ROLE OF ADIPONECTIN IN THE REGULATION OF CARBOHYDRATE AND LIPID METABOLISM

Adiponectin, an adipocyte-derived plasma protein, has been shown to play an important role in the regulation of fatty acid and glucose metabolism. Adiponectin enhances fatty acid oxidation both in skeletal and cardiac muscle as well as in the liver, thus reducing triglyceride content in these tissues. Moreover, it stimulates glucose uptake by skeletal and cardiac muscle, and inhibits glucose production by the liver; consequently decreasing blood glucose levels. This review focuses on the molecular mechanisms underlying adiponectin effects on carbohydrate and lipid metabolism in skeletal muscle, cardiac muscle and liver.

Key words: adiponectin, adiponectin receptor, glucose metabolism, fatty acid oxidation, muscle, heart, liver

ADIPONECTIN, THE ADIPOCYTE-DERIVED HORMONE

Adiponectin is an adipocyte-derived plasma protein which was identified by four research groups independently in the mid-1990s and was named AdipoQ, apM1 - adipose most abundant gene transcript 1, GBP28 - gelatin-binding protein, or Acrp30 - adipocyte complement-related protein 30 (1 - 4). Human adiponectin is encoded by the ADIPOQ gene (previously named APM1 or ACDC), which spans 17 kb on chromosome locus 3q27 (5, 6). Interestingly, human chromosome 3q27 has been identified as a region carrying susceptibility genes for type 2 diabetes and metabolic syndrome (7, 8). The gene for human adiponectin contains three exons, with the start codon in exon 2 and stop codon in exon 3 (5, 6).

Adiponectin is expressed and secreted predominantly by adipose tissue; nevertheless, its expression and serum levels decrease with obesity and are
positively associated with whole-body insulin sensitivity (1, 9, 10). Moreover, weight loss significantly elevates plasma adiponectin levels (10). In the plasma of non-obese subjects adiponectin levels lie in the range from 2 to 17 μg/ml (9). Plasma adiponectin levels in men are significantly lower than in women among non-obese and obese subjects (9). Although the ADIPOQ gene is expressed mainly in adipocytes, recent studies have found that adiponectin gene expression can be induced in hepatocytes (11), in myotubes (12), and in skeletal muscle (13). Moreover, adiponectin expression occurs in bone-forming cells (14) and cardiomyocytes (15).

REGULATION OF ADIPONECTIN GENE EXPRESSION

Regulation of adiponectin gene expression remains to be elucidated. Several studies have shown that adiponectin is induced during adipocyte differentiation and its secretion is stimulated by insulin (1, 4, 16). It has also been observed that IGF-1 up-regulates adiponectin gene, whereas TNF-α and glucocorticoids decrease adiponectin gene transcription (16 - 18). Recently, a functional PPAR-responsive element (PPRE) in the promoter region of the human adiponectin gene has been identified (19). Moreover, it has been shown that peroxisome proliferator-activated receptor γ (PPARγ), which is a well-known transcriptional activator of many adipocyte-specific genes, is required for adiponectin gene induction (19). Up-regulation of PPARγ gene expression in rat adipose tissue is accompanied by an increase in adiponectin gene expression (20, 21). Furthermore, PPARγ activators, thiazolidinediones (TZD), which are widely used to ameliorate insulin sensitivity and glucose tolerance in type 2 diabetes, increase adiponectin expression and secretion by adipocytes, elevating plasma adiponectin levels (17, 22, 23). These experimental observations suggest that PPARγ plays a significant role in the transcriptional activation of adiponectin gene expression via the PPRE in its promoter; however, the exact mechanism of adiponectin gene induction needs further investigation.

PROTEIN STRUCTURE OF ADIPONECTIN

Secreted adiponectin consists of an N-terminal species-specific variable region followed by a conserved collagenous domain highly homologous in sequence to collagen VIII and collagen X, and a C-terminal globular domain which shows significant sequence similarity with the complement factor C1q (2, 24). Circulating adiponectin forms a wide range of multimers, including trimers, hexamers and high molecular weight (HMW) multimers (25, 26). The globular domains of adiponectin form homotrimers (24, 25). The crystal structure of the adiponectin globular trimer reveals an unexpected homology to trimeric TNF-α (24). Both proteins feature the ability to trimerise via key conserved hydrophobic residues. Higher order structures of adiponectin are formed through the collagen like region (24, 25). Non-reducing gel electrophoresis analysis of human plasma
demonstrated that HMW multimers of adiponectin are less abundant in male than in female subjects (25). These results suggest that not only the total adiponectin concentration but also multimer distribution are different in two genders. Moreover, Fruebis et al. showed the presence of a truncated form of adiponectin, containing only the globular head, in human plasma (27). Mutations in the ADIPOQ gene result in an impaired multimerization and/or impaired secretion of adiponectin from adipocytes, both linked to the development of insulin resistance and type 2 diabetes.

**ADIPONECTIN RECEPTORS**

A few years ago, Yamauchi et al. cloned two different isoforms of adiponectin receptor, AdipoR1 and AdipoR2 (28). Both isoforms are expressed in many cell types, including adipocytes (20, 28, 29). Since adiponectin receptors are expressed in fat cells, adiponectin may play an important role in the regulation of adipose tissue metabolism via autocrine and/or paracrine manner. In human tissues AdipoR1 is expressed mainly in skeletal muscle, whereas AdipoR2 is predominantly expressed in the liver (28). Moreover, it has been demonstrated that two types of adiponectin receptor have different binding affinity for globular and full-length adiponectin, AdipoR1 is a high-affinity receptor for globular adiponectin but a very low-affinity receptor for full-length adiponectin, whereas AdipoR2 is an intermediate affinity receptor for globular and full-length adiponectin (28). *In vitro* studies have revealed that both isoforms of adiponectin receptor can mediate increased AMP-activated protein kinase (AMPK) phosphorylation and PPARα activity by adiponectin binding, thus activating fatty acid oxidation and glucose uptake (28).

Transcriptional regulation of genes encoding adiponectin receptors has not yet been clarified. So far, it has been shown that in human macrophages adiponectin receptor gene expression is regulated by PPAR (30) and that the induction of AdipoR1 in adipose tissue is correlated with an increase in the expression of PPARγ (20). These observations suggest that the AdipoR1 encoding gene may be regulated by PPARs.

**EFFECTS OF ADIPONECTIN ON CARBOHYDRATE AND LIPID METABOLISM IN SKELETAL MUSCLE**

Adiponectin has potent effects on carbohydrate and lipid metabolism in skeletal muscle (*Fig. 1*). Numerous studies have shown that treatment with the globular domain of adiponectin improves fatty acid utilization, both in isolated muscle as well as in cultured skeletal muscle cells (27, 31, 32). The action of adiponectin in muscle is mediated by adiponectin receptors, AdipoR1 and AdipoR2. In human skeletal muscle, AdipoR1 is expressed at the highest level, with lower levels of AdipoR2 (28). The binding of globular and full-length...
adiponectin to adiponectin receptors increased PPARα activity and stimulated glucose uptake and fatty acid oxidation in myocytes (28).

The molecular mechanisms underlying adiponectin-dependent increase in muscle fatty acid oxidation include up-regulation of several genes involved in muscle lipid metabolism, such as fatty acid translocase (FAT/CD36); acyl-CoA oxidase (ACO), the rate-limiting enzyme of the β-oxidation pathway in peroxisomes (33); and mitochondrial uncoupling protein 2 (UCP2), accompanied by the induction of PPARα gene expression and increase in PPARα activity (28, 32). The nuclear receptor PPARα is required for transcription of many genes involved in fatty acid oxidation pathway (34), thus its activation by adiponectin may improve fatty acid utilization in muscle. Additional effect of adiponectin on skeletal muscle is an increased phosphorylation of AMP-activated protein kinase (AMPK) (28, 31). Moreover, activation of AMPK has been shown to be
necessary for adiponectin effects on fatty acid oxidation in skeletal muscle cells (27, 31, 35). AMPK activation triggers many metabolic changes that act to restore energy balance in muscle cells, such as increased glucose uptake and metabolism, and increased oxidation of fatty acids (36). Regulation of fatty acid oxidation pathway by AMPK involves phosphorylation of acetyl-CoA carboxylase (ACC), which leads to the inhibition of ACC activity followed by a decrease in malonyl-CoA levels (36). Adiponectin-dependent AMPK activation in skeletal muscle was associated with an increase in ACC phosphorylation and a decrease in the concentration of malonyl-CoA (28, 31). Malonyl-CoA is an allosteric inhibitor of carnitine palmitoyl transferase 1 (CPT-1), an enzyme responsible for the transport of fatty acids into mitochondria, where fatty acid oxidation occurs (37). Thus a decrease in malonyl-CoA concentration after adiponectin treatment may be the reason for increased fatty acid oxidation in muscle (31).

In skeletal muscle, the pathways of glucose metabolism include glycogen synthesis, glucose oxidation and lactate production. Globular adiponectin has been reported to stimulate glucose transport both in isolated skeletal muscle as well as in cultured myocytes (31, 35, 38). Ceddia et al. have recently demonstrated that globular adiponectin increases glucose uptake into skeletal muscle cells via enhanced translocation of glucose transporter 4 (GLUT4) molecules to the cell membrane (39). Adiponectin also reduced the basal and insulin-stimulated rates of glycogen synthesis in muscle cells (39). Since AMPK can directly phosphorylate and inactivate glycogen synthase (36), the reduction of glycogen synthesis upon adiponectin treatment may be mediated by activation of AMPK. Moreover, it has been demonstrated that in adiponectin-treated myocytes glucose metabolism is shifted toward lactate production (39).

ADIPONECTIN IS INVOLVED IN CARDIAC CARBOHYDRATE AND FATTY ACID METABOLISM

Both isoforms of adiponectin receptor, AdipoR1 and AdipoR2, are expressed in the myocardium (Fig. 2). In recent years, Furuhashi et al. have provided indirect evidence for the binding of adiponectin to these receptors by demonstrating that serum adiponectin levels in the coronary sinus are significantly lower than in the aortic root (40). The gradient of adiponectin concentrations existing across the heart indicates that adiponectin binds to its receptors in the myocardium and/or accumulates in vascular walls. This finding, together with the observation that adiponectin receptors are expressed in the myocardium, suggests specific effects of adiponectin in the heart. Indeed, it has recently been reported that adiponectin treatment significantly enhances glucose and fatty acid uptake by cardiomyocytes (15). Moreover, adiponectin induces phosphorylation of AMPK in cultured cardiac myocytes (15, 41). Since AMPK is known to stimulate glucose uptake and translocation of the cardiomyocyte glucose transporter GLUT4 to the cell surface (42), it seems possible that the
Adiponectin-dependent increase in glucose uptake in cardiomyocytes is mediated by activation of AMPK (Fig. 3). Adiponectin deficiency is associated with impairment of glucose metabolism, insulin resistance and subsequent exacerbation of heart failure (43). Interestingly, AdipoR1, the predominant isoform of adiponectin receptor in the myocardium, is induced during cardiac hypertrophy (Fig. 2); suggesting increased adiponectin signalling in this condition.

Adiponectin is also involved in cardiac fatty acid metabolism. Treatment with the globular domain of adiponectin significantly increases fatty acid oxidation in the heart (26). It has been proposed that this effect is independent of AMPK activation (26); however, the exact mechanism by which adiponectin increases fatty acid oxidation in cardiac muscle remains to be elucidated.

**ADIPONECTIN MODULATES CARBOHYDRATE AND LIPID METABOLISM IN THE LIVER**

The liver, where adiponectin receptor AdipoR2 is expressed, is one of the adiponectin target organs (28). Several studies have shown that adiponectin modulates hepatic carbohydrate and lipid metabolism (Fig. 4). Long-term treatment with adiponectin improved insulin sensitivity and reduced triglyceride content in the liver (32). Adiponectin suppresses hepatic glucose production by down-regulation of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) gene expression, thus decreasing plasma glucose levels (35, 44, 45). An inhibitory effect of adiponectin on gluconeogenesis is probably mediated by AMPK phosphorylation. In the liver, AMPK activation is necessary...
for adiponectin-dependent inhibition of PEPCK and G6Pase gene expression and glucose production (35). Adiponectin has no effect on glycogen content and synthesis, glucose uptake or glycolysis in the liver (44, 45).

CONCLUSIONS

Over recent years, adipose tissue has been shown to secrete a variety of protein factors and hormones involved in many aspects of organs physiology. Adiponectin, an adipocyte-specific secretory protein, plays an important role in the regulation of glucose and lipid metabolism. In skeletal muscle, adiponectin improves fatty acid utilization and stimulates glucose uptake through activation
of AMPK (27, 28, 31, 32). Since skeletal muscle accounts for 80-90% of the insulin-stimulated glucose disposal (46), adiponectin-induced increase in glucose uptake may be beneficial in subjects with type 2 diabetes. Adiponectin has also been shown to enhance glucose and fatty acid uptake by cardiomyocytes, and to increase fatty acid oxidation in the heart (15, 26). Moreover, in various animal models adiponectin inhibits hepatic glucose production (35, 44, 45). In general, adiponectin increases insulin sensitivity and improves glucose tolerance (27, 44). In humans, plasma adiponectin concentrations are positively correlated with whole-body insulin sensitivity (9). Recently, an association between adiponectin concentrations in plasma and risk of type 2 diabetes in apparently healthy individuals has been reported (47). Moreover, there is increasing evidence that genetic variants in the adiponectin gene itself and/or in genes encoding

Fig. 4. Effects of adiponectin on carbohydrate and lipid metabolism in the liver.
adiponectin regulatory proteins, such as PPARγ, are associated with hypoadiponectinaemia, insulin resistance and type 2 diabetes. These observations suggest that adiponectin is probably a major insulin-sensitising hormone secreted by adipose tissue and may play an important role in the prevention and treatment of diabetes through modulation of insulin sensitivity and direct regulation of lipid and glucose metabolism.

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