

Exercise Physiology

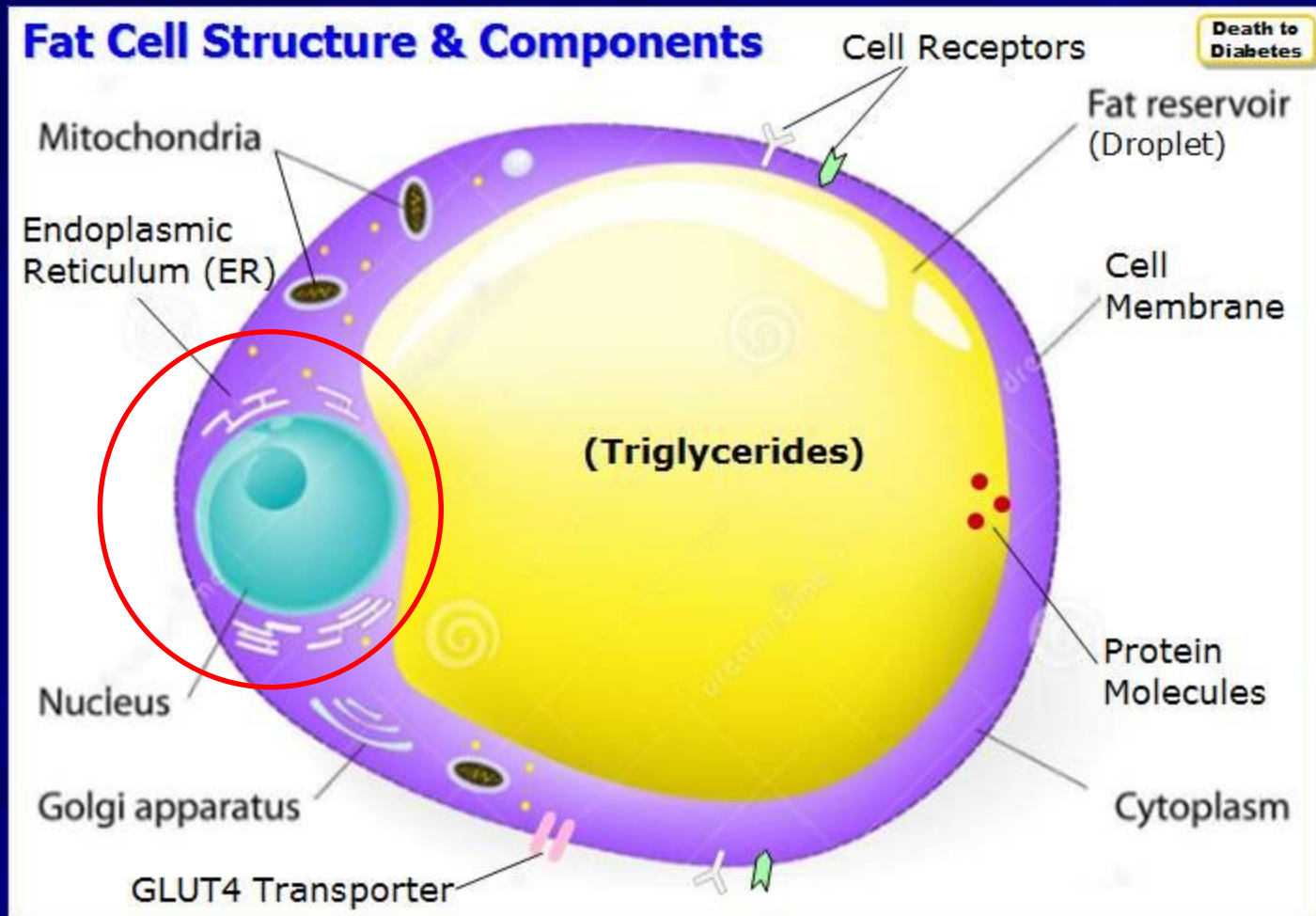
Cell Communication, Genetics and Body Weight Regulation

Aims

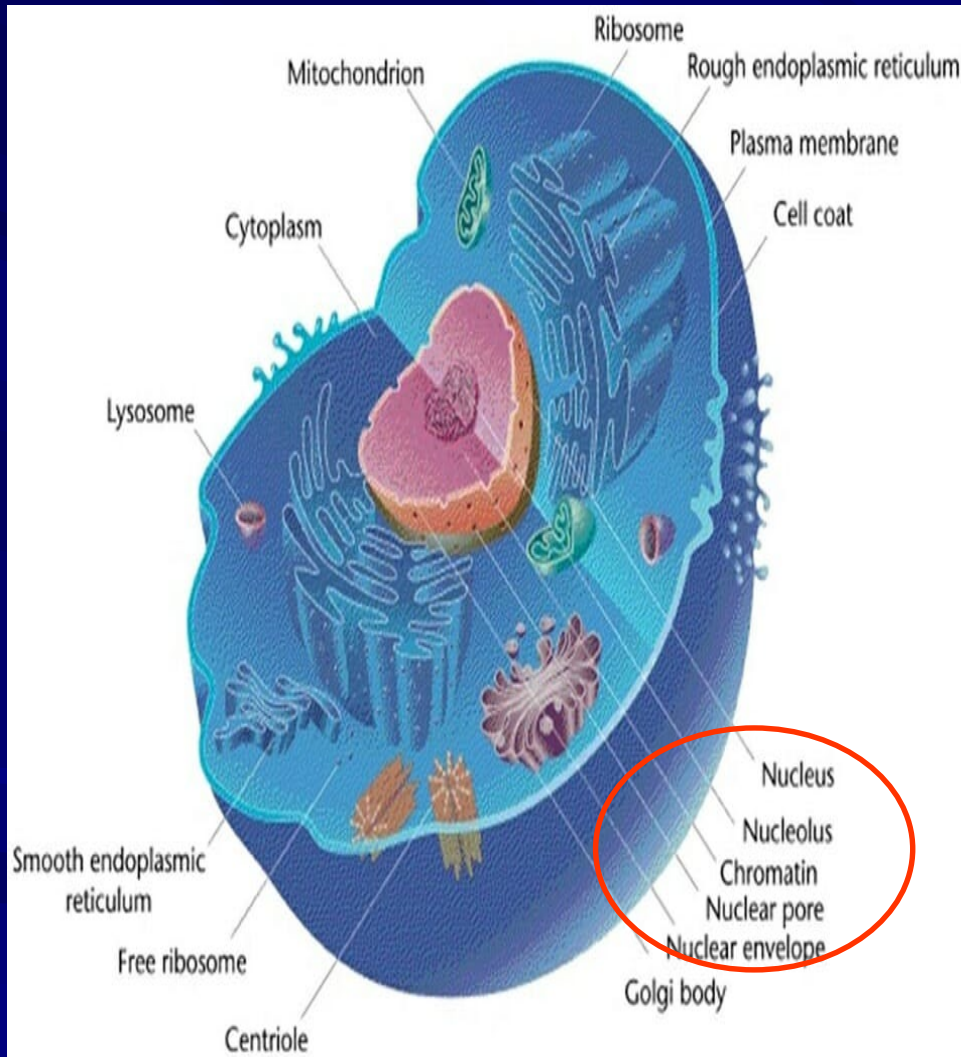
After this lecture you should be able to...

- Recognise that genes (sections of DNA) are found in the chromosomes in the cell nucleus and genes are responsible for the 'production' of proteins.
- Recognise that cells communicate with one another in a variety of ways, including by the production of hormone-like molecules.
- Recognise the difference between monogenic and polygenic disorders and the difference between genotype and phenotype.
- Recognise the function of leptin in the regulation of food intake as an example of how genes function and effect our physiology and behaviour.

The Adipocyte or Fat Cell is a Specialised Eukaryotic Cell for Storing Fat... **and much more**



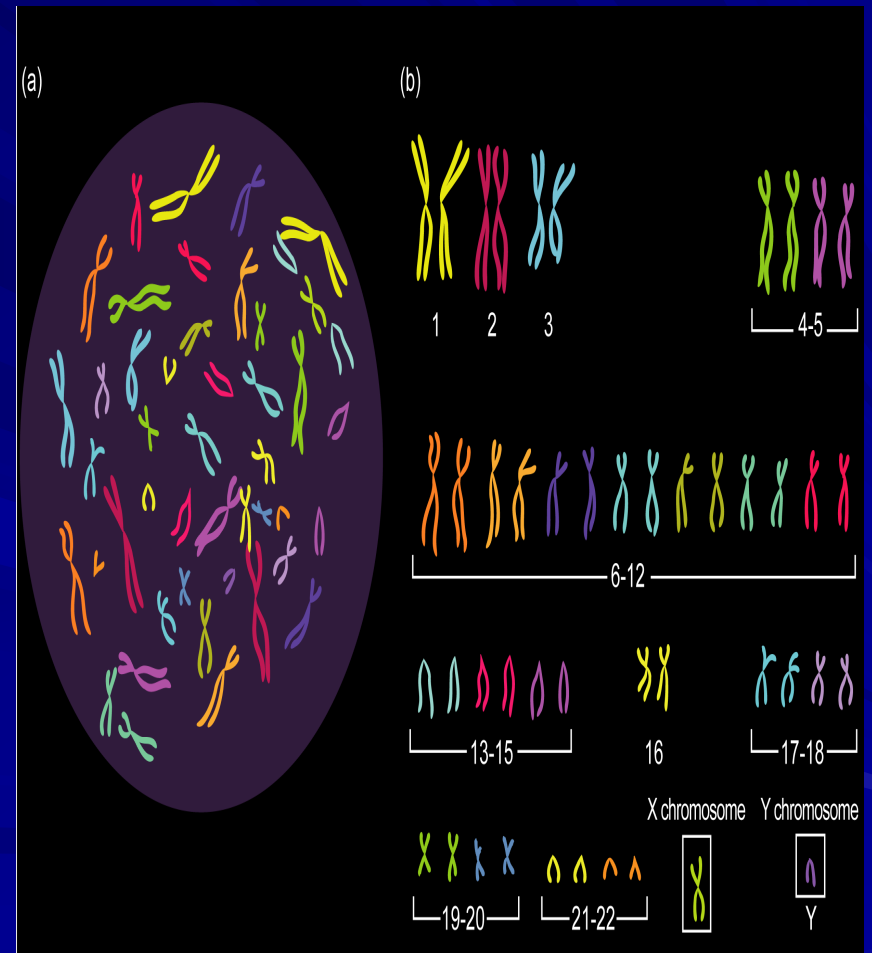
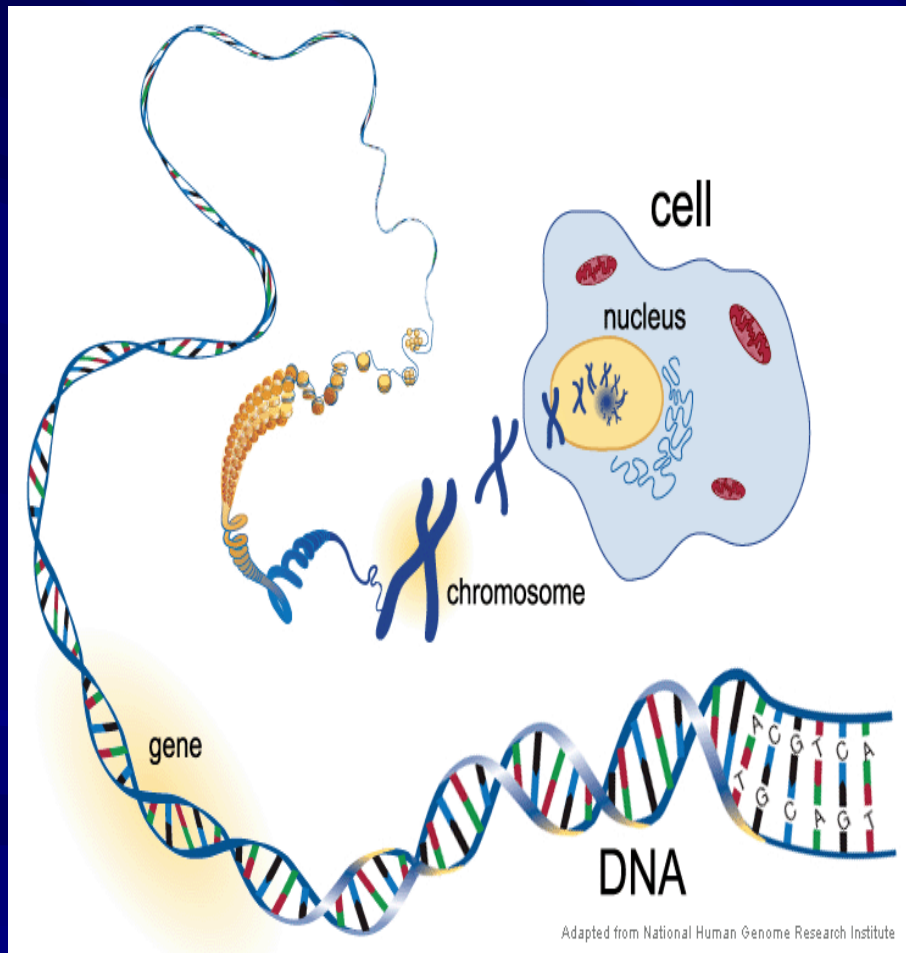
Eukaryotic Cell Structure



- Nucleus, nucleolus, chromatin, nuclear pore, nuclear envelope
 - Nucleus contains the DNA (deoxyribonucleic acid) which combines with proteins called histones to form chromatin
 - This is the genetic material of the cell
 - Nucleolus manufactures ribosomes

23 pairs of chromosomes

leptin gene is on chromosome 7

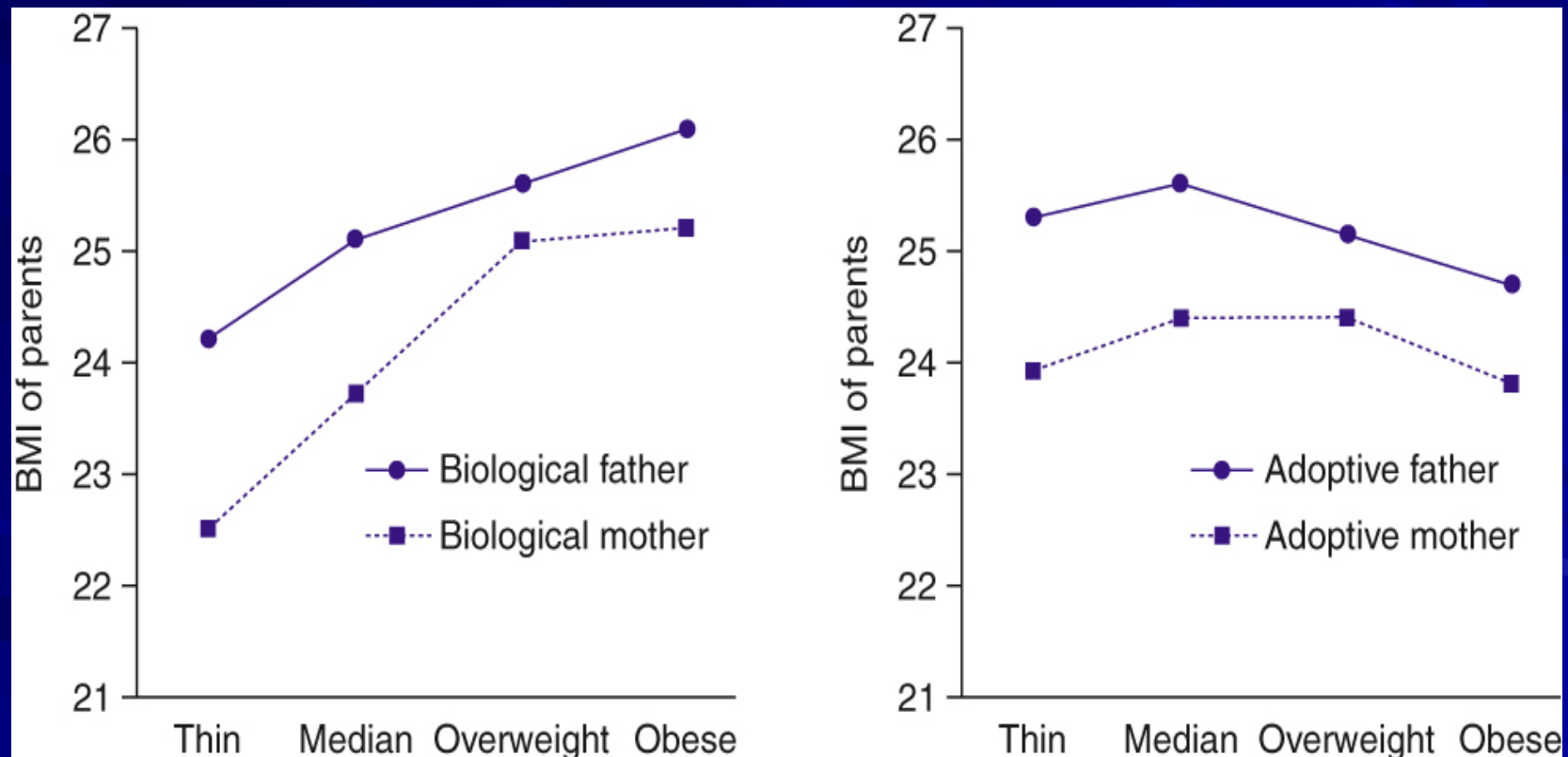


Genetics, genes and food intake

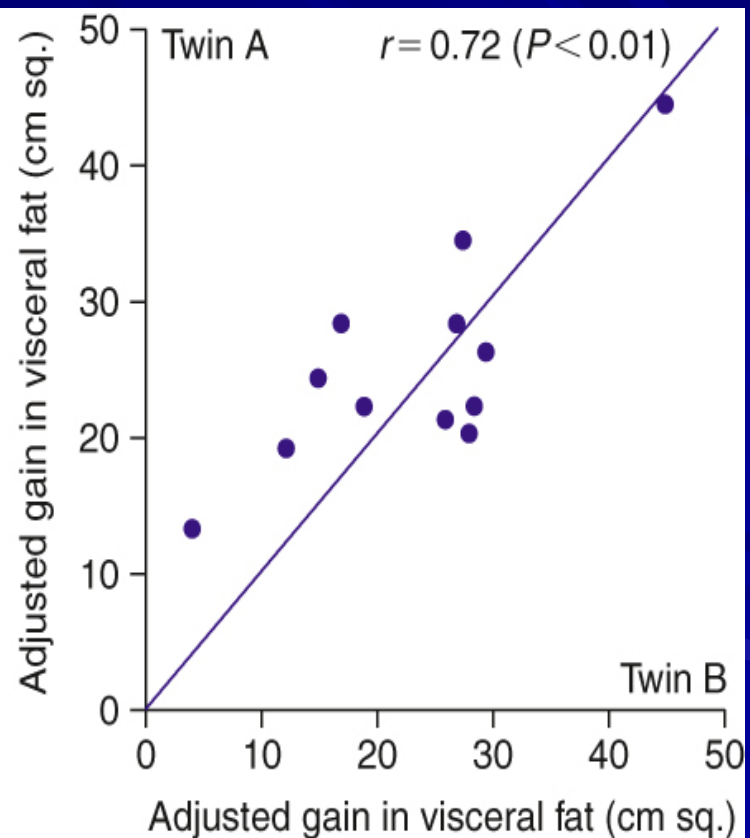
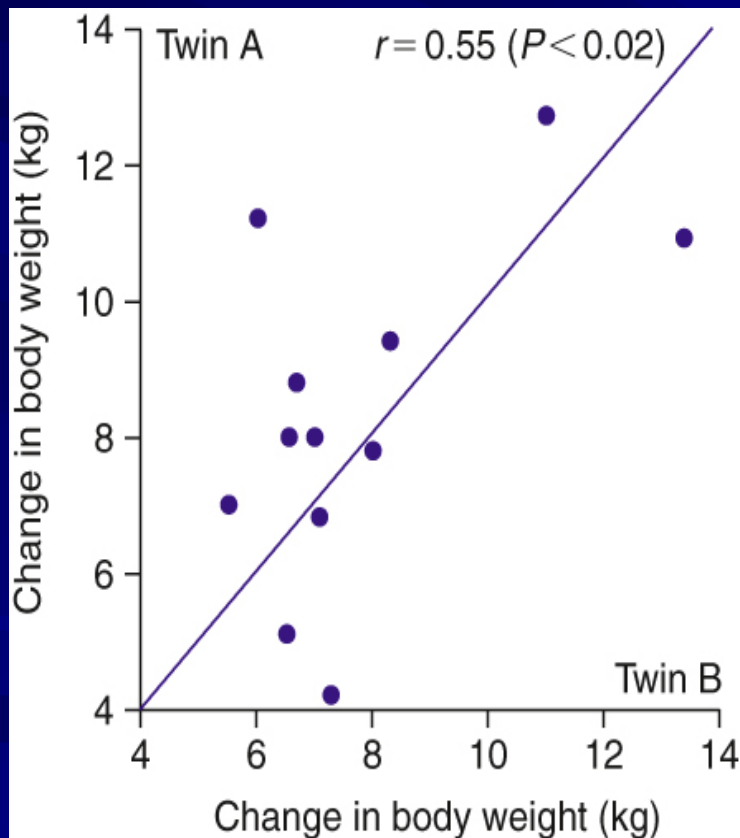


Genetics and Obesity – Clues of genetic variation from early studies.

BMI values of adopted children are associated with those of their biological parents



Gain in weight and visceral fat in monozygotic twins after overfeeding



What controls the amount we eat?

- Physiologically controlled:
 - glucostatic theory (insulin)**
 - lipostatic theory (leptin)**
 - gastrointestinal secretions (e.g. ghrelin, cholecystokinin)**
 - stretching of GI tract**

Also.....

- Food availability, food presentation, palatability, social gathering etc.....

Control of food intake - summary

- The control of food intake can be considered over the short term (meal-to-meal and day-to-day) or the longer term and involves many highly complex neural and hormonal regulatory systems.
- Hunger = the drive to eat
- Appetite = the desire to eat particular foods
- Satiation = the feeling of fullness which terminates eating
- Satiety = the feeling of repletion that inhibits future hunger

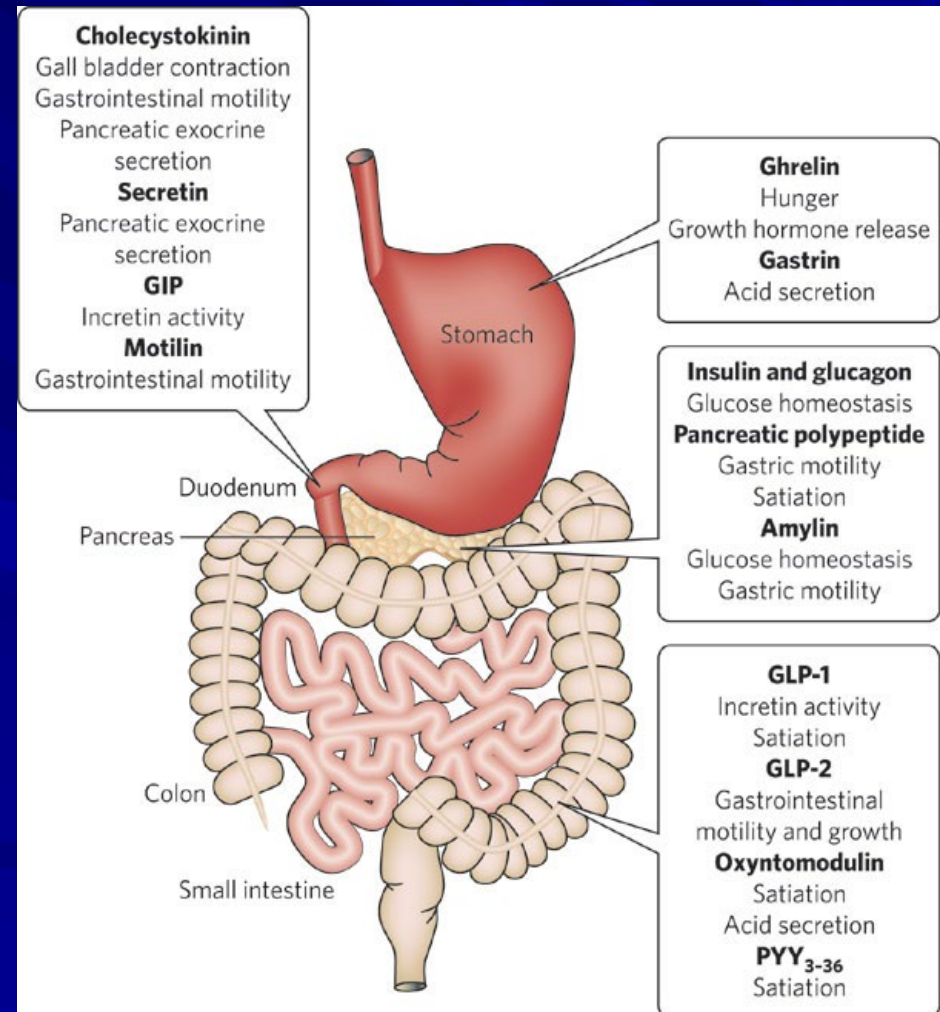
Short term control of food intake

- Short term food intake is controlled by the suppression of hunger at the end of a meal (satiation) and by a period of hunger absence between meals (satiety).

Short term control of food intake

covered on the 26th November

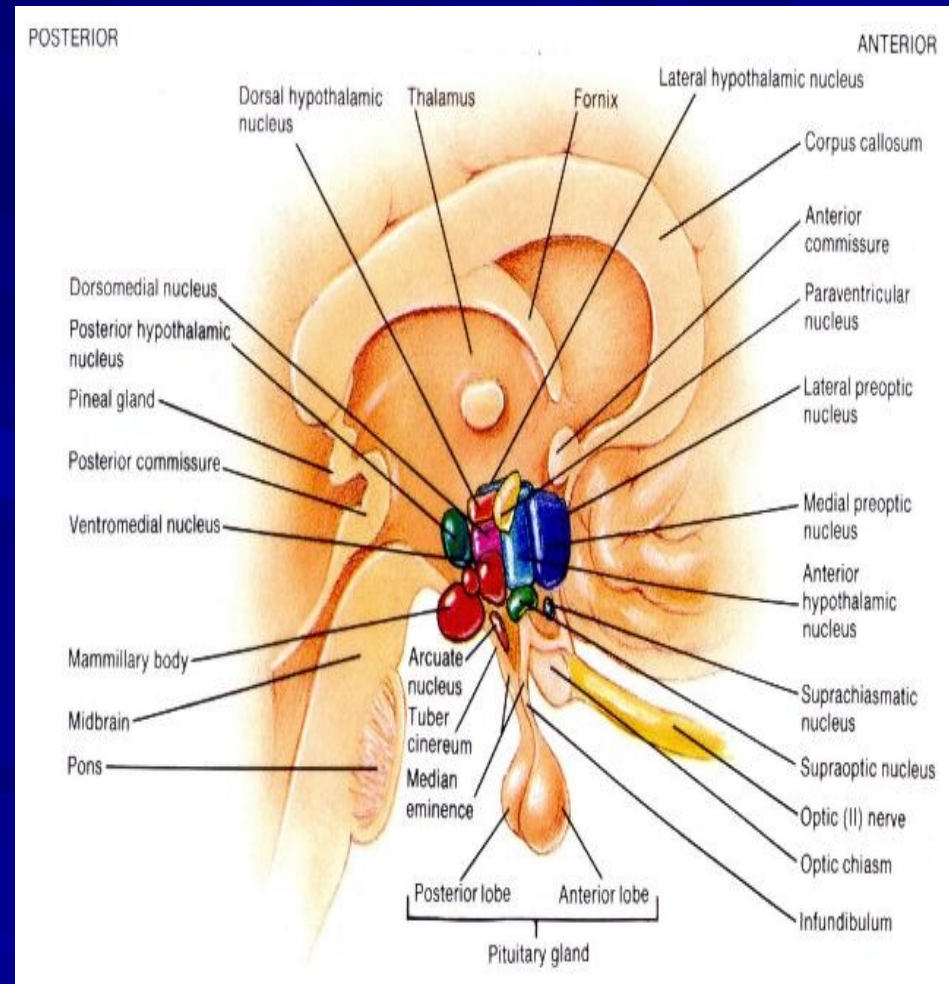
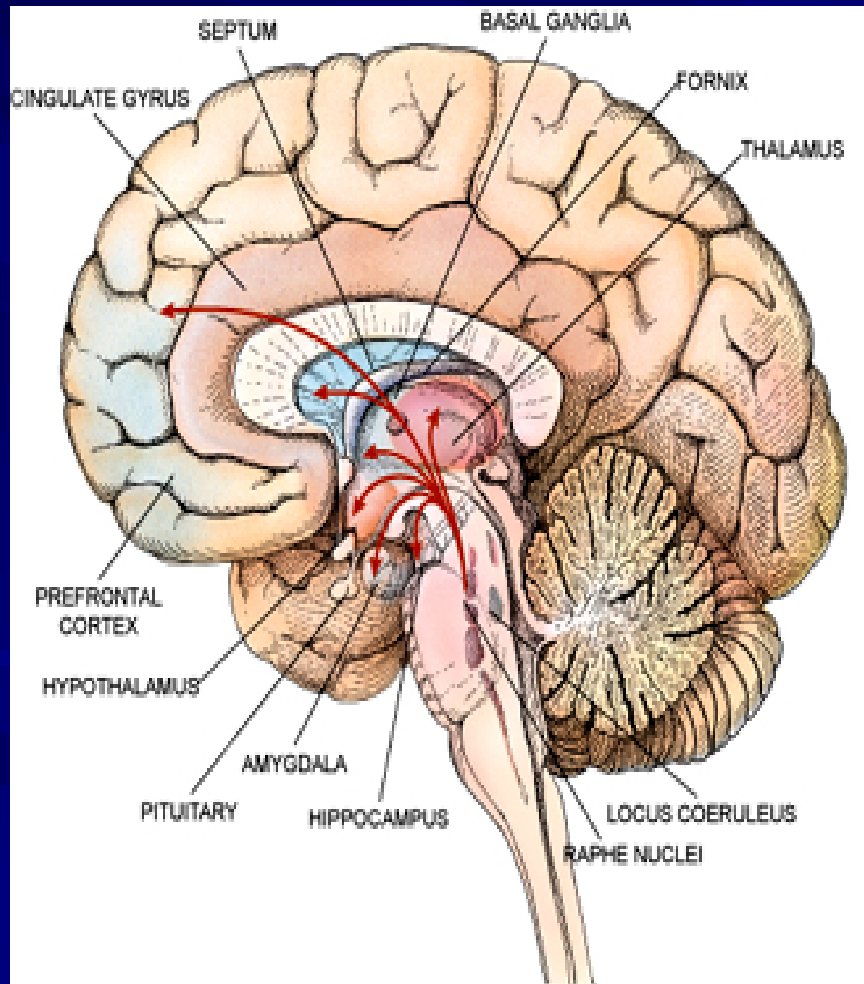
- Biological signals that arise in the gastrointestinal tract
 - **Inhibitors (anorexigenic or satiety signals)** such as:
 - cholecystokinin, Glucagon Like Peptide-1 (GLP-1), pancreatic polypeptide (PP) and protein YY (PYY)
 - **Stimulators (orexigenic signals)** such as:
 - ghrelin



Long term control of food intake

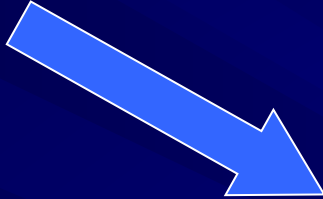
- Long term food intake is controlled by other neuroendocrine factors that communicate the size of the adipose mass (i.e. energy stores in the body) to the brain (in particular the hypothalamus).

The hypothalamus – a collection of neurons receiving & processing information and synthesising a variety of neuropeptides (small protein molecules that allow neurons to communicate)



The Discovery of Leptin & the homozygous ob/ob mouse

Lipostatic
Theory
(Kennedy,
1953)



*(These animals are: obese,
hyperphagic, infertile,
immature and susceptible
to type 2 diabetes)*

Discovery of the 'mutant'
mouse
by Douglas Coleman at the
Jackson Laboratory, USA.
[http://www.jax.org/thesea
rch/vol6no1/beyond-
news.html](http://www.jax.org/thesea_rch/vol6no1/beyond-news.html)



The Discovery of another mutant mouse in the 1960's, the homozygous db/db mouse



(These animals are ALSO obese, hyperphagic, infertile, immature and susceptible to type 2 diabetes)



What is the product of the *ob* and *db* genes?



Discovery of the product of the *ob* gene by Jeffrey Friedman at the Rockefeller University, NY.
<http://www.rockefeller.edu/research/faculty/labheads/JeffreyFriedman/>

The *ob* gene product was named leptin after the greek word *leptos* meaning “thin”. The product of the *db* gene is the leptin receptor, Lep-R or Ob-R



Why is the *ob/ob* mouse so fat? What causes the hyperphagia?



Normal *ob* gene produces leptin.
Leptin signals to the brain the
size of the body fat stores.
Food intake is controlled.



Mutated *ob* gene fails to produce leptin.
No signal to the brain about body fat.
Hyperphagia results.

How do these findings relate to humans?

Is human obesity the result of leptin deficiency?

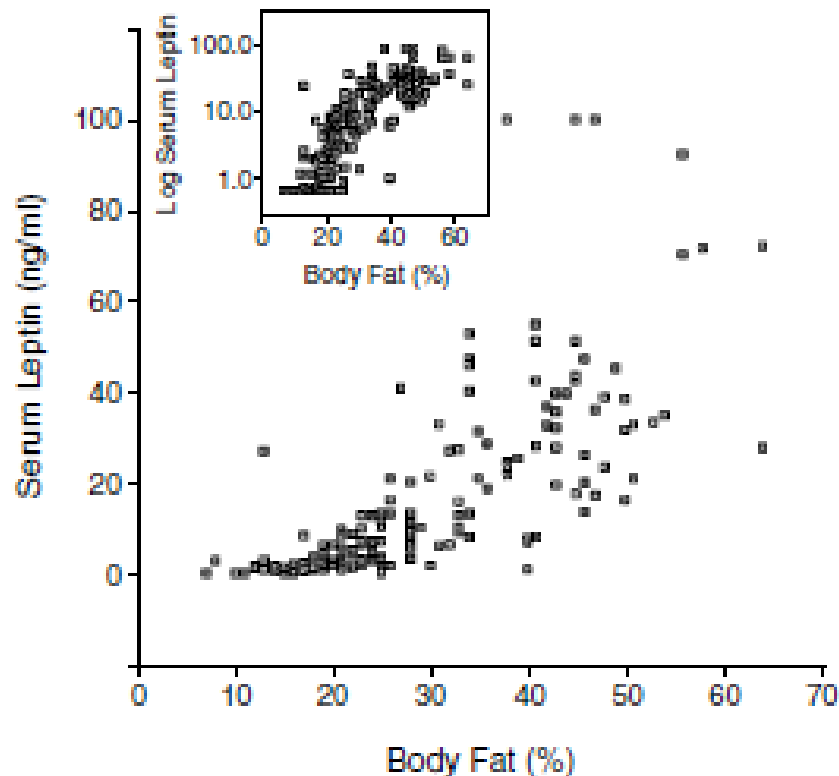


Figure 1. The Relation between the Percentage of Body Fat and the Serum Leptin Concentration in 136 Normal-Weight and 139 Obese Subjects.

The inset shows the natural log of the serum leptin concentration plotted against the percentage of body fat.

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Feb. 1, 1996

SERUM IMMUNOREACTIVE-LEPTIN CONCENTRATIONS IN NORMAL-WEIGHT AND OBESE HUMANS

ROBERT V. CONSIDINE, PH.D., MADHUR K. SINHA, PH.D., MARK L. HEIMAN, PH.D.,
AIDAS KRIAUCIUNAS, PH.D., THOMAS W. STEPHENS, PH.D., MARK R. NYCE, M.S.,
JOANNA P. OHANNESIAN, B.S.N., CHERYL C. MARCO, R.D., LINDA J. MCKEE, M.H.S.,
THOMAS L. BAUER, M.D., AND JOSÉ F. CARO, M.D.

NO...% body fat is positively related to serum leptin!

But there are very rare cases of extreme obesity, hyperphagia and leptin deficiency that respond to leptin therapy.

0021-972X/04/4515.00/0
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CLINICAL CASE SEMINAR

Congenital Leptin Deficiency Due to Homozygosity for the $\Delta 133G$ Mutation: Report of Another Case and Evaluation of Response to Four Years of Leptin Therapy

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University Department of Clinical Biochemistry, Cambridge Institute for Medical Research, Addenbrooke's Hospital (W.T.G., I.S.F., S.O.), Cambridge, United Kingdom CB2 2XY; Department of Pediatric Endocrinology, Alberta Children's Hospital (M.M., R.A.T.), Calgary, Alberta, Canada T2T 5C7; and Amgen, Inc. (A.M.D., E.L.), Thousand Oaks, California 91320-1799

Age (Years)



FIG. 3. Clinical photographs of the proband before initiation of therapy at age 5 yr (A) and after 48 months of leptin therapy at age 9 yr (B).

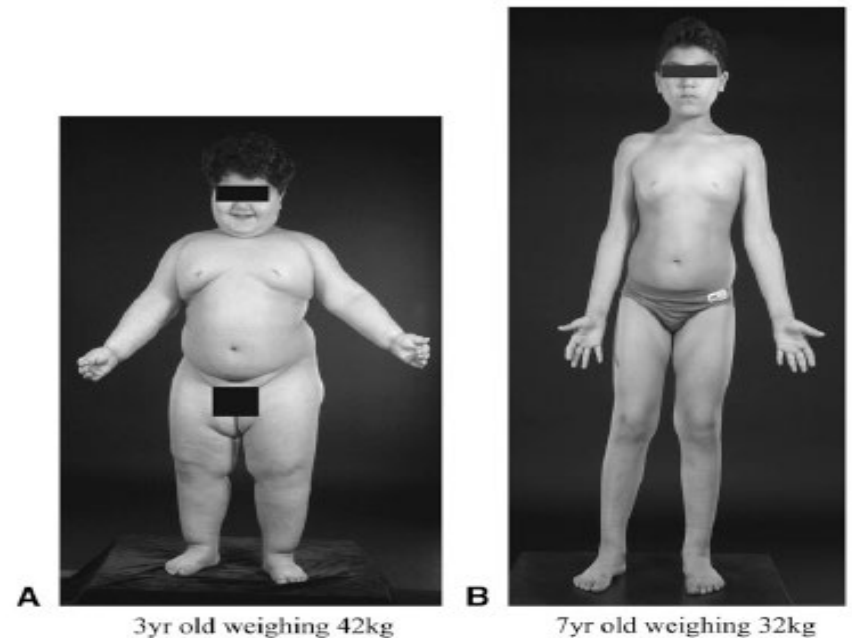
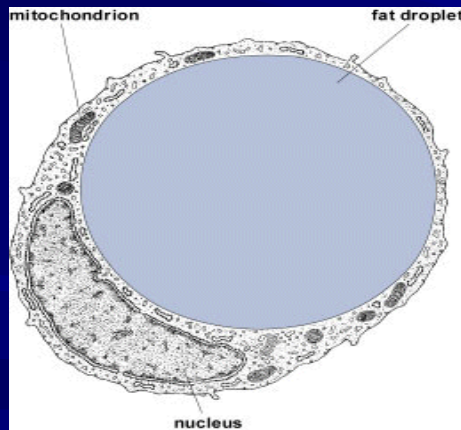
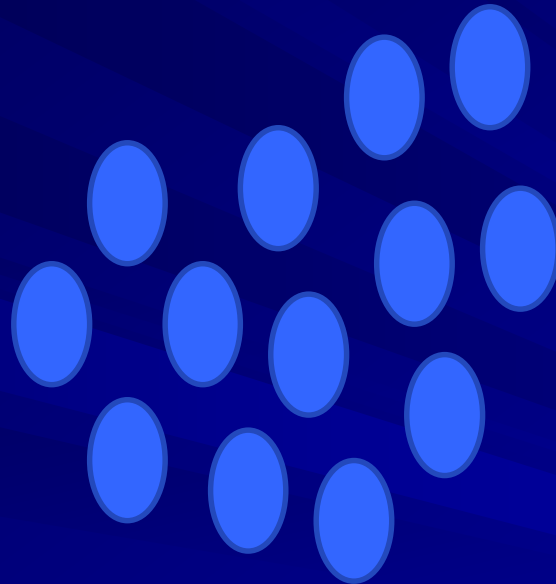


FIGURE 1. Effects of recombinant human leptin treatment in a patient with congenital leptin deficiency. (A) Before treatment. (B) After treatment.

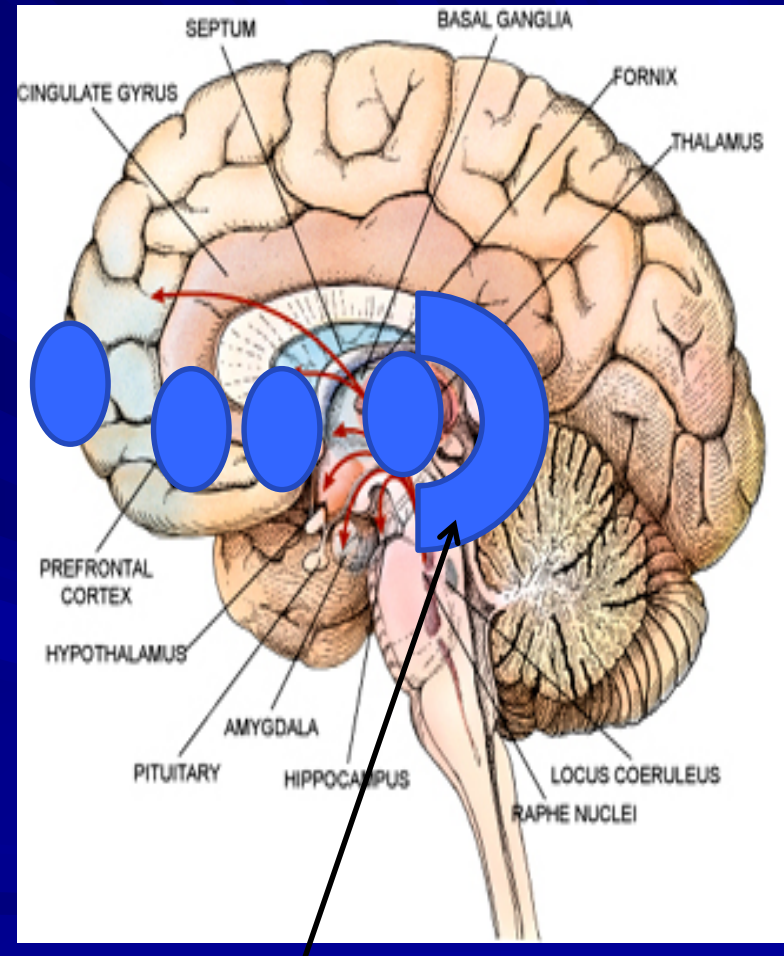
So what is leptin's action?



Enlarged fat cells



Increased leptin



Hypothalamic leptin receptor

What is the role of leptin?

- To prevent obesity?
- To prevent leanness?
- The expression of the 'thrifty genotype'

Summary

- Long term control of energy intake is (partly) regulated by afferent signals from the adipose tissue to the hypothalamus – i.e. Leptin.
- Body fat mass is directly related to leptin concentrations and leptin has multiple functions including a permissive effect on puberty, blood pressure control, reproductive health and bone health.
- Modern lifestyles and food availability/palatability mean that for many people food intake regulatory systems are overridden and overconsumption occurs.