Novel molecular targets for the treatment of obesity

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Advances in our understanding of the mechanisms underlying the development of obesity have occurred over the past few years, prompted by the discovery of leptin and its role in modulating energy balance. The discovery that leptin modulates neurotransmitter pathways in the CNS and the growing body of evidence suggesting that obesity in humans and rodent models is associated with leptin resistance have focused attention on downstream CNS pathways. From these neurotransmitter systems, a series of novel potential targets for the development of antiobesity agents is emerging.

The prevalence of obesity has increased dramatically over the past 20 years, prompting tremendous health concerns. Up to 35% of the population of the USA is overweight, reflecting a rapid increase in the incidence of obesity during this century. Increasingly, obesity has also become a serious medical problem in developing nations, with the incidence correlating with urbanization and a more plentiful food supply. The morbidities associated with obesity, including type II diabetes, cardiovascular disease, osteoarthritis and several forms of cancer, represent a major health risk to the obese population.

Physiologically, obesity is a disorder of energy balance: excess energy is stored as fat whenever energy intake exceeds energy expenditure. Thus, the optimal treatment for obesity would be one that both suppresses food intake and increases energy expenditure. Energy intake and energy expenditure are closely regulated processes, as reflected in the relative stability of body weight in the presence of large daily fluctuations in calorie intake. Energy balance is controlled by a complex system of metabolic pathways, integrated at the level of the CNS by a series of neurotransmitter signals. In recent years, the molecular architecture of some of these pathways has begun to be understood, opening new avenues for the discovery of novel therapeutic approaches to the treatment of obesity.

Leptin

The study of obesity has long been enhanced by the availability of several genetic models of the disease in rodents, including the obese, diabetic *ob/ob* and *db/db* mice and the Zucker *fa/fa* rat. The discovery in the past few years of the molecular basis for these genetic defects has provided new insights into the metabolic pathways that control body weight. The gene responsible for the metabolic abnormalities in the *ob/ob* mouse was identified by positional cloning and found to encode leptin, a cytokine-like hormone that is secreted from adipocytes[1]. Subsequently, the *db/db* mouse and *fa/fa* rat were found to have defects in the gene encoding the leptin receptor[2,3]. Chronic replacement of leptin was found to correct all of the phenotypic abnormalities of the *ob/ob* mice, including obesity, hyperphagia, hypothermia, hyperglycemia, hyperinsulinemia, hypercorticism and infertility[4–7].

Leptin has generally been shown to be more potent when given intracerebroventricularly than when given peripherally, suggesting that its primary site of action is in the CNS.

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Especially noteworthy is the observation that chronic leptin treatment of *ob/ob* mice appears both to decrease food intake and to increase energy expenditure, thus affecting both parameters of the energy balance equation. However, this analysis is complicated by the fact that food intake and energy expenditure are not independent variables: maintenance of an obese body mass requires a higher baseline energy expenditure than maintenance of a lean one, and the ingestion and metabolism of food causes an increase in energy expenditure (the thermogenic effect of food).

Early studies

Several early studies demonstrated clearly that leptin acutely decreases food intake in *ob/ob* mice, demonstrating a direct effect of leptin on energy intake[4–6]. More recently, two independent groups have reported that a single injection of leptin, given either peripherally[8] or intracerebroventricularly[8,9], to *ob/ob* mice leads to a significant increase in energy expenditure as determined by indirect calorimetry. This increase in energy expenditure occurs acutely, in the absence of significant changes in body weight. Also, because leptin causes a significant decrease in food intake, the thermogenic effect of feeding is reduced in the leptin-treated *ob/ob* mice. This decrease in diet-induced thermogenesis can be controlled by a pair-feeding paradigm, in which the food intake of control *ob/ob* mice is restricted to the levels consumed by the leptin-treated mice. Compared to the pair-fed controls, leptin caused a 47% increase in 22 h energy expenditure in *ob/ob* mice[8]. As the pair-fed and the leptin-treated *ob/ob* mice showed similar decreases in body weight, the thermogenesis is independent of changes in food intake or body weight, indicating that leptin can increase energy expenditure directly.

In addition to its effect on appetite and energy expenditure, leptin also regulates the partitioning of energy between fat and lean body mass by modulating the primary whole-body energy fuel source from carbohydrate to fat oxidation[8].

Recent studies using recombinant adenovirus to overexpress leptin *in vivo* have demonstrated that hyperleptinemia in rats caused a rapid disappearance of all grossly visible body fat[10]. *In vitro* studies on islet cells from hyperleptinemic animals showed that leptin lowers the triglyceride content of isolated cells by reducing esterification and increasing oxidation of free fatty acids (FFA)[11]. Since these changes did not occur in the islets of pair-fed rats, the changes in FFA metabolism were independent of the reduction in calorie intake[10]. These data suggest that leptin can directly regulate body adiposity by modulating energy fuel sources and increasing fatty acid oxidation.

Leptin resistance during obesity

The experiments summarized above indicate that leptin can reverse obesity in *ob/ob* mice by decreasing food intake, increasing energy expenditure and decreasing body adiposity by promoting fat oxidation. Thus, leptin, or a small molecule leptin receptor agonist, would appear to provide an optimal treatment for obesity. However, with the exception of two related obese children[12], human obesity is not associated with leptin deficiency. By contrast, recent experiments have suggested that leptin resistance may play a significant role in the development of obesity. Shortly after the discovery of leptin, it was determined that, with the exception of the *ob/ob* mouse, obese rodents exhibit increased levels of serum leptin[13,14]. At approximately the same time, it became apparent that obese humans also have increased levels of normal serum leptin, and that serum leptin is highly correlated with body mass index[13–19]. The concept that obese rodents and obese humans are resistant to their endogenous leptin began to emerge.

In a longitudinal study of peripheral leptin sensitivity during the development of obesity in mice, it was found that, as in obese humans, serum leptin levels were highly correlated with increasing adiposity in mice[18]. Young, lean mice responded to peripherally administered leptin with a decrease in food intake. However, these mice became resistant to leptin after obesity was induced by a high fat diet, demonstrating that murine obesity is correlated with peripheral leptin resistance. Interestingly, these obese mice remained sensitive to leptin delivered directly to the CNS via an intracerebroventricular infusion, suggesting that the CNS pathways activated by leptin remain intact during obesity-induced leptin resistance[20].

It is apparent that, despite some minor differences between studies, data are accumulating to support the concept of leptin resistance, which may also be referred to as reduced leptin sensitivity. One very recent study has shed some light on this subject[21]. The lethal yellow mouse (A^y/a), which overexpresses the agouti protein (see section on melanocortin, below), is obese, has high levels of serum leptin and is resistant to the actions of peripherally administered leptin. Deletion of the leptin gene from the A^y/a

mouse, thereby creating the A^y/a lep^{ob}/lep^{ob} mouse, generates a mouse that is more obese than either the A^y/a mouse or the leptin-deficient mouse. However, abolition of the leptin gene also restores leptin sensitivity to these mice; body weight falls dramatically and the very high levels of insulin and corticosterone are ameliorated in response to peripherally administered leptin[21]. This suggests that the chronic presence of high circulating levels of leptin rather than the presence of obesity *per se* is necessary for leptin resistance to develop.

Much work still needs to be carried out to determine the precise mechanism(s) by which leptin resistance might occur. Several hypotheses have been put forward, including the development of postreceptor signaling defects, reduced efficacy of leptin transport to the CNS or alterations in signal integration within the brain network[22]. Leptin appears to enter the brain by a saturable mechanism[23], and some studies in obese humans suggest that transport of leptin into the brain may be compromised, because leptin concentrations in the CSF of obese patients are proportionately low compared with the elevated serum concentrations[19–22].

Studies that address the question of whether leptin resistance can be reversed by environmental or other changes are also of great importance. What impact the apparent leptin resistance in obese humans will have on the potential efficacy of leptin as an antiobesity agent awaits the outcome of clinical trials. However, the observation of central leptin responsiveness in obese rodents in the face of peripheral leptin resistance suggests that the neurotransmitter pathways activated by leptin could provide fruitful targets for the discovery of antiobesity agents.

Neurotransmitters involved in the control of body weight

The brain plays a critical role in the regulation of body weight. Information about nutrient stores, satiety, hunger, palatability of food, etc. is communicated to the brain by endocrine molecules such as leptin or by neural pathways that connect the brain and the periphery. Cognitive and limbic centers of the brain also directly impact the quantity and type of food consumed and the overall metabolic rate of the body. These signals must be integrated by the brain and ultimately translated into appropriate changes in energy balance. The response to each input, the integration of the various inputs and the final compensatory response are mediated via the activation of discrete neurotransmitter and neuropeptide signaling pathways in the brain. Although the complex neuronal circuitry that regulates body weight is far from being fully defined, a number of specific neurotransmitters and neuropeptides have been implicated in this process.

Neuropeptide Y

Neuropeptide Y (NPY) is a 36-amino acid peptide that is widely distributed in both the central and peripheral nervous systems. Several lines of evidence suggest that NPY plays a key role in the control of body weight. Central administration of NPY increases food intake and decreases thermogenesis in satiated animals[24,25], while reduction in endogenous NPY via antisense oligonucleotide or immunoneutralization techniques leads to a decrease in food intake[26,27]. As would be expected for an orexigenic peptide, hypothalamic NPY and mRNA levels are increased after fasting and in genetically obese mice[28,29]. In fact, recent experiments with transgenic mice lacking NPY indicate that it is required for the maintenance of the obese phenotype of *ob/ob* mice[30]. Conversely, leptin appears to decrease food intake and body weight in part by decreasing NPY synthesis and release[29]. These data suggest that NPY is a key modulator of body weight and that NPY receptor antagonists might be useful antiobesity agents.

NPY mediates its physiological effects via interaction with at least six distinct G protein-coupled receptors (designated Y_1–Y_6)[31]. It is possible that additional subtypes remain to be cloned and characterized. The pharmacological properties of the Y_5 receptor subtype most closely match the pharmacological properties of the receptor mediating the effects of NPY on feeding[32]. Furthermore, antisense oligonucleotides directed against the Y_5 receptor decrease basal, deprivation-induced and NPY-induced food intake[33]. However, emerging pharmacological data suggest that NPY receptors other than or in addition to the Y_5 receptor may mediate the effects of NPY on feeding (see below). The ultimate determination of the NPY receptor subtype(s) that mediate(s) the effects of NPY on feeding must await the development of nonpeptide agonist and/or antagonist ligands that selectively bind to each receptor subtype.

Recently, progress has been made in the development of nonpeptide ligands for the Y_1 and Y_5 receptors (see Figure 1 and Table 1). The first nonpeptide NPY Y_1 receptor antagonist discovered, BIBP3226, has high affinity and selectivity for the Y_1 receptor[34]. Data on the ability of

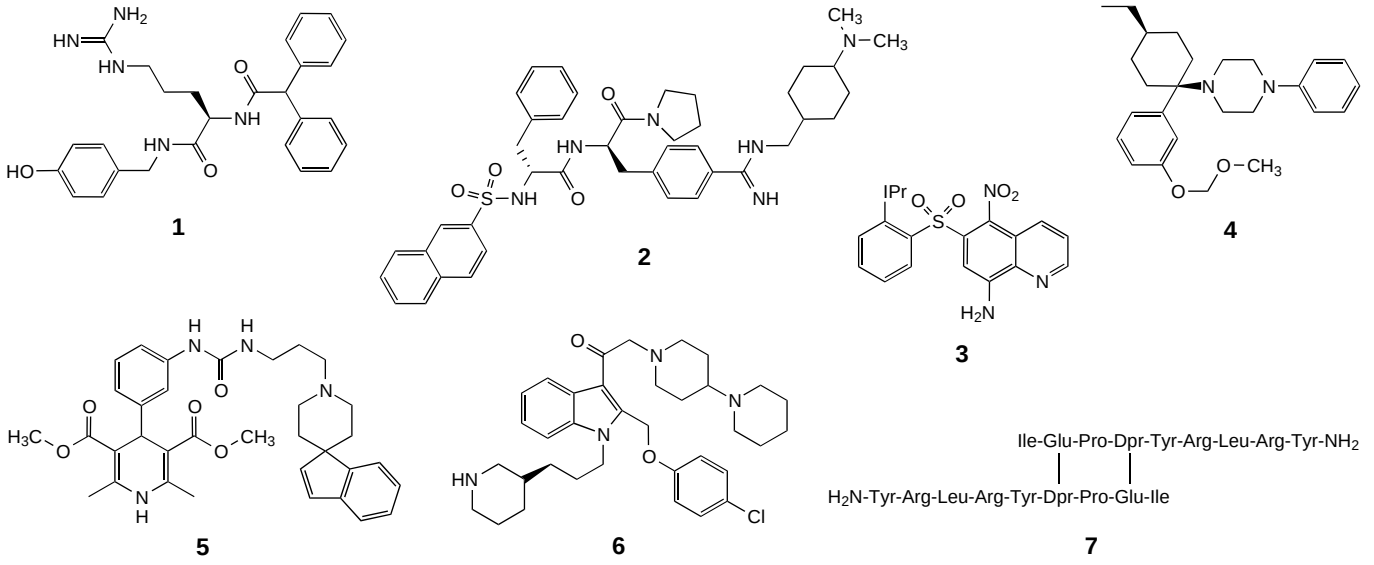

Figure 1. *NPY Y_1 receptor antagonists; for their pharmacological properties see Table 1 below.*

Table 1. Pharmacological properties of NPY Y_1 receptor antagonists[a]

Compound	Name (Developer)	K_i (nM) hY_1	hY_2	rY_3	hY_4	rY_4	hY_5	rY_5	Reference
1	BIBP3226 (Karl Thomae)	7.2	>10,000	>1,000	–	>1,000	–	>1,000	34
2	SR120819A (Sanofi)	15	10,000	>1,000	–	–	–	–	38
3	PD160170 (Parke-Davis)	48	>10,000	–	–	–	–	–	37
4	(Neurogen)[b]	29	–	–	–	–	–	–	39
5	(Bristol-Myers Squibb)[b,c]	1.6	>1,000	–	>1,000	–	>1,000	–	40
6	LY357897 (Eli Lilly)	0.75	>10,000	–	>10,000	–	>10,000	–	36
7	GR231118 (Glaxo Wellcome)[c]	0.063	63	–	0.25	0.20	100	100	41

[a]Receptor subtypes are: h, human; r, rat.

[b]Reported in the patent literature only; thus a representative compound is shown in Figure 1.

[c]Data obtained from Dr Deborra Mullins (pers. commun.).

BIBP3226 to inhibit NPY-induced food intake are conflicting, possibly because of the CNS toxicity associated with this drug[35] (H. Davis, pers. commun.). A compound from Eli Lilly, LY357897, has been reported to decrease NPY-induced food intake after central administration[36]. Sanofi, Parke-Davis, Neurogen and Bristol-Myers Squibb have also disclosed potent and selective NPY Y_1 receptor antagonists, but the effects of these compounds on NPY-induced feeding have not been reported[37–40]. A compound in the Neurogen series is in Phase II clinical trials for the treatment of obesity. The implication is that, like LY357897, Neurogen's Y_1 antagonists decrease food intake. These data implicate the Y_1 receptor in mediating the effects of NPY on feeding. This notion is supported by the recent observation that a peptide ligand known as GR231118, which is a potent Y_1 receptor antagonist but a very weak agonist at the Y_5 receptor[41], blocks spontaneous and NPY-induced feeding[42]. Novartis and Synaptic have recently

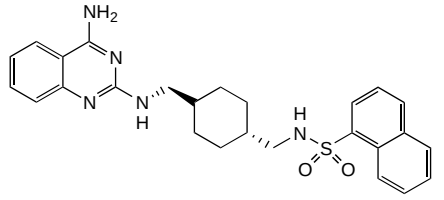

Figure 2. *NPY Y_5 receptor antagonist, CGP71683A (Novartis). The known affinities of this compound for various human NPY receptors are: hY_1, >1,000 nM; hY_2, >1,000 nM; hY_4, >1,000 nM; hY_5, 2 nM.*

disclosed a series of potent and selective NPY Y_5 receptor antagonists[43]. CGP71683A (Figure 2) has been reported to inhibit food intake in a variety of rodent feeding models, although the doses used are relatively high[43]. Development of additional NPY receptor antagonists will clearly be essential for determining the receptor subtype(s) involved in mediating NPY-induced feeding and in testing the utility of NPY receptor antagonists as antiobesity agents.

Melanocortins

The melanocortin peptide family, which includes α-melanocyte stimulating hormone (α-MSH), β-MSH, γ-MSH and ACTH, are all post-translationally processed products of the proopiomelanocortin gene. These peptides mediate their physiological effects by interacting with at least five structurally related G protein-coupled receptors designated MC1–MC5 (Ref. 44). Recent genetic evidence has strongly implicated melanocortin peptides and the MC4 receptor in the central control of body weight. The genetically obese *agouti* mouse develops late-onset obesity as a result of ectopic overexpression of the agouti signaling protein (ASP), which is a high-affinity antagonist of several melanocortin receptors[45]. As the MC4 receptor is localized exclusively in the brain, including hypothalamic regions involved in the control of body weight, it was presumed that antagonism of MC4 by ASP was responsible for the obese phenotype of the *agouti* mouse. This presumption has received strong support from the recent observation that transgenic mice lacking the MC4 receptor develop obesity and metabolic abnormalities that are quantitatively and qualitatively indistinguishable from those of the *agouti* mouse[46]. These data suggest that activation of the MC4 receptor by melanocortin peptides tonically restrains weight gain. The involvement of the melanocortin pathway in mediating the effects of leptin is controversial[21,47]. The emerging role of melanocortin peptides and the MC4 receptor in the regulation of body weight suggests that MC4 receptor agonists will be useful antiobesity agents. To date, there have been no nonpeptide MC4 receptor agonists described.

Galanin

Galanin is a 29–30 amino acid neuropeptide that is widely distributed in the brain and in peripheral tissues. Crawley and coworkers demonstrated that central administration of galanin increases food intake in satiated rats[48]. Conversely, reduction of central galanin levels by antisense oligonucleotide techniques or central administration of a peptide galanin receptor antagonist decreases food intake[49,50]. Galanin levels in the hypothalamic paraventricular nucleus are also positively correlated with fat intake[49]. These data suggest that galanin receptor antagonists might be useful antiobesity agents.

Galanin mediates its physiological effects via interaction with at least three distinct G protein-coupled receptors designated GALR1, GALR2 and GALR3 (Refs 51–53). There is evidence that additional galanin receptors remain to be cloned[54]. All three galanin receptors are expressed in the brain. However, the pharmacological characteristics of the receptor mediating the orexigenic effect of galanin are most closely related to the GALR1 receptor[48,51–53]. As discussed above for NPY, the ultimate determination of the galanin receptor subtype(s) that mediate(s) the effects of galanin on feeding must await the development of nonpeptide agonist and/or antagonist ligands that selectively bind to each receptor subtype. No such ligands have yet been described.

Biogenic amines

Activation of the SNS and the consequent release of norepinephrine in adipose tissue is known to lead to weight loss. The antiobesity effect of SNS stimulation results from activation of β-adrenoceptors (βARs) in two distinct types of adipose tissue. Activation of βARs in white adipose tissue (WAT) stimulates lipolysis, which depletes fat stores and releases FFAs. Activation of βARs in brown adipose tissue (BAT) increases energy expenditure via thermogenesis[55]. This is accomplished by βAR-mediated induction of the expression of uncoupling protein 1 (UCP1) and by activation of UCP1 by FFA released from WAT during lipolysis. Uncoupling proteins are mitochondrial proteins that

dissipate energy as heat by uncoupling oxidative phosphorylation from ATP synthesis – that is, they promote energy expenditure over energy storage. Recently, two additional uncoupling proteins structurally related to UCP1 have been cloned and designated UCP2 and UCP3 (Refs 56,57). UCP2 and UCP3 are widely expressed in human tissues, but are particularly enriched in skeletal muscle, WAT and BAT. Expression in skeletal muscle and adipose tissue is especially interesting because these tissues are the major sites of regulated thermogenesis in humans. It remains to be seen if activation of UCP2 and/or UCP3 is involved in thermogenic responses in humans and whether pharmacological modulation of UCP2 and UCP3 activity will be useful in the treatment of obesity.

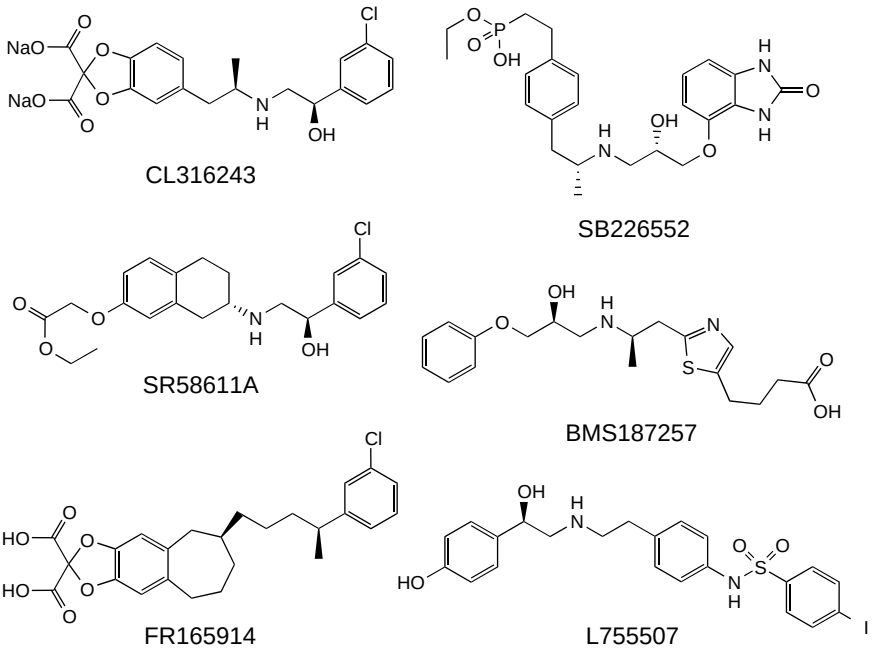

Figure 3. *Representative β_3AR agonists. These compounds were developed by the following companies: CL316243, American Home Products; SB226552, SmithKline Beecham; SR58611A, Sanofi; BMS187257, Bristol-Myers Squibb; FR165914, Fujisawa; L755507, Merck.*

Pharmacological characterization of the βAR subtype that mediates lipolysis and UCP1 activation in rodent adipose tissue has indicated that the β_1-, β_2- and β_3AR subtypes are all involved[58]. β_3AR is expressed primarily in adipose tissue, whereas β_1AR and β_2AR are more widely expressed. Pharmaceutical companies have therefore focused on the development of selective β_3AR agonists as potential antiobesity agents. Several such agents have been identified[59] (Figure 3). Selective β_3AR agonists increase metabolic rate, lead to weight loss and improve glucose tolerance in rodents[60]. For a variety of reasons, however, these agents have been only modestly effective in man and have been associated with side effects[61]. Many of the β_3AR agonists tested in clinical trials have not been sufficiently selective and have produced side effects due to activation of β_1AR and/or β_2AR. This lack of selectivity in humans may be because the pharmacological profile of human β_3AR is markedly different from that of rodent β_3AR (Ref. 62). Therefore, compounds that are selective agonists of rodent β_3AR are not necessarily selective or full agonists for human β_3AR. Moreover, humans have much less BAT than rodents and it remains to be seen if increases in thermogenesis in human BAT elicited by β_3AR agonists will be sufficient to lead to a significant antiobesity effect. Clinical trials with compounds selective for human β_3AR will be required to answer this question.

Biogenic amines in the brain also play a role in the regulation of body weight. Dexfenfluramine and fluoxetine induce their antiobesity effects by increasing synaptic levels of serotonin. This suggests that serotonin is involved in the central pathways that control body weight. Recently, transgenic mice lacking the 5-HT_{2C} receptor were found to be hyperphagic and mildly obese[63]. Therefore, serotonin might effect weight loss by interacting with 5-HT_{2C} receptors, and specific 5-HT_{2C} receptor agonists may be useful

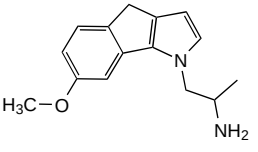

Figure 4. *Selective 5-HT_{2C} agonist (Roche). The reported K_i for this compound is 1 nM at the 5-HT_{2C} receptor, 125 nM at the 5-HT_{2A} receptor and >1,000 nM at all other 5-HT receptors.*

antiobesity agents. Roche has described a series of 5-HT_{2C} receptor selective agonists[64] (Figure 4); however, the effect of these agents on body weight has not been reported.

Conclusion

Recent advances in the genetics and physiology of obesity have increased our understanding of the mechanisms that control energy balance. It has become increasingly clear that, while the symptoms of obesity are expressed in the periphery, the mechanisms underlying the disorder are, in large part, centrally mediated. With this understanding has come a new series of potential targets for therapeutic intervention. By focusing on the neurotransmitter pathways that integrate the afferent signals of metabolic status, such as leptin and glucose, to activate the efferent pathways that affect appetite and energy utilization, it should be possible to modulate overall energy balance during obesity. The experience with leptin in rodent obesity models suggests that it is possible to modulate these pathways to decrease appetite and increase energy expenditure simultaneously, ultimately leading to the discovery of novel antiobesity agents.

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In short…

Cambridge Molecular (Cambridge, UK) has launched a genome research organization (GRO), **Cambridge Molecular Services**. The GRO is founded on Cambridge Molecular's expertise in DNA technologies and will provide services aimed especially at research in high-throughput screening.

BioFocus (Sittingbourne, UK) will support the antiviral programme of **Scriptgen Pharmaceuticals** (Medford, MA, USA) with new lead optimization. BioFocus has ongoing agreements with Roche Discovery Welwyn (Welwyn Garden City, UK) and ViroPharma (Malvern, PA, USA).