# Pharmacotherapy of obesity and insulin resistance

## Regulation of appetite

Ilona Benkő M.D., Ph.D.

University of Debrecen, Faculty of Medicine,
Dept. of Pharmacology and Pharmacotherapy

DEBRECENI EGYETEM

# BMI = body mass index

- **BMI = body mass in kg / square of the height in metres = $kg/m^2$**

| | |
|---|---|
| • **BMI < 18.5 $kg/m^2$** | **underweight** |
| • **18.5 < BMI < 25** | **normal or acceptable weight** |
| • **25 < BMI < 30** | **obesity grade 1** |
| • **30 < BMI < 40** | **obesity grade 2** |
| • **BMI > 40** | **obesity grade 3 or morbidly obese** |

# FAT TISSUE is an endocrine organ !!!

**and produces a lot of adipokines**

| Increase of insulin resistance | In obese people | Insulin sensitizers | In majority of obese people |
|---|---|---|---|
| resistin<br>TNF alpha | ↑<br>↑ | leptin<br>adiponectin | ↑<br>↓ |

**The leptin receptorial resistance is common**

# PHARMACOTHERAPY OF OBESITY

**pharmacotherapy is indicated in**

- **Patients with BMI >30**
- **Patients with BMI >28 with additional risk factors.**

**First-line therapy : change diete and lifestyle**

**1. Drugs that affect appetite**

**A. Sympathomimetics, psychostimulants**

**B. Peptides**

**C. Drugs influencing behaviour and moodness**

**2. Drugs that decrease absorption of fat, cholesterol or carbohydrates**

**3. Drugs that increase metabolic rate**

**4. Drugs for lowering risk of complications in obese people**

**e.g. insulin sensitizing, lipid lowering drugs, antihypertensive therapy**

# Recently used weigt reducing drugs

| group | WHO name | Brand name |
|---|---|---|
| Psychostimulant+antiepileptic anorexigen | phentermine + topiramate | Qsymia |
| Psychostimulant, anorexigen | mazindol | Mazanor, Sanorex |
| Psychostimulant, anorexigen | lorcaserin | Belviq |
| Psychostimulant, anorexigen | **bupropion+ naltrexon** | Mysimba |
| Leptin analog, anorexigen | metreleptin | Myalept |
| Inhibitor of lipid absorption Lipase inhibitor | orlistat | Xenical |
| Inhibitor of glucose absorption Alpha glucosidase inhibitor antidiabetics | acarbose | Glucobay |
| Inhibitor of glucose absorption Alpha glucosidase inhibitor antidiabetics | miglitol | Glyset |
| GLP-1 receptor agonist antidiabetics | exenatide | Byetta sc inj. |

# 1. Drugs affecting appetite

## 1. A. Sympatomimetic drugs, psychostimulants

### HYPOTHALAMUS

**Lateral nucleus**

**Control of HUNGER**

***Inhibitory type dopamin effect***

**first anorexigenes have *amphetamine-like effects***

**Phentermine which has amphetamine-like effect in combination with topiramate is used today**

**DA uptake inhibitor**

***mazindol***

**Ventromedial nucleus**

**Control of SATIATION**

**Serotonin 5HT2C receptor, alfa 1**

**Dexfenfluramine REDUX, Isolipan - withdrawal**

Side effect: Endocardial fibrosis mostly in the right heart

**lorcaserin is used even today**

**NA and serotonine uptake inhibitor:**

***sibutramine (Reductil, Meridia)* - withdrawal**

***because of increased cardiovascular toxicity***

### TOXICITY

**They are CENTRALLY ACTING STIMULANTS (in CNS) and result in high- sympathetic activity:**

**Headache, nausea, nervousness, insomnia, tremor, palpitation, tachycardia, hypertension, dry mouth , constipation, taste disorders**

**Psychosis, depression**

**CONTRAINDICATION:** **Pregnancy, during breast-feeding, cardiovascular diseases, psychosis, childhood and in elderly**

# Lorcaserin (Belviq) (USA 2012)

**Target in CNS:** in control of satiety in hypothalamus

selective agonist of $5HT_{2C}$ receptors

**Effect on $5HT_{2C}$ 100x than on 5-$HT_{2B}$ receptors**

Side effect: Mitral regurgitation, valvulopathy in clinical trials (2014)

Pathomechanism:

5-$HT_{2B}$ receptors are found in valvula in heart and in pulmonary arteries

⇩

phospholipase $C_{beta}$ ⇨ protein kinase C (PKC)

⇩

ERK1,2

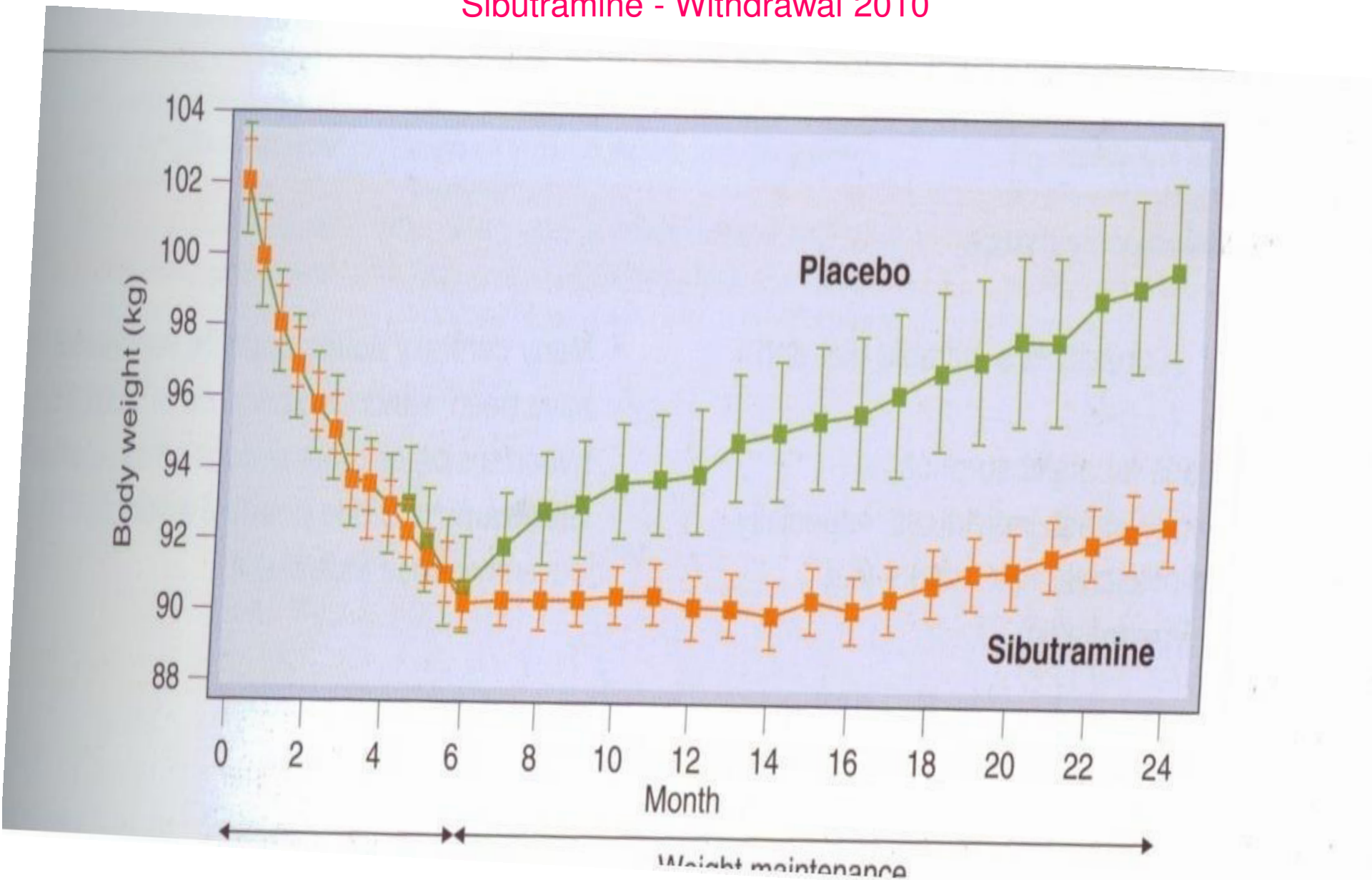
⇩

TGF-béta receptor1

⇩

increased production of the glucose amino glycan in valvular interstitial cells

# Sibutramine - Withdrawal 2010



# Toxicity of amphetamine-like drugs and psychostimulants: too much stimulatory effects in sympathetic vegetative centre of Hypothalamus

**Synonym names of this syndrome:**
**Sympathetic overflow, serotonine syndrome, disco fever, amfetamine intoxication**

**The following symptomes even in combination**

**Disorder in control of body temperature**

**malignant hypertermia** → **DEATH**

**Hypertonia with high amplitudes**

**hypertonic crisis** **stroke** → **DEATH**

**Overstimulation of cardiac muscle**

**ischaemia** **myocardial infarction** → **DEATH**

# Bupropion+ naltrexon (MYSIMBA)

**Effects in CNS:** mesolimbic dopaminergic reward pathways and hypothalamus
bupropion has dopamin + NA uptake weak inhibitory effect
+ naltrexon which is μ (mu) opioid receptor antagonist and potentiates effects of bupropion

Anorexigene + decrease of fat tissue even in visceral fat

Pharmacokinetics: p.o. bioavailability: 5-6 %, with meals is higher
T1/2 : naltrexon 5 hours
bupropioné 21 h - 2x a day administration
excretion even to the breast milk !

bupropion inhibits **CYP 2D6 – drug interactions** !!
CYP2B6 inductors enhance toxicity of bupropion e.g. carbamazepine, phenytoin

Adverse effects:
Epileptiform convulsions, psychotic symptoms with suicid actions, anxiety, insomnia, tremor, head-ache, tinnitus, vertigo, fever
hypertension, palpitation, angina pectoris, arthralgia,myalgia,,
nausea, mild hepatotoxicity, colica abdominalis, pruritus, sweating

CONTRAINDICATION: epilepsy, risk for suicid actions, MAO-I therapy, uncontrolled haypertension, addiction of opioids/etanol/benzodiazepines, malignancies in CNS, hepatic and renal insufficiencies, pregnancy, childhood

# *Ephedra sinica*

Ephedra distachya L.

*Ephedra sinica*: about 0,5 m in height, Northeast-China
Active ingredient:
**ephedrin and pseudoephedrin alkaloids.**

Mode of action of ephedrin :

Indirect + direct mixed type sympatomimetics
Effects in CNS+ periferally.

Indirect : neurotransmitter release from adrenerg neurons – amfetamin-like effect

CNS sympathetic overflow sy – stimulatory amfetamine-like effect - euphoria

Direct effect:

| | alfa1 | beta1 | beta2 |
|---|---|---|---|
| adrenalin | +++ | ++++ | +++ |
| efedrin | + | +++ | ++ |

# *Ephedra sinica*/ Ma Huang

ephedra is one of the most infamous dietary supplement

use: body building, sportmen, obesity,
for weight reducing, enhancement of performance

effects: weight reducing effect within 1-12 months
synergistic effect in combination with caffeine

Acute sympathomimetic effects in CNS+periferally

Reduced sensation of fatigue, enhance breath volume + cardiac output

Adrenergic effects , e.g. enhanced blood sugar ⟹ excess energy

⇓

Enhancement of performance

# *Ephedra sinica withdrawal*

Ephedrin therapeutic use:

as a drug, the synthetic ephedrin is the component of Mixtura pectoralis FoNo

Bronchodilatation in obstructive bronchitis, asthma bronchiale

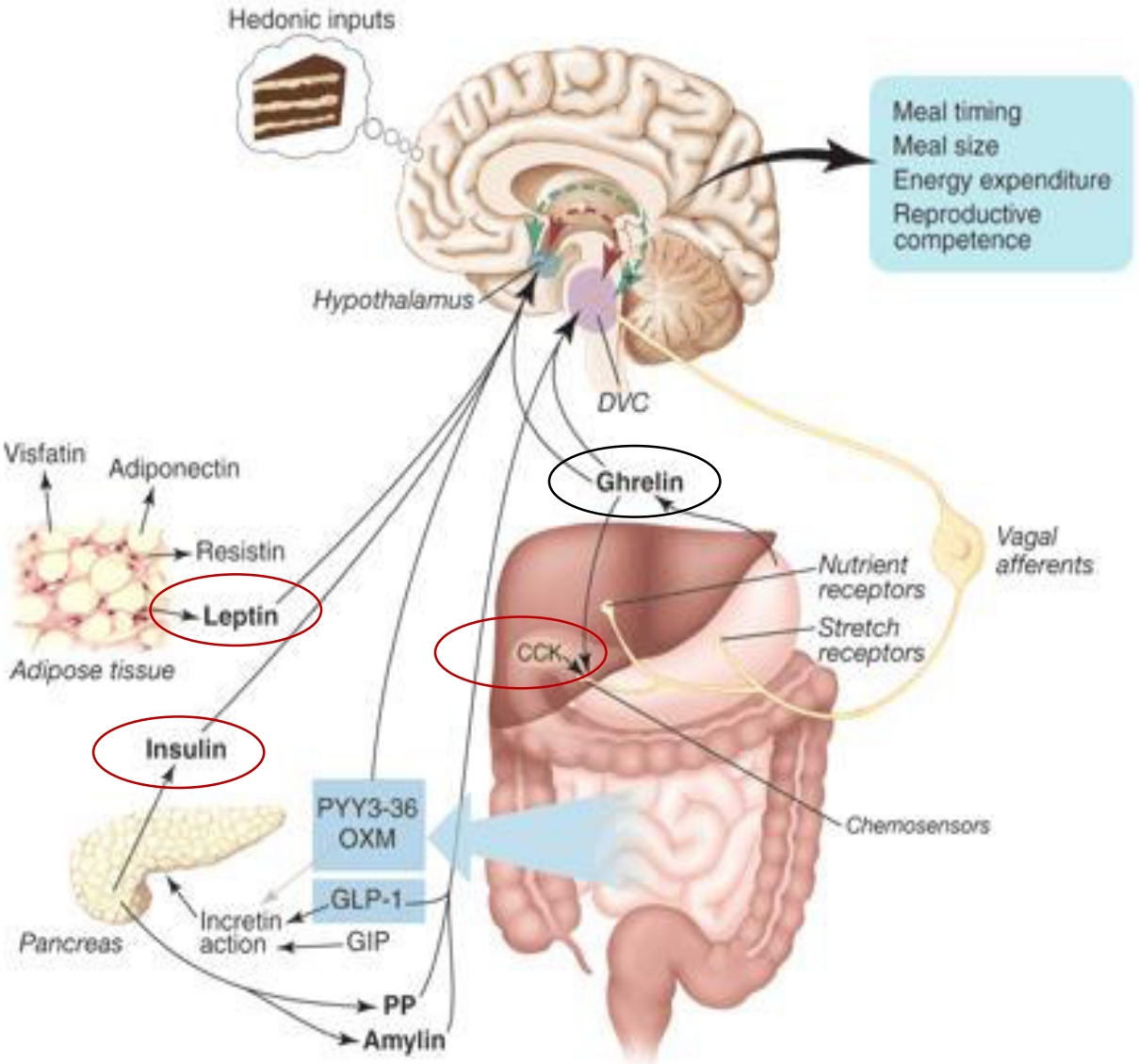
Ephedrin-containing dietary supplements: are PROHIBITED to sell

2004.U . S . Food and Drug Administration ( FDA ) banned dietary supplements, herbs containing *ephedra sinica*

2005. in Utahban tried to delibarate, but several months later it was banned again.

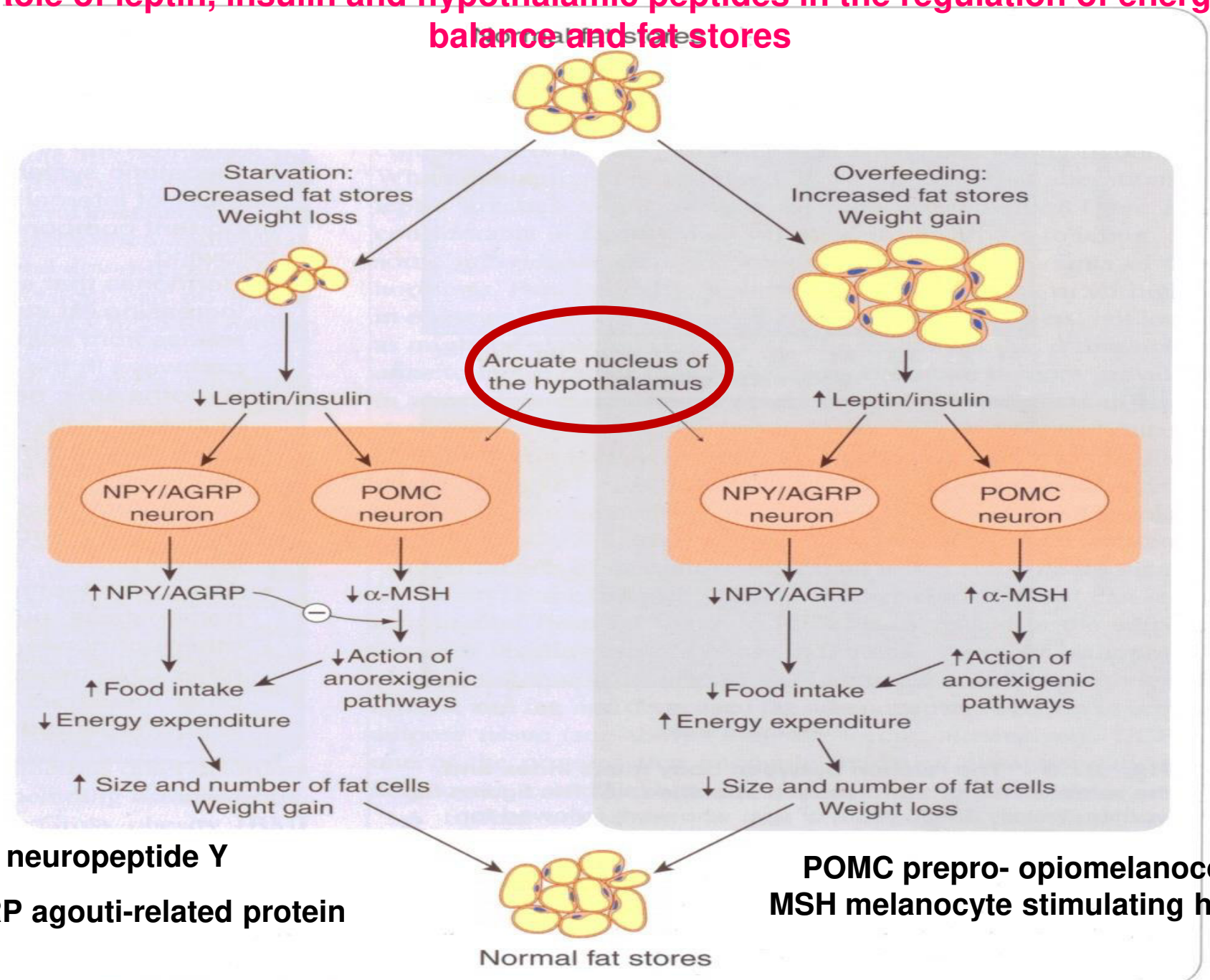
Many DEATH of young men due to the uncontrolled use of *ephedra sinica*

# Regulation of appetite




Badman M.K. and Flier J.S.
Science, 307,1909-1914 , 2005

# Role of leptin, insulin and hypothalamic peptides in the regulation of energy balance and fat stores




**NPY neuropeptide Y**

**AGRP agouti-related protein**

**POMC prepro- opiomelanocortin**

**MSH melanocyte stimulating hormon**

| OREXIGENS | ANOREXIGENS |
| --- | --- |
| increase food intake | decrease food intake |
| NA alpha2 | NA alpha 1 |
| GABA $_A$ | dopamine |
| Beta-endorphins | serotonine |
| NPY | CCK |
| peptid YY | leptin |
| galanin | adiponectine |
| GHRH | CART peptide cocain-amphetamine regulated peptid |
| endocannabinoids CB1 | CRH |
| | POMC |

## RIMONABANT CB1 ANTAGONIST

SITE OF ACTIONS IN CNS: both in hypothalamus and limbic system

u opiod receptor antagonists potentiate its effect, e.g. naloxone

SITE OF ACTIONS IN PERIPHERAL TISSUES:

liver: inhibits lipogenesis

visceral fat: inhibits lipogenesis and adiponectin production, increases beta oxidation of fats

sceletal muscles: increases glucose uptake and thermogenesis

PHARMACOKINETICS:

plasma protein binding high
T1/2 = 9-16 days !!
CYP 3A4 interactions !
excretion to milk

SIDE EFFECTS

Withdrawal (2008) because of doubling risk of psychosis

# Peptides under investigation

| | | | |
|---|---|---|---|
| **Peripheral peptides**[c] | | | |
| Leptin (adipocyte hormone) | Leptin receptor agonists, leptin sensitizers, leptin mimics: ciliary neurotrophic factor (CNTF) and axokine | Preclinical (mutant mice, leptin treatment in rodents)<br>Clinical (human mutations, leptin trial) | 7,41<br>9–11 |
| Cholecystokinin (CCK) | CCK analogues, $CCK_1$ and $CCK_2$ receptor agonists | $CCK_1$ receptor KO mice and mutant rats controversial | 37,41 |
| | Inhibitors of degradation | In clinical studies | |
| Enterostatin | Enterostatin analogues<br>Enterostatin receptor agonists | Clinical evidence (i.v. study) negative<br>Receptor not yet known | 1,37 |
| Glucagon-like peptides GLP-1 and GLP-2 | GLP analogues or receptor agonists | Clinical | 37 |
| | Inhibitors of degradation | No validation | |
| Amylin | Amylin and analogues | No validation | |
| | Amylin receptor agonists | Receptor not yet cloned | |
| Bombesin | Bombesin analogues<br>Bombesin-related receptor subtype 3 ($BRS_3$) agonists | Preclinical ($BRS_3$ KO mice) | 41 |

[a]Validation refers to confirming data from knockout, transgenic or mutant animals, or from human studies, including clinical trials and reported mutations.

[b]Abbreviations: i.v., intravenous injection; KO, knockout.

[c]Most of the peripheral peptides are released from the gastrointestinal (GI) tract in response to a meal and regulate food intake, mainly as satiety factors. Some peptides can, in addition, modulate nutrient absorption and passage through the GI tract. Many peripheral peptides were shown to reduce food intake when administered centrally.

...and CoA synthetase in the endoplasmic reticulum by

# 1. Drugs affecting appetite

## 1.B. In the rare leptin deficiency: rh leptin

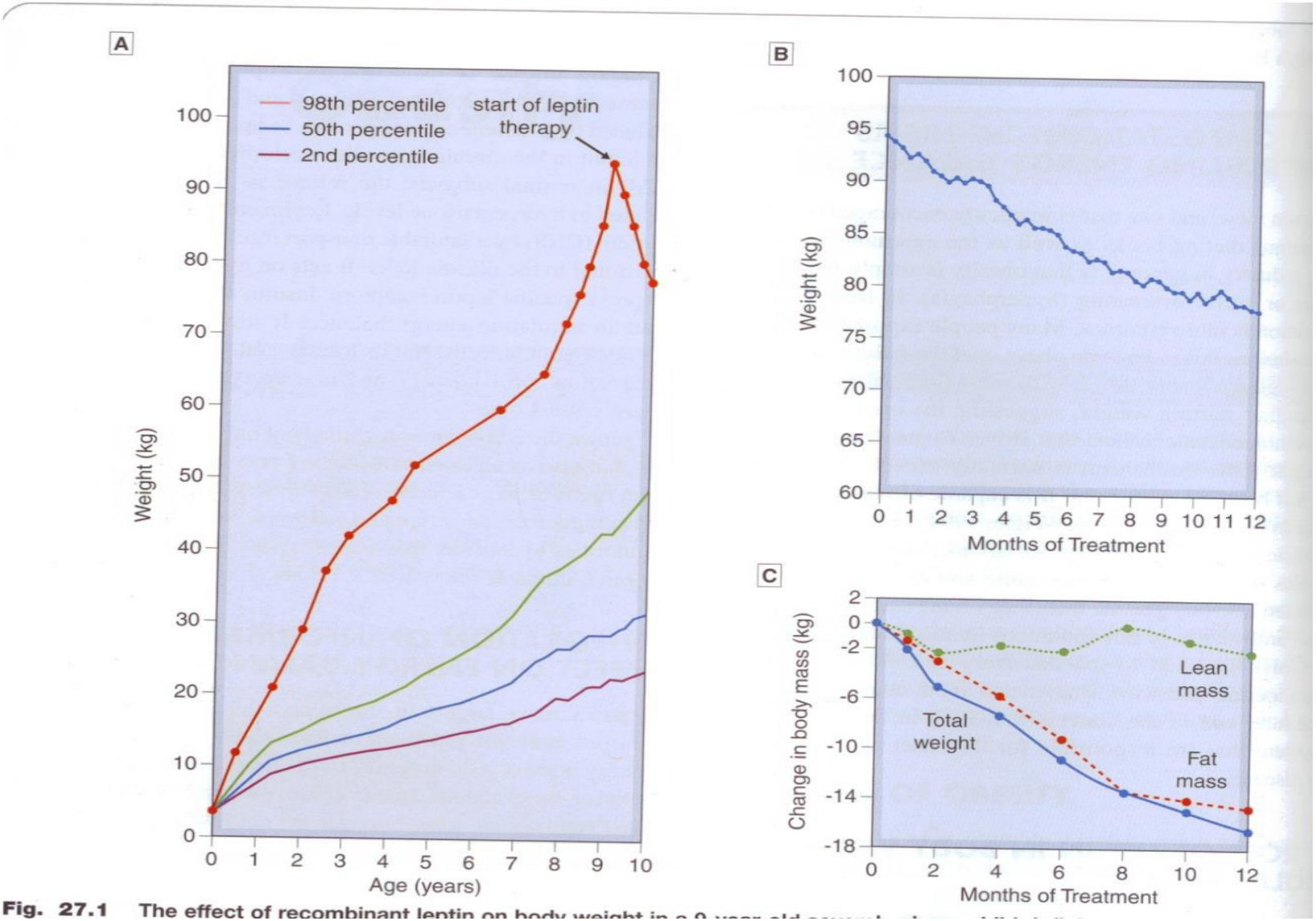



**Fig. 27.1** The effect of recombinant leptin on body weight in a 9-year-old

# Leptin

**Insulin increases leptin release**

**To date, only leptin and insulin are known to act as an adiposity signal.**

**In general,**

**Leptin circulates at levels proportional to body fat and BMI**
**It enters the CNS in proportion to its plasma concentration.**
**Its receptors are found in brain neurons involved in regulating energy intake and expenditure.**
**It controls food intake and energy expenditure by acting on receptors in the mediobasal hypothalamus**

**periferally it increases insulin sensitivity,**
**influences maturation of hemopoietic cells**

**glucocorticoids and oestrogenes decrease leptin blood level**

**beta3 receptor agonists decrease insulin-induced leptin release**

| | | |
|---|---|---|
| **Animal models:** | **ob/ob mice (obesity)** | **lack of leptin gene** |
| | **db/db mice (+diabetes)** | **leptin receptor defect** |

## 1.C. Drugs influencing behaviour and moodness

**CNS side effects, which led withdrawal of the most effective drugs show the importance of psychological factors.**

**•Antidepressants especially serotonin reuptake inhibitors have good effect on weight loss.**

**•Some antiepileptics (e.g. topiramate, zonisamide) may decrease attacks in food intake**

# 2. Drugs that decrease absorption of fat, cholesterol or carbohydrates

A. GI lipase inhibitors: **orlistat** (Xenical)

**Target** : lipase inhibitor in GUT
**Mechanism of action**: reduces absorption of fats since triglicerides not split

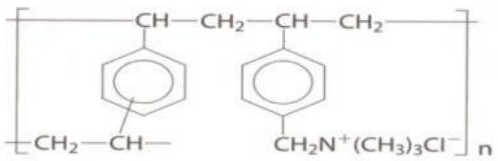
**Side effects**: flatulance, steatorrhea, fecal incontinence

**Clinical use**:
obesity for weight reducing and education of obese people for the proper diete !
In education it has similar role than disulfiram therapy in alcoholism

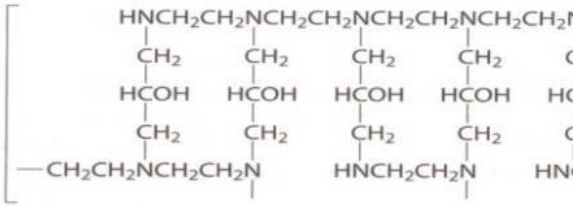
OTC drug

## 2. Drugs that decrease absorption of fat, cholesterol or carbohydrates (cont)

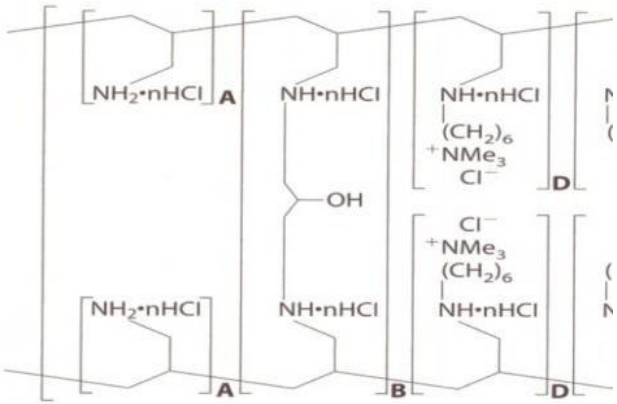
Cholestyramine



Colestipol



Colesevelam



A = Primary Amines

B. Bile acid binding resins
Plant fibers

C. Ezetimibe

D. Alpha glucosidase inhibitors: acarbose, miglitol

Side effects: flatulence, diarrhoae,
colica abdominalis
Hepatotoxicity

Contraindication: ulcus pepticum
inflammatory bowel diseases

## 3. Drugs that increase metabolic rate

A. Beta 3 agonists

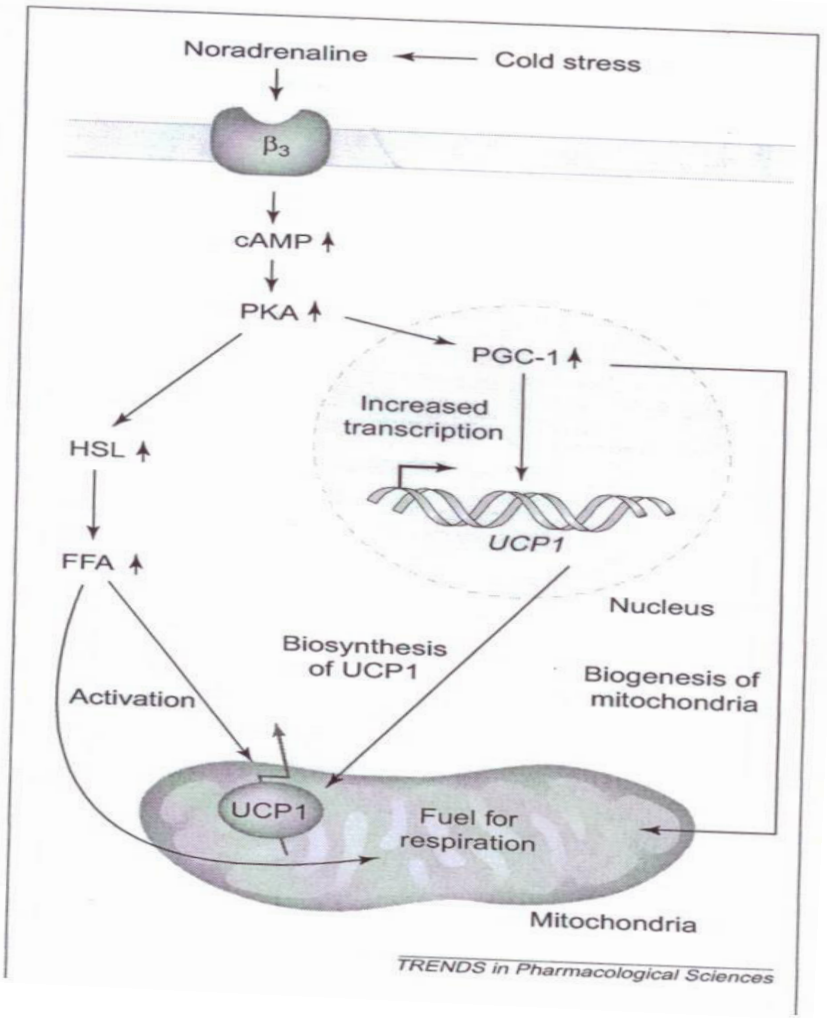
nebivolol (beta1 antagonist) effective in metabolic sy

B. UCP (uncoupling protein) analogues

**Uncoupling from ATP production a gooc theoretical mechanism but that compounds which have been investigated with this mechanism of action have a great toxicity.**

**One of the pollutants of fat-burning dietary supplements is**

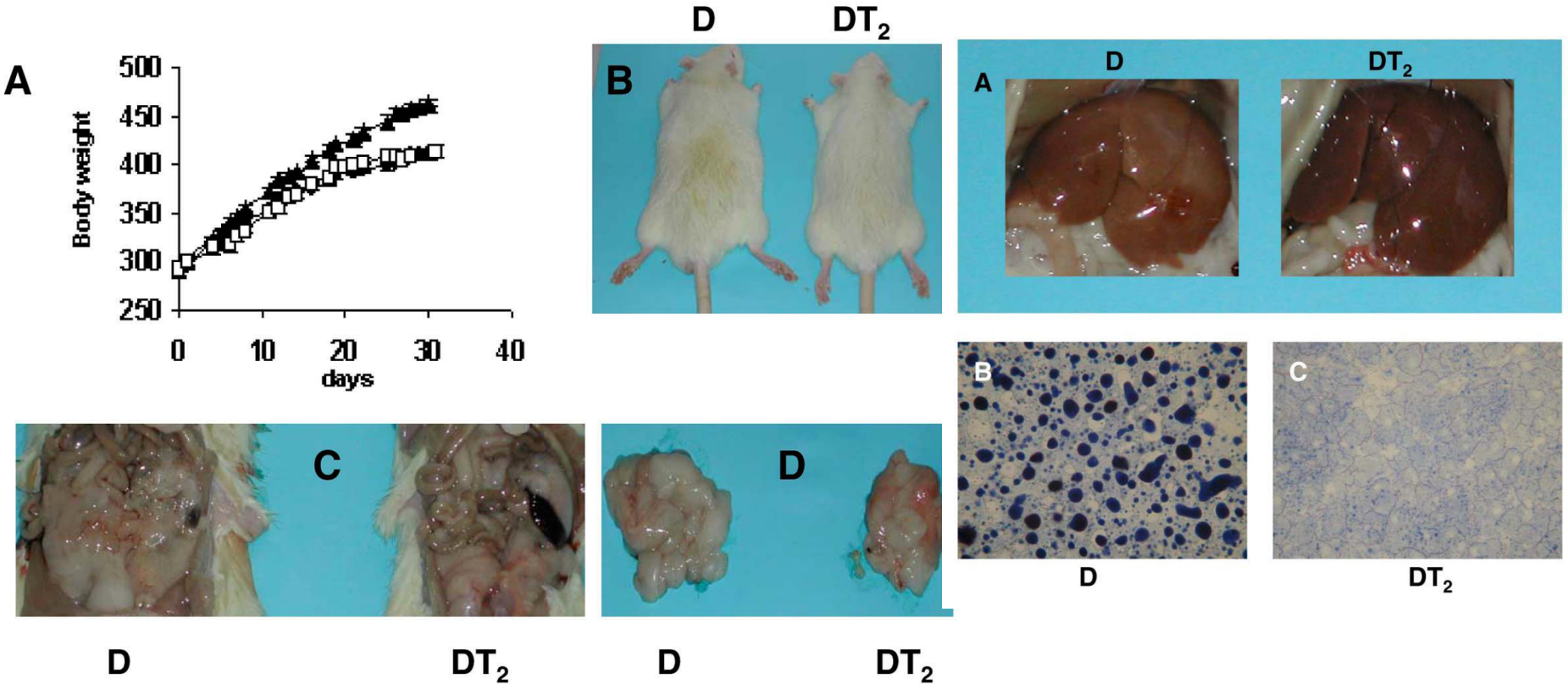
**DNF = dinitrophenol is very toxic !!**




C. Adipose tissue specific Thyroid hormone analogues

*The FASEB Journal express article 10.1096/fj.05-3977fje. Published online July 12, 2005.*

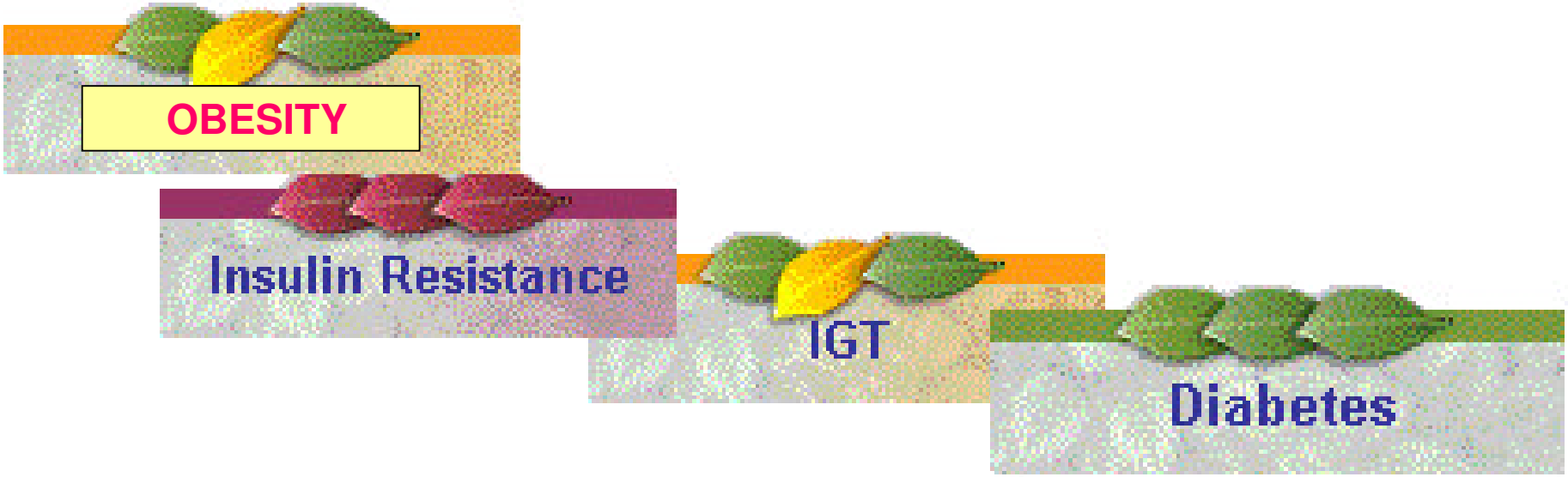
# 3,5-Diiodo-L-thyronine (T2) powerfully reduces adiposity in rats by increasing the burning of fats




**AMPK: AMPactivated protein kinase**
**CPT :carnitin palmytoil transferase**
**Mitochondrial uncoupling**

## 4. Drugs for lowering risk of complications in obese people

- insulin sensitizing
- lipid lowering and
- antihypertensive drugs




# Insulin sensitizer therapy

1. **Weight loss and exercises**
2. **Metformin (biguanide derivative)** side effect: lactic acidosis

   Contraindicated in renal, hepatic, hypoxic pulmonary diseases, heart failure or shock
3. **PPAR (peroxisome proliferator-activated receptor) gamma agonists :**

   troglitazone was withdrawn because of hepatotoxicity
   rosiglitazone was withdrawn (2010) because of increased bood volume and its consequencies
   pioglitazone

suppress resistin production and increase insulin sensitivity in muscle cells