

Short communication

Role of adiponectin and its target receptors to control deposition of fat in obesity related disorders

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ARTICLE INFO

Keywords:

Obesity
Adipose tissue
Adiponectin
Receptor

ABSTRACT

Background: Adiponectin is a protein hormone secreted by adipocytes.

Aim: The aim of present review is to enlist them all, and mention their significance in obesity, which helps researchers in drug discovery and future medicine.

Material and methods: The last 20 years data has been searched and studied to mention their current role in obesity treatment and ailments of disease.

Results and conclusion: Adiponectin exert its action through receptors AdipoR1, AdipoR2, T-cadherin. In muscle AdipoR1 is exhibit, while in liver AdipoR2 is mainly exhibit. AMPK and PPAR α pathway in liver and skeletal muscle are magnified by adiponectin. Adiponectin show many function like expand fatty acids oxidation, control glucose level and manage receptor activity. Circulating level of adiponectin is lower in case of obesity, insulin resistance and other metabolic disorder. In this review we will focus on role of adiponectin and its receptors in metabolic disorder obesity.

1. Introduction

Obesity is become now a day's one of the serious health issue in every part of the world, due to its relation with group of vascular, metabolic and psychosocial complication (Field et al., 2001; Must et al., 1999). Obesity is a condition when abnormal or excess fat accumulation in adipose tissue, to the extent that health may be diminish (echnical Report Seri, 2000). According to WHO overweight and obesity is calculated by body mass index (BMI) [(weight in kg)/(height in m)²]: BMI = 25–29 kg/m² for overweight and BMI \geq 30 kg/m² for obesity. Fat tissue constitutes a source of, 600 active regulative molecules (Blüher and Mantzoros, 2015). Among them, adiponectin play critical roles in management of the carbohydrate metabolism as well as the sensitivity to insulin (Blüher and Mantzoros, 2015; Blüher, 2012, 2014). These active molecules may compose a “bridge” in the middle of fat tissue and metabolic disorders and they are also responsible for take part in the progress of insulin resistance and pathogenesis of type2 diabetes (T2DM). Firstly, as a peptide of adipose tissue adiponectin was reported that is not regulated properly in case of obesity. After, sometime later adiponectin prospective as an anti-atherogenic factor was identified that have ability to control the endothelial adhesion molecules expression and atherogenesis (Prashar et al., 2017). After it, then

so many experiments and studies have survey the role of adiponectin in vascular homeostasis and in cardiovascular diseases its prospect value as a molecule that occur naturally providing inconstant results (Filho et al., 2006). In case of obesity, insulin resistant, T2DM, high blood pressure and coronary heart disease the levels of adiponectin become lower (Frystyk et al., 2007). The aim of present article is to explore the molecular mechanism of adiponectin and provide sufficient information to researcher so they can target or consider adiponectin as new therapeutic approach in controlling metabolic disease (Fig. 1).

2. Adipose tissue: overview

The massive and highly specific tissue is Adipose tissue in connective tissues and the cell of dissimilar types composed them. In adipose tissue variety of cells are present that represents its huge function and significance in distinct systems involving metabolic system and osteogenic system (Hattori et al., 2004). With the help of connective tissue AT is made which is ordinarily highly flexible in a low density. During obesity collagenous, calcified and rigid in a fibrotic state all are condition take place in connective tissue. The significant place for modulation of systemic metabolism is extracellular matrix of adipose tissue (Khan et al., 2009). Two types of adipose tissues are present in

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<https://doi.org/10.1016/j.obmed.2019.100148>

Received 20 September 2019; Received in revised form 5 October 2019; Accepted 7 October 2019

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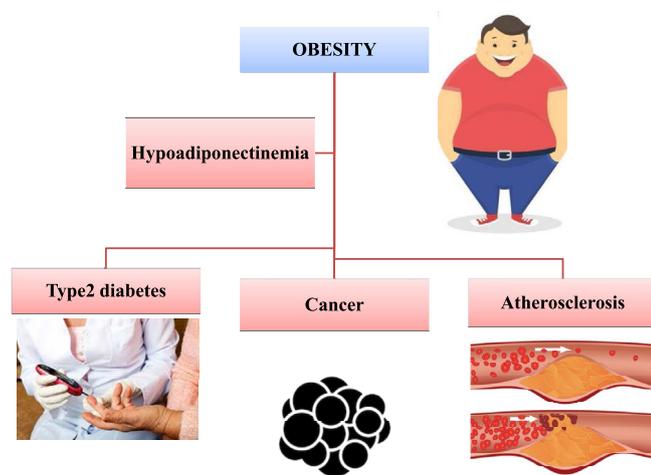


Fig. 1. Adiponectin in Obesity and its associated disorders.

human: White adipose tissue (WAT) and Brown adipose tissue (BAT). The adipocytes present in both types show different morphology and function. In organism WAT represents the vast majority of adipose tissue. In small mammals and human neonates particularly brown adipocytes are present and it contain several smaller droplets of lipid. BATS are in multilocular appearance. Brown adipose tissue are specialized for heat production (thermogenesis) that is almost absent in adult humans, but present in birth stage. Brown adipocytes average diameter is smaller than white adipocytes. Brown adipocyte stores energy, in the format of triglycerides in lipids that produces heat by oxidizing fatty acids, rather than supplying free fatty acids for use of another cell types (Bernlohr et al., 2002; Fonseca-Alaniz et al., 2007; Saely et al., 2012). WAT are in unilocular appearance and contain lipid of unique type because in high energy density they are able to store triglycerides (TGs) (Cinti, 2002; Nishino et al., 2008). Energy stored in this form is efficient because two types of reasons are responsible (1) As compared to carbohydrates the caloric value of lipids are significant. (2) With little associated water be can stored the Triglycerides in variance to carbohydrates. Then, weight of white adipocytes is approximately 60–85% made up of lipids and AT-weight water-weight is abolish (Trayhurn, 2007). This property of TGs in an obese state decreases the total weight of Adipose tissue as compared to the muscular body having skeletal muscle of same mass. The communication between adipose tissue and other biological systems is possibly done by bioactive moderator which is known as adipokines.

3. Adiponectin

Adiponectin is one of the adipokine secreted by adipose tissue, which is helpful to perform different biological procedure of human body. Adiponectin is a type of protein hormone with 244 amino acid and they flow in very high quantity (5–30 $\mu\text{g/ml}$), In total serum proteins its accounting is 0.01%. The expression and serum levels of adiponectin are reduced in obese patients, pigs, and rodent (Daniele et al., 2008; de Rosa et al., 2013). Males showing lower levels of Sexual dimorphism as compare to female when adiponectin expression is observed (Daniele et al., 2008). Monomer of 28–30 kDa synthesis of adiponectin manifested and they gathered in homo-oligomers having different molecular weights, low molecular weight (LMW) is a trimeric form, medium molecular weight (MMW) is a hexameric form and high molecular weight (HMW) is a multimeric form (Kadowaki and Yamauchi, 2005a; Shamaa et al., 2019; Schraw et al., 2008). The monomeric appearance of adiponectin in serum is available as a full-length form (*f*Adiponectin) or as a globular form of protein (*g*Adiponectin) (Fruebis et al., 2001a; Kishida et al., 2003). Generated

*g*Adiponectin by proteolytic cleavage product of *f*Adiponectin and contains the globular head without any collagen like domain the formation of trimers is qualified but not HMW type of oligomers (Ge et al., 2010; Waki et al., 2005). The monomeric form increased the fatty acid oxidation, bracing the AMPK activation in muscle and uptake of peripheral glucose (Almer et al., 2011). The secreted protein expressed in both WAT and BAT is encoded by adiponectin gene. Domains present in adiponectin is amino-terminal collagen domain and carboxyl-terminal globular domain and they are similar by structure to complement 1q (Shapiro and Scherer, 1998). Adiponectin show beneficial effect in insulin-sensitive organs including skeletal muscle via activation of AMPK and PPAR α , liver appears to moderate an increase in glucose utilization and fatty-acid oxidation (Kadowaki and Yamauchi, 2005b). Adiponectin biosynthesis and secretion in adipocytes is tightly controlled by some molecular protector in the endoplasmic reticulum including ERp44 (Endoplasmic Reticulum resident protein 44), Ero1-La (ER oxidoreductase 1-La) and DsbA-L (disulfide-bond A oxidoreductase-like protein) (Kadowaki and Yamauchi, 2005b; Wang et al., 2007; Qiang et al., 2007; Liu et al., 2008).

4. Adiponectin receptor

Two mainly effective and universal expressed receptors are AdipoR1 and AdipoR2 through which adiponectin acts. In skeletal muscle the abundant form of AdipoR1, while in liver the most abundant form of AdipoR2 (Kadowaki and Yamauchi, 2005a). For *g*Adiponectin the AdipoR1 have a very potent affinity while for *f*Adiponectin the AdipoR2 have a very potent affinity. Both receptors are G-protein coupled receptors having seven transmembrane and they are members of the PAQR (progesterone and Adipo Q receptor) family, In cell the N-terminus end is found in cytoplasmic region while externally the C-terminus end is found (Kadowaki and Yamauchi, 2005a). After adiponectin activation, in both homo and heterodimeric complexes AdipoR1 and AdipoR2 are assemble. Member of the cadherin superfamily is T-cadherin and they are able to bind with hexameric and multimeric forms of adiponectin but not bind with trimeric forms. T-cadherin is globally exhibit in the heart, aortic, carotid, iliac, and kidney arteries. T-cadherin was not communicated with hepatocytes, liver (Liu et al., 2008) and another important target organ but when adiponectin in muscle and C2 C12 myoblasts than T-cadherin was capable for binding (Hug et al., 2004; Combs et al., 2001; Kubota et al., 2006). In T-cadherin the intracellular domain is not present so they have no effect on adiponectin function and cellular signaling. The possibility from this data show that T-cadherin is may be one of the adiponectin binding proteins.

5. Signal transduction of adiponectin receptor

AdipoR1 activate AMPK. The mechanism latent have insulin-sensitizing action when induce adiponectin, so when found in skeletal muscle and liver the *f*Adiponectin stimulated AMPK phosphorylation, whereas *g*Adiponectin stimulation only in skeletal muscle (Nechamen et al., 2007). AMPK activation is blocked by using the dominant-negative mutant and they inhibit the effects of both *f*Adiponectin or *g*Adiponectin, this activity indicate that through activation of AMPK stimulation of glucose for utilization and fatty acid breakdown is proceeding. Lodish, Ruderman and colleagues also showed that via AMPK activation or inhibit acetyl-CoA carboxylase then globular domain of adiponectin could increase fat oxidation and glucose transport (Yamauchi et al., 2002). The proposed roles when adiponectin in liver then AMPK is active, Scherer et al. reported that presence of adiponectin in transgenic mice, gluconeogenic enzymes expression is reduced (Tomas et al., 2002). PPAR Activate via AdipoR2. PPAR pathway activated via AdipoR2 when adiponectin is induced then fatty acid combustion is elevated and energy consumption is increased via molecules ACO and UCP (Combs et al., 2004; Yamauchi et al., 2003b). To measured endogenous PPAR α ligands activities and the mechanisms by

Table 1
List of various drugs used to target Adiponectin for obesity treatments.

Component	Class	Consequence	Ref.
Natural and synthetic products	Inducer adiponectin	<ul style="list-style-type: none"> • Anthocyanin magnify the secretion of adiponectin. • Xanthohumol boost the levels of adiponectin and impaired diabetes in mice. • Rimonabant reduced the waist size and elevates levels of adiponectin. • Telmisartan raised levels of adiponectin in plasma. • Benzafibrate in serum of mice and in adipocytes increases the levels of adiponectin. • Sulfatide in adipocytes raised the production of adiponectin. • Catechins in adipocyte dose and time dependent way increased the expression and secretion of adiponectin. 	(Drolet et al., 2009; Forny-Germano et al., 2019; Tsuda et al., 2004; Nozawa, 2005; Moriuchi et al., 2007)
Biguanide (Metformin)	Inducer adiponectin	In serum increase the adiponectin levels and depletion of BMI and insulin resistance.	Hiuge et al. (2007)
Statin	Inducer adiponectin	Raised the adiponectin levels.	Bruun et al. (2007)
Curcumin, capsaicin, and gingerol	Inducer adiponectin	Encourage of adiponectin endogenous production.	Adamia et al. (2007)
Thiazolidinedione Pioglitazone Rosiglitazone Trogliatzone	Inducer adiponectin	<ul style="list-style-type: none"> • In adipocytes and in macrophages increases AdipoRs receptors. From adipocytes raised secretion of adiponectin and serum adiponectin concentration and ratio of HMW/total adiponectin.	(Sahebkar, 2013; Yamazaki et al., 2018; Tsuchida et al., 2005; Otvos et al., 2011; Sun et al., 2013; Okada-Iwabu et al., 2013; Combs et al., 2002; Phillips et al., 2003)
fAdiponectin	Adiponectin recombinant	<ul style="list-style-type: none"> • Modification of amino acids metabolism changed by high-fat diet. • Defence in case of injury in pigs with myocardial ischemia-reperfusion by apoptosis, suppression of inflammation. 	(Phillips et al., 2008; Liu and Liu, 2009)
gAdiponectin	Adiponectin recombinant	Free fatty acids levels in mice plasma decrease. Aware of the weight reduction in mice on high/fat/sucrose diet. Atherosclerosis ameliorated.	(Liu et al., 2013; Kondo et al., 2010)
gAdiponectin fused in Fc fragment ADP 355	Adiponectin recombinant Agonists AdipoRs	Ameliorate of the fasting glucose levels and the endurance to glucose in mice. Cancer cell lines and mice prevention of tumor growth.	Combs et al. (2001)
Natural compounds AdipoRon	Agonists AdipoRs Agonists AdipoRs	Agonist reveal by <i>in vitro</i> tests. Rectify of diabetes in genetically obese rodents and extension of the shortness life span of rodents on high-fat diet.	(Fruebis et al., 2001b; Yamauchi et al., 2003a; Tumminia et al., 2019; Otvos et al., 2011; Sun et al., 2013) Otvos et al. (2011) (Sun et al., 2013; Okada-Iwabu et al., 2013; Combs et al., 2002; Phillips et al., 2003; Yamauchi et al., 2001)

which adiponectin increased the levels of ACO and UCP, Both genes ACO and UCP possess as a PPRE in its promoter regions. Exciting, PPAR α ligands activity and expression is increased by adiponectin (Yamauchi et al., 2007). AdipoR1 activate AMPK than Ca²⁺, Fatty Acid Combustion, Mitochondrial Biogenesis, Mitochondrial OXPHOS, and ROS is done. Induces adiponectin in AdipoR1 then extracellular Ca²⁺ is influx which is valuable for the activation of Ca²⁺/calmodulin dependent protein kinase kinase β (CaMKK β), AMPK. Then operate the SirT1 by PPAR pathway and result is increased expression and decreased acetylation of PPAR γ coactivator1 α (PGC-1 α), and increased mitochondria present in myocytes. In fact, when muscle specific disturbance of AdipoR1 then suppressed the adiponectin-mediated intracellular result in increase Ca²⁺ concentration and decreased the CaMKK, AMPK, and SirT1. Suppression of AdipoR1 show decreased expression of PGC-1 α , deacetylation, decreased enzymes and mitochondrial content, decreased oxidative type I myofibers and in skeletal muscle decreased oxidative stress-detoxifying enzymes that are related with insulin resistance and decreased endurance for exercise. Level of Adiponectin and AdipoR1 decrease in obesity and may have consider this roles in case of mitochondrial dysfunction and insulin resistance (Yamauchi et al., 2003a).

6. Role of APPL1 and APPL2 in signal pathway

Adiponectin signaling in mammals is positively mediates when Adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1 (APPL1) an adaptor protein, binds to the adiponectin

receptors. APPL1 have three functional domains, which are important for adiponectin receptor intracellular signal transduction pathway. This includes N-terminus (BAR) domain have 18–226 amino acid, pleckstrin homology (PH) domain have 278–377 amino acids and a phosphotyrosine binding (PTB) domain have 597–636 amino acids it is near the COOH terminus (Nawrocki et al., 2006). APPL1 acts as an connecting partner of both AdipoR1 and AdipoR2. The BAR domain have multiple biological action like sensing and inducing membrane curvature, small GTPase binding, transcriptional repression, apoptosis, and secretory vesicle fusion (Parker-Duffen et al., 2013; Ren et al., 2006). Normally, proteins of specific membrane compartments targeted by PH domain then the lipid specificity of the BAR domain is increased (Dawson et al., 2006). The well established function of PTB domain is to act as an adaptor or scaffold for the binding of proteins. Away from BAR-PH domain and COOH terminus near PTB domain of APPL1 is present which make binding partners an easily accessible structure. APPL2 is an isoform of APPL1, and these both proteins display 54% identity in protein sequences (Peter et al., 2004). APPL2 (isoforms of APPL1) also have an N-terminal BAR domain, central PH domain, and C-terminal PTB domain. Follicle-stimulating hormone is involved by APPL2 in signal transduction pathway by binding to APPL1 via their respective BAR domains (Mao et al., 2006).

7. Adiponectin in obesity

Obesity is a serious health issues that increasing risk of metabolic syndrome including cardiovascular disorder, respiratory disorders,

diabetic retinopathy, and cancer. Abnormal creation of adipokines in obese person, than visceral body fat may attack the physical fitness. For energy metabolism adiponectin plays a crucial role. Total adiponectin and multimeric (HMW) concentration decreases in obesity and after weight loss increases (Daniele et al., 2008; de Rosa et al., 2013; Iwabu et al., 2010; Kaser et al., 2008). Total adiponectin and High molecular weight oligomers are inversely connected to body mass index, glucose level, insulin level, triglyceride levels, degree of IR, visceral fat collection (de Rosa et al., 2013). Various studies indicate a strong relationship of HMW and metabolic disorder, whereas the role of MMW and LMW oligomers has been poorly explored (Meyer et al., 2013; Fitzgerald, 2013; Daniele et al., 2012). The way by which adipose tissue amplify (increase size, hypertrophy, hyperplasia, number of cells) could regulate adiponectin synthesis and secretion. Drolet et al. exhibit an opposite connection in middle of mean adipocytes diameter and secretion of adiponectin (Hamilton et al., 2011; Drolet et al., 2009). In obesity and T2DM condition the receptor AdipoR1 and AdipoR2 is remarkably lowered. Adiponectin and oligomers HMW levels after weight loss rise together.

8. Earlier benefits to target adiponectin release

Adiponectin has shown different properties, including clinical benefits to control obesity. Adiponectin expression will be increase by different ways:

(1) Reduction of calories (2) somatic efforts (3) Addition of adiponectin inducer and recombinant adiponectin (4) Peptide emulative commence. This type of involvement reveals therapeutic effect in metabolic diseases (Table 1).

9. Conclusion

Adiponectin is an adipose tissue derived protein that plays an important role in preventing insulin resistance, diabetes and cardiovascular disorders. Decreased level of adiponectin in obese, diabetic and coronary artery disease patients. Adiponectin and its receptor AdipoR1 and AdipoR2 and T-cadherin were identified have beneficial effect like glucose hemostasis and expand fatty acid oxidation. Thus adiponectin is a novel target to treat obesity.

Declaration of competing interest

All authors have none conflict of interest.

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