Molecular Mechanisms of Insulin Resistance

Interactions with adipose tissue's molecules

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INTRODUCTION Insulin resistance is the cell's incapacity to respond to the normal actions of the hormone that leads to a decrease in cell survival, glucose uptake and the synthesis of protein, glycogen and fatty acids. Insulin exerts its immediate effects via the activation of the **IR/IRS/PI3K/PKB signaling pathway**. Molecules related with the adipose tissue can modulate this pathway, increasing or decreasing insulin sensitivity. Some of these molecules are **adiponectin**, **leptin**, **resistin** and inflammatory factors such as **tumor necrosis factor alpha** (TNF-α) and **interleukine 6 (**IL-6).

Adiponectin

It **increases fatty acid oxidation** and **improves insulin sensitivity**.

Targets: **AMPK** and **PPAR**.
Activates: TSC and fatty acid transporters.
Reduces: mTORC, ACC, IKK, SREBP and ChREBP.
Increases glucose uptake via GLUT 4 translocation. Reduces gluconeogenesis by blocking PEPCK and G6P.

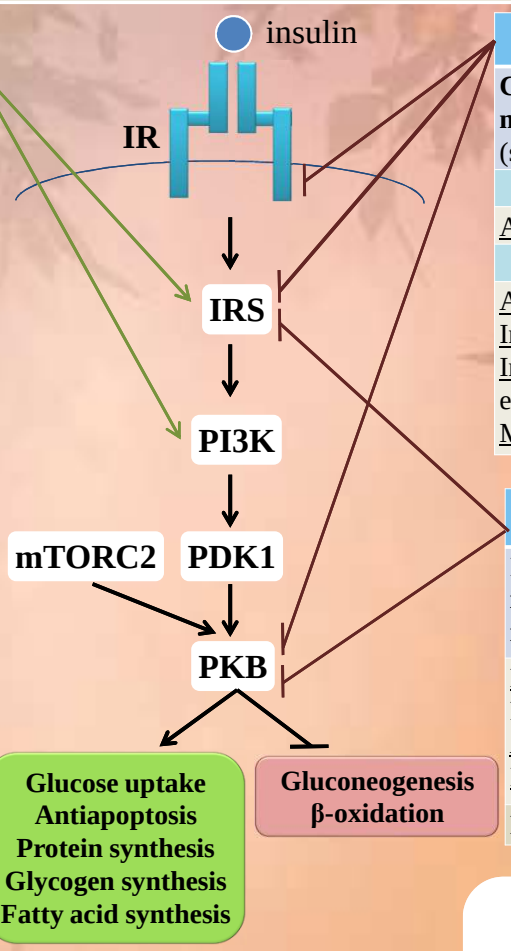
↓ insulin resistance

Leptin

It **decreases hunger, thermogenesis** and **fatty acid oxidation**.

Leptin resistance State: hormone levels are high but cells don't respond to it. It appears in obese patients.
Caused by: BBB transport deficiency AND SOCS3 activation: inhibits JAK/STAT leptin signaling pathway.
Increases lipogenesis (c-fos and SREBP activation).

↑ insulin resistance



TNF-α & IL-6

Cytokines mostly produced by **macrophages**. Higher expression in obesity (systemic inflammatory state).

IL-6

Activates: SOCS3, MAPKs and PKC.

TNF-α:

Activates: IKK → NF-κB, S6K, JNK1.
Inhibits: GLUT 4, ACS, JNK and perilipin.
Increases cytokine production and expression and lipid accumulation.
Modulates gene expression.

↑ insulin resistance

Resistin

It recruits **proinflammatory factors** and **immune cells**. It's mostly produced by **monocytes** and **macrophages**.

Decreases: AMPK, PPAR, PKB activity, ROR activation and Foxo1 expression.
Activates: GSK3, ERK1/2 and SOCS3.
Increases gluconeogenesis and lipogenesis.

Human relevance not proved.

↑ insulin resistance

Antidiabetic Drugs

Biguanides

Metformin is the most used biguanide.
Targets: **AMPK** and **PPAR** → fatty acid oxidation increase/ lipogenesis block.
Insulin sensitivity increase: ↑ peripheral glucose and glucose uptake
↓ hepatic glucose production.

Thiazolidinediones (TZDs)

Targets: **AMPK** and **PPARɣ**
Insulin sensitivity increase: ↑ glucose use for energy expenditure
inflammatory cytokines block

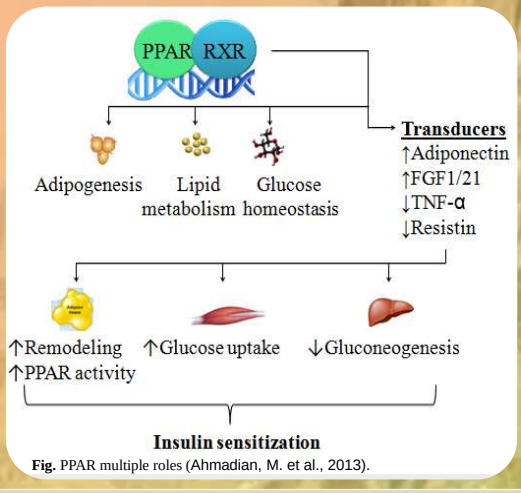


Fig. PPAR multiple roles (Ahmadian, M. et al., 2013).

CONCLUSIONS Adipose tissue's related molecules modulate insulin resistance, promoting this pathology in overweight status. Insulin resistance can also be seen in **veterinary medicine**, with a lower prevalence, mostly related with an animal's **inadequate nutrition** or **life style** that lead to obesity. Two antidiabteic drugs broadly used, **Metformin** and **TZDs,** have the same targets: **AMPK** and **PPAR**, making clear that both molecules have a **crucial role** in insulin resistance. There is a **need for further research** since many of the **mechanisms** involved in this pathology remain **incompletely understood** and the **perspectives** of finding **new drugs** are **favorable.**

ABBREVIATIONS: Insulin receptor (IR); insulin receptor substrates (IRS); phosphoinositide-dependent kinase-1 (PDK1); protein kinase B (PKB); AMP-activated protein kinase (AMPK); peroxisome proliferator-activated receptors (PPAR); tuberous sclerosis complex (TSC); mammalian target of rapamycin complex 1&2 (mTORC1/2); acetyl Co-A carboxylase (ACC), IκB kinase (IKK); sterol regulatory element-binding protein (SREBP); carbohydrate-responsive element-binding protein (ChREBP); phosphoenolpyruvate carboxykinase (PEPCK); glucose 6-phosphatase (G6P); blood-brain barrier (BBB); supressor of cytokine signaling 3 (SOCS3); janus-kinase/signal transducers and activators of trascription (JAK/STAT); mitogen-activated protein kinase (MAPKs); protein kinase C (PKC); nuclear factor-κB (NF-κB); c-Jun N-terminal kinases (JNK); glycogen synthse kinase 3 (GSK3); extracellular signal-regulated kinases 1&2 (ERK1/2); tyrosine-protein kinase transmembrane receptor (ROR).