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Adiponectin: A defence hormone of vascular physiology- A review

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Abstract
Adiponectin, a hormone product of APM1 gene, composed of 244 amino acids with a molecular weight of 30 kDa, performs a very important role in vascular physiology thus prevents from atherosclerosis and other cardiovascular diseases. Its structure is divided into three domains: the N-terminal domain, collagen-like domain and the globular domain of the C-terminal region. Adiponectin is largely secreted by adipocytes, also secreted from cardiomyocytes, hepatocytes and placenta but in lower concentrations. Secretion of adiponectin is strictly controlled by the retention of protein thiols, so that two molecular endoplasmic reticulum chaperones play a critical role: 44 kDa ER proteins (endoplasmic reticulum protein 44, ERp44) and Ero1-La (endoplasmic reticulum oxidoreductin 1-like alpha), both induced during adipogenesis. ERp44 forms the disulphide bond with adiponectin whereas Erol-La weakens the disulphide bond, responsible for its release. Atheroprotection is conferred by different actions of this protein, including anti-inflammatory effects, stimulation of nitric oxide production, mitigation of pro-atherogenic mediators and coronary plaque vulnerability modulation.

Keywords: Adiponectin, atherosclerosis, ERp-44, Ero1-La, Nitric oxide production

1. Introduction
Adipose tissue is not simply an inert storage depot for lipids but is also an important endocrine organ that plays a key role in the integration of endocrine, metabolic, and inflammatory signals for the control of energy homeostasis. The white adipose tissue secretes a variety of bioactive proteins into the circulation collectively called adipocytokines. Not only adiponectin is included in adipocytokines but leptin, tumor necrosis factor (TNF), plasminogen activator inhibitor type-1 (PAI-1), adipsin and resistin are also included in the adipocytokines [1]. Adiponectin is a protein of collagenous type that is only synthesized in white adipose tissue and circulates at relatively high (microgram/millilitre) concentrations. Synthesis and production of this hormone is induced during adipocyte differentiation.
With industrialization, obesity is advancing and is not only associated with increase in total fat cell mass but also causes different physiological and pathological disturbances like atherosclerosis, diabetes, metabolic syndrome and other cardiovascular complications. The pathogenic relationship between obesity, metabolic syndrome and their cardiovascular complications is well established; however, the mechanisms by which excess body fat causes these conditions has not yet been clarified. The direct vascular and metabolic effects of plasma proteins especially adiponectin that originate from adipose tissue have received growing attention [2]. Even though the mechanisms underlying the anti-inflammatory properties of adiponectin are not well understood but the anti-atherogenic and anti-inflammatory properties of adiponectin may be related to its ability to stimulate the production of nitric oxide by the vascular endothelium [3].
Adiponectin was first described as a peptide of adipose tissue that becomes dysregulated in obesity. Shortly after, its potential as an anti-atherogenic factor was recognized for its ability to modulate the expression of endothelial adhesion molecules and affect key mechanisms involved in atherogenesis. Since then, many experimental and clinical studies have thoroughly examined the role of adiponectin in vascular homeostasis and its potential value as a clinical biomarker in cardiovascular diseases.

2. Structure
Adiponectin, a product of the APM1 gene, is a protein composed of 244 amino acids with a molecular weight of 30 kDa, also known as GBP-28 (galatin binding protein-28), ADOPOQ

and ACRP30. Its structure is divided into three domains: the N-terminal domain, which has a variation in amino acids between species, the collagen-like domain and the globular domain of the C-terminal region (fig 1) [4]. The collagen domain allows for the trimeric or hexameric formation and other multimeric isoforms before being secreted (fig 2). A cysteine residue at collagenous rod is an essential mediator of multimeric complexes, which may represent the most biologically active form of the protein. Adiponectin is structurally related to proteins of the complement system (C1q) and tumor necrosis factor alpha (TNF-α), which are prototype members of a growing family of proteins known as CTRPs (C1q/TNF bonds) [5].

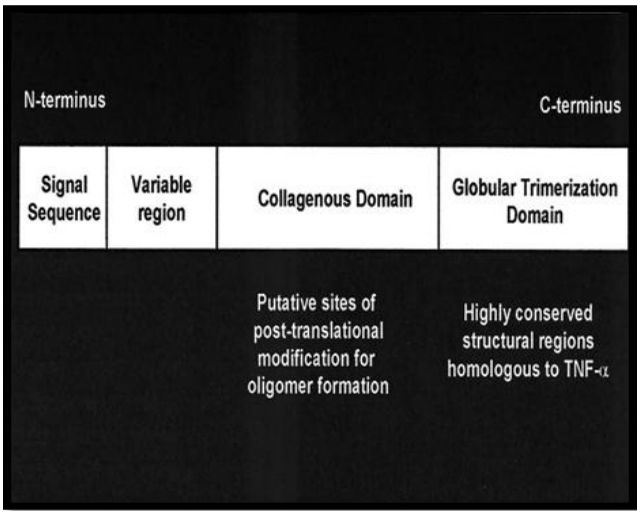

Fig 1: Structure of Monomeric adiponectin

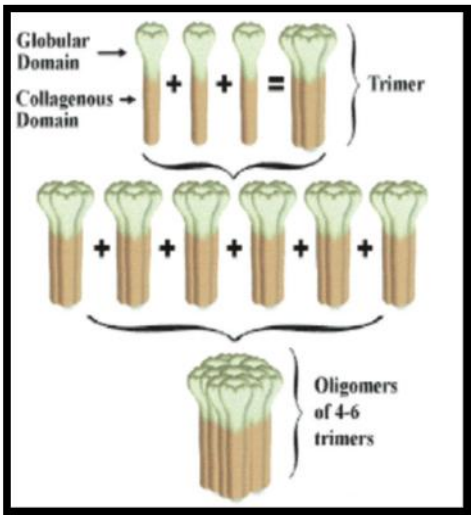

Fig 2: Formation of Trimeric and Multimeric forms of adiponectin.

3. Biosynthesis of adiponectin

The protein Adiponectin is largely secreted by adipocytes, although it can also be secreted by cardiomyocytes, hepatocyte, placenta, liver, skeletal muscle, colon, salivary gland, hypophysis and epicardial fat, but the contributions of these tissues to the circulating adiponectin are considerably very less. Also minute concentrations of adiponectin can also be measured in breast milk and cerebrospinal fluid [6]. Retention of two protein thiols controls the secretion of this hormone so that two molecular endoplasmic reticulum chaperones play a critical role (a) 44 kDa ER proteins (endoplasmic reticulum protein 44, ERp44) (b) Ero1-La (endoplasmic reticulum oxidoreductin 1-like alpha). However induction these protein thiols occurs during adipogenesis. Endoplasmic reticulum protein 44 (ERp44) is important for the maturation of trimeric and hexameric forms of protein as it forms a disulfide bond with adiponectin. It also controls the overexpression of ERp44 for the optimum secretion of the adipokine, which is possible by intracellular retention of adiponectin. Whereas, endoplasmic reticulum oxidoreductin 1-like alpha (Ero1-La) is responsible for consistent release of adiponectin as it is involved in the weakening of the disulfide covalent bond. This disulfide covalent bond is present between adiponectin and ERp44. As this disulphide bond is weaken there is optimum release of adiponectin [5].

4. Receptors

The role of adiponectin is mediated by receptors known as adiponectin receptors 1 and 2 (Adipor1 and Aipor2) (fig 3). AdipoR2 has 66.7% amino acid identity with AdipoR1 with seven transmembrane portions and are functionally different from the G-protein coupled receptors particularly, because they have opposite polarity (i.e., the N-terminal faces the intracellular compartment). Although, in relative proportions Adipor1 and Adipor2 receptors may vary from tissue to tissue and in general are expressed simultaneously [7].

An additional cell surface molecule called T-cadherin shows significant affinity for adiponectin. T-cadherin binds to adiponectin, which is not a signaling receptor due to lack of intracellular signaling domains, to confer full cardioprotective potential of the latter. Adiponectin works in an autocrine and paracrine manner in the adipose tissue, and in an endocrine manner in distal tissues. The autocrine effects are illustrated by their role in adipocyte differentiation. Induction is greater than 100 times that of adiponectin mRNA during the course of differentiation of adipose cells [8]. Also, recent *in vivo* and *in vitro* studies provided evidence of a regulatory feedback loop by which adiponectin controls its own production and the expression of its receptor.

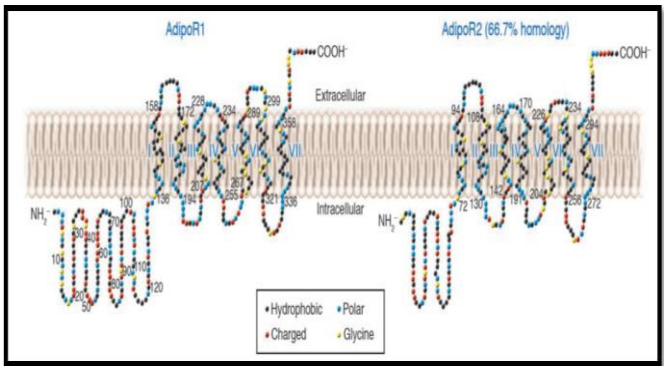

Fig 3: Structure and types of adiponectin receptors**.**

5. Adiponectin influence on endothelial and vascular function

During the early stages of atherosclerosis, various lipoproteins such as low density lipoprotein (LDL) are deposited in the intima of the vascular wall. These lipoproteins are closely connected to oxidation and they induce many adhesion molecules on endothelial cells, such as vascular cell adhesion molecule (VCAM)-1, intracellular adhesion molecule (ICAM)-1, and E-selectin (fig 4). Mononuclear cells bind to endothelial cells via these adhesion molecules and migrate into the subendothelial space. This process is induced by several bio-reactive mediators, including monocyte chemotactic protein (MCP-1), which plays a prominent role. Since they are located on the vessel wall, the monocytes

develop into macrophages and while the LDL oxidizes, they differentiate into foam cells. This process is performed by acyl-coenzyme A [cholesterol acyltransferase-1 (ACAT-1)] in the macrophages, which catalyzes the formation of cholesterol esters. As a secondary event, the synthesis of nitric oxide by the enzyme endothelial nitric oxide synthase (eNOS) is decreased [9].

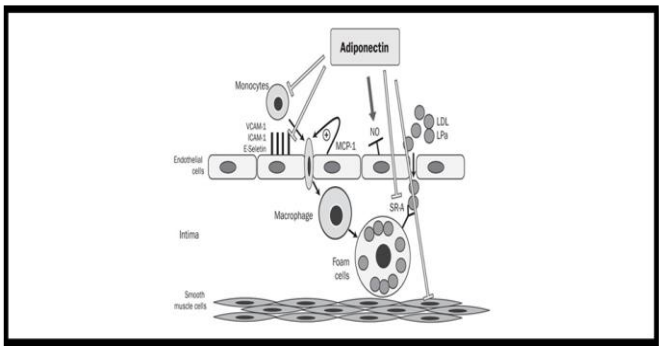

Fig 4: Adiponectin inhibits the up-regulation of adhesion molecules, the binding of monocytes to endothelial cells, the transformation of macrophages into foam cells and the proliferation and migration of vascular smooth muscle cells. In addition, the production of nitric oxide from endothelial cells is stimulated by this adipokine. Vascular cell adhesion molecules (VCAM-1), intracellular adhesion molecules (ICAM-1), Attractive monocyte chemo protein (MCP-1), nitric oxide (NO) low density lipoprotein (LDL), lipoprotein (LPA).

The main role of adiponectin in vascular physiology is to modulate the cross-link between endothelial cells, smooth muscle cells, leukocytes, platelets, and protect against vascular injury and atherogenesis. Atheroprotection is conferred by different actions of this protein, including anti-inflammatory effects, stimulation of nitric oxide production, mitigation of pro-atherogenic mediators and coronary plaque vulnerability modulation [10]. Furthermore, in humans, plasma adiponectin levels are positively associated with arterial vasodilation in response to nitro-glycerine (an endothelium-independent vasodilation measure), which does not depend on insulin sensitivity [6]. Adiponectin inhibits the production of proinflammatory cytokines and chemokines in endothelial cells, diminishing its ability to become activated in response to several inflammatory stimuli. Adiponectin also down-regulates receptor expression. The anti-inflammatory properties of adiponectin are mediated in part by activation of Adipor1 & Adipor2 receptors in monocytes, macrophages and endothelial cells and lessen the accumulation of inflammatory cells at sites of vascular injury.

A variety of substances that adversely affect the endothelial function are known, including free fatty acids, cytokines (such as TNF-α), and pro-oxidant molecules, including oxidized low density lipoprotein (oxLDL). These mediators activate signalling kinases and are also closely related to the production of endothelial reactive oxygen species (ROS) (superoxide and H2O2), which play a key role in the development of atherogenesis in the context of metabolic syndrome and diabetes mellitus [11]. Recent evidence also suggests that adiponectin potently inhibits the vascular endothelial growth factor (VEGF), which is induced by the formation of ROS, suggesting a broad anti-oxidant effect of adiponectin on blood vessels [12].

6. Conclusion

Adiponectin, a product of the APM1 gene is not only a hormone secreted from the adipose tissues plays a key role in the integration of endocrine, metabolic, and inflammatory signals for the control of energy homeostasis. It also acts as a protective factor for diseases like atherosclerosis and other cardiovascular diseases. Adiponectin emerges to playing a key role in the protection and integrity of vasculo-endothelium.

7. Acknowledgement

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