiposity as well as many other signals. The presence of opposing hypothalamic circuits for controlling energy homeostasis enables rapid and fine-tuned control over energy homeostasis since the brain can simultaneously turn up one system (e.g. catabolic or anabolic) while turning down the other. Insulin and leptin cause a net reduction of activity in hypothalamic anabolic circuits and a net increase of activity in hypothalamic catabolic circuits.

It is axiomatic that the brain exercises regulatory control over body fat content, and that this is manifest at least partly via the control of food intake. It is just as obvious that the brain influences blood glucose levels as well, in part via direct control of autonomic nervous system projections to the pancreatic islets and liver. Only recently, however, has it become recognized that the same or closely allied neurons in the hypothalamus control both food intake and the impact of islet hormones on hepatic glucose production, and that the same receptors and signals evidently control both responses.

As reviewed above, when insulin is administered near or directly into the arcuate, animals become hypophagic, and when insulin is low or absent in the brain, animals become hyperphagic, and this can be attenuated by local administration of insulin into the brain (Sipols *et al.* 1995). Increased insulin in the arcuate also reduces hepatic glucose production via the vagus nerve (Obici *et al.* 2002*c*; Pocai *et al.* 2005); likewise, arcuate administration of oleic acid also reduces both food intake and hepatic glucose production (Obici *et al.* 2002*b*; Lam *et al.* 2005*b*). Thus, molecules that signify ample available energy (insulin or certain fatty acids) initiate a signal to the liver to stop producing so much glucose while simultaneously sending a message to eat less food.

Evidence suggests that normal control of hepatic glucose output relies on an adequate insulin signal both locally in the liver as well as within the hypothalamus, and that an adequate fatty acid signal locally within the hypothalamus is also important. When either signal is compromised in the brain, animals gain excess weight and become systemically insulin resistant (Brüning *et al.* 2000; Obici *et al.* 2002*c*; Okamoto *et al.* 2004; Lam *et al.* 2005*b*), these being two key symptoms of the metabolic syndrome. Leptin elicits comparable actions as insulin in the hypothalamus (Niswender & Schwartz 2003; Munzberg & Myers 2005) although it should be noted that the way the two adiposity signals innervate specific arcuate neurons differs (Xu *et al.* 2005). As with insulin, leptin in the arcuate reduces food intake and body weight (Campfield *et al.* 1995; Seeley *et al.* 1996), and reduced leptin signalling results in hyperphagia and obesity as well as systemic (Coleman 1978; Zhang *et al.* 1994) and central (Ikeda *et al.* 1986) insulin resistance. Administration of leptin into the brain reverses insulin-deficiency hyperphagia (Sindelar *et al.* 1999) and lessens systemic insulin resistance (Haluzik *et al.* 2004). Hence, convergent signals from insulin and leptin act in the brain to regulate both energy and glucose homeostasis and a defect in either leptin or insulin signalling in the brain can result in overeating, weight gain, insulin resistance and other sequellae of the metabolic syndrome (Porte *et al.* 2005; Schwartz & Porte 2005).

In sum, plasma insulin is a signal that reflects both circulating energy in the form of glucose and stored energy in the form of visceral adipose tissue. Insulin acts directly at the liver to suppress the synthesis and secretion of glucose, and some plasma insulin is transported into the brain where it provides an important and indeed necessary input for the appropriate regulation of both stored energy and glucose secretion by the liver. As occurs in the brain, the liver is also simultaneously influenced by competing signals with regard to glucose secretion since glucagon both stimulates insulin secretion and increases hepatic glucose output.

## 6. AMYLIN AND INGESTIVE BEHAVIOUR

Islet amyloid polypeptide or amylin, is co-secreted with insulin from pancreatic B-cells. Whereas with regard to food intake, insulin functions mainly as an adiposity signal and glucagon functions mainly as a satiety signal, amylin has characteristics of both kinds of signal. Like insulin, plasma amylin levels are low during fasting and increase during meals and following glucose administration, and the levels are all directly proportional to body fat. Amylin and insulin are normally co-secreted in a fixed molecular ratio (insulin to amylin) of between ten and one hundred. Obesity, diabetes mellitus, pancreatic cancer and certain pharmacological interventions all tend to increase the amount of amylin relative to insulin.

### (a) *Amylin as a satiety signal*

Eating results in a rapid increase in plasma amylin that is directly proportional to meal size (Butler *et al.* 1990; Moore & Cooper 1991; Young & Denaro 1998). Administration of exogenous amylin prior to a meal dose-dependently reduces food intake in rats and mice (Chance *et al.* 1991; Morley & Flood 1991; Lutz *et al.* 1994, 1995; Morley *et al.* 1994; Arnelo *et al.* 1996*a*), mainly due to a reduction in meal size (Lutz *et al.* 1995, 2001*b*; Reidelberger *et al.* 2002; Mollet *et al.* 2004), without producing a conditioned taste aversion (Chance *et al.* 1992; Lutz *et al.* 1995; Morley *et al.* 1997; Asarian *et al.* 1998; Rushing *et al.* 2002). The effect of exogenous amylin on meal pattern is therefore similar to that of CCK. As discussed below, plasma amylin is thought to function as a satiety signal by accessing receptors in the AP in the hindbrain, a region with a relatively permeable blood–brain barrier. Nonetheless, some plasma amylin probably does enter the brain via facilitated transport through the blood–brain barrier (Banks *et al.* 1995), and when amylin is administered directly into the lateral or 3rd-cerebral ventricle, it elicits a potent and long-lasting anorectic effect at very low doses (Rushing *et al.* 2002). Consistent with this, blockade of central amylin receptors produces a long-lasting increase in food intake, body weight and body adiposity (Rushing *et al.* 2001).

### (b) *Disruption of amylin signalling*

Several amylin antagonists are available (e.g. amylin 8-37, AC 253 and AC 187), and when administered prior to meals either systemically or directly into the AP, each attenuates the anorectic action of exogenous amylin (Lutz *et al.* 1996, 1997*b*, 2000; Mollet *et al.* 2004; Reidelberger *et al.* 2004) and increases food intake when administered alone (Grabler & Lutz 2004; Mollet *et al.* 2004; Reidelberger *et al.* 2004). These data strongly imply a physiological role of endogenous amylin in the regulation of food intake, specifically in the regulation of meal size. Consistent with this, mice

lacking amylin have a significantly increased rate of body weight gain and slightly increased cumulative food intake relative to controls (Gebre-Medhin *et al.* 1997, 1998; Lutz 2005). Little is known of the post-receptor intracellular signalling mechanisms elicited by amylin, although its anorectic action has been linked to the formation of cGMP in the AP (Riediger *et al.* 2001; Becskei *et al.* 2004).

### (c) *Interactions of amylin with other signals*

Amylin and CCK have been reported to interact synergistically to reduce meal size (Bhavsar *et al.* 1998). While CCK antagonists do not affect the anorectic action of amylin, amylin antagonists attenuate CCK's anorectic action (Morley *et al.* 1994; Lutz *et al.* 1996, 1997*a*, 2000), and the anorectic effect of CCK is almost absent in mice lacking amylin (Mollet *et al.* 2003). These data have been interpreted to indicate that endogenous amylin has a neuromodulatory function within the AP/NTS region of the hindbrain that facilitates or amplifies other satiety signals such as those elicited by CCK that are conveyed to the NTS via afferent vagal nerves (Ritter & Ladenheim 1985; Moran *et al.* 1997; Lutz *et al.* 1998; Mollet *et al.* 2003). This mechanism would therefore be analogous to that by which the adiposity signals insulin and leptin act in the hypothalamus to influence the brain's sensitivity to meal-generated signals.

Amylin and glucose activate the same neurons in the AP (Riediger *et al.* 2002), as do amylin and glucagon-like peptide-1 (GLP-1) (Riediger *et al.* 2002). AP neurons responsive to glucose are also responsive to CCK (Funahashi & Adachi 1993; Wang *et al.* 2000). Perhaps analogous to what occurs in the arcuate nucleus, AP neurons are therefore able to integrate several metabolic and hormonal signals important in the control of energy homeostasis.

### (d) *Central neural circuits stimulated by amylin*

The AP is the predominant site of action of circulating amylin in the brain. Amylin's anorectic action is completely abolished following lesions in the AP/NTS region (Lutz *et al.* 1998, 2001*b*), and amylin dose-dependently stimulates AP neurons in vitro, with a threshold concentration in the range of circulating plasma amylin concentrations (Riediger *et al.* 2001, 2002). Amylin also induces Fos expression in the AP (Rowland *et al.* 1997; Rowland & Richmond 1999; Riediger *et al.* 2001, 2004; Becskei *et al.* 2004), and amylin antagonists that attenuate amylin's anorectic action also eliminate the Fos response in the AP (Riediger *et al.* 2001, 2002, 2004). Finally, when rats are refed after being deprived, there is an increase of Fos in the AP/NTS that is subsequently attenuated in the AP when an amylin antagonist is administered (Riediger *et al.* 2004). The point is that the AP/NTS is able to integrate diverse signals related to meals, and amylin appears to render the region more sensitive to other metabolic signals that reduce food intake.

There is no unique amylin receptor gene. Rather, the functional amylin receptor in the AP (and elsewhere) utilizes a calcitonin receptor (CTR) whose amylin-specificity and affinity are bestowed via the co-expression of one of several receptor activity modifying proteins (RAMPs) (McLatchie *et al.* 1998; Christopoulos *et al.* 1999; Foord & Marshall 1999; Muff *et al.* 1999; Sexton *et al.* 2001; Fischer *et al.* 2002). The prototypical amylin receptor results from the interaction of RAMP 1 or RAMP 3 with the CTR. RAMP1 and RAMP3 mRNA have been co-localized with amylin-induced Fos mRNA in the rat AP (Ueda *et al.* 2001; Barth *et al.* 2004), and most amylin-sensitive AP neurons also express the CTR (Becskei *et al.* 2004).

In addition to the AP/NTS, amylin elicits a strong Fos response in the lateral parabrachial nucleus (lPBN), the central nucleus of the amygdala (CeNA) and the bed nucleus of the stria terminalis (Rowland *et al.* 1997; Rowland & Richmond 1999; Riediger *et al.* 2004). All of these Fos responses are markedly attenuated in AP-lesioned rats (Rowland & Richmond 1999; Riediger *et al.* 2004), implying that the other sites are downstream of direct amylin action in the AP. The NTS and the lPBN are critical relay points for satiety and other signals to reach forebrain areas (Berthoud 2002).

There is no conclusive evidence that peripheral amylin has a direct effect on the hypothalamus. However, fasting-induced Fos activation in lateral hypothalamic neurons that is reversed by refeeding can also be reversed by administering systemic amylin to rats without access to food (Becskei *et al.* 2004). Further, peripheral amylin or its agonist salmon calcitonin down-regulates the expression of both orexin and melanin concentrating hormone (MCH) in the lateral hypothalamus (LHA; Barth *et al.* 2003). Since the LHA is devoid of amylin binding sites (Beaumont *et al.* 1993; Sexton *et al.* 1994; Christopoulos *et al.* 1995), the presumption is that the LHA receives inhibitory input from amylin-activated neurons in the brainstem. As discussed above, LHA neurons expressing orexin and MCH are also inhibited by signals coming from insulin and leptin, whether directly or indirectly.

### (e) *Amylin as an adiposity signal*

Besides having a strong satiating effect, amylin also shares many characteristics with the adiposity signals insulin and leptin, not the least of which is that its levels are highly correlated with body fat (Cooper 1994; Pieber *et al.* 1994; Wimalawansa 1997). When amylin is infused chronically via osmotic minipumps placed in the abdominal cavity, there is a sustained reduction in food intake and body weight gain that is abolished in rats with AP/NTS lesions (Arnelo *et al.* 1996*b*; Lutz *et al.* 2001*b*). Consistent with this, and as discussed above, mice lacking amylin gain weight more rapidly than controls, especially when young (Gebre-Medhin *et al.* 1997, 1998; Lutz 2005). Obese Zucker *fa/fa* rats have dysfunctional leptin receptors. Besides being hyperinsulinemic and hyperleptinemic, these rats are also hyperamylinemic. Administering an amylin antagonist to these rats results in increased food intake, presumably by blocking endogenous amylin (Grabler & Lutz 2004). Amylin may therefore function as an important adiposity signal in these animals since their brains are insensitive to insulin's (Ikeda *et al.* 1986) as well as leptin's catabolic action. Consistent with this, the ability of amylin to reduce meal size is normal in rats on a high-fat diet that develop diet-induced obesity (Eiden *et al.* 2002).

(**f**) ***Pathophysiology of amylin's anorectic action***

Few studies have considered amylin's anorectic action under pathophysiological conditions. Amylin has been suggested to contribute to the anorexia occurring during certain pancreatic neoplastic diseases that are characterized by supraphysiological plasma amylin levels (Stridsberg *et al.* 1995; Permert *et al.* 1997). Lack of amylin may also contribute to the hyperphagia that occurs in IDDM since these individuals also lack amylin. Consistent with this, long-term treatment of late-stage type-2 diabetics who are overweight and insulin resistant with an amylin analogue in addition to insulin resulted in far greater weight loss than occurred in diabetics receiving insulin only. Thus, co-administration of insulin plus amylin might help to circumvent the increase in body weight that occurs in type-2 diabetics treated with insulin, insulin secretagogues or insulin sensitizers (Weyer *et al.* 2001; Hollander *et al.* 2004).

To summarize, blood-borne amylin reduces meal size by stimulating neurons in the AP. Besides enhancing the action of other satiety signals at the level of the hindbrain, the amylin signal interacts with other signals controlling energy homeostasis at the level of the LHA and probably elsewhere. Finally, there is evidence that amylin functions as an adiposity signal in addition to a satiety signal.

## 7. GLUCAGON AND INGESTIVE BEHAVIOUR

As mentioned above, pancreatic glucagon's metabolic functions are in many respects opposite to those of insulin. Glucagon's most prominent physiological role is to stimulate glucose production via hepatic glycogenenolysis or gluconeogensis, thereby helping maintain euglycemia during states of rapid glucose utilization or fasts, respectively. Pancreatic glucagon is also secreted as food is ingested, and this is thought to provide a satiety signal leading to termination of the meal (Geary 1990, 1998). In contrast to insulin and amylin, neither basal, prandial, nor stimulated glucagon secretion is related to body adiposity (Holst *et al.* 1983*b*; Raben *et al.* 1994), and repeated administration of glucagon in amounts sufficient to reduce food intake have few metabolic side effects (Geary 1990, 1998). Therefore, unlike insulin and amylin, glucagon appears not to be an adiposity signal.

(**a**) ***The glucagon family of peptides***

The proglucagon gene is expressed in A-cells of the endocrine pancreas and L-cells of the intestinal wall. It is also expressed in the NTS in the hindbrain (Larsen *et al.* 1997; Lovshin & Drucker 2000). The control of proglucagon expression and of proglucagon post-translational processing differs among these tissues. Brain and L-cell proglucagon-derived peptides include glicentin (proglucagon 1-69), oxyntomodulin (proglucagon 33-69), glucagon-like peptide-1 (GLP-1; proglucagon 78-107 amide), and GLP-2 (proglucagon 126-158). Pancreatic A-cells synthesize only true pancreatic glucagon (proglucagon 33-61). The hepatocyte glucagon receptor is highly selective for glucagon, with little affinity for any other proglucagon-derived peptides (Hjorth *et al.* 1994). Other proglucagon-derived molecules that have been implicated in the control of food intake include GLP-1 (Tang-Christensen *et al.* 1996; Thiele *et al.* 1998; Rinaman 1999; van Dijk & Thiele 1999; Kinzig *et al.* 2002; Schick *et al.* 2003), GLP-2 (Tang-Christensen *et al.* 2000) and oxyntomodulin (Cohen *et al.* 2003; Baggio *et al.* 2004). Only glucagon is considered here.

(**b**) ***Prandial glucagon secretion***

Eating stimulates an immediate, brief increase in glucagon secretion. It occurs within one minute of the onset of spontaneous meals (de Jong *et al.* 1977) and also increases during sham feeding (Nilsson & Uvnas-Wallensten 1997). These observations, coupled with the absence of prandial glucagon secretion in patients with transplanted pancreata (Secchi *et al.* 1995), collectively imply that glucagon secretion can be elicited by cephalic stimuli. Consistent with this, stimulation of the ventromedial hypothalamus, the dorsal vagal complex, or the gastric or hepatic branches of the vagus nerve increase glucagon secretion (Marliss *et al.* 1973; de Jong *et al.* 1977; Berthoud *et al.* 1990). Although most meals, except pure carbohydrate meals, stimulate glucagon secretion, high-protein meals are most effective (Langhans *et al.* 1984).

The magnitude of the prandial increase in *systemic* glucagon concentration during most meals is modest (Muller *et al.* 1971; Holst *et al.* 1983*a*; Geary 1996) because first-pass hepatic extraction is very efficient. Portal vein glucagon concentration is considerably higher (Ishida *et al.* 1983) and can be substantial without any detectable change in systemic plasma glucagon concentration (Dencker *et al.* 1975; Langhans *et al.* 1984). For this reason, the primary target of prandial pancreatic glucagon secretion is likely the liver, and, consistent with this, prandial glucagon secretion stimulates hepatic glycogenolysis during meals (Langhans *et al.* 1982*a*, 1984). As described below, glucagon's satiety effect also originates in the liver.

(**c**) ***Glucagon decreases meal size***

Subcutaneous, intramuscular, intraperitoneal, systemic intravenous and intra-hepatic portal administration of glucagon all reduce feeding (Geary 1990, 1998). Hepatic-portal infusions are most reliable, eliciting rapid, dose-dependent decreases in food intake at doses ten times lower than vena caval infusions (Geary *et al.* 1993), thus providing compelling evidence that glucagon acts in the liver to inhibit eating. Hepatic-portal infusions of glucagon selectively decrease the size of the meal without affecting the duration of the subsequent intermeal interval (Le Sauter *et al.* 1991), and following intraperitoneal glucagon injections, rats display normal postprandial satiety behaviour (Geary & Smith 1982*a*), indicating that glucagon contributes to satiation as opposed to postprandial satiety. Intravenous infusion of glucagon also decreases meal size in humans (Geary *et al.* 1992). The subjects reported feeling equally satiated as during control meals and reported no side effects, and the dose administered produced systemic plasma glucagon concentrations that approximated the range produced by normal meals (Geary 1998).

The signal to reduce meal size generated by glucagon reaches the brain via sensory axons of the vagus nerve since total subdiaphragmatic vagotomy,

selective hepatic vagotomy, or lesion of the vagal afferent terminal fields within the NTS all prevent glucagon's feeding-inhibitory effect (Geary & Smith 1983; MacIsaac & Geary 1985; Weatherford & Ritter 1986, 1988; Geary *et al.* 1993). The transduction mechanism by which glucagon generates a vagal afferent signal is unknown. Glucagon receptors have not been identified on vagal sensory neurons, implying an indirect mechanism. However, glucagon's feeding-inhibitory potency has been dissociated from its glycogenolytic and hyperglycemic effects (Geary & Smith 1982*b*; Geary *et al.* 1987) as well as from insulin-mediated effects (De Castro *et al.* 1978; Geary *et al.* 1997). Glucagon does have vascular and smooth muscle actions in the liver, and the majority of hepatic vagal afferent fibers innervate the biliary tree and hepatic vasculature (Sawchenko & Friedman 1979; Berthoud *et al.* 1992); however, the glucagon fragment, glucagon (1-21), which is a full agonist for the vascular and smooth muscle effects, does not inhibit feeding (Geary 1987). Glucagon also inhibits feeding in the absence of any effect on gastric emptying (Stockinger & Geary 1989).

Another possibility is that glucagon affects the hepatocyte in a way that reduces its membrane potential, leading to an electrotonic effect that is transmitted to vagal afferents, as originally proposed by Russek (1981). Glucagon could affect the hepatocyte membrane potential directly (Petersen 1974), as a consequence of increasing intracellular fatty acid oxidation (McGarry & Foster 1980), or as a consequence of decreasing hepatocyte Na+/K+-ATPase activity (Langhans & Scharrer 1987*a*,*b*; Rossi *et al.* 1995). Lutz *et al.* (2001*a*) recently established the physiological relevance of glucagon's effect on the hepatic membrane potential by demonstrating that glucagon antibodies depolarize the hepatocyte membrane in vivo. As yet, however, this mechanism has not been convincingly linked to glucagon satiety. Finally, almost nothing is known about the central processing of glucagon satiety, other than the necessity of the hindbrain areas where the signal is received from the vagus nerve (Weatherford & Ritter 1988).

### (d) *Reducing the glucagon signal increases meal size*

Langhans *et al.* (1982*b*) demonstrated that pre-meal intraperitoneal administration of a highly specific polyclonal glucagon antibody significantly increased meal size and reduced hepatic glucose secretion, presumably as a result of decreased hepatic glycogenolysis. Hepatic-portal but not vena caval infusions of the same antibody also increased meal size (Le Sauter *et al.* 1991; Geary *et al.* 1993). These findings imply that endogenous glucagon, secreted during meals, normally contributes to meal cessation by an action in the liver.

### (e) *Interactions with other signals*

The ability of glucagon to reduce meal size depends upon functional interactions with other meal-related signals because even massive doses of glucagon fail to inhibit sham feeding in rats with open gastric cannulas, in which food does not accumulate in the stomach or enter the intestines in significant amounts (Geary & Smith 1982*b*). CCK has been implicated as one such signal, since at doses that are insufficient to reduce sham feeding, CCK is able to reinstate glucagon's dose-dependent satiety effect (Le Sauter & Geary 1987). Oestradiol also interacts with glucagon since both the feeding-inhibitory effect of glucagon and the feeding-stimulatory effect of glucagon antibodies are increased by estradiol treatment in ovariectomized rats (Geary & Asarian 2001). Thus, glucagon contributes to the marked sexual differentiation of the control of eating in rats. Whether or not glucagon interacts with the adiposity signals insulin and leptin has not been investigated. Pretreatment with the amylin receptor antagonist, calcitonin gene-related peptide-(8-37), however, blocked the satiety effect of glucagon under some, but not all, test conditions (Lutz *et al.* 1996). Whether this potential interaction with glucagon signalling relates to amylin's function as a satiety signal, an adiposity signal, or both, is unclear.

### (f) *Pathophysiology of glucagon satiety*

Changes in glucagon secretion and disruptions of food intake have been associated in various diseases, but no causal relationships have been established. For example, glucagonoma produces extremely elevated glucagon levels and severe anorexia (Wynick *et al.* 1993; Madsen *et al.* 1995). Whether this involves overstimulation of normal glucagon satiety or some non-specific feeding-inhibitory effect is unknown (see Geary 1998, for a review). Postprandial glucagon levels are increased in type-2 diabetes mellitus and may contribute to hyperglycemia in both type-1 and type-2 diabetes mellitus (Dinneen *et al.* 1995), but these changes would seem to predict increased satiety and consequently reduced caloric intake, whereas as discussed above, diabetes is associated with hyperphagia. On the other hand, a missense mutation in the glucagon receptor gene that reduces glucagon signalling has been found in some patients with late-onset type-2 diabetes mellitus (Hager *et al.* 1995), a phenomenon which potentially could contribute to reduced satiety and overeating.

## 8. CONCLUSIONS

Hormones of the endocrine pancreas are collectively at the crossroads of many aspects of energy homeostasis. Glucagon, amylin and PP act in the short term to reduce meal size, and insulin sensitizes the brain to short-term meal-generated satiety signals; and insulin and perhaps amylin and PP as well act over longer intervals to modulate the amount of fat maintained and defended by the brain. Hormones of the endocrine pancreas interact with receptors at many points along the gut–brain axis, from the liver to the sensory vagus nerve to the hindbrain to the hypothalamus; and their signals are conveyed both neurally and humorally. Finally, their actions include gastrointestinal and metabolic as well as behavioural effects. Thus, the production and release of all of these hormones of the endocrine pancreas (insulin, glucagon, amylin and PP) are influenced by food intake and (at least in part) by body fat (insulin and amylin), and they in turn control caloric intake (insulin, glucagon, amylin, PP) and body

weight (insulin, amylin and PP) through peripheral (glucagon, PP and maybe insulin) as well as central (amylin and insulin) mechanisms.

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