FUTURE TREATMENT FOR TYPE 2 DIABETES: ADIPONECTIN RECEPTOR AGONIST AS ''EXERCISE MIMETIC''

Raghav Goyal, Vaibhav G. Sheth, Kulbhushan Tikoo*

Laboratory of Epigenetics and Diseases, Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, S.A.S. Nagar, Mohali, 160062, Punjab, India.

***Corresponding author: Prof. Kulbhushan Tikoo,** Laboratory of Epigenetics and Diseases, Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, S.A.S. Nagar, Mohali, 160062, Punjab, India.
E-mail: tikoo.k@gmail.com; Telephone: +91 1722214682-87; Fax: +91 1722214692.

ABSTRACT

Recent research provides evidence that proteins secreted by adipocytes are linked to type 2 diabetes mellitus. These secretory proteins, collectively called as adipokines includes leptin, tumor necrosis factor (TNF)-α, plasminogen-activator inhibitor type 1 (PAI-1), adipsin, resistin, and adiponectin. Dysregulation of these adipokines contributes to development of insulin resistance and type 2 diabetes mellitus. Unlike other adipokines, adiponectin appears to have a regulatory role in insulin resistance and type 2 diabetes mellitus. Adiponectin is an adipocyte-related complimentary protein, which decreases in cases of insulin resistance and type 2 diabetes mellitus. Upregulation of it by adiponectin-inducers such as thiazolidinediones, statins and metformin; recombinant adiponectin and adiponectin receptor agonists has been associated with insulin sensitization and anti-diabetic effect, which indicates that adiponectin can serve as a potential therapeutic target for the treatment of insulin resistance and type 2 diabetes mellitus. The recent discovery of first orally active adiponectin receptor activator, AdipoRon by Okada-Iwabu *et al.* signifies potential of adiponectin receptors as therapeutic target. AdipRon exerts multiple effects similar to those of adiponectin, including reduced tissue triglyceride content in the liver and muscle, and oxidative stress in the liver, muscle and white adipose tissues (WAT). AdipoRon also increased exercise endurance and energy expenditure via AdipoR, modulates the longevity pathways, improves health and collectively prolongs the shorten lifespan.

KEY WORDS: Type 2 diabetes mellitus, insulin resistance, adiponectin, AdipoRon, exercise mimetic.

INTRODUCTION

Type 2 diabetes mellitus is a heterogeneous group of metabolic diseases resulting from defect in insulin secretion, insulin action, or both resulting in hyperglycemia and is one of the leading cause of morbidity and mortality (Nyenwe et al., 2011). Globally, an estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980. The global prevalence of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population, while type 2 diabetes is much

more common and accounts for around 90% of all diabetes cases worldwide., thus prevention of type 2 diabetes mellitus is one of the priority issues. (WHO, 2016).

Insulin resistance is a complex pathophysiological process with a clear influence of genetics, obesity and unhealthy life practices with long-term sequelae including the risk of type 2 diabetes mellitus (Muoio and Newgard, 2008, DeFronzo and Tripathy, 2009).

Growing body of evidences suggest that dysregulation of adipokines have played a vital role in insulin signaling pathway. Adipokines, such as adiponectin and leptin have been demonstrated to increase insulin sensitivity while adipokines such as TNF-α, PAI-1, adipsin, resistin, IL-6 have been evidence to induced insulin resistance (Bouzid et al., 2016). One of the major cause of insulin resistance is a low level of adipokine, adiponectin. Adiponectin is produced by adipocytes in an inverse manner based on the amount of fat stored. Studies demonstrate that genetic deletion of adiponectin or its receptors results in hypoadiponectinemia and thereby involved in the development of insulin resistance. Administration of exogenous adiponectin has been proved to restore insulin signaling (Ahlstrom et al., 2017). So, it could be hypothesized that substances that enhance or mimic adiponectin, which activate its receptors and/or post receptor signaling pathway can be a promising therapeutic strategy in the prevention and treatment of insulin resistance and type 2 diabetes mellitus (Blüher, 2014, Yamamoto et al., 2014).

ADIPONECTIN

Adiponectin (also known as 30-kDa adipocyte complement-related protein;

Acrp30, adipose most abundant gene transcript 1; APM1, AdipoQ or gelatin-binding protein; GBP28) is a hormone secreted by adipocytes (Haluzik et al., 2004), which binds to two distinct adiponectin receptors (AdipoR1 and AdipoR2) and exerts anti-diabetic effects through activation of AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor (PPAR-α) pathways in liver and skeletal muscles. The insulin sensitizing action of adiponectin results primarily from decrease in hepatic gluconeogenesis and increase in muscle glucose transport and secondly through enhancement of energy consumption and fatty acid oxidation in peripheral tissues which finally leads to an increase in ATP production (Kadowaki and Yamauchi, 2005, Holland et al., 2017).

Structure of adiponectin

Adiponectin is a 247 amino acids containing protein with four domains. The N-terminal signal peptide consisting of 17 amino acids, the variable region consisting of 28 amino acids, the collagenous domain with 65 amino acids, the receptor binding effector C-terminal globular domain consisting of 137 amino acids. Adiponectin shares sequence similarities with collagens X and VIII as well as complement factor C1q, which belongs to a family of proteins that form characteristic multimers. Adiponectin exists in a wide range of multimer complexes in plasma and combines via its collagen domain to create three major oligomeric forms: Trimers (3 adiponectin molecules), LMW isoform (hexamers of adiponectin molecule), HMW isoform (12-18 adiponectin molecules) (Kadowaki et al., 2006).

Adiponectin receptors

Adiponectin binds to a number of receptors: Adiponectin receptor 1 (AdipoR1), Adiponectin receptor 2 (AdipoR2) and T-cadherin - CDH13. AdipoR1 and AdipoR2 appear to be integral membrane proteins, the N-terminus is internal, and the C-terminus is external, opposite to the topology of all other reported G protein–coupled receptors (GPCRs). AdipoR1 is ubiquitously expressed, with abundant expression in skeletal muscle, whereas AdipoR2 is most abundantly expressed in the hepatocytes (Okada-Iwabu et al., 2015, Kadowaki et al., 2006).
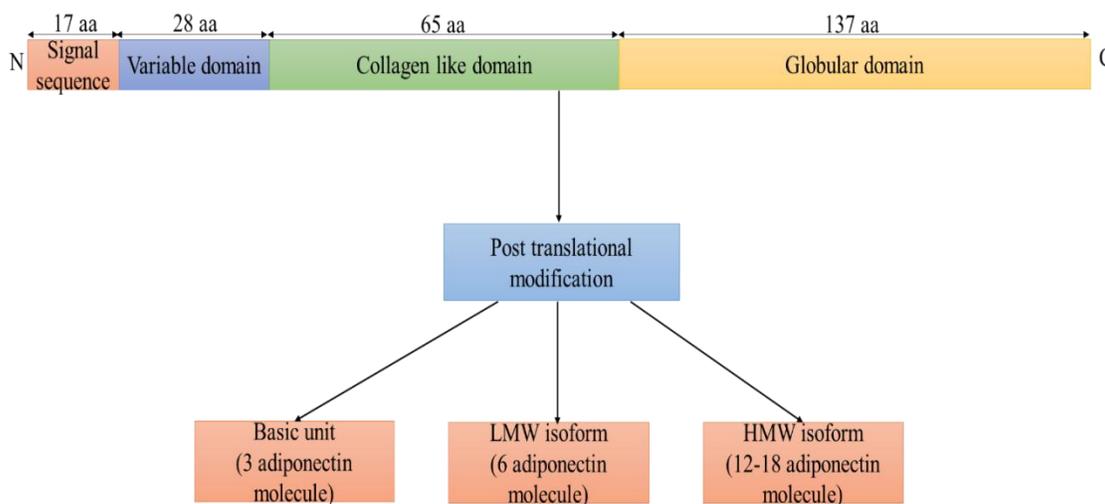

Figure 1: Domains and structure of adiponectin (Kadowaki et al., 2006).

ADIPONECTIN AND TYPE 2 DIABETES MELLITUS

Various environmental and genetic factors cause decrease in the levels of adiponectin, which results in high blood glucose level and fat circulation, ultimately leading to insulin resistance. The decrease in plasma adiponectin led to decreased glucose uptake, increased gluconeogenesis, decreased fatty acid oxidation in the skeletal muscles and liver. The decrease of fatty acid oxidation causes the increase of free fatty acids (FFA), following an increase in insulin resistance, which results in high plasma glucose level and increased gluconeogenesis, ultimately contributing to the development of type 2 diabetes mellitus (Okamoto et al., 2006, Lee and Kwak, 2014).
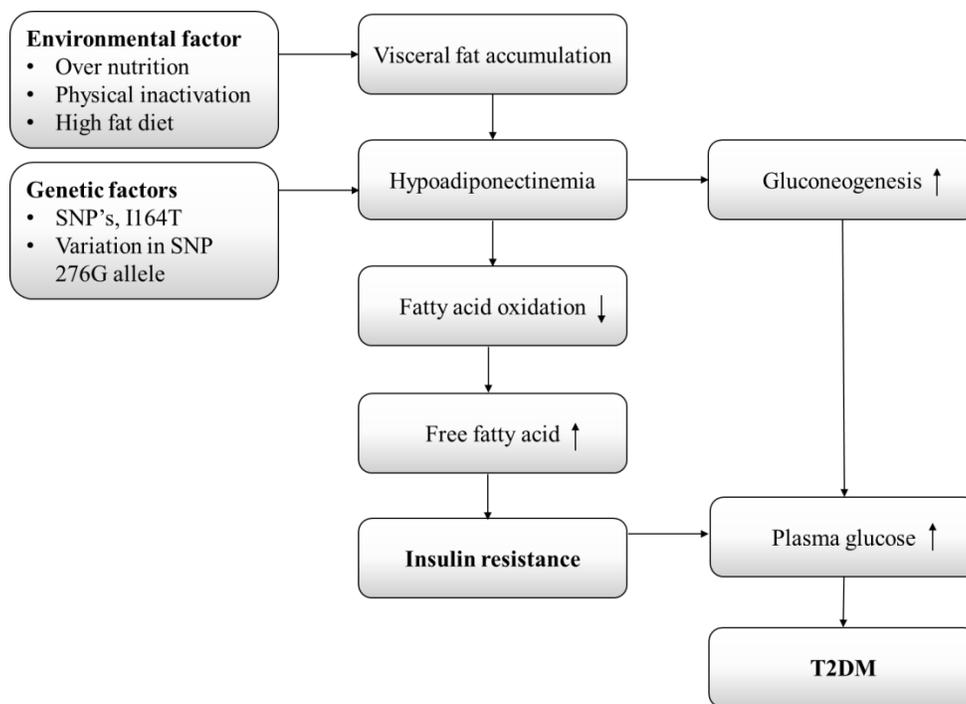
Figure 2: Role of adiponectin in type 2 diabetes mellitus. ↑, increased; ↓, decreased; T2DM, type 2 diabetes mellitus (Caselli, 2014, Kawano and Arora, 2009).

Mechanism of action of adiponectin

Adiponectin reduces tissue triglyceride content and up-regulates insulin signaling in skeletal muscle and liver. In skeletal muscle, activation of AMPK is stimulated by globular and full-length adiponectin, while in the liver only by the full-length form. The glucose-lowering effects of adiponectin may account for the phosphorylation of acetyl coenzyme A carboxylase (ACC), increased fatty-acid combustion, glucose uptake and lactate production in myocytes. These activities stimulated by adiponectin limit gluconeogenesis in the liver. Adiponectin increases fatty-acid and energy consumption through activation of PPAR-α, leading to reduced triglyceride content and thereby increasing insulin sensitivity in the liver and skeletal muscle (Kadowaki et al., 2006, Caselli, 2014, Nigro et al., 2014).

Adiponectin and adiponectin receptors as therapeutic targets

Therapeutic strategy for type 2 diabetes mellitus and insulin resistance may include the up-regulation of plasma adiponectin, up-regulation of adiponectin receptors or the development of AdipoRs agonists (Kadowaki et al., 2006). Few such drugs have been listed in the Table 1.

ADIPONECTIN ACTIVATING AGENTS–CURRENT STATUS

In 2013, University of Tokyo's Open Innovation Center for Drug Discovery and Okada-Iwabu et al., succeeded in identifying a small-molecule AdipoR-activating compound AdipoRon. It is the first orally active adiponectin receptor activator which binds to AdipoR1 and AdipoR2 directly via both AMPK-dependent and AMPK-

30

independent signaling. AdipoR agonist AdipoRon is useful in improving the metabolic capacity of the liver, skeletal muscle and adipose tissue, thereby exerting anti-diabetic effects Additionally, AdipoRon leads to normalization of obesity-shortened lifespan despite a high-fat diet. AdiponRon improves insulin resistance via AdipoR1, which involves AdipoR1-mediated AMPK activation by adiponectin in the liver and skeletal muscle. AdipoRon also upregulates adiponectin via AdipoR2 in the liver, and activates AMPK and PPARα pathway (Okada-Iwabu et al., 2015, Zhang et al., 2015, Lee and Hung, 2015, Okada-Iwabu et al., 2013).
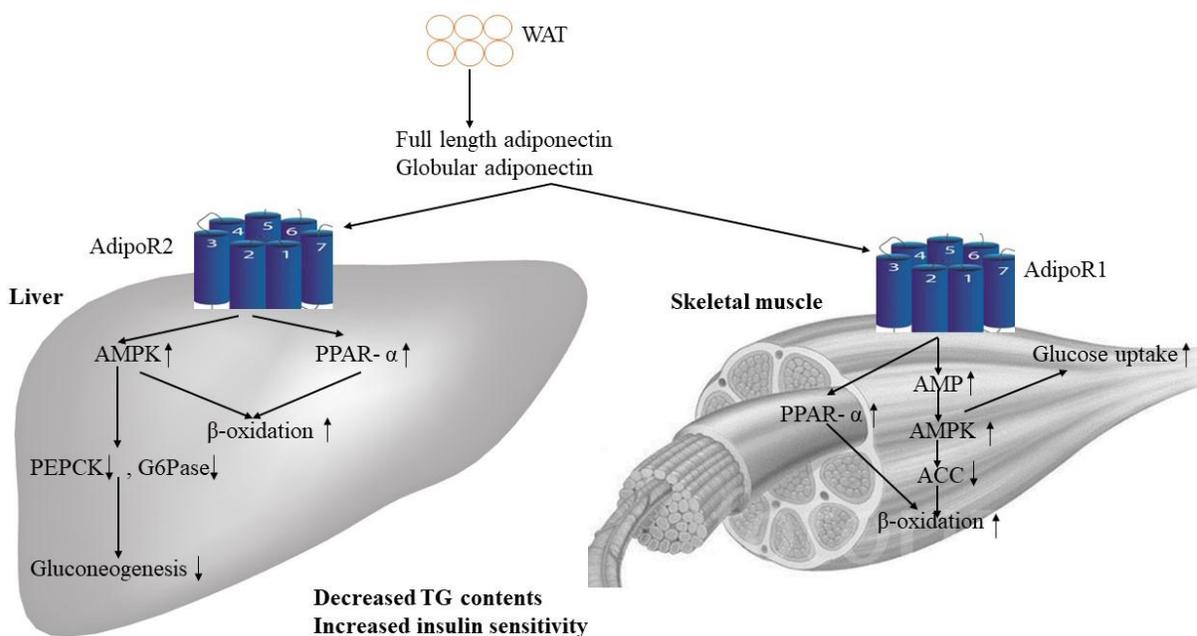

Figure 3: Mechanisms of adiponectin in the liver and skeletal muscle. WAT, White adipose tissue; PEPCK, phosphoenolpyruvate carboxykinase; G6Pase, glucose-6-phosphatase; TG, triglycerides; ACC, acyl-coenzyme A oxidase; AMP, Adenosine monophosphate; AMPK, AMP kinase (Kadowaki et al., 2006).

FUTURE PROSPECTS

Discovery of adiponectin undoubtedly represents a very important step to further understand the mechanism of obesity-induced insulin resistance and type 2 diabetes mellitus. In order to understand the biology and exact mechanism of adiponectin a number of crucial steps are still needed to be performed. Recombinant adiponectin administration in human can be more effective in order to treat insulin resistance and type 2 diabetes mellitus. Identification of crystal structures of the AdipoRs may accelerate the development and optimization of AdipoR-targeted small molecule. Also, AdipoR-activating agents are expected to be further refined and developed as effective therapeutic modalities for the treatment of insulin resistance and type 2 diabetes mellitus. The development of AdipoR-activating drugs or AdipoR agonists is

31

eagerly awaited as they have high potential as "exercise-mimetic" and provide similar effects to those of exercise (Okada-Iwabu et al., 2017). This will pave the way for definitive treatment of the metabolic syndrome and type 2 diabetes mellitus.

Table 1: Adiponectin activator agents

Drugs	Category	Mechanism of action	References
Fenofibrate, Clofibrate	Adiponectin inducer	PPARα agonists	(Rahman et al., 2009)
Rosiglitazone, Pioglitazone	Adiponectin inducer	PPARγ agonists	(Liu and Liu, 2010)
Muraglitazar, Tesaglitazar, Ragaglitazar, Naveglitazar, Ragaglitazar, Naveglitazar	Adiponectin inducer	PPAR dual agonists(α/γ)	(Wei et al., 2012)
Anthocyanin	Adiponectin inducer	Activation of PPARα and PPARγ	(Kim and Park, 2016)
Cinacalcet	Adiponectin inducer	Activation of PGC-1a	(Kuczera et al., 2015)
Curcumin, Capsaicin, and Gingerol	Adiponectin inducer	Promotion of adiponectin endogenous production	(Yamazaki et al., 2008)
Metformin	Adiponectin inducer	Increase of adiponectin serum levels and reduction of BMI and insulin resistance	(Adamia et al., 2007)
fAdiponectin	Recombinant adiponectin	Correction of amino acids metabolism altered by high-fat diet	(Rothan et al., 2013)
gAdiponectin	Recombinant adiponectin	Decrease of plasma free fatty acids levels in mice. Induction of weight reduction in mice on high/fat/sucrose diet	(Yamauchi et al., 2003)

Drugs	Category	Mechanism of action	References
ADA 355	AdipoR agonist	Mimic adiponectin action, suppression of tumor growth in cancer cell lines and mice	(Otvos et al., 2011)
AdipoRon and 112254	Orally active adipoR agonists	Amelioration of diabetes in genetically obese rodents and prolongation of the shortness life span of rodents on high-fat diet	(Okada-Iwabu et al., 2013, Balasubramanian et al., 2017)

CONCLUSION

Adiponectin is a key marker in development of obesity-induced insulin resistance, in contrast to other known adipocyte-derived hormones. In obese individuals, adiponectin concentration is found to be decreased. This fact suggests the possibility that adiponectin replacement might become a new therapeutic approach towards the treatment of insulin resistance and type 2 diabetes mellitus.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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