LEADING ARTICLE

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Promising New Approaches to the Management of Obesity

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Abstract

The pathophysiology of obesity is complex with many different pathways involved. A better understanding of these weight-regulating mechanisms has lead to the identification of new targets for anti-obesity agents. Most attention has been given to the centrally acting neuropeptides regulating food intake. Leptin, playing a key-role, exerts its action through several neuropeptides such as neuropeptide Y, α-melanocyte stimulating hormone and agouti related protein. Cocaine– and amphetamine-regulated transcript peptide and the orexins are the latest discovered peptides acting at the level of the hypothalamus. Targets for new drugs acting on peptides secreted from the periphery are cholecystokinin and glucagon-like peptide 1. Another potential target in the treatment of obesity is increasing energy expenditure via β3 adrenoceptors or uncoupling proteins. These new pharmacological agents in development could be valuable adjuncts to more traditional treatment strategies such as dietary treatment, behavioural/psychological counselling and physical activity.

Obesity is a major problem in our modern society and recent data indicate that the prevalence of obesity is still increasing, for both children and adults, not only in industrialised countries but also in developing countries.[1,2] The aetiology of obesity is multifactorial and is the result of a complex interaction between genetic, environmental (predominantly dietary) and psychosocial factors. Because of this complexity, obesity is difficult to treat and comprehensive treatment programmes combine diet, exercise and behavioural therapy. In the morbidly obese patient surgical treatment can be a valuable treatment option.[3] In recent years, a lot of attention has been given to the role of pharmacotherapy as an additional treatment option with new drugs such as orlistat and sibutramine being marketed. With the discovery of the *ob* gene and its product leptin,[4] a boom of research has emerged in the field of genetics and molecular biology, increasing our understanding of the physiology of weight regulation mechanisms. This in turn has lead to the identification of a series of promising new pharmacological approaches for the treatment of overweight and obesity. In this article we focus on a few of these new potential targets and compounds in development for pharmacological treatment of obesity which can be divided into those that act on energy intake and those that act on energy expenditure. Recently, reviews were published in this journal on the new drugs orlistat[5] and sibutramine,[6] and for this reason they are not discussed in this article.

1. Drugs Altering Energy Intake

Food intake is regulated by several key neurotransmitters which are in a complex interaction with each other. In the last few years, a lot of research has been performed in this area with the development of new agonists or antagonists acting on specific receptors. Peptides regulating food intake can be divided into orexigenic peptides increasing food

intake and anorexigenic peptides leading to a decrease in food intake (table I).

1.1 Peptides Secreted from the Periphery

1.1.1 Leptin

The discovery of leptin in 1994 by Friedman and colleagues[4] has been a landmark in the field of obesity research. Leptin, the product of the *ob* gene, is secreted by adipocytes and signals to the brain about the fat stores of the body (fig. 1). Since its discovery, it has been shown that leptin is more than a simple adipocyte-derived factor playing an important role in energy balance. It also acts as a mediator of different endocrine and metabolic pathways such as the onset of puberty and insulin secretion.[7]

Unlike in the obese *ob/ob* mouse, where no leptin secretion could be demonstrated due to a mutation in the *ob* gene,[4] obese humans show increased levels of leptin, correlating with the amount of body fat.[8]

Table I. Peptides decreasing or increasing energy intake

Peptides decreasing food intake	Peptides increasing food intake
Glucagon-like peptide-1 (GLP-1)	Neuropeptide Y (NPY)
α-Melanocyte-stimulating hormone (α-MSH)	Melanin concentrating hormone (MCH)
Corticotropin-releasing hormone (CRH)	Agouti related protein (AGRP)
Cocaine- and amphetamine-regulated transcript (CART)	Orexins/hypocretins
Cholecystokinin (CCK)	Galanin
Bombesin	β-Endorphin
Glucagon	
Amylin	
Enterostatin	
Anorectin	

It has been suggested that the failure of leptin to normalise fat stores in obese humans is the result of the presence of leptin resistance in obese humans, analogous to insulin resistance in type 2 (non-insulin dependent) diabetes mellitus. However, there seems

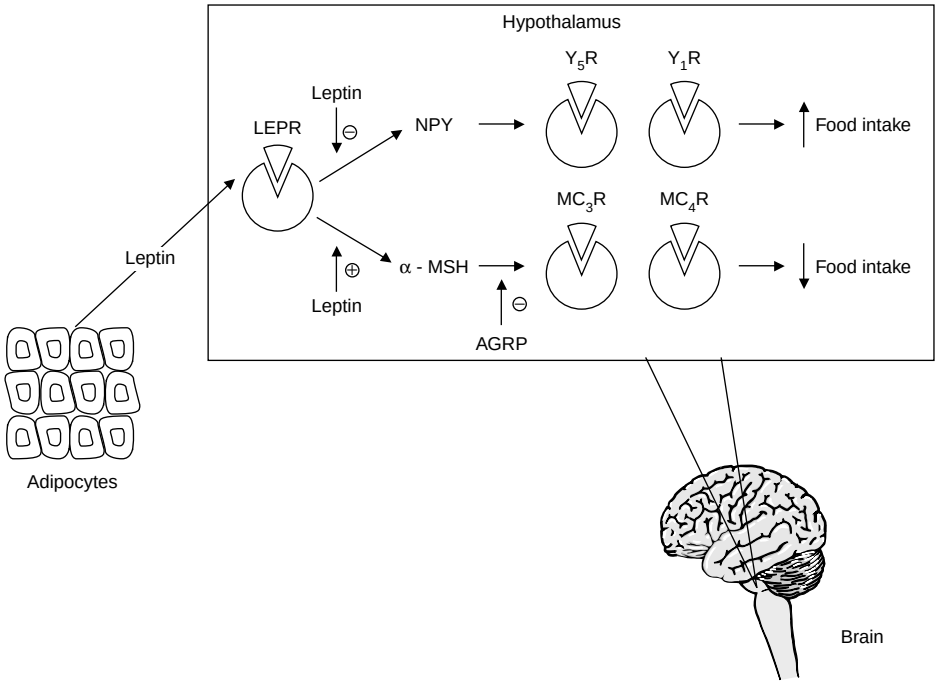

Fig. 1. Secretion of leptin by adipocytes and post-signalling effects of leptin at the level of the hypothalamus. **AGRP** = agouti related protein; **LEPR** = leptin receptor; **MC_3R** = melanocortin 3 receptor; **MC_4R** = melanocortin 4 receptor; **MSH** = α-melanocyte stimulating hormone; **NPY** = neuropeptide Y; **Y_1R** = neuropeptide receptor 1;**Y_5R** = neuropeptide receptor 5.

to be little direct evidence supporting this hypothesis as recently reviewed by Arch et al.[9]

In humans, only a few reports have been published on mutations in the *ob* gene[10,11] or the leptin receptor gene.[12] In 1997, Montague et al.[10] identified two nine-year old cousins homozygous for a frame-shift mutation in the leptin gene, resulting in severe obesity. Treatment of one of these girls with recombinant leptin, administered subcutaneously, led to a sustained reduction in bodyweight, which was predominantly a reduction of body fat.[13]

The post-receptor signalling effects of leptin are mediated through different neurotransmitters including neuropeptide Y (NPY), glucagon-like peptide-1 (GLP-1), α-melanocyte stimulating hormone (α-MSH), corticotrophin releasing hormone (CRH) and cocaine– and amphetamine–regulated transcript (CART), each of these being a possible target for anti-obesity treatment.[14,15] Whether leptin itself may show some possible therapeutic benefit still remains an open question, although initial preliminary findings only suggest limited success.[16] Important limitations are that leptin has to be given subcutaneously and in very high doses, which could result in inflammatory reactions at the injection site. Leptin analogues and leptin receptor agonists, such as LY-355101[17] are currently under investigation and could offer more promising perspectives.

1.1.2 Cholecystokinin

Cholecystokinin (CCK) is an endogenous gastrointestinal hormone and neurotransmitter which seems to play an important role as a peripheral satiety factor (fig. 2). It is secreted from the duodenum in the presence of food, and has both central and gastrointestinal effects such as inhibition of gastric emptying, contraction of the pyloric sphincter, stimulation of gallbladder contraction and pancreatic exocrine secretion.[18] Clinical studies in humans have shown that intravenous infusion of cholecystokinin significantly reduces feelings of hunger and increases satiety in both lean and obese volunteers.[19] Two types of cholecystokinin receptor have been identified, CCK-A and CCK-B. Type A receptors are found mainly in the periphery (gallbladder, pancreas, pyloric sphincter and vagal afferent fibres), but are also found in some areas of the central nervous system. The type B receptor is found predominantly in the brain.[18] The satiety effects of cholecystokinin are thought to be mediated through the type A receptor.[20] Cholecystokinin stimulates CCK-A receptors on the vagus nerve passing signals to the hypothalamus.[21] Recently a synergistic interaction between cholecystokinin and leptin has been demonstrated,[22,23] suggesting an interaction between the short term, meal-related satiety signal with CCK and the long term regulator of bodyweight, leptin.[24]

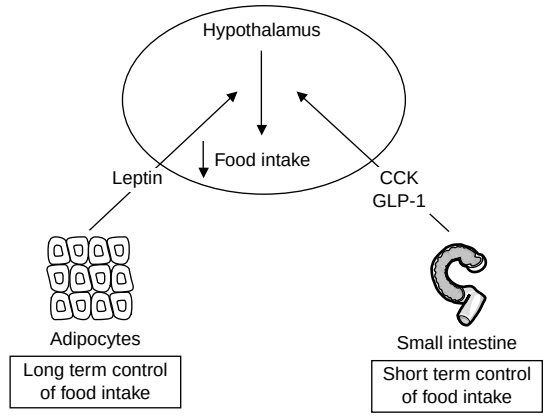

Fig. 2. Schematic representation of food-regulating peptides secreted from the periphery. Two major systems can be identified: the short term regulation of food intake with cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1) and the long term regulation of food intake through the leptin system.

Cholecystokinin agonists are potential anti-obesity agents targeting CCK-A receptors. The challenge is to find orally active and CCK-A selective agonists that have a long biological half-life, show no adaptive responses and are effective in obese humans.[25] Butabindide, which blocks an enzyme that metabolises CCK, could also be of therapeutic value.[26]

1.1.3 Glucagon-Like Peptide 1

GLP-1, a peptide with a 50% sequence homology with glucagon, is produced in and secreted from the L-cells of the intestinal mucosa after intake of a mixed meal (see fig. 2).[27] GLP-1 is an incretin

hormone, which means that an oral load of glucose elicits a greater insulin response than an intravenous glucose infusion.[28] For this reason, GLP-1 has been extensively studied as an anti-diabetic agent.[29] Studies have shown that an intravenous infusion of GLP-1 also slows gastric emptying in obese men,[30] and reduces energy intake in lean[31] and obese men[32] and in male patients with type 2 diabetes.[33] Obese women seem to have attenuated GLP-1 secretion in response to an oral carbohydrate load compared with lean women.[34] A recent study by Flint et al.[35] showed that peripherally infused GLP-1 in healthy males decreased diet-induced thermogenesis and carbohydrate oxidation, most probable secondary to a retarded absorption of nutrients.

It is not clear whether the effect on food intake is mainly a result of reduced gastric emptying or whether it is mainly a central effect. GLP-1 and its receptors are present in the hypothalamus[36] and it has been shown that GLP-1 can cross the blood brain barrier.[37] In a recent paper by Turton et al.,[38] it has been shown that intracerebroventricular injection of GLP-1 inhibits feeding in rats and injection of the specific GLP-1 receptor antagonist exendin (9-39) blocked this effect. However, knock out of the GLP-1 receptor gene is not associated with the development of obesity or glucose intolerance.[39]

GLP-1 could be used to treat obese patients with type 2 diabetes, by acting on both hyperglycaemia and food intake.[33] Unfortunately the effects of GLP-1 are very short-lived, since it is metabolised very quickly by the dipeptidyl-peptidase IV (DPP-IV) enzyme.[40] DPP-IV, or CD 26, seems to play a role in many physiological processes such as in immune, inflammatory and endocrine responses.[41] Different approaches are currently being investigated to turn GLP-1 into a clinically useful therapeutic agent.[29] DPP-IV resistant analogues of GLP-1[42] and DPP-IV inhibitors[43] are being developed for use in type 2 diabetes. Exendin 4, a 39 amino acid polypeptide isolated from the salivary secretions of the Gila monster (*Heloderma suspectum*), shows 53% amino acid identity to mammalian GLP-1 and is a full GLP-1 receptor agonist. Exendin 4 has been shown to have prolonged duration of glucose lowering action, and is being explored as an anti-diabetic agent.[44] These types of agents could also have inhibitory effects on food intake and in this way be of potential benefit for obese patients.

1.2. Peptides Mainly Found Centrally

1.2.1 Neuropeptide Y

NPY, a 36 amino acid peptide, seems to play a role in different biological functions such as regulation of blood pressure, anxiety and memory.[45] It is also one of the most potent stimulators of food intake,[46] with a most prominent effect on carbohydrate consumption.[47] Central administration of NPY in rats increases lipoprotein lipase activity in white adipose tissue and decreases sympathetic nervous system activity leading to a decrease in brown adipose tissue thermogenesis.[48] Administration of leptin to mice results in inhibition of NPY synthesis and release, explaining in part the hypothalamic anorectic effect of leptin.[49] However, the fact that leptin still inhibits food intake in NPY knockout mice, suggests that other peptides than NPY also play a role in the leptin signalling system.[50]

NPY is synthesised mainly in the hypothalamus and 6 different receptor subtypes have been cloned of which type 1 and type 5 seem to be the most important in the regulation of food intake.[51,52] Different NPY receptor antagonists are being developed; selective for the Y1[53,54] or the Y5 receptor.[55]

1.2.2 α-Melanocyte Stimulating Hormone/Agouti-Related Protein

Another pathway through which leptin exerts its actions is the pro-opiomelanocortin (POMC) system, with an effect opposite to that of the NPY pathway, leading to a decrease in food intake.[56] Melanocortins are peptides cleaved from the pro-opiomelanocortin (POMC) precursor with α-MSH playing the most important role in the regulation of food intake.[57] α-MSH binds to the melanocortin receptors (MC-R), MC3-R and MC4-R[58] and α-MSH agonists have been shown to promote satiety.[59] Evidence for the importance of MC4-R in bodyweight regulation was obtained from the *A^{vy}/-agouti* mouse, a yellow-coated obese mouse model, which ectopically expresses the agouti protein. This protein was found

to be a potent antagonist of MC1-R, causing the yellow coat colour, and MC4-R, leading to obesity.[60] Mice lacking MC4-R become hyperphagic and develop obesity.[61]

Agouti-related protein (AGRP), a protein nearly identical to the agouti protein has been shown to be a potent, selective antagonist of MC3-R and MC4-R, increasing food intake.[62] Leptin injection in *ob/ob* mice inhibits AGRP mRNA expression and AGRP mRNA expression is stimulated by fasting in wild-type mice.[63] These data show that the pro-opiomelanocortin system is a very interesting target for pharmacological intervention.

1.2.3 Melanin Concentrating Hormone

Melanin concentrating hormone (MCH) is a neuropeptide involved in different physiological processes. Recently, a role for MCH in feeding behaviour was suggested as overexpression of MCH mRNA was found in *ob/ob* mice.[64] Fasting increases expression of MCH mRNA in both the *ob/ob* mice and control animals, and intracerebroventricular administration of MCH to rats stimulates feeding.[64] MCH–deficient mice have been shown to have a reduced bodyweight due to hypophagia.[65] Recently, Chambers et al.[66] showed that MCH binds to the orphan G-protein coupled somatostatin-like receptor SLC-1. MCH and α-MSH are functional antagonists, but unlike AGRP which antagonises α-MSH by acting on the same receptor, MCH and α-MSH act on different receptors.[66] Antagonists of SLC-1 may be useful in the treatment of obesity.

1.2.4 Cocaine- and Amphetamine-Regulated Transcript Peptides

CART was originally discovered as mRNA whose levels were increased after administration of cocaine and amphetamine.[67] The peptide products of CART have been shown to play an important role in different physiological processes, including feeding behaviour.[68,69] Different CART peptides affect feeding with different potencies, of which CART 55-102 seems to be the most important.[70] Intracerebroventricular administration of CART peptide fragment[68] or recombinant CART peptide[69] inhibits feeding in rats.[68] In addition, CART peptides have been shown to completely block the feeding response induced by NPY.[69] In the *ob/ob* mouse and the Zucker rat, 2 animal models with disturbances in the leptin system, CART mRNA levels are almost absent from the arcuate nucleus.[69] Peripheral administration of leptin to obese mice stimulates CART mRNA expression.[69] Further research will have to establish whether there is a role for a synthetic CART agonist in the treatment of obesity.

1.2.5 Orexins/Hypocretins

The newest family of hypothalamic peptides are the orexins[71] or hypocretins[72] which were identified almost simultaneously by two different groups. Both orexin A and orexin B[71] (or hypocretin I and II[72]) are derived by proteolytic processing from the same precursor prepro-orexin. When administrated to the rat brain, the peptides bind to the orexin receptors OX_1R and OX_2R to stimulate feeding behaviour.[71] A 48-hour fast upregulates hypothalamic prepro-orexin mRNA expression.[73] Leptin injected intraperitoneally in Long-Evans rats significantly decreased orexin A levels in the lateral hypothalamus, leading to a decrease in food intake and bodyweight.[74]

The orexin receptors, which belong to the G-protein coupled receptor superfamily, have been shown to be broadly distributed in the rat brain, suggesting additional functions for orexins.[74] A recent paper by Lin et al.[75] has shown that a mutation in the hypocretin (orexin) receptor 2 gene in dogs causes narcolepsy. This suggests a broader role for orexins than the regulation of feeding and a major physiological role could be in the regulation of sleeping behaviour.

1.2.6 Other Peptides

Many other central peptides may play a role in the regulation of feeding behaviour (table I). Galanin increases food intake, with a most prominent effect on fat intake.[76] Corticotropin-releasing hormone (CRH; corticorelin), or its relative urocortin, reduce food intake and their release seems to be increased by leptin.[77]

2. Drugs Altering Energy Expenditure

2.1 β3 Adrenoceptor

The existence of an 'atypical' adrenoceptor, which is now referred to as β3 adrenoceptor next to β1 and β2 adrenoceptors, was first suggested in the early eighties,[78] and the receptor was cloned in 1989.[79] The β_3 adrenoceptor is located mainly in adipose tissue and plays an important role in the adrenergic stimulation of lipolysis and thermogenesis in white and brown adipose tissue. The role of β_3 adrenoceptors in human obesity and type 2 diabetes has been suggested by the fact that a Trp64Arg mutation in the β_3 adrenoceptor gene has been associated with weight gain in morbidly obese patients,[80] with features of the insulin resistance syndrome[81] and with the time of onset of type 2 diabetes.[82] However, there is still a lot of controversy concerning the importance of the polymorphism in the pathophysiology of obesity or type 2 diabetes.[83,84]

In the last 15 years, different β3 agonists have been developed by several pharmaceutical companies with positive results in different animal models.[85,86] However, clinical studies in humans with these early compounds were rather disappointing, which could partly be explained by the fact that there are substantial differences between the animal and the human receptor, and that it is difficult to find a compound with sufficient bioavailability that is highly selective and a full agonist at the human receptor.[87,88] Some of these early studies demonstrated increased thermogenesis and weight loss in obese participants treated with β3 agonists,[89] but also produced tachycardia and tremor, attributable to additional β2 agonist properties.

New β3 adrenergic compounds specifically targeted to human the β3 adrenoceptor are currently being investigated.[88] One of these compounds, L-755507 has been shown to stimulate energy expenditure in rhesus monkeys.[86] However, it can still be argued that the amount of brown fat tissue in the adult human body is insufficient for β3 adrenoceptor agonists to produce a substantial weight loss effect.[87] A recent randomised controlled trial with CL-316243 (BTA-243)[90] in lean male volunteers showed an increase in insulin-stimulated glucose disposal, fasting free fatty acid concentration and 24-hour fat oxidation. However, no effects on energy expenditure or bodyweight were observed. Another study with this compound in patients with upper body obesity, could not show an effect on bodyweight.[91]

2.2 Uncoupling Proteins

Uncoupling proteins (UCPs) are inner mitochondrial membrane transporters which uncouple mitochondria respiration from ATP synthesis thereby dissipating energy as heat. UCP1 has been known for several years and is found only in brown adipose tissue.[92] There does not seem to be any direct evidence for a significant role for brown adipose tissue and UCP1 in regulation of energy expenditure and bodyweight in adult humans.[93] However, some genetic studies suggested a link between UCP1 polymorphism and weight gain in morbid obesity[94] or body fat gain in adulthood,[95] while more recent studies could not find any association with obesity-related phenotypes.[96,97]

Recently two new uncoupling proteins have been discovered: UCP2 which is widely expressed in human tissues[98] and UCP3 which is found predominantly in skeletal muscle.[99] UCP3 gene expression in rodents has been shown to be regulated by thyroid hormone, leptin and β3 adrenergic agonists.[100] Different papers have focused on UCP2 and UCP3 gene expression and polymorphisms in human obesity and type 2 diabetes. Bouchard et al.[101] found a significant linkage between markers in the vicinity of the *UCP2* gene and resting metabolic rate (RMR) in humans. However, no linkage could be demonstrated between obesity markers and UCP2 polymorphism in patients with type 2 diabetes.[102] Schrauwen et al.[103] showed a negative correlation between skeletal muscle UCP3 gene expression and BMI, and a positive correlation between UCP3 mRNA levels and RMR in Pima Indians.

Even if no defects in the *UCP2* or *UCP3* genes can be associated with human obesity, UCPs are still promising targets for anti-obesity drugs by in-

creasing energy expenditure,[104] but no data on clinical studies in humans are available yet.

3. Conclusion

These are exciting times for researchers and clinicians working in the field of obesity. Obesity has been recognised as a chronic disease, requiring lifelong treatment in which pharmacological agents could play an important role. The increasing knowledge about the systems regulating food intake and energy expenditure has lead to the identification of different potential targets for drug treatment. However, the gap between the identification of these new targets for weight management and the development of effective compounds with an acceptable safety profile that can be used for the treatment of human obesity remains. As has been shown for leptin and β3 adrenergic agonist, findings in rodents are not always reproducible in humans. Hopefully, the boom of research in the field of genetics and molecular biology will, in the long term, lead to the availability of different types of medications for the long term treatment of human obesity. This will probably make it easier to match the individual patient with the most effective treatment.

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