LEPTIN- AN ENERGY BAROMETER AND NEUROENDOCRINAL REGULATOR!!

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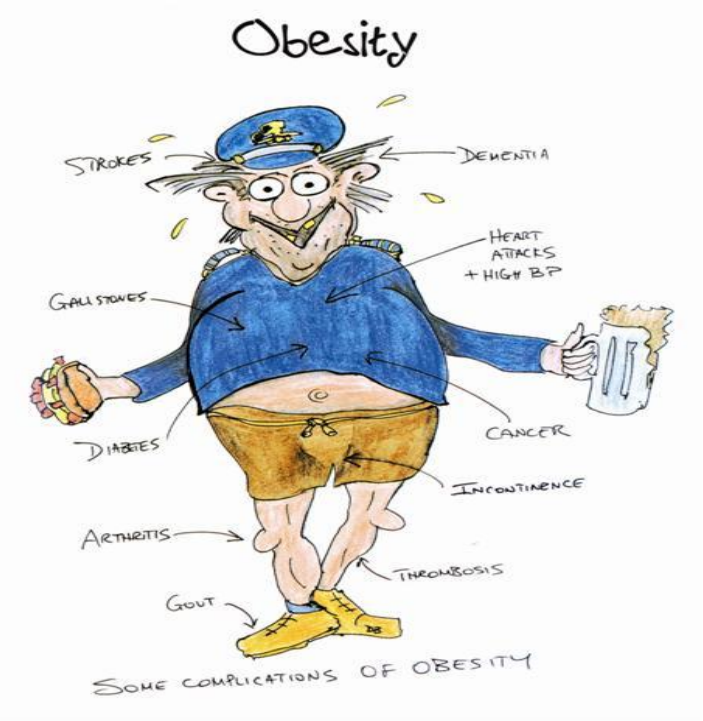
Is Obesity really **caused only due to greed, laziness** or a lack of willpower to exercise ?

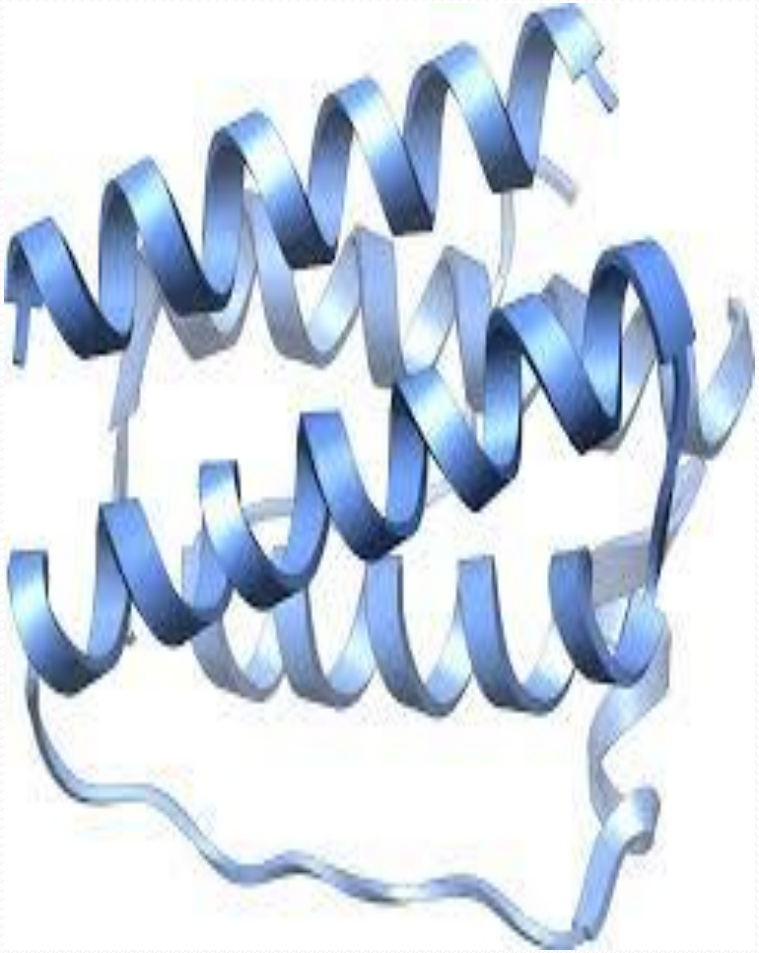


OVERVIEW

- INTRODUCTION
- SOURCES OF LEPTIN
- CENTRAL AND PERIPHERAL EFFECTS OF LEPTIN
- CLINICAL IMPLICATIONS
- OBESITY- A LEPTIN PARADOX !!
- M.C.Q's

INTRODUCTION

Human leptin is a protein of **167 amino acids** with a **four-helix bundle motif** similar to that of a cytokine



INTRODUCTION

- Leptin (Greek – *leptos*) means **thin**
- It is a protein hormone that plays a key role in **regulating energy intake and energy expenditure**
- It is one of the most important **adipose derived** hormones
- The ***Ob* (*Lep*)** gene (***Ob*** for **obese**, ***Lep*** for **leptin**) is located on **chromosome 7** in humans

DISCOVERY

The effects of leptin were observed by studying mutant obese mice within a mouse colony at the Jackson Laboratory in 1950

Leptin was discovered in 1994 by Jeffrey M. Friedman and Douglas L. Coleman through the study of such mice at Rockfeller University.

SOURCES OF LEPTIN

Major source of leptin is **white adipose tissue**

can also be produced by

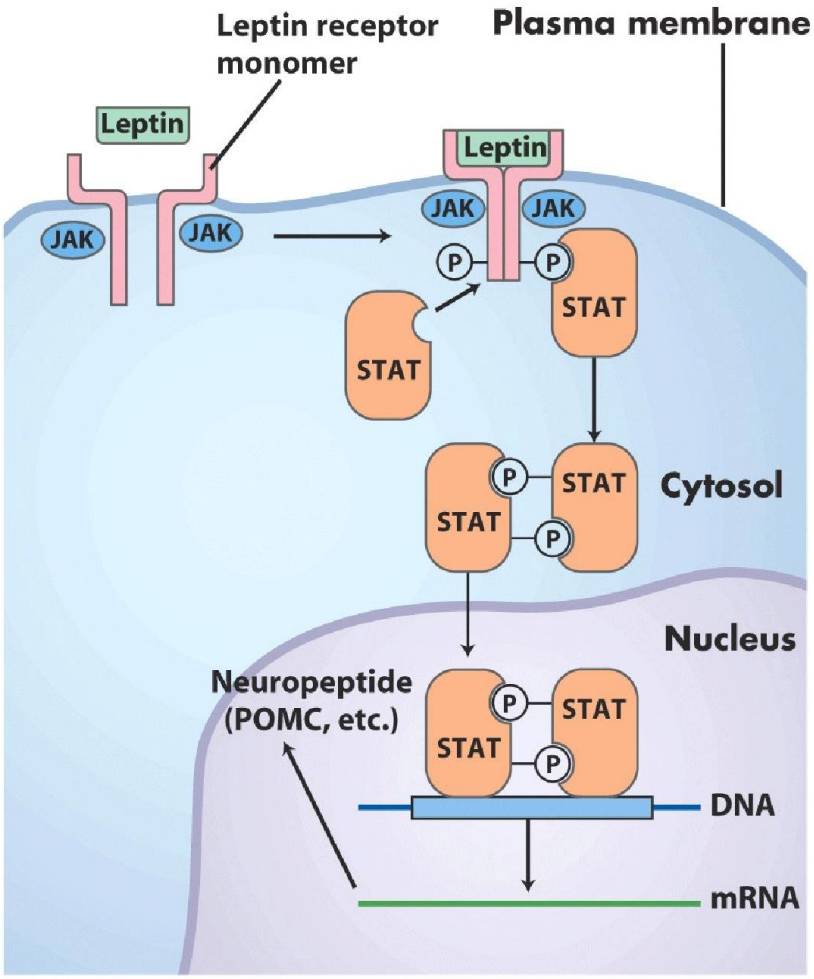
- **brown adipose tissue**
- **placenta**
- **ovaries**
- **skeletal muscle**
- **stomach**
- **mammary epithelial cells**
- **bone marrow**
- **pituitary**

RECEPTORS

Leptin interacts with **six types** of receptors :

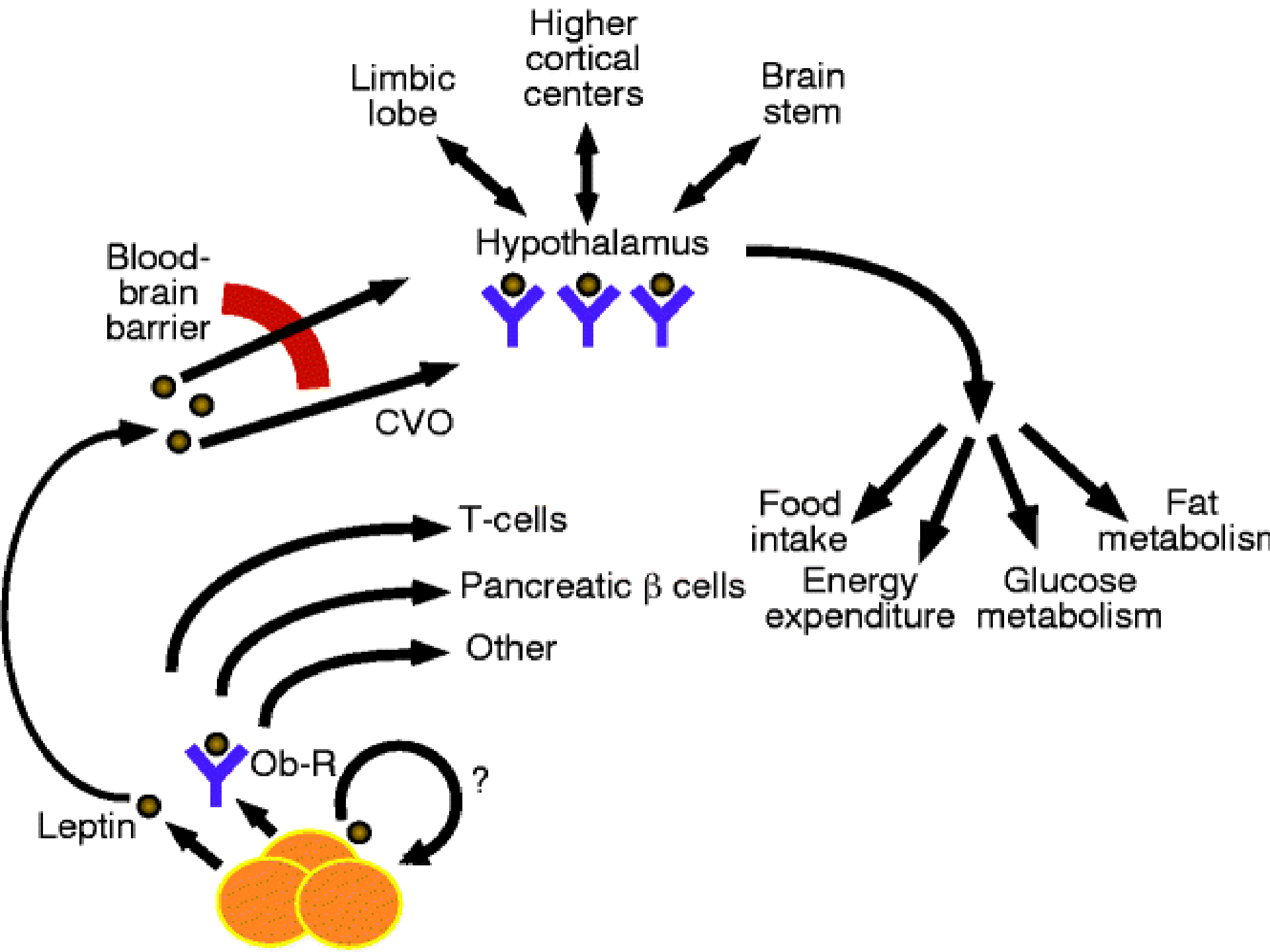
- *Ob-Ra* to *Ob-Rf*
- encoded by a single gene, LEPR
- ***Ob-Ra* and *Rc*** → transport leptin across BBB
- ***Ob-Rb*** → Hypothalamus , regulates energy homeostasis and neuroendocrine function
- ***Ob-Re*** → binds circulating leptin

MECHANISM OF ACTION



Once leptin has bound to the Ob-Rb receptor, it activates the **JAK-stat**, which is phosphorylated and travels to the nucleus to effect changes in gene expression.

CENTRAL AND PERIPHEPRAL EFFECTS OF LEPTIN


Higher cortical centers
Limbic lobe
Brain stem
Hypothalamus
Blood-brain barrier
CVO
T-cells
Pancreatic β cells
Other
Food intake
Energy expenditure
Glucose metabolism
Fat metabolism
Ob-R
?
Leptin

CENTRAL EFFECTS OF LEPTIN

REGULATING FOOD INTAKE AND ENERGY EXPENDITURE

Leptin

↓

binds to its receptor

(expressed primarily in hypothalamus)

↓

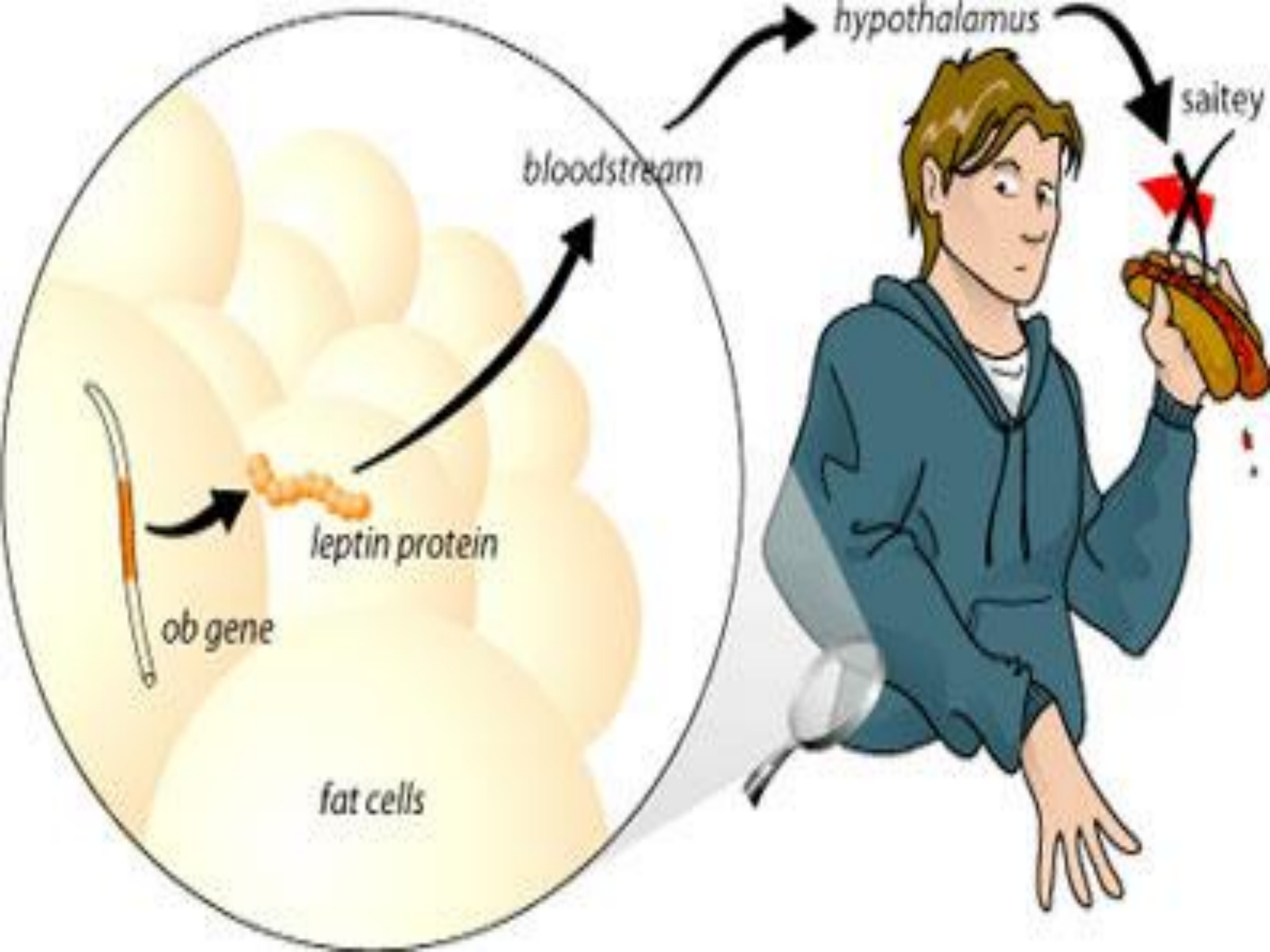
Hypothalamus modulates food intake and energy expenditure

LEPTIN - AN INDICATOR OF ENERGY BALANCE

When low leptin levels are detected by brain, the body is warned of limited energy supplies

If high leptin levels are detected, the hypothalamus senses the body as being overweight.

This then triggers the body to eat less and expend more energy


hypothalamus
saitey
bloodstream
leptin protein
ob gene
fat cells

PEPTIDES THAT INCREASE FOOD INTAKE

- **Orexin (lateral hypothalamus)**
- **NPY (arcuate and PVN)**
- **AgRP (arcuate and PVN)**
- **MCH (lateral hypothalamus)**

PEPTIDES THAT DECREASE FOOD INTAKE

- **POMC (αMSH) (arcuate and PVN)**
- **CART (arcuate nucleus)**
- **CRH (PVN)**

LEPTIN SENSITIVE NEURONES

- Contained within the hypothalamus
- One of these subsets expresses NPY and AgRP, peptides that stimulate food intake and inhibit energy expenditure, thereby promoting positive energy balance .
- These NPY/AgRP neurons are inhibited by both leptin and insulin.

LEPTIN SENSITIVE NEURONES (contd.)

POMC neurons are stimulated by leptin

↓

POMC

↓

α - MSH

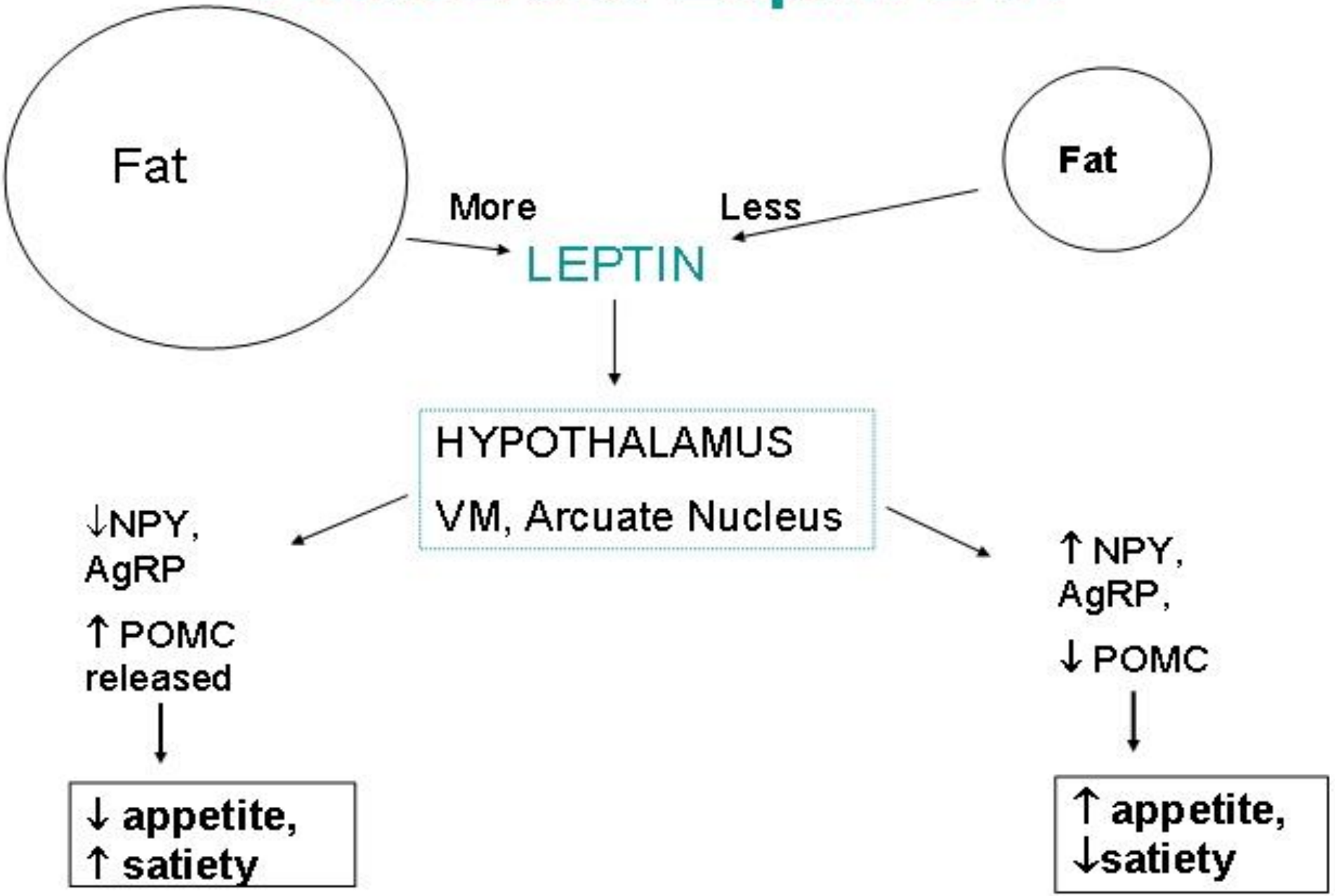
↓

Inhibit food intake

increase energy expenditure and

promote weight loss

What Does Leptin Do?



PERIPHERAL EFFECTS

- Reproductive system
- Immune system
- Bone metabolism
- Circulatory system
- Glucose homeostasis
- Obesity and weight loss

EFFECT ON REPRODUCTIVE SYSTEM

LEPTIN

↓

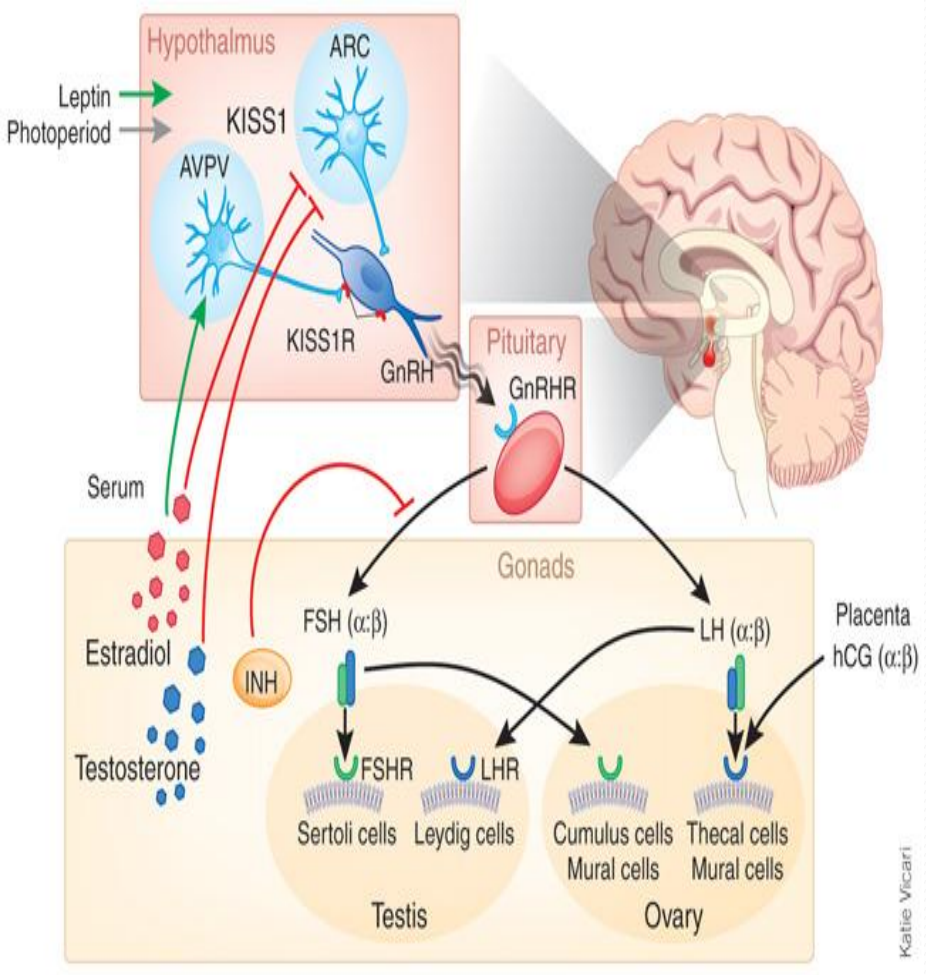
Kisspeptin

↓

↑ Release of GnRH

↓

↑ LH, FSH and Testosterone



EFFECT ON REPRODUCTIVE SYSTEM (contd.)

- Leptin regulates reproductive functions by activating neurons that project **afferent input to GnRH neurons** in the preoptic area and other hypothalamic areas

- Several neurons involved in energy homeostasis are **anatomically associated with GnRH neurons** (*e.g.*, Ag RP , NPY and POMC neurons) and may thus link changes in energy balance with subsequent alterations in energy balance with subsequent alterations in reproductive function.

EFFECT ON REPRODUCTIVE SYSTEM (contd.)

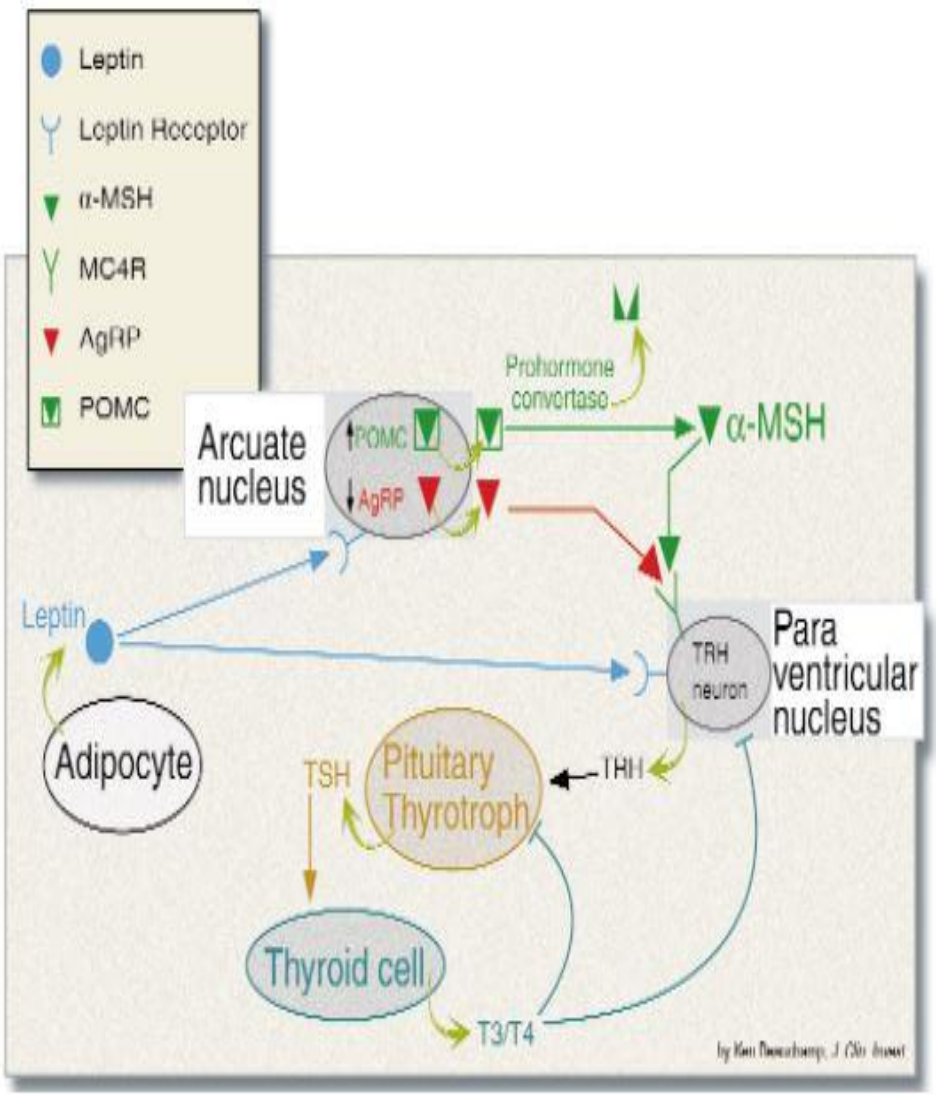
- Leptin administration **normalizes LH** levels in females and **restores testosterone** level in males.

- Normal leptin levels may have a permissive role and thus be necessary for normal progression of puberty and reproductive maturity

EFFECT ON HYPOTHALAMIC-PITUITARY-THYROID AXIS

- Leptin **directly** stimulates neurons in PVN of the hypothalamus to upregulate pro-TRH gene expression

- **indirectly** influences TRH neurons in the PVN through signals from the arcuate nucleus.



EFFECT ON HYPOTHALAMIC-PITUITARY-THYROID AXIS

- TSH and Leptin secreted in a pulsatile fashion

- Congenital leptin deficiency

↓

Highly disorganized TSH secretion pattern

↓

Induce changes on metabolism

EFFECT ON HYPOTHALAMIC-PITUITARY-GROWTH HORMONE AXIS

Leptin

↓

GHRH

↓

Increase in GH secretion

EFFECT ON HYPOTHALAMIC-PITUITARY-GROWTH HORMONE AXIS (contd.)

In humans, leptin may regulate not GH secretion *per se* but mainly the effect of GH to **regulate** secretion of **IGF-I** and its **binding proteins** in the periphery

EFFECT ON HYPOTHALAMO - PITUITARY - ADRENAL AXIS

Leptin

↓

stimulation of CRH release

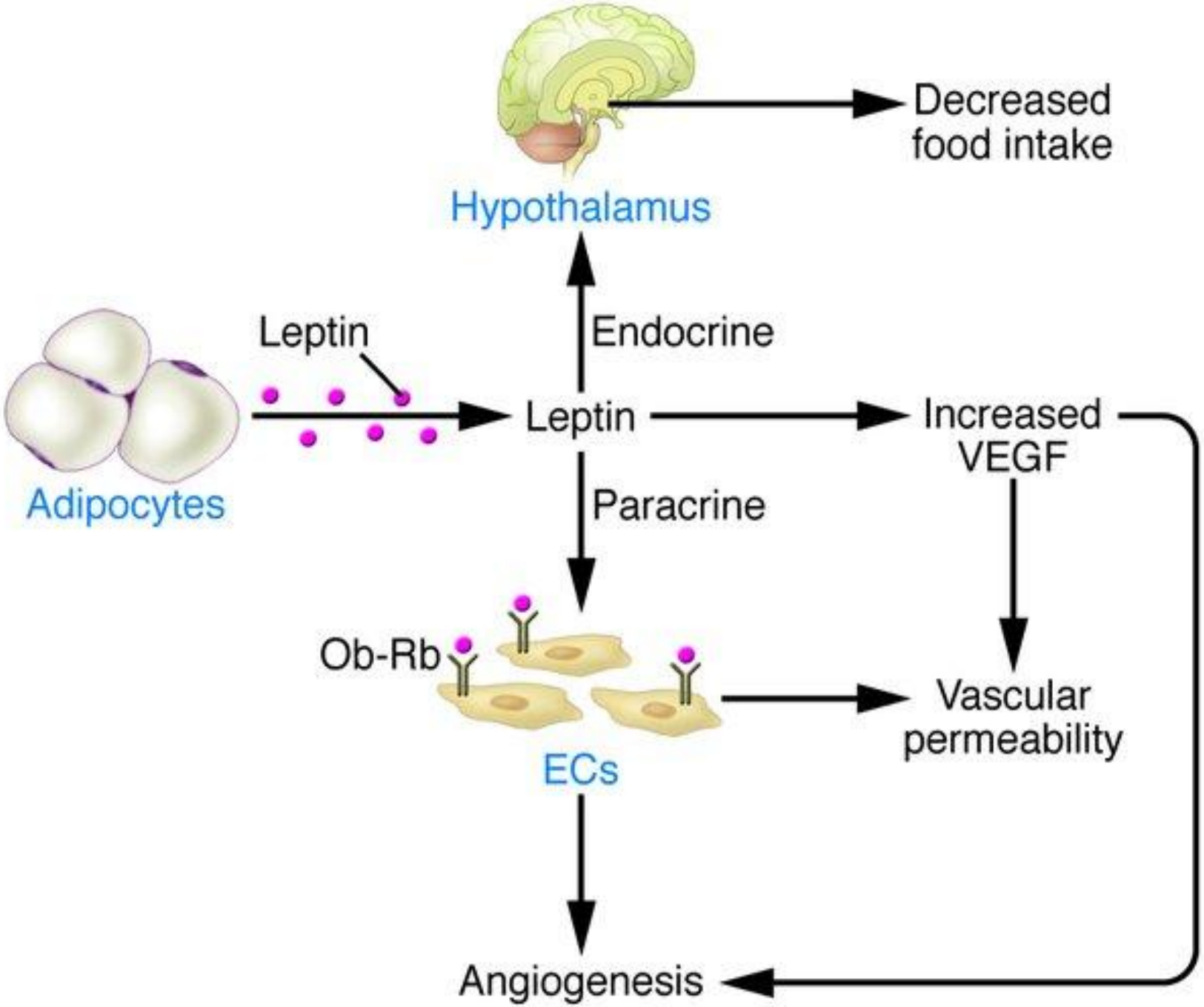
↓

increase in ACTH and cortisol

EFFECT ON CIRCULATORY SYSTEM

The role of **leptin/leptin receptors** in modulation of T cell activity in immune system was shown in experimentation with mice

Exogenous leptin can promote angiogenesis by increasing vascular endothelial growth factor levels


Decreased
food intake
Hypothalamus
Leptin
Endocrine
Adipocytes
Leptin
Increased
VEGF
Paracrine
Ob-Rb
Vascular
permeability
ECs
Angiogenesis

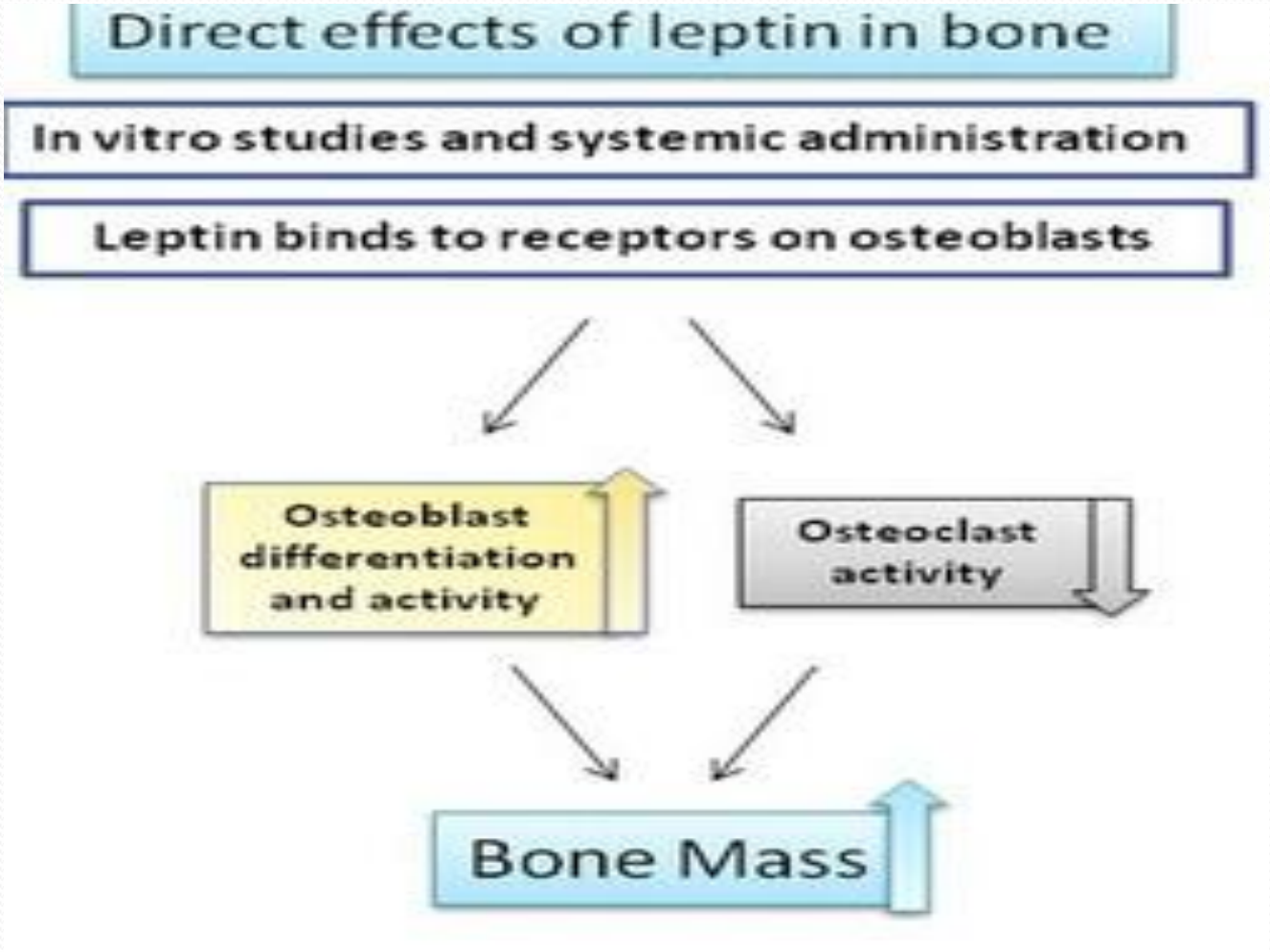
LEPTIN AND NITRIC OXIDE

- Leptin can modulate vascular tone through local mechanisms involving nitric oxide (NO) release mediated through Endothelial Nitric Oxide Synthase Phosphorylation pathway.

EFFECT ON BONE METABOLISM

Leptin decreases cancellous bone, but increases cortical bone. This "**cortical-cancellous dichotomy**" may represent a mechanism for enlarging bone size, and thus bone resistance to cope with increased body weight.

EFFECT ON BONE METABOLISM (contd.)



EFFECT ON BONE METABOLISM (contd.)

There is a potential for treatment of diseases of bone formation - such as impaired fracture healing – with leptin.

EFFECT ON IMMUNE FUNCTION

Leptin :

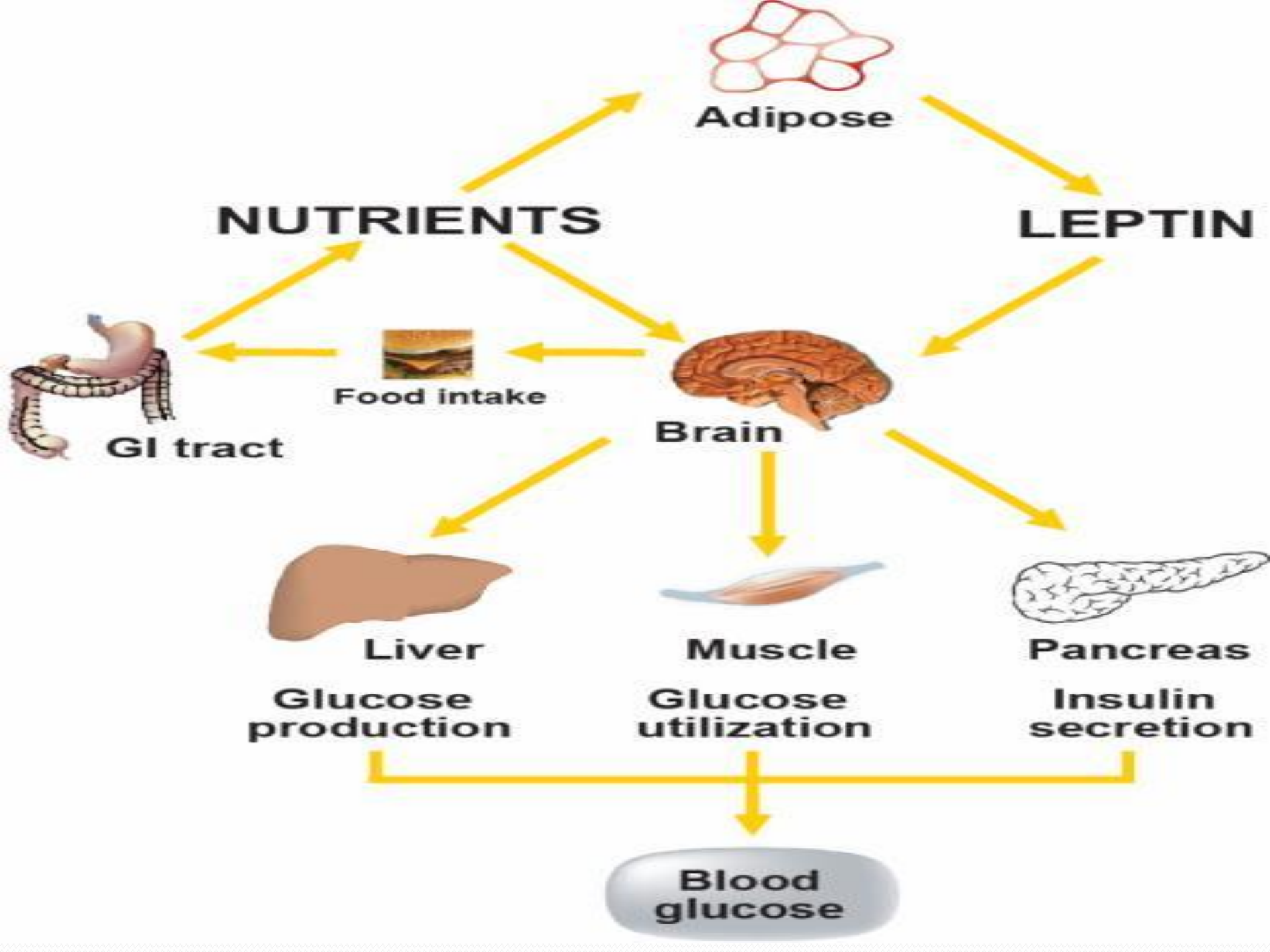
- enhance **phagocytic activity in macrophages**
- promote **production of pro-inflammatory cytokines** such as TNF-α, IL-6 and IL-12
- stimulate **chemotaxis in polymorphonuclear cells**
- promotes **lymphocyte survival in-vitro by suppressing Fas-mediated apoptosis**

Hypoleptinemic states → **increased risk of infection**

EFFECT ON GLUCOSE METABOLISM

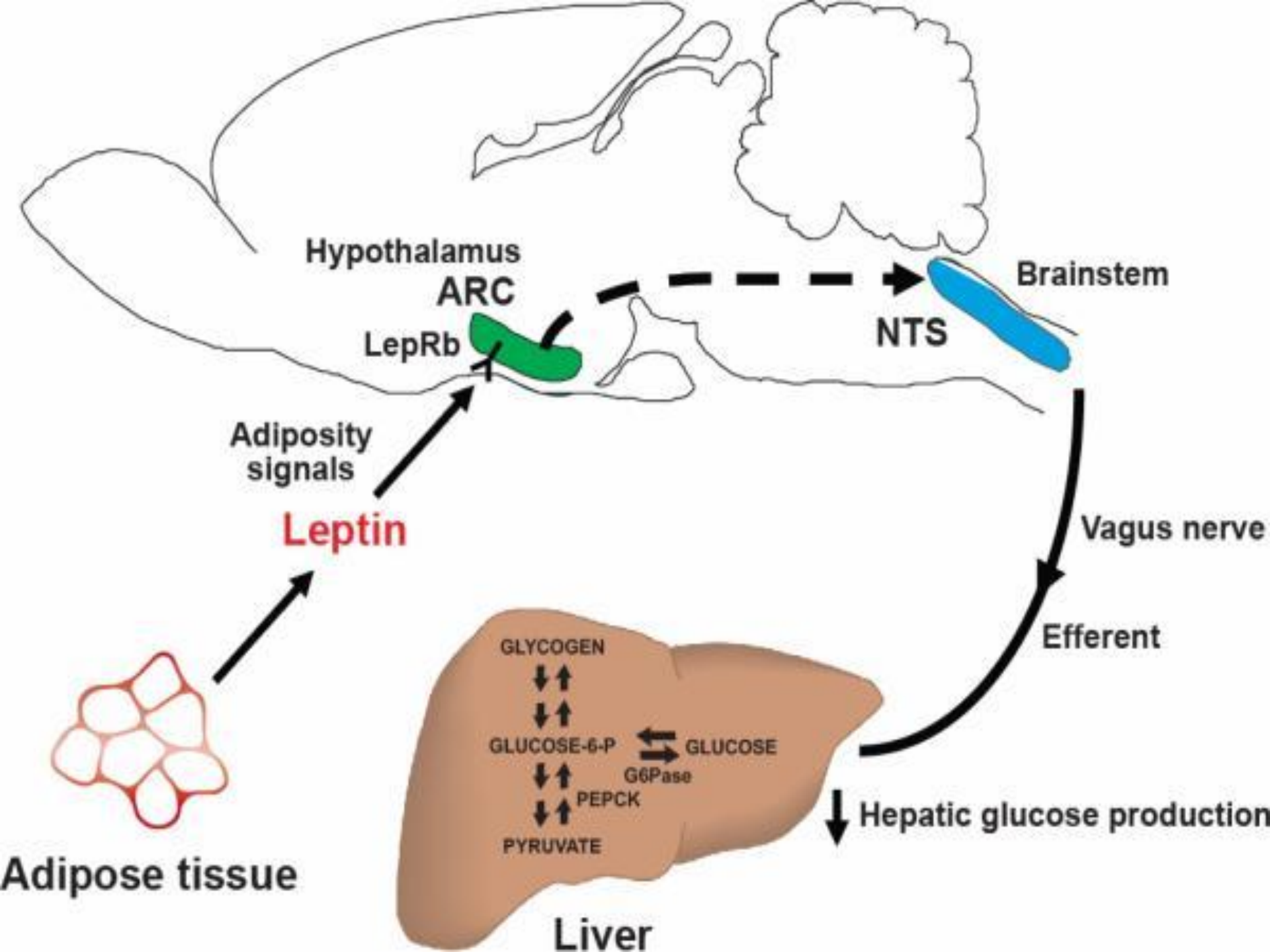
- Growing evidence implicates leptin in glucose homeostasis as well, particularly in the control of peripheral tissue insulin sensitivity.

- Mice with genetic leptin deficiency or leptin receptor deficiency exhibited not only hyperphagia and obesity, but insulin resistance and diabetes as well


Adipose
NUTRIENTS
LEPTIN
GI tract
Food intake
Brain
Liver
Muscle
Pancreas
Glucose production
Glucose utilization
Insulin secretion
Blood glucose

EFFECT ON GLUCOSE METABOLISM (contd.)

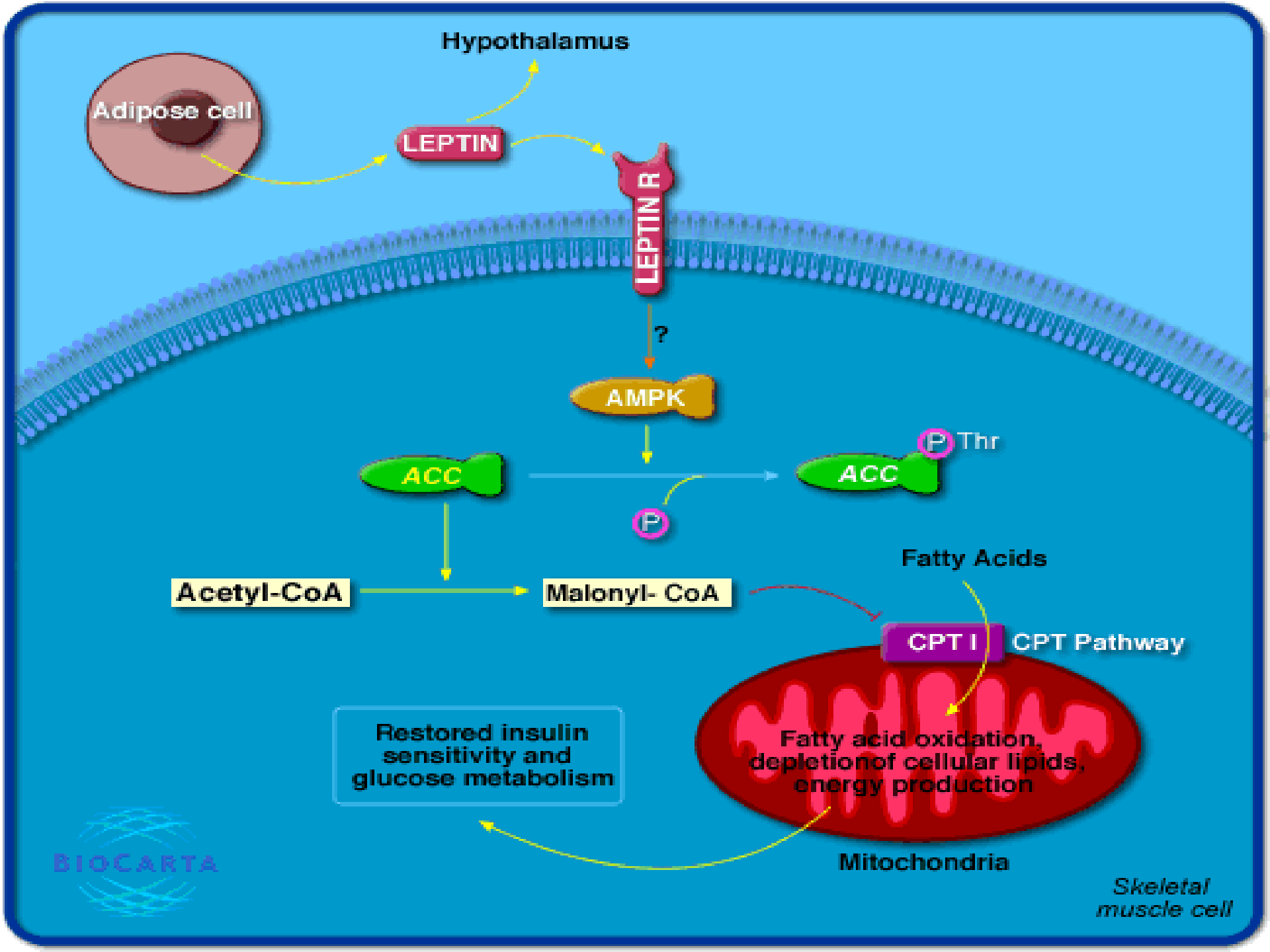
Findings suggest that hypothalamic leptin signaling is an important determinant of glucose metabolism and that the underlying neuronal mechanism involves **Phosphatidylinositol - 3 kinase (PI3K) signaling**


Hypothalamus
ARC
LepRb
Brainstem
NTS
Adiposity signals
Leptin
Vagus nerve
Efferent
GLYCOGEN
GLUCOSE-6-P
GLUCOSE
G6Pase
PEPCK
PYRUVATE
Hepatic glucose production
Adipose tissue
Liver

INDIRECT EFFECTS OF LEPTIN ON GLUCOSE METABOLISM

- Effects on **lipid metabolism**

- Decreases intracellular lipid concentration through **reduction of fatty acid and triglyceride** synthesis and a concomitant **increase in lipid oxidation**


Hypothalamus
Adipose cell
LEPTIN
LEPTIN R
?
AMPK
ACC
P
Thr
ACC
P
Acetyl-CoA
Malonyl- CoA
Fatty Acids
CPT I
CPT Pathway
Restored insulin sensitivity and glucose metabolism
Fatty acid oxidation, depletionof cellular lipids, energy production
Mitochondria
BIOCARTA
Skeletal muscle cell

EFFECT ON GLUCOSE METABOLISM (contd.)

Leptin treatment restores euglycemia and normalizes peripheral insulin sensitivity in animal models of type-I diabetes

CLINICAL APPLICATIONS :

Leptin replacement has been studied in:

- **Congenital leptin deficiency**
- **Lipodystrophy**
- **Hypothalamic amenorrhoea**

CONGENITAL LEPTIN DEFICIENCY

- marked obesity (hyperphagia)
- hypogonadotrophic hypogonadism (inadequate secretion of GnRH)
- failure to reach puberty, including absence of growth spurt, secondary sex characteristics and menarche

Leptin replacement reverses several of the changes seen with congenital leptin deficiency

LIPODYSTROPHY

- **Loss of subcutaneous** adipose tissue
- **increase in visceral** adipose tissue
- **It is a rare autosomal recessive condition**

Leptin replacement therapy dramatically **improves dyslipidemia** and **insulin sensitivity** in these individuals and **reduces hepatic gluconeogenesis** and **intrahepatic fat content**

HYPOTHALAMIC AMENORRHOEA

- Common cause of **absent menstrual periods** and **infertility**

- Leptin may be a promising treatment for **infertility** in women with **hypothalamic amenorrhoea**

- Leptin can **normalize** **LH concentrations** and pulse frequency within **weeks** of treatment and can **restore** **ovulatory function** after only **months** of treatment

- Leptin is a hormone that is produced by the body's fat cells
- It is often referred to as the **"satiety hormone"** or the **"starvation hormone"**
- Leptin's primary target is in the brain, particularly an area called the hypothalamus

- Various Central and Peripheral effects.

- Leptin is ***supposed*** *to* tell the brain that we have enough fat stored, that we don't need to eat, and that we can burn calories at a normal rate.

- We eat → body fat goes up → leptin goes up → we eat less and burn more.
- Or…
- We don't eat → body fat goes down → leptin goes down → we eat more and burn less.

PARADOX OF LEPTIN- OBESITY !!

- Obese have a lot of body fat in their fat cells.

- Very high levels of leptin .

- People shouldn't be eating… their brain should ***know*** that they have plenty of energy stored.

PARADOX OF LEPTIN- OBESITY !!

- There's a whole ton of leptin floating around, but the brain doesn't **"see"** that it is there .

- **Leptin resistance-** It is now believed to be **the main biological abnormality in human obesity**

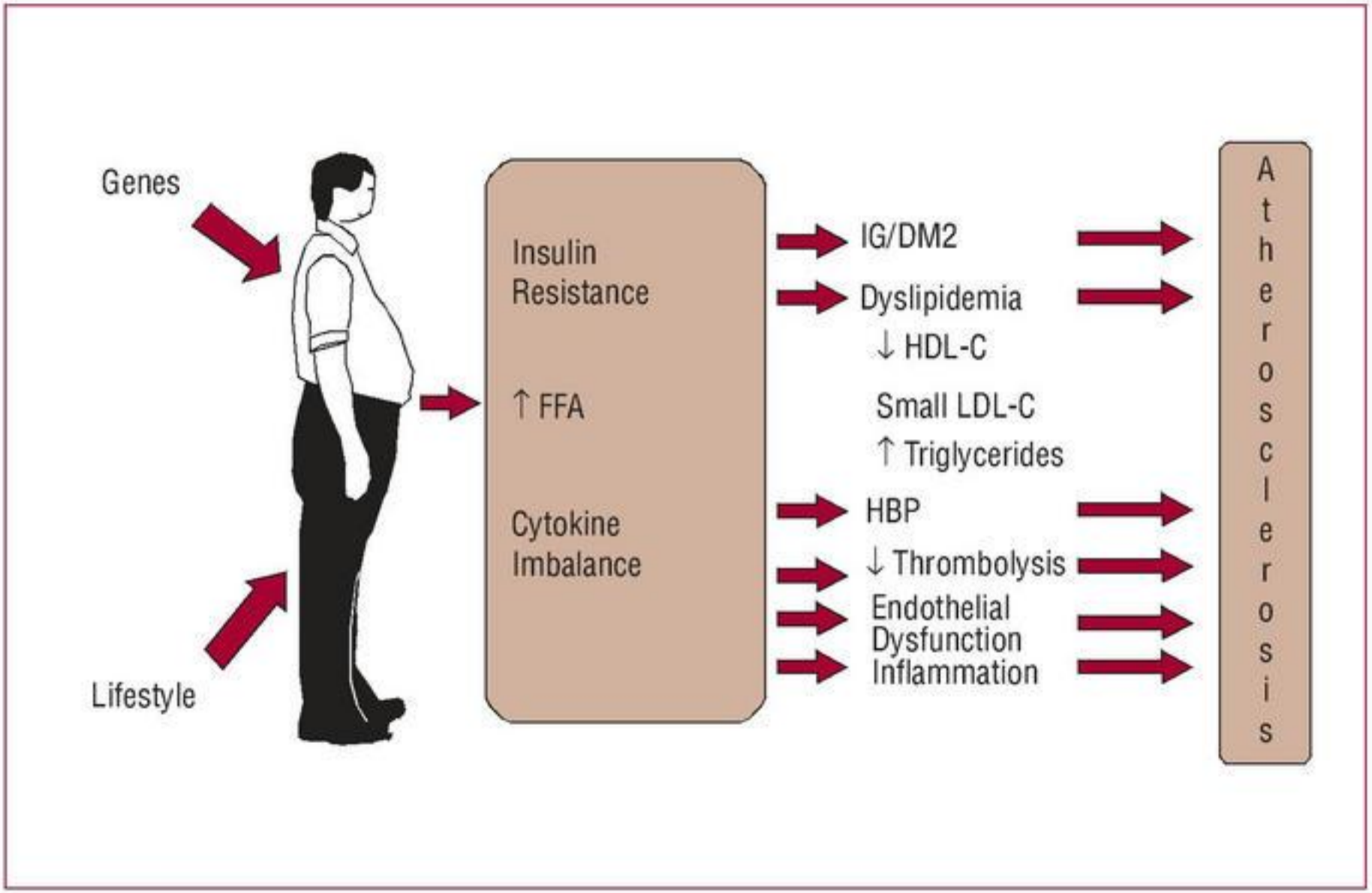
↓

Change our physiology and behavior in order to regain the fat that the brain thinks we're missing.

LEPTIN RESISTANCE

- Hunger and reduced energy expenditure.

PARADOX OF LEPTIN-OBESITY


Genes
Lifestyle
Insulin Resistance
↑ FFA
Cytokine Imbalance
IG/DM2
Dyslipidemia
↓ HDL-C
Small LDL-C
↑ Triglycerides
HBP
↓ Thrombolysis
Endothelial Dysfunction
Inflammation
Atherosclerosis

WEIGHT LOSS DIETS

Most “diets” don’t provide good long-term results. This is a well known problem in weight loss studies.

↓

Significant reduction in leptin levels

↓

Brain doesn’t necessarily reverse its leptin resistance.

↓

Hunger, increased appetite, reduced motivation to exercise and decreased amount of calories burned at rest

LEPTIN RESISTANCE

- Leptin resistance or tolerance was first thought to be due to mutations of the leptin receptor and other rare monogenic obesity syndromes.

- Leptin transport across the blood-brain barrier is impaired in obesity. This is partially due to saturation of the transporter as a result of hyperleptinemia and a subsequent decrease in transport activity.

LEPTIN RESISTANCE

- Endoplasmic reticulum stress in the liver, adipose tissue, and pancreatic β-cells has recently been shown to play a role in the development of leptin resistance.

LEPTIN RESISTANCE

- Targeting these mechanisms of leptin resistance has led to development of leptin sensitizers.

- Amylin may act synergistically with leptin to induce fat-specific weight loss, and the amylin analog pramlintide has been tried in conjunction with leptin in clinical trials for weight loss with modest effects.

CELLULAR MECHANISMS BEHIND LEPTIN RESISTANCE

- **Inflammation:** Inflammatory signaling in the hypothalamus (IL-6,IL-8, IL-10, TNF-α, FABP4)

- **Free Fatty Acids:** Having elevated free fatty acids in the bloodstream may increase fat metabolites in the brain and interfere with leptin signaling.

- **Having high leptin:** Having elevated levels of leptin in the first place seems to cause leptin resistance.

WHAT SCIENCE KNOWS ABOUT REVERSING LEPTIN RESISTANCE ?

- The best way to know if one is leptin resistant, is to **look in the mirror**

REVERSING LEPTIN RESISTANCE

- If there is a lot of **body fat**, especially in the **belly area**, then one is almost certainly **leptin resistant**

- A key to preventing (or reversing) leptin resistance, is reducing **diet-induced inflammation**

REVERSING LEPTIN RESISTANCE

- **Avoid processed food:** Highly **processed foods** (foods high in **sugar**, refined flour and vegetable oils)

may compromise the integrity of the gut and drive to inflammation.

- **Eat Soluble Fiber:** Eating **soluble fiber** can help improve gut health and may protect against obesity

REVERSING LEPTIN RESISTANCE

- **Sleep:** Poor sleep has been **implicated in problems with leptin**

- **Lower your triglycerides:** Having high blood triglycerides can prevent the transport of leptin from blood and into the brain . The best way to lower triglycerides is to **reduce carbohydrate intake**

- **Eat Protein :** Eating plenty of **protein** can cause automatic weight loss. There are many reason for that, one of them may be an **improvement in leptin sensitivity**

REVERSING LEPTIN RESISTANCE

- **Exercise:** Physical activity may help to reverse leptin resistance .

- The effect of long-term exercise training on leptin concentration has shown that regular exercise allows "resetting" of the leptin concentration so that a lower concentration can be maintained at a certain body fat content.
- Physical activity is known to increase sympathetic nerve activity that promotes down-regulation of plasma leptin concentrations.

REVERSING LEPTIN RESISTANCE

MIND-BODY PRACTICES

- Chronic stress is a multi-pronged dagger that has felled many. Unmitigated stress increases cortisol levels directly interferes with how leptin functions.

- Mind-Body Practices –**Mindfulness meditation**, intentionally bringing awareness to "present-moment" experience.

- Mindful eating is considered a form of meditation and is associated with decreased craving for food, improved sugar control, feeding behavior, and weight management.

NUTRACEUTICAL "FOOD AS MEDICINE" APPROACHES

- **Curcumin** from turmeric downregulates leptin.
- **Omega 3 fatty acids** found in fish, nuts, seeds, and some plants may help modulate release of leptin.
- **Probiotics** improve gastrointestinal integrity and immune balance, improving production of short chain fatty acids which will have direct influence on leptin.
- **Aloe leaf**, **licorice extract**, **vitamin D**, **ginger**, **garlic**, **green tea extract** offer positive benefits on gut bacteria, gut-brain interactions and general immune health.

REVERSING LEPTIN RESISTANCE

- Unfortunately, there is no simple way to do this !!

- Eating **real food** (not modern processed foods high in **sugar** i.e fructose, refined flour and vegetable oils) , maintaining a healthy gut, exercising, sleeping well, mind- body practices etc…

↓

- **Drastic shift in lifestyle with all interventions.**

TAKE HOME MESSAGE

- Obesity is **not caused by only greed, laziness or a lack of willpower**
- There are **strong biochemical forces** at play… which promote increased hunger and decrease energy consumption.
- Individual is still responsible to help oneself.

TAKE HOME MESSAGE

Although the causes of obesity are complicated and diverse, **leptin resistance is the main reason.**

↓

Drastic shift in lifestyle.

CONCLUSION

- Regulation of leptin in the body will have a profound impact on the treatment of obesity, diabetes mellitus and infertility .

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Thank you

MCQ's

1)Major source of leptin is :

a. White adipose tissue
b. Skeletal muscle
c. Liver
d. ovary

MCQ's

Leptin is also known as:

a. Satiety hormone
b. Starvation hormone
c. Both the above
d. None of the above

MCQ's

Mechanisms behind leptin resistance :

a. Inflammation
b. Free fatty acids
c. High leptin levels
d. All the above

MCQ's

Effect of Leptin on glucose metabolism :

a. ↑ses hepatic glucose production and glucose utilization in muscles

b. ↓ses hepatic glucose production and glucose utilization in muscles

c. ↓ses hepatic glucose production and ↑ses glucose utilization in muscles

d. None of the above

MCQ's

Peptides which decrease food intake:

a. Proopiomelanocortin (POMC)
b. Orexin
c. Agouti related peptide (AgRP)
d. Neuropeptide Y (NPY)