Appetite Control

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Please Note

The slides marked with a yellow star * comprise the most important (basic) pieces of information in this topic.
The presentation focuses on the physiological control of appetite and some pathophysiological aspects of feeding disturbances (obesity) with a specific emphasize on the neurohormonal factors.
I. Physiology of neuroendocrine regulation of food intake

- Central regulation of food intake – hypothalamus, neurohormones
- Short- and long-term peripheral regulation of satiety and energy balance
  - GIT hormones
  - Adipose tissue hormones
  - Pancreatic hormones

II. Pathophysiological aspects of feeding disturbances (obesity)
The physiological regulation of food intake is a complex homeostatic process that is regulated by many endocrine and metabolic factors in a combination with visual, olfactory, and taste sensation, emotions, memory, and the life conditions.
Our prehistorical progenitors clearly did not have the opportunity to suffer either from obesity or anorexia nervosa.

**Thrifty genes theory** – genes predisposing to effective energy storage enabled to survive during starvation, however they predispose to obesity nowadays.
The Progression of Development...

Adapted from R. Unger
A short historical overview...

- 1953, Kennedy put the **lipostatic hypothesis**; adipose tissue produces a specific „lipostatic“ factor.

- 1967, Mayer and Thomas put the **glucostatic hypothesis**; fluctuations in glycaemia lead to stimulation or inhibition of food intake (brain and liver – regulatory organs)
The balance between energy intake and expenditure is tightly regulated and body weight is stable despite day-to-day food intake fluctuations......

...... unless the border is overestimated and the balance is broken.
I. Physiology of neuroendocrine regulation of food intake

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  - Adipose tissue hormones
  - Pancreatic hormones

II. Pathophysiological aspects of feeding disturbances (obesity)
The energy homeostasis is strongly influenced by emotions, stressful conditions and learned feelings (Are you able to eat spinach after which you vomited 20 years ago at school???).

Especially in humans all regulations are under tight control of higher nervous centres (neocortex) and so called „will“ can dramatically effect mood and feelings associated with eating.

Figure 1: Schematic diagram depicting possible interactions between “cognitive” and “emotional” brain with the “metabolic” brain. Behavioral and anatomical observations suggest that accumbens→hypothalamus projections are involved in reward-driven food intake by modulating hypothalamic feeding circuits thought to be crucial for homeostatic control of energy balance. Indirect projections through the ventral pallidum and projections from the amygdala and relevant cortical areas may also be important. Hypothalamus→accumbens projections are also present and may provide modulation of feeding motivation by metabolic state signals.
Hypothalamus and brain stem are crucial in central regulation of feeding - responsible for integration of brain neurotransmitters, peripheral neurohumoral afferents; adipocyte-derived signals, and GIT peptides.

Source: Morton et al. 2005
**Factors which decrease appetite are called anorexigenic**

<table>
<thead>
<tr>
<th>Decrease Feeding (Anorexigenic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Melanocyte-stimulating hormone (α-MSH)</td>
</tr>
<tr>
<td>Leptin</td>
</tr>
<tr>
<td>Serotonin</td>
</tr>
<tr>
<td>Norepinephrine</td>
</tr>
<tr>
<td>Corticotropin-releasing hormone</td>
</tr>
<tr>
<td>Insulin</td>
</tr>
<tr>
<td>Cholecystokinin (CCK)</td>
</tr>
<tr>
<td>Glucagon-like peptide (GLP)</td>
</tr>
<tr>
<td>Cocaine- and amphetamine-regulated transcript (CART)</td>
</tr>
<tr>
<td>Peptide YY (PYY)</td>
</tr>
</tbody>
</table>

**Factors which increase appetite are called orexigenic**

<table>
<thead>
<tr>
<th>Increase Feeding (Orexigenic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropeptide Y (NPY)</td>
</tr>
<tr>
<td>Agouti-related protein (AGRP)</td>
</tr>
<tr>
<td>Melanin-concentrating hormone (MCH)</td>
</tr>
<tr>
<td>Orexins A and B</td>
</tr>
<tr>
<td>Endorphins</td>
</tr>
<tr>
<td>Galanin (GAL)</td>
</tr>
<tr>
<td>Amino acids (glutamate and γ-aminobutyric acid)</td>
</tr>
<tr>
<td>Cortisol</td>
</tr>
<tr>
<td>Ghrelin</td>
</tr>
</tbody>
</table>

*Table 71-2*

*Neurotransmitters and Hormones That Influence Feeding and Satiety Centers in the Hypothalamus*
The main structures involved in regulation of appetite include: hypothalamus and brain stem.

- **N. arcuatus (ARC)** –
  - pivotal role in the integration of signals regulating appetite
  - receptors for hormones and neuropaetides that regulate feeding

- **N. paraventricularis (PVN)** – integration of signals from ARC with thyroid and HPA axes

- **N. vagus** – satiety signals to the brain stem after ingestion of meal

- **N. tractus solitarius + PVN** – connection of brainstem with hypothalamus

- **N. suprachiasmaticus** – timing (lesions in humans lead to night hyperphagia and obesity)

Source: Morton et al. 2005
There are two distinct types of neurons in the arcuate nuclei (hypothalamus) that are especially important as controllers of appetite and energy expenditure:

(1) Proopiomelanocortin (POMC) neurons that produce melanocyte-stimulating hormone (α-MSH) and cocaine- and amphetamine-related transcript (CART)

*Activation of the POMC neurons decreases food intake and increases energy expenditure*

(2) Neurons producing the orexigenic substances: neuropeptide Y (NPY) and agouti-related protein (AGRP).

*Activation of the NPY-AGRP neurons increases food intake and reduces energy expenditure.*
Figure 71-2

Control of energy balance by two types of neurons of the arcuate nuclei: (1) pro-opiomelanocortin (POMC) neurons that release α-melanocyte-stimulating hormone (α-MSH) and cocaine- and amphetamine-regulated transcript (CART), decreasing food intake and increasing energy expenditure; and (2) neurons that produce agouti-related protein (AGRP) and neuropeptide Y (NPY), increasing food intake and reducing energy expenditure. α-MSH released by POMC neurons stimulates melanocortin receptors (MCR-3 and MCR-4) in the paraventricular nuclei (PVN), which then activate neuronal pathways that project to the nucleus tractus solitarius (NTS) and increase sympathetic activity and energy expenditure. AGRP acts as an antagonist of MCR-4. Insulin, leptin, and cholecystokinin (CCK) are hormones that inhibit AGRP-NPY neurons and stimulate adjacent POMC-CART neurons, thereby reducing food intake. Ghrelin, a hormone secreted from the stomach, activates AGRP-NPY neurons and stimulates food intake. LepR, leptin receptor; Y1R, neuropeptide Y1 receptor. (Redrawn from Barsh GS, Schwartz MW: Nature Rev Genetics 3:589, 2002).
Hypothalamic neuropeptides have different effects:

[Diagram showing effects on various physiological functions]

Initially, hypothalamic nuclei involved in appetite control were divided into satiety centre and hunger centres. However, this is not the precise division now.

- **Ventromedial nuclei „satiety centre“ - VMH**
  (lesion leads to hyperfagia)

- **Lateral nuclei „hunger centre“ - LH**
  (lesion leads to anorexia)
I. Physiology of neuroendocrine regulation of food intake

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  - GIT hormones
  - Adipose tissue hormones
  - Pancreatic hormones

II. Pathophysiologival aspects of feeding disturbances (obesity)
Energy homeostasis is controlled by peripheral signals from adipose tissue, pancreas, and the GI system. Gut-derived peptides and adiposity signals influence central circuits in the hypothalamus and brain stem to produce a negative (−) or positive (+) effect on energy balance. Thus the drive to eat and energy expenditure are adjusted so that over time, body weight remains stable.
Peripheral factors involved in regulation of food intake:

- Gastrointestinal hormones
- Pancreatic hormones
- Adipose tissue hormones

They are either

- **Orexigenic** – stimulating appetite (e.g., ghrelin)
  
or

- **Anorexigenic** – decreasing appetite (e.g., insulin, peptide YY, CCK, leptin)
Long-term adiposity signals (leptin) interact with short-term satiation signals (CCK)

- Leptin and insulin acts in hypothalamus to enhance central sensitivity to short-term satiety signals (CCK)
- Satiety signals are integrated with fat amount

Cummings and Overduin 2007
# Factors regulating food intake

<table>
<thead>
<tr>
<th>SATIETY FACTORS</th>
<th>HUNGER FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach and duodenum distension (n.vagus)</td>
<td>Hungry contractions</td>
</tr>
<tr>
<td>heat</td>
<td>cold</td>
</tr>
<tr>
<td>↑ glucose, amino acids, lipids in blood</td>
<td>↓ glucose, amino acids, lipids in blood</td>
</tr>
<tr>
<td>catecholamines</td>
<td>orexins</td>
</tr>
<tr>
<td>serotonin</td>
<td>endorphins</td>
</tr>
<tr>
<td>ACTH</td>
<td>Galanin</td>
</tr>
<tr>
<td>Insulin (food in stomach)</td>
<td>Glutamic acid</td>
</tr>
<tr>
<td>Leptin</td>
<td>cortisol</td>
</tr>
<tr>
<td>CCK (lipids in duodenum)</td>
<td>Neuropeptide Y</td>
</tr>
<tr>
<td>MSH</td>
<td>GABA</td>
</tr>
<tr>
<td>glucagon</td>
<td>ghrelin</td>
</tr>
<tr>
<td>Peptide YY</td>
<td>AMPK</td>
</tr>
</tbody>
</table>
Adipose Tissue
The size and endocrine profile of adipocytes reflects obesity or leanness.

Malnutrition (Anorexia nervosa)  
Normal (Slightly overweight)  
Obese
Thus adipose tissue plays an important role in the regulation of energy homeostasis...

**and leptin started the recognition of adipose tissue as an endocrine organ**
In 1994 – discovery of **leptin** („satiety hormone“)
*Hormon produced by adipose tissue*

It has been found, that mutation of **ob gene** encoding protein hormone leptin produced by adipocytes results in morbid obesity in mice.

**Zhang et al, Nature, 1994.**

Leptin treatment of leptin-deficient **ob/ob** mice normalized their body weight and recovered their fertility.
LEPTIN (167 AA, 16 kDa)

- Regulator of energy metabolism and body fat mass
- „Satiety hormone“ – decreases appetite
- Marker of body fat mass

*Obesity is often associated with resistance to leptin*
Leptin acts in hypothalamus:
- stimulates anorexigenic / catabolic pathway
- inhibits orexigenic / anabolic pathway
LEPTIN (167 AA, 16 kDa)

A pleiotropic hormone/cytokine involved in regulation of fat mass - coordination of feeding behavior, metabolism, ANS, and energy balance, e.g.:

- ↑ sympathetic activity
- ↑ GH – effect on growth
- ↑ TSH
- ↑ LH, FSH – puberty, reproduction
- ↑ hematopoiesis

Decreased leptin is an indicator of energy imbalance involved in adaptive response to fasting/starvation characterized by:

- Shorter stature
- ↓ thyroid hormones
- Delayed puberty
- ↑ cortisol
- Thermogenesis, hyperfagia after fasting
Adipose tissue produces many hormones and cytokines

These factors are produced not only by adipocytes, but also by macrophages, fibroblasts, endothelial cells and other cells present in adipose tissue

Adipose tissue- derived factors:
1. Proinflammatory (TNF-α, IL-6, resistin)
2. Antiinflammatory (adiponectin)

These factors significantly contribute to metabolic regulation
Product of adipose tissue - **Adiponectin**

- Predominantly produced by adipocytes
- Circulates in 1000-times higher concentration than other hormones
- Insulin-sensitizing, anti-atherogenic, and anti-inflammatory
- Regulates food intake (acts in hypothalamus)
- Most promising therapeutic properties among adipokines in treatment of diabetes
Effects of adiponectin:

Stimulation ➔ Inhibition

Adipocytes

Cells proliferation & migration

Adiponectin

Endothelium

Smooth muscle cells

HB-EGF, PDGF, bFDF, EGF

↓(?) Food intake

↑ Insulin sensitivity

Effects of adiponectin:

Stimulation ➔ Inhibition

Matsuda M. et al., JBC, 2002
Product of adipose tissue - Resistin

Mice:
• Produced mainly by adipocytes
• Prodiabetic properties
• Regulated nutritionally

Humans
• Produced mainly by macrophages
• Proinflammatory cytokine
• Nutritional regulation (?)
• Effect on insulin sensitivity (?)
Central administration of resistin promotes short-term satiety in rats

- These effects are modest and transient
- Administration of resistin for several days did not affect body weight
- Resistin mRNA was found in n.arcuatus and ventromedial n. (brain-derived resistin acts in energy homeostasis?)
- Therapeutic and physiological effects probably limited
These adipose tissue-derived hormones: leptin, adiponectin, resistin, and others have been found to regulate food intake; have receptors in CNS.
The next part of the appetite control story is the gastrointestinal (GI) system and its hormones...
Over 40 gastrointestinal hormones have been discovered so far
GIT and pancreatic peptides are anorexigenic (satiety) except for ghrelin which is the only orexigenic (hunger) peptide

Table 1
Selected GI and pancreatic peptides that regulate food intake

| Peptide       | Main site of synthesis     | Receptors mediating feeding effects | Sites of action of peripheral peptides germane to feeding | Effect on food intake
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CCK</td>
<td>Proximal intestinal I cells</td>
<td>CCK1R</td>
<td>Hypothalamus: X; Hindbrain: X; Vagus nerve: X</td>
<td>↓</td>
</tr>
<tr>
<td>GLP1</td>
<td>Distal-intestinal L cells</td>
<td>GLP1R and other</td>
<td>X? X? X</td>
<td>↓</td>
</tr>
<tr>
<td>Oxyntomodulin</td>
<td>Distal-intestinal L cells</td>
<td>GLP1R</td>
<td>X? X? X</td>
<td>↓</td>
</tr>
<tr>
<td>PYY3-36</td>
<td>Distal-intestinal L cells</td>
<td>Y2R</td>
<td>X? X? X</td>
<td>↓</td>
</tr>
<tr>
<td>Enterostatin</td>
<td>Exocrine pancreas</td>
<td>F1-ATPase β subunit</td>
<td>X? X? X</td>
<td>↓</td>
</tr>
<tr>
<td>APO AIV</td>
<td>Intestinal epithelial cells</td>
<td>Unknown</td>
<td>X? X? X</td>
<td>↓</td>
</tr>
<tr>
<td>PP</td>
<td>Pancreatic F cells</td>
<td>Y4R, Y5R</td>
<td>X? X? X</td>
<td>↓</td>
</tr>
<tr>
<td>Amylin</td>
<td>Pancreatic β cells</td>
<td>CTRs, RAMPs</td>
<td>X? X? X</td>
<td>↓</td>
</tr>
<tr>
<td>GRP and NMB</td>
<td>Gastric myenteric neurons</td>
<td>GRPR</td>
<td>X? X? X</td>
<td>↓</td>
</tr>
<tr>
<td>Gastric leptin</td>
<td>Gastric chief and P cells</td>
<td>Leptin receptor</td>
<td>X? X? X</td>
<td>↓</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>Gastric X/A-like cells</td>
<td>Ghrelin receptor</td>
<td>X? X? X</td>
<td>↑</td>
</tr>
</tbody>
</table>

CTRs, calcitonin receptors; RAMPs, receptor activity-modifying proteins; GRP, gastrin-releasing peptide; NMB, neuropeptide B; GRPR, GRP receptor. X? indicates that it is unclear whether physiologically relevant quantities of GLP1 from the gut evoke DPP4-mediated degradation in blood to activate GLP1 receptors in the brain, although these receptors might interact with CNS GLP1 to regulate food intake. ? indicates that it seems very unlikely that gastric leptin interacts in a physiologically meaningful way with leptin receptors in the hypothalamus or hindbrain, which are important targets of leptin secreted from adipocytes. ↑Effect of peripheral peptides on food intake. In some cases, central administration yields opposite results.

Cummings and Overduin 2007
Satiety signals arise from different parts of GI system – stomach, proximal and distal small intestine, colon, pancreas.

Ingested food evokes satiation by 2 main effects on GI system:
- Gastric distension
- Release of peptides from enteroendocrine cells

Hindbrain – the principal central site for short-term signals that are transmitted:
- *neurally* (vagus to n. tractus solitarius)
- *hormonally* (gut peptides acting directly on area)

Cummings and Overduin 2007
Release of peptides from enteroendocrine cells

(Similarities between enteroendocrine cells of the intestine (L cell) and taste receptor cells of the tongue).
Intestinal satiety peptide
Cholecystokinin (CCK)

- Secreted by I cells of duodenal and jejunal mucosa, brain, enteric nervous system
- Secreted in response to luminal nutrients (lipids, proteins and/or products of their digestion)
- Has a satiating effect
- Inhibits gastric emptying
- Triggers the stereotyped sequence of eating behavior in rats
Intestinal satiety peptide

**Glucagon-like Peptide 1 (GLP-1)**

- Secreted by L cells of distal small intestine and colon
- Biphasic stimulation by ingested nutrients (lipids, carbohydrates)
- Inhibits food intake and reduces body weight
- Modulator of the stress response related to taste aversion (contact with CRH in n.paraventricularis)
- Potent insulinotropic and glucagonostatic hormone (improves insulin release, attenuates glucagon release, improves glucose disposal)
- Ideal candidate for treating diabetes (GLP-1 analogue - exenatide)
Intestinal satiety peptide - Peptide YY

- Produced by distal intestinal cells
- Physiological role in appetite by signaling the end of a meal in n. arcuatus (inhibits NPY)
- Slows gastric emptying and GI motility, inhibits secretion of gastric acid
- Increases shortly after a meal (while fasting reduces its level in healthy subjects)
- Secreted postprandially in proportion to caloric load (L > C > P) in a biphasic manner (neural, nutrient)
- Involved in both short-term regulation of satiety and long-term regulation of energy expenditure and body weight
Ghrelin – orexigenic (hunger) peptide

Ghrelin acts in hypothalamus on NPY/AgRP and POMC/CART neurons in an opposite manner to leptin.
GHRELIN (28 AA)

- Produced mainly in the stomach (Kojima 1999)
- Orexigenic and prokinetic effects
- Inverse relationship with leptin
- The regulator of postprandial satiety (physiological meal initiator)
- Dual action - short-term reg. of satiety and long-term reg. of body weight - low in obesity (postprandially) and high in anorexia nervosa (fasting)
- Obestatin - the product of the same gene as ghrelin

The only known peripheral orexigenic hormone
The secretion of ghrelin is regulated by the combination of mechanical, chemical, neural, and hormonal signals with unknown priority.

SST = somatostatin, CCK = cholecystokinin, GH = growth hormone

Source: Casanueva F, Diaguez C. 2004
Pancreatic peptides regulating food intake

Pancreatic polypeptide:
- Secretion stimulated postprandially in proportion to caloric load (vagal control)
- Influences exocrine pancreatic function, GI motility, gastric acid secretion
- Peripheral administration reduces feeding (vs. central administration increases feeding?)

Amylin:
- Cosecreted with insulin postprandially by pancreatic beta cells
- Inhibits gastric emptying, gastric acid and glucagon secretion
- Decreases meal size and food intake
- Amylin analogue pramlintide – used in diabetes treatment

Insulin:
- Marker of adipose tissue mass
- Secretion in response to caloric influx (but not the meal initiator as ghrelin)
- Regulation of satiety and meal termination
- Potent signal for leptin secretion
Content:

I. Physiology of neuroendocrine regulation of food intake

- Central regulation of food intake – hypothalamus, neurohormones
- Short- and long-term peripheral regulation of satiety and energy balance
  - GIT hormones (ghrelin and others)
  - Adipose tissue hormones (leptin and others)
  - Pancreatic hormones (insulin)

II. Pathophysiologial aspects of feeding disturbances (obesity)
OBESITY
Obesity is classified by Body Mass Index (BMI)

\[ \text{BMI} = \frac{\text{Weight (kg)}}{\text{Height (m}^2)} \]

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m(^2))</th>
<th>Metabolic c.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal weight</td>
<td>18.5–24.9</td>
<td>average</td>
</tr>
<tr>
<td>Overweight</td>
<td>25–29.9</td>
<td>increased</td>
</tr>
<tr>
<td>Obesity I</td>
<td>30.0–34.9</td>
<td>middle</td>
</tr>
<tr>
<td>Obesity II</td>
<td>35.0–39.9</td>
<td>high</td>
</tr>
<tr>
<td>Obesity III</td>
<td>≥40.0</td>
<td>Very high</td>
</tr>
</tbody>
</table>

WHO, 1998
Waist circumference is a helping indicator of visceral fat – this fat is the most metabolically active and thus the most harmful.

Women

>88 cm = highly increased risk\(^1\)
>80 cm = increased risk\(^1\)

Men

>102 cm = highly increased risk\(^1\)
>94 cm = increased risk\(^1\)

Consequences of Obesity

Mechanical – joint illness, dyspnoe, sleeping apnoe, heart hypetrophy,…..

Metabolic - diabetes, hypertension, hyperlipoproteinaemia, ischemic heart disease, ictus, tumours, sterility, depression,….. = Reaven metabolic syndrome
Obesity and Leptin

Leptin gene mutation causes morbid obesity in human, but....

Obesity and Leptin

• Leptin deficiency is not epidemiologically significant cause of obesity (3 cases of leptin-gene mutation in humans accompanied by morbid obesity)

• Most of obese patients have hyperleptinemia i.e. circulating leptin levels correlate with body fat content

• Body weight loss induces decrease in circulating leptin levels

• Clinical trials focused on the treatment of obesity with leptin did not show significant benefit of leptin treatment to body weight loss
Obesity and Leptin

Why hyperleptinemia does not suppress food intake in patients with obesity?

• **Resistance to leptin**: either on the levels of leptin transport across the blood-brain barrier or on the postreceptor level

*Primary leptin function is not to suppress food intake, but to trigger complex adaptive reaction of human body to starvation*
Obesity leads to subclinical inflammation in adipose tissue

A strong positive correlation between adipocyte size and the number of macrophages in adipose tissue has been found.

Obesity in mice is accompanied by decreased adiponectin

Haluzik et al, 2003
Obesity and GIT hormones

• Decreased satiety perception represents an important risk factor for the development of obesity (Degado-Aros 2004)

• Alterations in hormonal responses to food intake contribute to the decreased satiety in obesity (Schwartz and Morton 2002)

• GIT hormones are hot candidates for regulators of appetite and satiety in obese patients
Food fails to suppress ghrelin in obesity

Postprandial ghrelin response in obesity is (in contrast to healthy subjects) independent on caloric content and macronutrient composition of meal.

Does it contribute to resistance to weight loss by some obese patients?

Figure 1. Mean (± SEM) ln(ghrelin) response in lean and obese subjects following a test meal. There is a significant fall in ln(ghrelin) at 30 minutes following the meal in lean subjects (p=0.003, ANOVA for multiple comparisons with baseline), but no fall in obese subjects.

English et al. 2002
Obesity and pancreatic polypeptide (PP)

• PP low in obese vs. normal patients in morbid obesity
• Obesity associated with impaired intestinal peak of PP postprandial response
Obesity and Peptide YY

- Fasting PYY low or normal in obesity
- Obese subjects exhibit normal sensitivity on PYY-induced anorexia
- PYY deficiency rather than PYY resistance may contribute to the pathogenesis of obesity
- Postprandially, PYY response blunted in obese
- Caloric load required to evoke the same response in obese as in lean was more than double
- Obese subjects may have weaker PYY-induced satiety signal for an equivalent meal – contribute to reduce satiety of obese
Obesity and Cholecystokinin

- Fasting CCK increases in obesity
- Postprandial response of CCK on mixed-meal is normal
Short Quiz:

1. Which of the following peripheral factors is orexigenic?
   A. Insulin
   B. peptide YY
   C. CCK
   D. Leptin
   E. Ghrelin

2. Antiinflammatory cytokine produced by adipose tissue is
   A. adiponectin
   B. resistin
   C. ghrelin
   D. insulin
   E. CCK

3. Body Mass Index (BMI) equal to 23 (kg/m$^2$) means
   A. normal body weight
   B. overweight
   C. obesity I
   D. obesity II
   E. obesity III

4. Anorexigenic pathway in hypothalamus involves
   A. Neuropeptide Y (NPY)
   B. Proopiomelanocortin (POMC) neurons
   C. Agouti-related protein (AGRP)
   D. All the above
   E. None the above
Answers:

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Thank you