Biochimica et Biophysica Acta 1852 (2015) 1887–1894

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review article

The emerging role of adiponectin in cerebrovascular and neurodegenerative diseases

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ARTICLE INFO

Article history:
Received 2 April 2015
Received in revised form 10 June 2015
Accepted 23 June 2015
Available online 26 June 2015

Keywords:
Adiponectin
Cerebrovascular diseases
Neurodegenerative diseases

ABSTRACT

Adiponectin is an anti-atherogenic protein secreted by adipose cells that improves insulin sensitivity. Notably, adiponectin receptors are expressed in the brain, suggesting that adiponectin signaling disruption may impact neurologic function. Recently, studies have demonstrated the association of adiponectin levels with cerebrovascular disorders and neurodegenerative diseases (NDDs), and these results have drawn significant attention. In this review, we discuss the association between the adiponectin levels and the incidence, progression, and prognosis of cerebrovascular disorders and NDDs. We describe the controversial issues surrounding current studies and present our hypothesis concerning the possible mechanism underlying adiponectin function in neurological disorders. Finally, we explicate obstacles preventing clinical adiponectin administration, including available routes of drug delivery and the central nervous system regulation of adiponectin. Collectively, the data assembled herein serve as a comprehensive reference regarding the role of adiponectin in neurological disorders to support the future clinical potential of adiponectin as a therapeutic agent.

1. Introduction

Neurological diseases constitute a group of disorders affecting the spinal cord and the brain. Cerebrovascular diseases and neurodegenerative diseases (NDDs), which carry high morbidity and mortality, are two major types of neurological diseases that are presently garnering significant attention [1,2]. Cerebrovascular diseases induce brain dysfunction via cerebral ischemia and hemorrhage (the leading causes of adult disability and death [2]). Treatments for cerebral ischemia and hemorrhage remain limited. Tissue plasminogen activator (tPA) is the only treatment approved by the FDA for cerebral ischemia, and tPA must be administered within 3 h of ischemia symptom onset [3]. Limited by low recanalization rates, <5% of patients receive rapid intervention [4]. Both medical and surgical treatments are available for cerebral hemorrhage, but outcomes remain unsatisfactory [5–7]. There is an urgent need for new therapeutic targets and biomarkers that can predict the incidence and the prognosis of cerebral ischemic and hemorrhagic events. Neurodegeneration is the umbrella term covering the progressive loss of neuronal structure or function, resulting in irreversible brain damage. The incidence of NDDs, including Alzheimer's disease (AD), multiple sclerosis (MS), Parkinson's disease (PD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS), is increasing at an alarming rate worldwide [1,8,9]. However, the etiologies of NDDs are not well understood. No cures exist for these disorders, and new therapeutic targets and biomarkers are urgently needed.

Secreted by adipose cells, adiponectin increases insulin sensitivity, possesses anti-atherogenic properties, and regulates glucose levels and fatty acid breakdown [10,11]. Low adiponectin levels are an independent risk factor for the development of metabolic syndrome [10,12] and diabetes mellitus [11,13]. Additionally, hypoadiponectinemia and adiponectin gene polymorphisms are risk factors for coronary heart disease and cardiovascular disease [14]. However, the relationship between the adiponectin levels and neurological disorders is unclear. The receptors for adiponectin, AdipoR1 and AdipoR2, are prominently expressed in the brain [15], suggesting that adiponectin signaling may be intricately related to neurologic function and, consequently, neurological pathology. Recently, marked attention has been directed toward the association of adiponectin with cerebrovascular disorders and NDDs. Based on these studies, we discuss the association of the

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http://dx.doi.org/10.1016/j.bbadis.2015.06.019
0925-4439/

adiponectin levels and adiponectin gene polymorphisms with the incidence, progression and prognosis of cerebrovascular disorders and NDDs.

In the current review, we summarize the latest progress regarding the association of adiponectin with cerebrovascular disorders and NDDs. First, we review the discovery of adiponectin, its structure, and its known receptors. Next, we discuss the known associations of adiponectin with cerebrovascular disorders and NDDs. Finally, we identify several controversial issues concerning these associations and explicate the future prospects of the clinical application of adiponectin for treating neurological disorders. We aimed to compile a comprehensive reference concerning the current information concerning adiponectin and neurological disorders; we hope that this information will aid in the design of further experimental research advancing the therapeutic potential of adiponectin against neurologic disease.

1.1. Discovery of adiponectin

In 1995, Scherer et al. first characterized adiponectin as a novel 30-kDa secretory protein (Acrp30) expressed in differentiating 3 T3-L1 adipocytes [16] (Fig. 1). In 1996, adiponectin was described in mouse and rat models as "GBP28" (mRNA transcripts of gelatin-binding protein of 28 kDa size), "apM1" (adipose most abundant gene transcript 1), and "AdipoQ" (a protein found highly expressed in adipose tissue) [17–19]. The human adipose-specific and most abundant gene transcript, apM1, was isolated [18], and the apM1 gene product was termed adiponectin [20]. Arita et al produced monoclonal and polyclonal antibodies against human adiponectin and developed an enzyme-linked immunosorbent assay (ELISA) to quantify the plasma adiponectin concentration; these tools produced dramatic breakthroughs in this field of study [20].

Significant work was subsequently performed by others to determine the connections between adiponectin and visceral adiposity, insulin resistance, and vascular diseases [21,22]. In 2007, Lara-Castro et al. [11] identified adiponectin as a highly expressed transcript in preadipocytes differentiating into adipocytes. These studies ultimately demonstrated the pleiotropic effects of adiponectin, indicating adiponectin as an attractive therapeutic target for obesity-related conditions.

Previous studies assured a promising future for adiponectin in terms of therapeutic applications for pathophysiological conditions. However, further studies revealed the nature of adiponectin physiology to be complex. Despite its adipose origin, adiponectin expression decreased in obesity, and adiponectin administration induced weight loss. The mechanism by which adiponectin expression decreases during obesity is not fully understood [23]. As evidence substantiating the association between adiponectin and the metabolic/cardiovascular complications of obesity has accumulated [23–25], new relationships between adiponectin and adaptive immunity, inflammation, cancer, and neurological disease have been discovered [26–29]. In the current review, we direct our focus to the association of adiponectin with neurological disease.

1.2. Structure and receptors of adiponectin

Adiponectin is a 244-amino-acid polypeptide encoded by the *ADIPOQ* gene in humans [18] that has previously been referred to as GBP-28, apM1, AdipoQ, or Acrp30. Adiponectin possesses four distinct structural domains [30]. The first domain is a short signal sequence targeting the protein for secretion outside the cell. The second domain is a short region that is variable between species, and the third domain is a 65-amino acid collagenous region. Interestingly, the final globular domain possesses stronger signaling activity in isolation than the full protein [31]. Overall, the *ADIPOQ* gene shows similarity to complement 1Q factors (C1Qs) [30]. When the three-dimensional structure of the globular region was determined, a striking similarity to TNFα was observed, despite their unrelated protein sequences [30].

Adiponectin binds to numerous receptors. Two receptors (AdipoR1 and AdipoR2) share homology to G protein–coupled receptors; a third receptor, CDH13, is similar to cadherin family proteins [32,33]. AdipoR1 and AdipoR2 are predicted to contain seven transmembrane helices with a topology opposite to that of G-protein–coupled receptors. Their seven-transmembrane helices, which are conformationally distinct from those of G-protein–coupled receptors, enclose a large cavity in which three conserved histidine residues coordinate with a zinc ion. The zinc-binding structure may play a role in adiponectin-stimulated adenosine monophosphate (AMP)-activated protein kinase (AMPK) phosphorylation and uncoupling protein 2 (UCP2) upregulation. The primary biological effects of adiponectin occur via its stimulation of AdipoR1 and AdipoR2, which increase the activities of 5′AMP and peroxisome proliferator-activated receptor (PPAR), respectively [34]. The overall structures, large internal cavities and extracellular faces of AdipoR1 and AdipoR2 are presented in Figs. 1, 4 and 5, respectively, in the study by Hiroaki et al. [34]. AdipoR1 and AdipoR2 are distributed throughout the body with varying tissue specificity and exhibit different affinities for the varying adiponectin isoforms. AdipoR1 is predominantly located on skeletal muscle and endothelial cells [35–37], and AdipoR2 is most highly expressed in the liver [32]. Recently, many studies have demonstrated that AdipoR1 and AdipoR2 are also expressed in the brain [15,38,39].

In turn, AdipoR1 and AdipoR2 target downstream AMPK and UCP2, which serve as important cellular metabolic rate control points. Adiponectin receptor expression correlates with the insulin levels. The

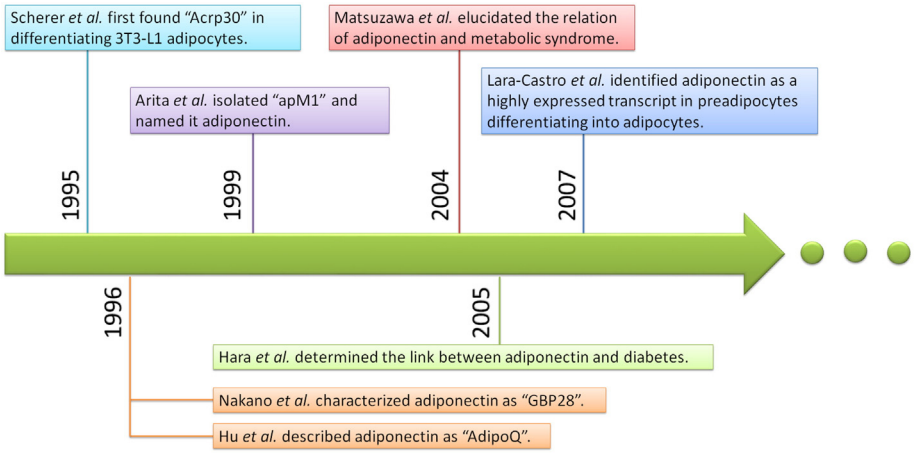

Fig. 1. *The discovery of adiponectin.* The flow chart describes main events in the history of adiponectin.