ADIPOCYTOKINES and ITS ACTION

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OBESITY

- a systemic illness caused by energy transformation homeostasis disorder
- Increase the amount of body fat mass
• **WAT:** white adipose tissue
  – accumulation of triacylglycerols: SAT, IAT(+VAT)
  – an endocrine gland producing bioactive adipocytokines
  – a group of a few glands acting differently
  – Glucose and lipid metabolism

• **BAT:** brown adipose tissue
  – heat generation
  – located along vessels active
  – may prevent obesity and insulin resistance

(Činti 2011, Wójcik and Górski 2011).
ADIPOSE TISSUES

White Fat

Beige Fat

Brown Fat

Excess fat is stored in lipocytes, which expand in size until the fat is used for fuel.

Fat reservoir

Nucleus

Brown fat cell
Converts chemical energy to heat to protect against cold weather.

Beige fat cell
Immature cell in white fat tissue matures to burn fat.

White fat cell
Most common fat cell, used to store fat and found beneath the skin and abdomen.
Timeline and mechanisms of adipocyte hyperplasia and hypertrophy

During periods of positive energy balance, such as overfeeding or sedentary lifestyle, adipose tissue expansion can be achieved by hyperplasia and/or hypertrophy.
Hyperplasia produces more adiponectin and less inflammatory adipokines.

Physiological balance between hypertrophy and hyperplasia

By the other side, hypertrophied adipocytes produce less adiponectin and more inflammatory adipokines.

Physiological balance between hypertrophy and hyperplasia
Adipose tissues & Adipocytokines

- A adipose tissue is now considered an active endocrine organ.
- Adipocytokines are bioactive proteins secreted from adipose tissues acting locally or at distant sites to regulate metabolism.
- In 1994, discovery of leptin known as the satiation hormone regulating body energy homeostasis and maintenance of body mass.
**Leptin**: a satiation hormone, released from fat cells, regulating body energy homeostasis and maintaining of body mass/an appetite suppressor

- Circulate in the blood and acts on a receptor localized in the hypothalamus and elsewhere in brain to regulate food intake
- Inhibit appetite
- Reduce the mass of the adipose tissue
- Increase the amount of energy expenditure

- When fat mass increases, leptin levels increase, suppressing appetite until weight is lost.
- When fat mass falls, plasma leptin concentrations fall too, stimulating appetite and suppressing energy expenditure until fat mass is restored.

• Leptin biosynthesis is stimulated by insulin, glucose, corticosteroids, large amounts of fat and carbohydrates in the diet, and regular meals and hampered by glucagon, catecholamines and low temperature.

• Leptin release is low during the day and increases at night explained as an effect of not eating.

• Leptin regulates the metabolism of an organism via the central and peripheral nervous system.

• Via the peripheral nervous system:
  – Leptin regulates the metabolism of an organism through inhibition of lipogenesis, stimulation of lipose, and an increase of β-oxidation of fatty acids.
  – Leptin increases glycolysis and insulin sensitivity of tissues, and inhibits hepatic gluconeogenesis.

Leptin regulates the metabolism of an organism via the central nervous system. Leptin is a protein whose transcription is stimulated by cocaine, amphetamine, and corticotropin-releasing hormones.

Fig. 1. Schematic of leptin activity.
Adipokines

- Since the identification of leptin in 1994, adipose tissue has emerged as an extremely active endocrine organ secreting a huge variety of adipokines
  - hormones
  - cytokines
  - growth factors
  - vasoactive factors
Adipocytokines

Proinflammatory

Adipokines
• Leptin
• Resistin
• Apelin, visfatin
• Omentin
• Retinol-binding protein 4 (RBP4)

Cytokines
• Tumor necrosis factor (TNF-α)
• Interleukin-6 (IL-6)

Anti-inflammatory and insulin-sensitizing adipocytokine

• Adiponectin
  • Leptin, TNF-α, and IL-6 are well-characterized proinflammatory adipocytokines
ANGPTL4, angiopoietin-like 4; ASP, acylation-stimulating protein; BP, blood pressure; CCL, chemokine (CC motif) ligand; CRP, C-reactive protein; FGF-21, fibroblast growth factor-21; FIAF, fasting induced adipose factor; FNDC5, fibronectin type III domain containing 5; HMGB1, high-mobility group B1; IL, interleukin; MCP-1, monocyte chemoattractant protein 1; MIF, macrophage migration inhibitory factor; MMP, matrix metalloproteinase; PAI-1, plasminogen activator inhibitor-1; PEDF, pigment epithelium-derived factor; PGI₂ and PGF₂α, prostaglandin I₂ and F₂α; RBP4, retinol binding protein-4; SAA, serum amyloid A; STAMP2, six-transmembrane protein of prostate 2; TGFβ, transforming growth factor-β; TIMP-1, tissue inhibitor of matrix metalloproteinase-1; TNF-α, tumor necrosis factor-α; TWEAK, TNF-like weak inducer of apoptosis; VEGF, vascular endothelial growth factor; WISP1, Wnt1-inducible signaling pathway protein-1; YKL-40, chitinase-like 1 protein.
Adipokines

<table>
<thead>
<tr>
<th>Adipokine</th>
<th>Main Metabolic Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin</td>
<td>Hormone with antidiabetic, antiatherogenic, and anti-inflammatory properties</td>
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<tr>
<td>Adipsin</td>
<td>Protein involved in activation of the alternative complement pathway</td>
</tr>
<tr>
<td>Angiotensinogen</td>
<td>Precursor molecule of angiotensin II that causes vasoconstriction, increased BP, and release of aldosterone from the adrenal cortex</td>
</tr>
<tr>
<td>Apelin</td>
<td>Peptide implicated in control of BP and one of the most potent stimulators of cardiac contractility; inhibits insulin secretion; involved in lipolysis</td>
</tr>
<tr>
<td>ASP</td>
<td>Hormone produced by the complement pathway that regulates whole body glucose and lipid metabolism</td>
</tr>
<tr>
<td>Calprotectin</td>
<td>Proinflammatory factor involved in cell adhesion, chemotaxis, and antimicrobial activity</td>
</tr>
<tr>
<td>Cardiotrophin-1</td>
<td>Cytokine involved in hypertrophy of cardiomyocytes</td>
</tr>
<tr>
<td>Cathepsins S, L, K</td>
<td>Cysteine proteases that promote adipogenesis and extracellular matrix remodeling</td>
</tr>
<tr>
<td>Chemerin</td>
<td>Chemoattractant protein involved in adaptive and innate immunity and in adipogenesis</td>
</tr>
<tr>
<td>CCL2, 3, 5, 7, 8, 11</td>
<td>Chemokines involved in monocyte chemotaxis</td>
</tr>
<tr>
<td>Clusterin</td>
<td>Lipoprotein that promotes tumor progression and angiogenesis and is involved in metabolic and cardiovascular diseases</td>
</tr>
<tr>
<td>CRP</td>
<td>Acute-phase reactant involved in inflammatory processes</td>
</tr>
<tr>
<td>Fetuin A</td>
<td>Protein that reflects liver fat content; associated with lipid-induced inflammation and insulin resistance; promotes cancer progression</td>
</tr>
<tr>
<td>FGF-21</td>
<td>Hormone that stimulates glucose uptake into adipocytes and increases thermogenesis, energy expenditure, and fat utilization</td>
</tr>
<tr>
<td>FIAF/ANGPTL4</td>
<td>Protein induced by fasting and hypoxia</td>
</tr>
<tr>
<td>FNDC5/irisin</td>
<td>Myokine/adipokine involved in promotion of myogenogenesis and fat browning</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>Orexigenic and adipogenic hormone that exerts a depressor effect on BP control and acts as a cardioprotective agent</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>Acute-phase reactant with angiogenic and chemotactic properties</td>
</tr>
<tr>
<td>Hepcidin</td>
<td>Proinflammatory cytokine that activates MMP-9</td>
</tr>
<tr>
<td>HGF</td>
<td>Factor that stimulates proliferation and development in adipocytes and antiinflammatory effects</td>
</tr>
<tr>
<td>HMGB1</td>
<td>Alarmin involved in DNA repair and secretion of insulin in pancreatic β-cells</td>
</tr>
<tr>
<td>Hsp72</td>
<td>Damage-activated protein that induces neutrophil and natural killer cell recruitment</td>
</tr>
<tr>
<td>IGF-I</td>
<td>Factor that stimulates proliferation and differentiation in adipocytes</td>
</tr>
</tbody>
</table>
Table 1. Adipokines secreted by adipose tissue

<table>
<thead>
<tr>
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<tr>
<td>IL-1β</td>
<td>Proinflammatory cytokine involved in a paracrine inflammatory pathway in adipose tissue</td>
</tr>
<tr>
<td>IL-6</td>
<td>Proinflammatory cytokine implicated in acute-phase responses</td>
</tr>
<tr>
<td>IL-8/CXCL8</td>
<td>Chemokine involved in pathogenesis of atherosclerosis and cardiovascular diseases</td>
</tr>
<tr>
<td>IP-10/CXCL10</td>
<td>Chemokine produced by T cells</td>
</tr>
<tr>
<td>Leptin</td>
<td>Anorexigenic hormone with lipolytic and vasoactive effects in addition to other pleiotropic activities</td>
</tr>
<tr>
<td>Lipocalin-2</td>
<td>Adipokine showing anti-inflammatory properties</td>
</tr>
<tr>
<td>MCP-1</td>
<td>Chemoattractant protein that promotes inflammation and macrophage infiltration in adipose tissue</td>
</tr>
<tr>
<td>MIF</td>
<td>Factor involved in proinflammatory processes and immunoregulation.</td>
</tr>
<tr>
<td>MMP2 and 9</td>
<td>Proteins implicated in adipogenesis</td>
</tr>
<tr>
<td>NUCB2/Nesfatin-1</td>
<td>Anorexigenic peptide also involved in the inflammatory response</td>
</tr>
<tr>
<td>NGF</td>
<td>Neurotropin involved in development and survival of sympathetic neurons</td>
</tr>
<tr>
<td>Omentin</td>
<td>Novel adipokine that modulates insulin sensitivity and exerts anti-inflammatory properties</td>
</tr>
<tr>
<td>Osteopontin</td>
<td>Proinflammatory factor involved in vascular and myocardial remodeling; cytokine implicated in insulin resistance and cancer</td>
</tr>
<tr>
<td>PAI-1</td>
<td>Potent inhibitor of fibrinolysis implicated in development of atherosclerotic plaques</td>
</tr>
<tr>
<td>PEDF</td>
<td>Secreted glycoprotein that belongs to the noninhibitory serpin group with antiangiogenic, antioxidant, antiinflammatory, and lipolytic effects</td>
</tr>
<tr>
<td>PGI2 and PGF2α</td>
<td>Factors implicated in regulatory functions such as inflammation, blood clotting, ovulation, menstruation, and acid secretion</td>
</tr>
<tr>
<td>Progranulin</td>
<td>Chemoattractant protein involved in adipose tissue inflammation and neurodegenerative diseases</td>
</tr>
<tr>
<td>RBP4</td>
<td>Factor involved in development of insulin resistance, visceral fat distribution, and dyslipidemia</td>
</tr>
<tr>
<td>Resistin</td>
<td>Hormone involved in development of insulin resistance, which participates in the proinflammatory response</td>
</tr>
<tr>
<td>SAA</td>
<td>Acute-phase reactant produced in response to injury, infection, or inflammation</td>
</tr>
<tr>
<td>SRFP5</td>
<td>Inhibitor of WNT5a signaling with anti-inflammatory properties</td>
</tr>
<tr>
<td>STAMP2</td>
<td>Metalloreductase that plays a role in cellular import of copper and iron and in reduction of macrophage recruitment and polarization toward the M1 phenotype</td>
</tr>
<tr>
<td>Tenascin C</td>
<td>Damage-activated protein that induces immune responses and extracellular matrix remodeling</td>
</tr>
<tr>
<td>TGFβ</td>
<td>Regulatory factor of preadipocyte proliferation, differentiation, and apoptosis</td>
</tr>
<tr>
<td>Tissue factor</td>
<td>Major cellular initiator of the coagulation cascade</td>
</tr>
<tr>
<td>TIMP-1</td>
<td>Inhibitor that decreases adipogenesis and impairs glucose tolerance</td>
</tr>
<tr>
<td>TNFα</td>
<td>Proinflammatory cytokine involved in systemic inflammation and development of insulin resistance in obesity</td>
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<tr>
<td>TWEAK</td>
<td>Proinflammatory cytokine of the TNF superfamily that inhibits adipose tissue growth</td>
</tr>
<tr>
<td>Vaspin</td>
<td>Adipokine of the serine protease inhibitor family showing insulin-sensitising effects</td>
</tr>
<tr>
<td>VEGF</td>
<td>Factor involved in angiogenesis stimulation in adipose tissue</td>
</tr>
<tr>
<td>Visfatin/NAMPT</td>
<td>NAD⁺ biosynthetic enzyme involved in regulation of β-pancreatic cells</td>
</tr>
<tr>
<td>WNT5a</td>
<td>Secretned glycoprotein of the WNT family with anti-adipogenic and proinflammatory actions</td>
</tr>
<tr>
<td>WISP1</td>
<td>Secreted matricellular protein that regulates adipogenesis and adipose tissue inflammation</td>
</tr>
<tr>
<td>YKL-40</td>
<td>Proinflammatory factor that stimulates innate immune system, extracellular matrix remodeling, and angiogenesis</td>
</tr>
<tr>
<td>Zinc α2-glicoprotein</td>
<td>Soluble glycoprotein with lipolytic effects</td>
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ANGPTL4, angioptoeitin-like 4; ASP, acylation-stimulating protein; BP, blood pressure; CCL, chemokine (CC motif) ligand; CRP, C-reactive protein; FGF-21, fibroblast growth factor-21; FIAF, fasting induced adipose factor; FNDC5, fibronectin type III domain containing 5; HMGB1, high-mobility group B1; IL, interleukin; MCP-1, monocyte chemoattractant protein 1; MIF, macrophage migration inhibitory factor; MMP, matrix metalloproteinase; PAI-1, plasminogen activator inhibitor-1; PEDF, pigment epithelium-derived factor; PGI₂ and PGF₂α, prostaglandin I₂ and F₂α; RBP4, retinol binding protein-4; SAA, serum amyloid A; STAMP2, six-transmembrane protein of prostate 2; TGFβ, transforming growth factor-β; TIMP-1, tissue inhibitor of matrix metalloproteinase-1; TNFα, tumor necrosis factor-α; TWEAK, TNF-like weak inducer of apoptosis; VEGF, vascular endothelial growth factor; WISP1, Wnt1-inducible signaling pathway protein-1; YKL-40, chitinase-like 1 protein.
Insulin sensitivity
- Adiponectin, Apelin
- Lipocalin-2
- Omentin
- Vaspin, Visfatin

Adipose tissue proliferation
- Calprotectin, HGF, Hepcidin
- IGF-1, MMP2, MMP9, TGFβ, VEGF

Adipocytokines

Insulin resistance
- Fetuin A, RBP4, Resistin
- Osteopontin

Cardiovascular
- Angiotensinogen, Apelin
- Cardiotropin-I, Clusterin
- Ghrelin, IL-8
- Osteopontin, PAI-1

Proinflammation
- CRP, Hepcidin, IL-1B, IL-6
- MCP-1, PGI2, PGF2α
- Progranulin, SAA
- TNFα, TWEAK, WISP1

Anti-inflammation
- Adiponectin
- PEDF, SRFP5
Adiponectin

- A polypeptide hormone of antidiabetic, anti-inflammatory and anti-atherogenic activity
  - an antagonist of receptor IL-1
  - stimulate secretion of IL-10
- **Its secretion is stimulated by insulin and inhibited by TNF and IL-6**
- Play a key role in carbohydrate and fat metabolism
  - Increase insulin sensitivity of tissues
  - Stimulate muscle glucose uptake
  - Inhibit hepatic gluconeogenesis
  - Decrease the concentration of free fatty acids by increasing oxidation

TNF-α

- Cause insulin resistance by blocking the receptors for this hormone
- Has an impact on pancreatic beta cells inhibiting insulin secretion
- Inhibit its ability to estrificate fatty acids
- Decrease secretion of adiponectin
- Inhibit the transport of glucose to the liver cells and fatty acid oxidation

Kuryszko et al., 2016, Lui 1998)
- Approximately 30% of the circulating IL-6 comes from the adipose tissue
- **Synthesis in VAT is about 3 times higher than in SAT**
- High concentrations of IL-6 cause insulin resistance
- **Decrease expression of insulin receptors**
- Decrease adipogenesis and secretion of adiponectin and visfatin
- **Stimulate liver gluconeogenesis**

(Kern et al. 2001; Ruan and Lodish 2003).
Dysfunctions of adipose tissues

- In 2004, Bays introduced the notion of adiposopathy, defined as dysfunction of the adipose tissues
  - Insulin and leptin resistance
    - Concentration of leptin in blood serum in obese individuals is higher
    - Administration of exogenous leptin does not reduce body mass
  - Productions of inflammatory cytokines (TNF and IL-6) and monocyte chemoattractant protein
  - Adipocytes enlarge and die while macrophages massively infiltrate the adipose tissues

Normal fat tissue metabolism

1. Fat tissue contains 10-15% macrophages

2. Fat globule

3. Enhanced insulin sensitivity

4. M2 anti-inflammatory activation

5. M2-activated macrophage

Adiponectin and omega-3 fatty acids block inflammatory pathways.

Adipose tissue metabolism in obese individuals

1. Fat tissue contains 50-60% macrophages
2. Apoptotic fat cells
3. TNF-α and other inflammatory factors
4. Inflammation recruits additional immune cells
5. Inflammation causes fat tissue to become insulin-resistant

Both outcomes accelerate and activate additional steps in developing diabetes.
Metabolic dysfunctions in adipose tissues

These changes mediate development of obesity-related metabolic dysfunctions such as insulin resistance, dyslipidemia, nonalcoholic fatty liver disease, and atherosclerosis.
Three most likely causes of inflammatory reaction

1) Inflammatory reaction in the adipose tissue
   - in response to adipocyte hypoxia
   - hypertrophied adipocytes in adipose tissue, an increasing fat cell moves away from blood vessels, leads to a reduction in blood flow with subsequent hypoxia and macrophage infiltration
   - hypoxia causes the release of IL-6
   - In addition, cytokines produced by macrophages inhibit adipogenesis

(Kuryszko et al. 2016, Trayhurn et al. 2008)
Three most likely causes of inflammatory reaction

2) **Oxidative stress** caused by an increased supply of glucose to the fat cells

- sugar is taken up by endothelium cells of the stroma vessels
- increases the production of free radicals
- damages the cells by triggering an inflammatory reaction

(Kuryszko et al. 2016, Lin et al. 2005)
Three most likely causes of inflammatory reaction

3) **Cell stress theory**
   - adipocyte hypertrophy, contributes to the impairment of the functions of the endoplasmic reticulum and the activation of stress-sensitive proteins which occur in it

(Kuryszko et al. 2016, Persegin et al 2003)
Detailed action of adipocytokines will not only help understand the pathophysiology of metabolic dysfunction associated with obesity but also assist to identify therapeutic targets to prevent or reverse these metabolic derangements.