Mechanisms regulating energy metabolism by adiponectin in obesity and diabetes

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Abstract

Nutritional control of molecular events has become of great interest given the increased incidence of diet-induced obesity, and consequently Type 2 (non-insulin-dependent) diabetes, in recent years. The altered adipose tissue content in obese individuals results in an altered profile of circulating adipokines, and here we focus on adiponectin, whose circulating levels decrease in obese individuals. Adiponectin is a 30 kDa protein but circulates primarily as hexameric, oligomeric and, to a lesser extent, trimeric forms. Full-length adiponectin can also be cleaved to produce a fragment containing the globular domain that exerts potent metabolic effects. Adiponectin has insulin-mimetic and -sensitizing actions including stimulation of glucose uptake in skeletal muscle and suppression of glucose production in liver. Hence, adiponectin has attracted great interest as an antidiabetic agent. Adiponectin acts via two receptor isoforms, AdipoR1 (adiponectin receptor 1) and AdipoR2, which have distinct tissue distributions and affinities for recognition of the various adiponectin forms. Expression of AdipoR isoforms can be regulated by hyperinsulinaemia and hyperglycaemia with the consequence of increased sensitivity or resistance to specific forms of adiponectin. In summary, regulation of adiponectin or AdipoR expression may be of great importance in the development of metabolic perturbations characteristic of Type 2 diabetes in obese individuals.

Obesity and the metabolic syndrome

Diet-induced obesity and the subsequent development of features of the metabolic syndrome have become major worldwide health problems [1,2]. Almost 70% of adults in U.S.A. are overweight but, perhaps more alarmingly, 16% of juveniles are overweight and there is a trend towards decreased age of onset of Type 2 (non-insulin-dependent) diabetes, which was typically only found in adults. A weight loss of 5–10% can improve insulin resistance in obese individuals [2] and nutrition has become an important target for management of obesity, insulin resistance and diabetes [3]. Given that attempts to regulate food intake and content are futile in most of the at risk patients, a clearer understanding of the cellular events underlying the pathophysiology of features of the metabolic syndrome is required to allow therapeutic synergism of novel medications along with diet and exercise. Here, we provide an up-to-date mini-review on control of molecular regulation of adiponectin action.

Adiponectin structure and function

Adipose tissue, once considered simply a lipid storage depot, is now known to be a dynamic endocrine organ that secretes various factors (adipokines) [4,5]. Obese and Type 2 diabetic patients or animal models exhibit altered profiles of adipokines and energy metabolism and insulin action are markedly impaired in individuals with visceral obesity [6]. Adiponectin is one of the most abundant plasma proteins (~1–17 µg/ml) and, whereas adipokine levels typically show an inverse correlation with body mass index, adiponectin is distinct in that circulating levels decrease in obesity. Adiponectin has antidiabetic properties due to insulin-mimetic and insulin-sensitizing actions, while anti-inflammatory and anti-atherosclerotic effects have also been consistently reported. Since it is impossible to cover here, readers are referred to several excellent reviews discussing the various effects of adiponectin [7–9]. To manipulate the function of adiponectin, or prevent obesity-related defects in adiponectin action, it is imperative to appreciate the complex yet intriguing nature of its structure and regulation.

The adiponectin gene product is a 30 kDa protein but these monomers can form trimeric [LMW (low-molecular-mass form)] or higher order complexes including hexamers [MMW (medium-molecular-mass form)] and oligomers [HMW (high-molecular-mass form)] (see Figure 1), which each have different potency for, and end-point responses in, different tissues [10,11]. In addition, fAd (full-length adiponectin) multimers may be cleaved to liberate a fragment containing the C-terminal globular domain (gAd), which exhibits potent metabolic effects, particularly in skeletal muscle [12–14]. Furthermore, an intracellular signalling role for gAd was recently proposed [15] and the cleaved N-terminal region of adiponectin was recently reported to bind...
Figure 1 | Regulation of adiponectin synthesis and function
As highlighted in this Figure, the function of adiponectin can be regulated at many levels, including: transcription of the adiponectin gene; translation of RNA to protein; post-translational modifications resulting in oligomerization of fAd into trimers (LMW), hexamers (MMW) and oligomers (HMW); protease-mediated cleavage of fAd to produce the N-terminal fragment and the C-terminal globular domain. Binding of adiponectin forms to membrane receptors (e.g. gAd has high affinity only for AdipoR1) and LMW, MMW and HMW forms of fAd and gAd can mediate distinct cellular effects. It has also been suggested that the N-terminal fragment may mediate cellular responses.

AdipoRs (adiponectin receptors)
Two AdipoR isoforms, whose transcription has been shown to be regulated by PPAR and liver X receptor ligands, were recently discovered and it has been suggested that additional receptors may exist [8,16,23]. Both AdipoR1 and AdipoR2 are predicted to have seven transmembrane domains and AdipoR1 has a high affinity for gAd and low affinity for fAd oligomeric forms, whereas AdipoR2 exhibits intermediate binding affinity for both gAd and fAd forms. A potential pathophysiological role for alterations in AdipoRs is supported by a positive correlation between receptor expression in skeletal muscle with insulin resistance and plasma insulin levels, lower skeletal-muscle AdipoR1 and AdipoR2 expression in patients with a family history of diabetes and altered AdipoR1 expression in ob/ob, db/db or STZ (streptozotocin) diabetic mice [24–26]. The importance of AdipoR is being further highlighted by a growing literature on their regulation in response to changes in nutritional conditions, metabolic alterations and antidiabetic agents, which cannot be discussed further here. We have performed in vitro studies to examine direct regulation of AdipoR expression by hyperinsulinaemia and hyperglycaemia [13]. Both conditions decreased AdipoR1 mRNA levels and, importantly, reduced the metabolic effects of gAd in skeletal muscle. Hyperinsulinaemia also increased AdipoR2 and increased sensitivity of muscle cells to fAd (Figure 2). Demonstration of this potential for conditions prevailing during the progression of Type 2 diabetes to alter AdipoR expression and consequently the function of different forms of adiponectin confirms the recently proposed concept of gAd resistance, resulting in a vicious cycle of events that exacerbates the development of diabetes [8].

Adiponectin signalling
Relatively little detail is known at this moment regarding adiponectin-regulated intracellular signalling cascades. However, there is evidence that clearly suggests a central role for AMPK (AMP-activated protein kinase) in mediating the majority of adiponectin’s effects and others such as regulation of Akt, p38, ERK (extracellular-signal-regulated kinase), cAMP and NF-κB (nuclear factor κB) and generation of nitric...
Regulation of AdipoR isoform expression and adiponectin-sensitivity by hyperglycaemia and hyperinsulinaemia

In extensor digitorum longus or L6 muscle cells, there is approx. 6-fold more AdipoR1 than AdipoR2. Hyperinsulinaemia or hyperglycaemia can reduce AdipoR1 mRNA expression, resulting in gAd resistance, while hyperinsulinaemia also induced a switch towards increased fAd-sensitivity by enhancing AdipoR2 expression.

Oxide and ROS (reactive oxygen species) by adiponectin have also been shown [8]. A major step forward came recently with the identification of an AdipoR-binding protein [27]. One intriguing aspect of adiponectin action is that different tissue-specific effects, or indeed distinct signalling effects within the same cell type, can be mediated by different oligomeric forms of adiponectin [10,11]. Clearly defining the signalling pathways and end-point responses mediated by each form of adiponectin in specific tissues will be of great interest and perhaps of tremendous (patho)physiological significance. Furthermore, the potential for cross-talk [28] between adiponectin signalling and pathways regulated by other hormones should be realized (Figure 3). With this in mind, current studies in our laboratory are aimed at determining the metabolic function of adiponectin in the presence of physiologically relevant mixtures of adipokines, rather than in isolation.

Metabolic consequences of adiponectin gene KO (knockout) or supplementation

The insulin-mimetic and insulin-sensitizing effects of adiponectin on liver and/or skeletal muscle have been clearly shown by injection, acutely decreasing blood glucose in normal mice, preventing insulin-resistance associated with diet-induced obesity and ameliorating insulin resistance and improved glucose tolerance upon administration to various obese or lipoatrophic insulin-resistant animal models [7,8]. The direct insulin-sensitizing effect of gAd was further demonstrated by the fact that gAd transgenic ob/ob mice exhibited attenuated insulin resistance and diabetes compared with ob/ob mice and transgenic overexpression of adiponectin prevented diet-induced metabolic complications in rats. In addition, many interesting phenotypic consequences have been noted using adiponectin-KO mice generated by various groups [29–31]. Adiponectin-KO mice exhibited mild or moderate insulin resistance, particularly when fed a high-fat diet, developed atherosclerosis as a result of 2-fold more neointimal formation and developed hypertension when maintained on a high-salt diet and aortic banding-induced hypertrophic remodelling was greater in adiponectin-KO mice, all of which can be corrected by adiponectin administration. The potent and widespread physiological effects of adiponectin therefore make this adipokine extremely attractive as a drug discovery target.

Conclusion

Adiponectin mediates many advantageous physiological effects and decreased circulating levels or defects in adiponectin action may play a role in the pathophysiology of many disease states, for example in obesity and diabetes. Regulation of adiponectin action is complicated and occurs at many levels, including formation of oligomers, enzymatic cleavage and availability of its receptor isoforms. Future studies to clearly identify the mechanisms of adiponectin synthesis and action may allow exploitation of the undoubted therapeutic potential of adiponectin and overcome current limitations in this regard [32].
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References


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