Obesity

- Approx. 23% of adults are obese in the U.K. The number of obese children has tripled in 20 years. 10% of six year olds are obese, rising to 17% of 15 year olds. The overall cost to this country is estimated at up to £7.4 billion a year.
 Obesity is a major risk factor for diabetes mellitus, hypertension, cardiovascular disease and arthritis.

 Therapies based on nutritional and behavioural modifications alone have only partial and temporary benefits.

 The cause of obesity is usually straightforward - more food is eaten than is needed and the excess calories are stored as fat. However, the biochemical and genetic basis is complex.

 Most cases of human obesity probably arise from abnormal expression of multiple genes. Nonetheless, insulin and leptin are important hormonal signals and may play significant roles in the development of obesity.

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<td>• Myocardial infarction</td>
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<td>• Stroke</td>
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<td>• Breast</td>
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**Leptin**

- Leptin is the (146 aa) product of the ob (obese) gene; it influences food intake, energy expenditure, body weight and neuroendocrine function.

- It is secreted by adipose tissue and levels increase exponentially with increasing fat mass - prolonged fasting significantly decreases plasma leptin (and insulin) whereas overfeeding increases it.
Binding of leptin to receptors, on neurons in the hypothalamus, generates ‘satiety’ signals.

Mice lacking leptin (ob/ob mice) are obese (and will overeat when given access to unlimited quantities of food) and will lose weight if given exogenous leptin.

Mice that lack the leptin receptor are insensitive to leptin administration (‘leptin resistance’).
The Leptin gene (ob)

- The mouse ob gene is on chromosome 6. It encodes a 4.5 kb mRNA transcript with a highly conserved 167-amino acid open reading frame encoding a cytokine-like hormone. Human leptin is 84% identical to mouse leptin.

- A 21-amino acid signal peptide is cleaved before release of leptin into the circulation.

- Two distinct mutations have been identified. One mutant gives rise to no leptin mRNA. The other, over-expresses a truncated mRNA with a premature stop codon (arg105 - term), this is translated into a truncated leptin protein which is rapidly degraded in adipocytes.

The structure of leptin - a bundle of 4 $\alpha$ helices (labelled A-D).
The OB-R gene

- The leptin receptor (OB-R) gene has been mapped to the diabetes (db) locus of mouse chromosome 4.

- Mutations in the receptor produce a syndrome in db/db mice that is phenotypically identical to ob/ob mice - except that administration of recombinant leptin does not result in reduced food intake and body weight.
Multiple transcripts of the leptin receptor, resulting from alternative splicing, encode 6 OB-R isoforms.

These isoforms share a common N-terminus (the extracellular domain), but have cytosolic domains of different lengths.

Only OB-Rb contains motifs within its intracellular domain that are required for signal transduction.
Leptin binding at the receptor activates the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signalling cascade.

Janus kinase (JAK) domain structure - ERM favours membrane association, SH2 binds phosphotyrosine-containing peptides.

JAK phosphorylation-induced dimerization of STAT.
Leptin intracellular signalling pathway in the hypothalamus.
Proopiomelanocortin (POMC) neurons in the hypothalamus express the leptin receptor.

POMC is a 267 aa precursor protein, the post-translational processing of which is tissue-specific and results in the production of a number of peptides with different biological activities.

Active peptides are produced by endoproteolytic cleavage at adjacent pairs of basic amino acids by the prohormone convertases PC1 and PC2.

Occupation of the leptin receptor on POMC neurons leads to the secretion of α-melanocyte stimulating hormone (α-MSH), which in turn binds to neurons expressing the melanocortin-4 receptor (MC4-R) - it is these neurons that suppress appetite.
Leptin and obesity in humans

- The effectiveness of leptin in regulating body weight and food intake in mice generated considerable interest in its possible use in the management of obesity in humans.

- Although leptin and its receptor may well be involved in human obesity, its role is not clear cut.

- Obesity in humans is usually associated with leptin resistance (i.e. lack of sensitivity to increased circulatory levels of leptin) rather than lack of leptin expression and secretion.

- Leptin resistance may reflect mutation of the leptin receptor or a defect in the mechanism responsible for the transport of leptin across the blood-brain barrier.
Human mutations associated with obesity

A mutation in the 5'-untranslated region of the human ob gene has been identified in a number of obese subjects with low serum levels of leptin.

In these patients, administration of recombinant leptin, or leptin analogues or mimetics, may be possible approaches for treatment. Unfortunately, daily s.c. injection of leptin over extended periods may not be easily tolerated in humans.

Genetic cases of POMC deficiency have been described that are associated with obesity and increased appetite.

MC4-R mutations have also been found in some obese humans.
Adiponectin

- Secreted from adipocytes. Like leptin, it plays roles in regulation of glucose and lipid metabolism and body weight. Mutations in the gene for adiponectin implicated in insulin resistance, obesity, hypertension and cardiovascular disease in humans.

- A 244 amino acid protein, it exists in low (hexameric) and high (multimeric) molecular weight forms in the plasma.

- Circulating levels correlate with insulin sensitivity and are inversely related to the degree of obesity. Decreased levels are seen in insulin-resistant states such as obesity and type 2 diabetes.

- Administration of recombinant protein reduces serum glucose in normal and diabetic rats - without stimulation of insulin secretion.

- Adiponectin receptors are expressed in skeletal muscle (AdipoR1) and liver (AdipoR2) - they appear to be linked to AMP kinase activation.
Exercise and adipokines (leptin and adiponectin) activate AMP Kinase, which phosphorylates and inhibits acetyl CoA carboxylase (ACC). This reduces malonyl CoA synthesis, activating carnitine palmitoyl transferase (CPT1) and thereby increasing mitochondrial import and oxidation of long-chain acyl-CoAs in muscle. Leptin activates AMPK in muscle through two distinct mechanisms: one is a direct effect through the leptin receptor in muscle and the other is mediated by the hypothalamic-sympathetic nervous system (SNS) axis through gO adrenergic receptors in muscle.
Resistin

- Resistin is a 10 kDa protein secreted by adipose tissue in the mouse. In humans it is primarily secreted by macrophages and monocytes.

- Although resistin appears to regulate glucose and lipid metabolism in mice - this seems unlikely in humans.
Summary

- Obesity has become an epidemic in the U.K. and therapies based upon nutritional and behavioural modifications alone have only partial and temporary benefits.

- Insulin and leptin may play significant roles in the development of obesity.

- In mice, leptin is the product of the ob gene. It is secreted by adipose tissue. Binding to leptin receptors on POMC neurons in the hypothalamus leads to the secretion of a-melanocyte stimulating hormone (a-MSH), which in turn binds to neurons expressing the melanocortin-4 receptor (MC4-R) – it is these neurons that suppress appetite.

- Mice lacking leptin are obese and will lose weight if given exogenous leptin. Mice that lack the leptin receptor show 'leptin resistance'.

- Although leptin and its receptor may well be involved in human obesity, its role is not entirely clear.