Adiponectin Receptors: A Review of Their Structure, Function and How They Work

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The Council of Hypothalamic Metabolites
Intro
Agenda

1. AMPK Activation Pathways
2. PPARα & Ca^{2+} Activation Pathways
3. Pathway Regulation and More Pathways
4. Adiponectin and Receptors in Disease
5. Conclusion
AMPK Activation Pathways: Receptors, Structure & Function
Receptors & Structure

- AdipoR1
  - A protein which acts as a receptor for Adiponectin
  - Binding of Adiponectin at this receptor results in activation of an AMP-activated Kinase signaling pathway which affects levels of fatty acid oxidation and insulin sensitivity expressed mainly in the Liver, Muscle, and Hypothalamus
Receptors & Structure cont...

- Regulated by AMP:ATP Ratio
  - Energy Regulator
    - Drop in ATP
    - LKB1 Activation of AMPK
    - AMPK Regulates Glucose and Lipid Metabolism and drive to eat in order to keep body in a homeostatic condition
- Regulated by Ca²⁺/CaMKKβ activation
  - Product of PPAR Activation at AdipoR2
Function

- AMPK Increase of Activation
  - Skeletal Muscle:
    - Excitation of TBC1D1, Rab GTPase activating protein, which increases Glucose Uptake
  - Hypothalamus
    - Increase in Neuropeptide Y activation which can increase food intake
  - Liver:
    - ACC (Acetyl-CoA Carboxylase) is inhibited consequently decreasing FAS (Fatty Acid Synthesis)
    - HMG-CoA (HMG-CoA Reductase) is inhibited leading to the decrease of cholesterol synthesis
PPAR(α,β,γ) & Ca²⁺ Pathway: Receptors, Structure, and Function
Receptors

- **AdipoR2: PPARα**
  - Another protein that acts as a receptor to adiponectin → peroxisome proliferator-activated receptor (PPARα)
  - Found in liver, white adipose tissue (WAT), and vasculature
  - Glucose metabolism and insulin sensitivity

- **AdipoR1: CaMKKβ**
  - Found in liver, skeletal muscle, hypothalamus, etc.
  - Calmodulin-dependent protein kinase kinase (CaMKKβ)
**Structure**

- **Full-Length Adiponectin**
  - Found in the skeletal muscle and liver
- **Globular Adiponectin**
  - Found in the skeletal muscle
  - Proteolytic cleavage of FL Adiponectin
  - Increased binding in myocytes and skeletal muscle membrane
  - Decreased binding in hepatocytes and liver membrane
- **PAQR Family of Receptors**
  - Progesterone and adiponectin Q receptors

![Diagram of Adiponectin Structure](image)

"Not sure if Globular Adiponectin prefers ADIPO-R1 or R2"
Signalling Mechanisms
Function

- **AdipoR2: PPARα activation**
  - Fatty acid combustion and energy consumption
  - Increased insulin sensitivity
  - ACO and UCP genes: peroxisome proliferator response element (PPRE) in promoter regions

- **AdipoR1**
  - Extracellular influx of Ca2+ → activation of (CaMKK)β, AMPK
  - SirT1 is then activated which increases expression and decreases acetylation of PPARα gamma coactivator (PGC)-1α, increases mitochondria in myocytes

- **Both**
  - Ligand activities, fatty-acid oxidation, and glucose uptake
Function cont...

- Decreased adiponectin and hindered adipoR1
  - Insulin resistance and decreased exercise endurance
  - Linked to diabetes, mitochondrial dysfunction in obesity

- Ceramidase activity
  - Might lead to collective pleiotropic biological actions
  - Ceramidase and S1P (sphingosine 1-phosphate) activity further downstream
    - Ceramidase activation → increased sphingosine & reduced hepatic ceramide insulin sensitivity?
    - Increased S1P → protecting cells from apoptosis (myocytes and beta cells)
  - Independent of AMPK pathway
Pathway Regulation & Other Possible Receptors and pathways
Pathway Regulation

- AdipoR1
  - Heart, liver, skeletal **muscle***, brain, and cancer cell;
- AdipoR2
  - Artery, **liver***, adipocytes, brain, and cancer cell.
- Insulin, adiponectin and AdipoR(1&2)
  - Inversely correlated: Insulin↑ => ↓AdipoR
  - Insulin down-regulates AdipoR expression via PI3K/Akt/FOXO1-dependent pathway (Tsuchida et al. 2004)
  - Insulin inhibits adiponectin production through the same pathway

[Note: *Indicates tissue or cell type not fully described in the image.]
Pathway Regulation Cont.

- AdipoR and ob/ob mice (Tsuchida et al. 2004)
  - hyperinsulinemia/T2DB => ↓AdipoR expression
  - Decreased adiponectin sensitivity
    - Experiment: adiponectin administration to wild-type mice and ob/ob mice (skeletal muscle)
    - ↓ activation of AMPK in the skeletal muscle in ob/ob despite adiponectin injection
- “Vicious cycle”
The “vicious cycle”
Pathway Regulation Cont.

- Fasting and adiponectin
  - Caloric restriction $\Rightarrow$ ↑ adiponectin (Cawthorn et al. 2014) $\Rightarrow$ ↑ insulin sensitivity
  - Anorexia Nervosa?
    - AN patients still have increased level of adiponectin despite WAT depletion
    - Adiponectin produced by MAT in bone marrow
      - Paradoxical increase of bone marrow fat in AN patients (Scheller, Erica L et al, 2016)
Possible other receptors and pathways

T-cadherin (A.K.A Cadherin 13 or CDH13)

- An adiponectin receptor on cardiac muscle
- Evidence: adiponectin is unable to bind to cardiac muscle in T-cadherin-deficient mice
- T-cadherin protects against cardiac stress through association with adiponectin (Denzel et al, 2010)
  - Cardiac stress: hypertrophy
Possible other receptors and pathways Cont.

Calreticulin

- A protein found on the surface of macrophage
- Promotes phagocytosis
- Adiponectin-mediated removal of early apoptotic cells
  - Apoptosis, necrosis and inflammation (Haanen and Vermes, 1995)
    - Accumulation of dying cell and free cell content would trigger/enhance the inflammatory response
  - Lack of adiponectin => ↑ Inflammation
Adiponectin and receptors in disease
NASH

- AdipoR1/R2 regulate fatty acid metabolism in liver

- Study on obese Zucker rats
  - High fat/high cholesterol diet
  - Developed non-alcoholic steatohepatitis
    - Excess fat in liver, inflammation, fibrosis, cell damage
NASH continued

- Decreased expression of AdipoR1/R2 → decreased AMPK and PPARα
- Down-regulation of adiponectin → increased synthesis and decreased oxidation of fatty acids
- High fat diet → obesity/insulin resistance → receptor inhibition → decrease lipid metabolism → accumulation of fat → NASH
Obesity

- Cardiovascular tissue express adiponectin receptors
  - Decreased in hyperinsulinemia via PI3K/Akt pathway
  - PI3K/Akt pathway imbalance → obesity and Type II Diabetes

- Adipose hypertrophy
  - Reduces glucose uptake
  - Exacerbates insulin resistance
  - Block PI3K/Akt mediated inhibition of lipolysis
  - Reduce glucose utilization

- Decrease in AdipoR1 decreases AMPK-dependent angiogenic responses
Obesity continued

- Impaired adiponectin action → obesity-linked diseases
  - AdipoR1 in muscle, liver, macrophages → Type II Diabetes, atherosclerosis
  - AdipoR1/R2 in liver and cancer cells → fatty liver and cancer
  - AdipoR2 in endothelial cells → atherosclerosis
Cancer Cells

- AdipoR1/R2 expression decrease in gastric cell lines via TGFβ
  - TGFβ activated → signaling cascade → cell differentiation and proliferation
- Decreased mRNA expression of AdipoR1/R2 in gastric cancer cells
- Decrease receptor expression in endometrial adenocarcinoma tissue → development, invasion, metastasis
Cancer Cells continued

- Reduction of hyperinsulinemia
- Hyperinsulinemia promotes IGF1
  - Regulates cell proliferation
Exercise

- Exercise activates AMPK and increases longevity
- Adiponectin activates AMPK in skeletal muscle → activates SirT1 → longevity
- SirT1
  - Improves insulin sensitivity
  - Affects activity of proteins responsible for metabolic regulatory transcription factors
  - Mimic exercise → increase life span?
The antidiabetic effect

Adiponectin KO → obese, insulin resistant phenotype

-HFD given to mice = insulin resistance, hypertriglyceridemia and ↓ plasma adiponectin lVls
-Adiponectin administered to these mice highly improves insulin resistance and hypertriglyceridemia

Administration seems to increase fatty acid oxidation via seq activation of AMPK, MAPK and PPARα

Administration improves insulin sensitivity, promoting glucose uptake

↑adiponectin → ↓ weight, obesity, insulin resistance and T2D
Treatment Strategies

If a ↓ in adiponectin has a role in the development of diseases like T2D, increasing adiponectin receptors could help treat them.

PPARα activation by its agonist Wy-14,643 is being studied as a potential therapeutic strategy.

Future Research

Long term effect of adiponectin on insulin resistance

Analysis of 3D structure of AdipoR

Improvement of ARA using the 3D structure

Drug development
Conclusion
Reference

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4420556/