

REVIEW

Adiponectin receptor signalling in the brain

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Adiponectin is an important adipocyte-derived hormone that regulates metabolism of lipids and glucose, and its receptors (AdipoR1, AdipoR2, T-cadherin) appear to exert actions in peripheral tissues by activating the AMP-activated protein kinase, p38-MAPK, PPARα and NF-kappa B. Adiponectin has been shown to exert a wide range of biological functions that could elicit different effects, depending on the target organ and the biological milieu. There is substantial evidence to suggest that adiponectin receptors are expressed widely in the brain. Their expression has been detected in regions of the mouse hypothalamus, brainstem, cortical neurons and endothelial cells, as well as in whole brain and pituitary extracts. While there is now considerable evidence for the presence of adiponectin and its receptors in the brain, their precise roles in brain diseases still remain unclear. Only a few research studies have looked at this facet of adiponectins in brain disorders. This brief review will describe the evidence for important functions by adiponectin, its structure and known actions, evidence for expression of AdipoRs in the brain, their involvement in brain disorders and the therapeutic potential of agents that could modify AdipoR signalling.

Abbreviations

ACC, acetyl-CoA carboxylase; AD, Alzheimer's disease; AdipoR, adiponectin receptor; AMPK, adenosine monophosphate-activated protein kinase; APPL, adaptor protein containing a pleckstrin homology domain, a phosphotyrosine domain and a leucine zipper motif; EBP, enhancer-binding protein; eNOS, endothelial NOS; FOXO1, forkhead transcription factor O1; gAD, globular adiponectin; MS, multiple sclerosis; PAQR, progesterone and AdipoQ receptor; PI3K, phosphatidylinositol 3-kinase; RACK, receptor for activated C-kinase; SIRT1, silent mating type information regulation 2 homologue 1

Introduction

Adipose tissue has long been regarded as paramount for maintenance of life and exerting various physiological functions in mammals (Gesta *et al.*, 2008). In addition to regulating cold adaptation and non-shivering thermogenesis (Redinger, 2009), it is also an important passive fuel storage site, assisting in generation of ATP. Furthermore, research over the past two decades has shown that adipose tissue is not merely an inert tissue devoted to energy storage, but it is also a metabolically active organ capable of regulating

immunological and inflammatory processes under physiological and pathological states (Fantuzzi, 2005). In the last decade, the epidemic of obesity and its related pathologies such as hypertension, diabetes and strokes has prompted further research into this multitasking tissue. These studies have yielded the intriguing finding that adipose tissue can function as an endocrine organ because of its ability to secrete various hormones, tissue factors and cytokines, collectively known as adipokines (Trayhurn and Beattie, 2001; Trayhurn and Wood, 2004; Wood and Trayhurn, 2007; Vazquez-Vela *et al.*, 2008; Bastard *et al.*, 2009; Li *et al.*, 2009).

Adiponectin

One important adipocyte-derived hormone is adiponectin, which was first discovered by Scherer and colleagues in 1995 in 3T3-L1 adipocytes. Since then, other research groups have identified adiponectin in murine and human adipocytes (Scherer *et al.*, 1995; Hu *et al.*, 1996; Maeda *et al.*, 1996). Adiponectin was initially thought to be produced exclusively by adipose tissue. However, recent studies have shown it to be expressed, both at mRNA and protein levels, in other tissues such as human and murine osteoblasts (Berner *et al.*, 2004), liver parenchyma cells (Yoda-Murakami *et al.*, 2001; Jonsson *et al.*, 2005; Kaser *et al.*, 2005), myocytes (Delaigle *et al.*, 2004), epithelial cells (Shimada *et al.*, 2004; Patel *et al.*, 2008) and placental tissue (Camino *et al.*, 2005; Chen *et al.*, 2006).

Human adiponectin is a 28–30 kDa protein that comprises 244 amino acids and structurally belongs to the soluble defence collagen superfamily (Berg *et al.*, 2002). It bears 82% amino acid homology with its murine counterpart and its structure comprises multiple domains (Scherer *et al.*, 1995; Maeda *et al.*, 1996; Nakano *et al.*, 1996; Berg *et al.*, 2002). It has a signalling peptide region and a species-specific variable domain at the N-terminal, followed by a collagenous domain and a globular domain at the C-terminal (Figure 1). The N-terminal is quite unique, as it shows no structural homology to any other proteins and is structurally diverse among different species. On the contrary, the globular domain at the C-terminal bears the same amino acid sequence as that of the complement factor, C1q, and bears a striking structural similarity to the globular domains of other proteins such as collagens VIII and X, mannose-binding protein, TNF- α and

pulmonary surfactant proteins A and D (Brass *et al.*, 1992; Hu *et al.*, 1996; Shapiro and Scherer, 1998; Fruebis *et al.*, 2001; Yamauchi *et al.*, 2003). This domain facilitates the binding of adiponectin to its receptors. The collagenous domain in the centre comprises 22 G-X-Y repeats and facilitates the triple-helix formation of the protein structure (Berg *et al.*, 2002).

Adiponectin is a relatively abundant protein that accounts for about 0.01% of total serum proteins in humans and 0.05% in rodents (Matsuzawa, 2005). In humans, its serum concentration is 2–20 $\mu\text{g}\cdot\text{mL}^{-1}$, and it has been shown to undergo oligomerization in the circulation (Shimada *et al.*, 2004) (Figure 2). Adiponectin is released into the circulation as full-length trimers, hexamers, high molecular weight (HMW) multimers and a globular fraction called globular adiponectin (gAD), generated by proteolytic cleavage of the full-length adiponectin monomer (Waki *et al.*, 2003). Collectively, trimers and hexamers are referred to as low molecular weight (LMW) multimers, while larger complexes (18-mers and above) are known as HMW forms. The trimeric form is the basic form of circulating adiponectin, and it is formed through non-covalent disulphide bond linkages in its collagenous domains (Pajvani *et al.*, 2003). The hydrophobic interactions in the globular head help to maintain trimer stability (Waki *et al.*, 2003). The trimers undergo further post-translational modifications that include disulphide bond linkage between the cysteine residues located in the N-terminal variable region (Cys³⁶ in human and Cys³⁹ in mouse adiponectin, respectively), hydroxylation and glycosylation of four conserved proline and lysine residues in the collagenous domain of the trimers, to oligomerize into hexamers and larger complexes. (Tsao *et al.*, 2002; 2003; Pajvani

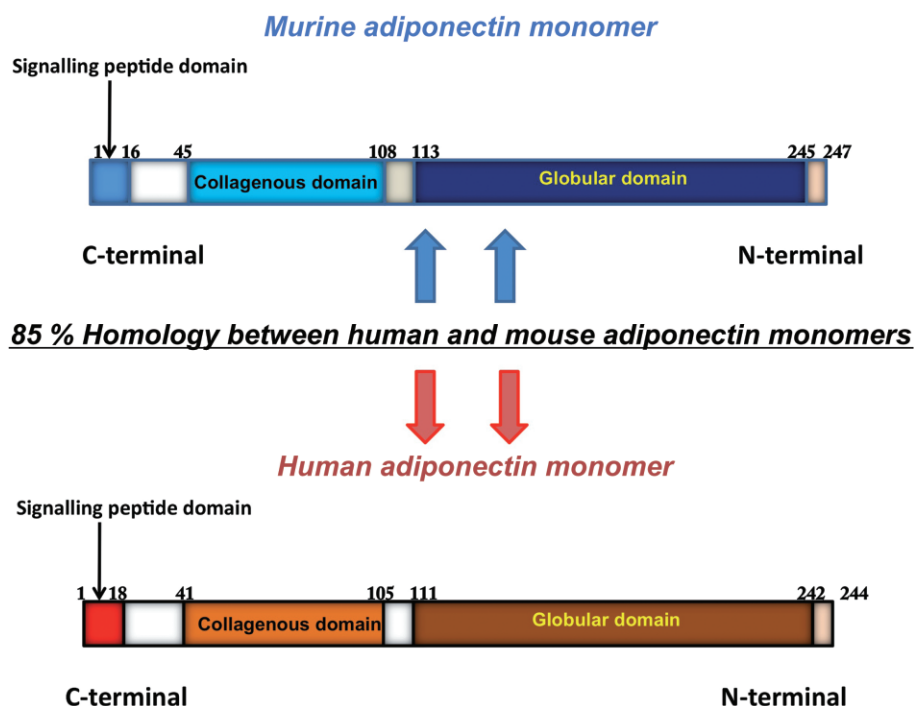


Figure 1

Schematic representation of adiponectin isoforms. The human and murine isoforms of adiponectin have 85% structural homology. Each of the adiponectin isoforms is composed of an N-terminal collagenous domain and a C-terminal globular region.

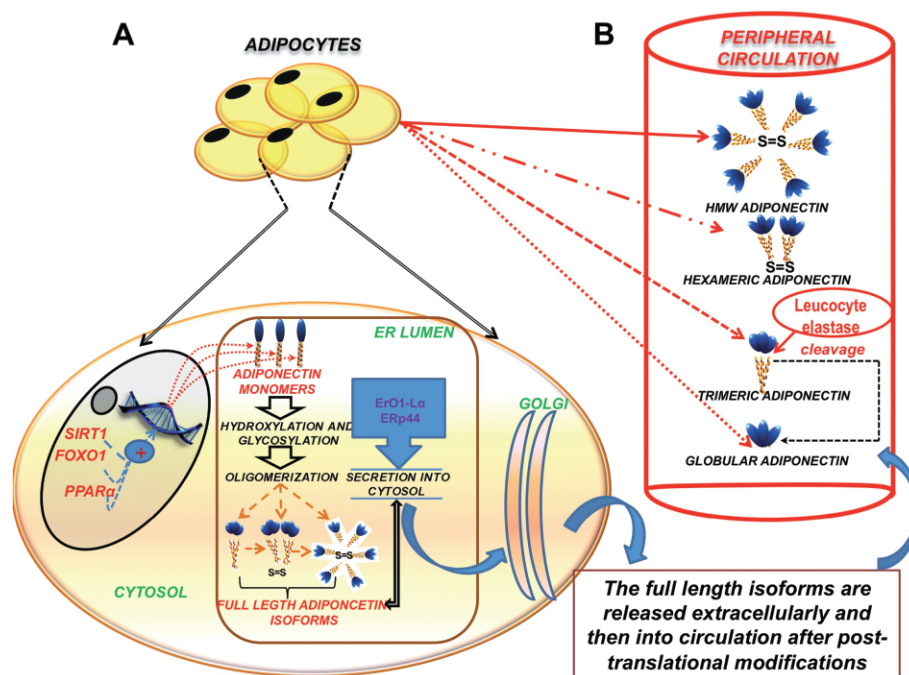


Figure 2

Regulation of synthesis, secretion and circulation of adiponectin. (A) Adipocytes synthesize adiponectin mRNA in its monomeric form within the nucleus. This transcription is regulated and promoted by SIRT1/FOXO-1 and PPAR α . Once transcribed, the adiponectin protein monomer is released into the ER, where it undergoes various post-translational modifications, regulated by ER chaperones like ERp44 and Ero1- α to form trimers, hexamers and HMW (full-length adiponectin) isoforms. (B) Following their packaging in the golgi, the adiponectin isomers are released into the peripheral circulation. The HMW isomer is the most abundant and biologically active form of adiponectin. Another form of circulating adiponectin is the gAd leukocyte elastase-mediated cleavage of the globular domain of the trimeric adiponectin.

et al., 2003; Waki *et al.*, 2003; Richards *et al.*, 2006; Wang *et al.*, 2006a). In addition, a small fraction of adiponectin is cleaved by leukocyte elastase and circulates as a proteolytic fragment that comprises the globular domain of the protein, known as gAd (Fruebis *et al.*, 2001) (Figure 2). Hexamers and HMW species are the two major oligomeric forms of circulating adiponectin (Nakano *et al.*, 1996). The lower plasma concentrations of trimeric and globular forms may be explained by their shorter half-lives (Pajvani *et al.*, 2003). Thus, adiponectin is a complex protein that circulates in the body as different oligomers.

The regulation of adiponectin expression and secretion of its oligomers into the circulation is not yet well understood. A sexual dimorphism is seen in the levels of circulating adiponectin, with males having lower adiponectin levels than females (Arita *et al.*, 1999). In addition, circulating adiponectin levels can be modified by various hormonal, nutritional, pharmacological factors, circulating cytokines, inflammatory conditions and disease states (Fasshauer *et al.*, 2002; Maeda *et al.*, 2002; Nishizawa *et al.*, 2002; Combs *et al.*, 2003; Bottner *et al.*, 2004; Tsou *et al.*, 2004; Brochu-Gaudreau *et al.*, 2010). Certain proteins, such as silent mating type information regulation 2 homologue 1 (SIRT1), NAD⁺-dependent protein deacetylase and forkhead transcription factor O1 (FOXO1)-C enhancer-binding protein α (EBP α) transcription complex, have also been shown to influence adiponectin release (Picard *et al.*, 2004; Qiao and Shao, 2006). Furthermore, a recently published study showed that the secretion of

these oligomers is tightly regulated by a pair of molecular chaperones in the endoplasmic reticulum, namely ERp44 (an ER protein of 44 kDa) and Ero1- α (ER oxidoreductase 1- α) (Wang *et al.*, 2008). While ERp44 was shown to inhibit the secretion of adiponectin oligomers through thiol-mediated retention, Ero1- α promoted the release of HMW adiponectin trapped by ERp44.

Adiponectin receptors (AdipoRs)

With obesity being a major factor in morbidities such as diabetes, hypertension and atherosclerosis, the discovery of adiponectin has led to a paradigm shift in the approach of research undertaken in this area. As a result of the extensive work examining adiponectin and its role in obesity, it is now regarded as an important protein, exerting a myriad of potentially beneficial effects ranging from body weight regulation, modulation of endothelial function, insulin-sensitization and anti-atherogenic and anti-inflammatory actions (Ouchi *et al.*, 1999; Berg *et al.*, 2001; Fruebis *et al.*, 2001; Yamauchi *et al.*, 2001; Okamoto *et al.*, 2002; Whitehead *et al.*, 2006; Kang *et al.*, 2009). Adiponectin exerts these effects by activating numerous signalling molecules, including adenosine monophosphate-activated protein kinase (AMPK), p38-MAPK, JNK, PPAR α transcription factor and NF- κ B in multiple tissues (Figure 3). These activating signals are transduced via the AdipoRs (Yamauchi *et al.*, 2003; Tang *et al.*, 2005), which

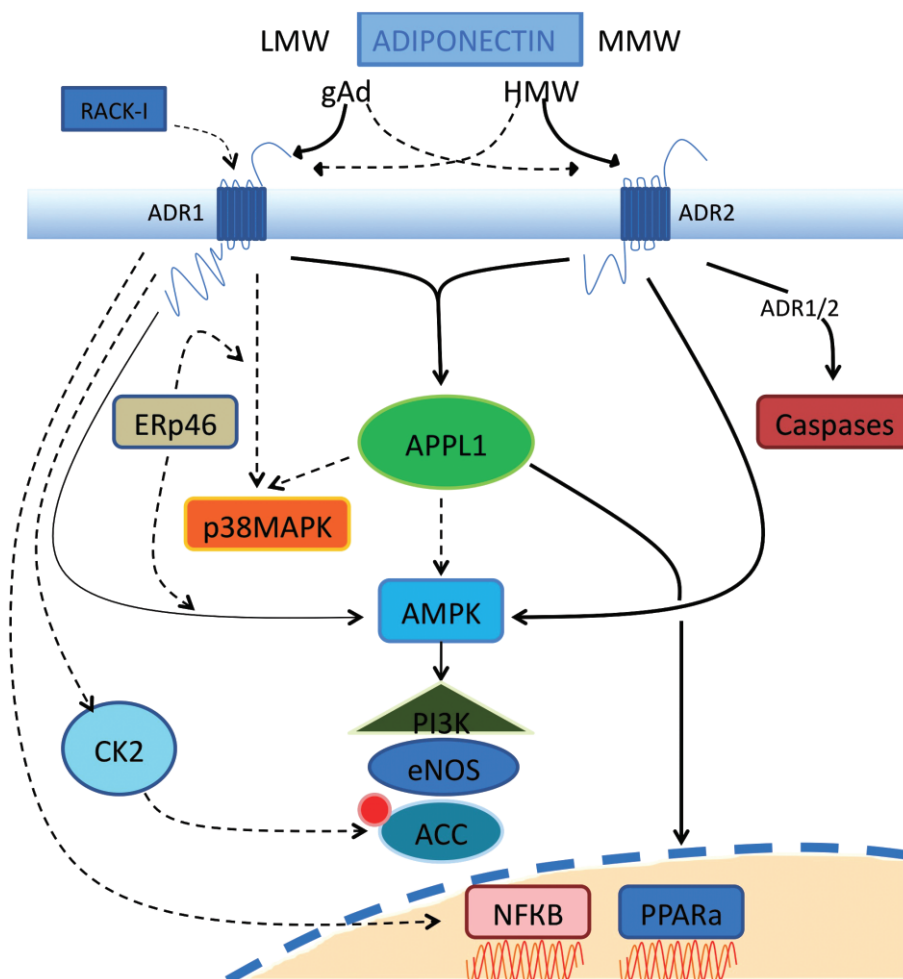


Figure 3

Representation of signalling transduction via adiponectin receptor activation. Adiponectin exists in full-length, globular, high molecular and low molecular weight forms. The binding of the different forms of adiponectin to the two known adiponectin receptors, AdipoR1 and AdipoR2, can lead to stimulation of AMPK, p38-MAPK, JNK and PPAR α . Interacting directly with the N-terminal of adiponectin receptors, APPL1 elicits signalling through PPAR α and along with AMPK modulates the PI3K pathway and eNOS levels. ACC phosphorylation occurs from CK2 adaptor protein at the AdipoR1 N-terminus whilst interaction of the scaffold protein RACK-I at AdipoR1 can mediate glucose metabolism. The ER chaperone, ERp46 helps mediate AdipoR1 signalling to p38 and AMPK. Signalling to NF- κ B is solely through AdipoR1, but evidence exists for both its activation and inhibition upon gAd binding. Activation of both receptors results in activation of the caspase cascade and alterations in cell survival.

include two seven transmembrane domain (7TM) receptors, AdipoR1 and AdipoR2, and a recently discovered cell surface protein called T-cadherin (Hug *et al.*, 2004). The first AdipoR to be discovered was AdipoR1, by Kadowaki and colleagues (Yamauchi *et al.*, 2003). This finding was followed by a search of human and mouse databases for AdipoR1-homologous genes, leading to the identification of a protein that exhibited a 68% identity to AdipoR1, which was termed AdipoR2 (Yamauchi *et al.*, 2003; Vasseur, 2006). The human AdipoR1 gene is located on chromosome 1(q32.1) and encodes a 375 amino acid 42 kDa protein. The human AdipoR2 gene is found on chromosome 12(p13.33), and it encodes a 43 kDa protein comprising 386 amino acids (Narasimhan *et al.*, 2005).

While the two main AdipoRs, AdipoR1 and R2, belong to the 7TM receptor family, they are structurally and functionally distinct from other 7TM receptor proteins (e.g. the

GPCRs), one of the striking differences is the reversed membrane topology that they possess (Yamauchi *et al.*, 2003). Hence, contrary to the conventional 7TM receptor protein structure, AdipoRs possess an intracellular amino terminus and an extracellular carboxyl-terminus. In addition to this structural variation, their downstream signalling mechanism bear no similarity to G-protein receptor-mediated signalling. Owing to these major differences, AdipoRs have now been categorised into a niche subset of the 7TM protein family, called the progestin and AdipoQ receptor (PAQR) family, which comprises 11 mammalian proteins that also includes the progestin receptors (Tang *et al.*, 2005).

AdipoRs are expressed in liver (Neumeier *et al.*, 2005; Bonnard *et al.*, 2008; Felder *et al.*, 2010), muscle (Civitaresse *et al.*, 2004; Staiger *et al.*, 2004; Beylot *et al.*, 2006; Dai *et al.*, 2006), heart (Neumeier *et al.*, 2005; Ding *et al.*, 2007; Palanivel *et al.*, 2007), adipose tissue (Fasshauer *et al.*, 2004;

Bluher *et al.*, 2005; Dai *et al.*, 2006; Rasmussen *et al.*, 2006; Liu *et al.*, 2008a, b), osteoblasts (Berner *et al.*, 2004; Kanazawa *et al.*, 2007), pancreas (Kharroubi *et al.*, 2003; Staiger *et al.*, 2005; Gu *et al.*, 2006), leukocytes (Chinetti *et al.*, 2004; Alberti *et al.*, 2007; Weigert *et al.*, 2008) and the brain (Kubota *et al.*, 2007) of humans, rodents and various other mammals. The expression profile of AdipoR1 is quite ubiquitous and is most abundant in skeletal muscle. On the other hand, the expression of AdipoR2 is most abundant in liver (Coope *et al.*, 2008). Recently, a third AdipoR, T-cadherin, was discovered. It bears no structural semblance to AdipoR1 and R2 as it lacks the *trans*-membrane and intracellular domains (Ranscht and Dourszimmernann, 1991; Takeuchi *et al.*, 2007). T-cadherin is highly expressed in the vasculature and to a lesser degree in muscle (Takeuchi *et al.*, 2007). However, the liver, a primary target tissue of adiponectin, does not show a high degree of T-cadherin expression. This raises an intriguing possibility that T-cadherin may not be a functional receptor of adiponectin but could be an adiponectin-binding protein.

Mechanisms regulating the expression of AdipoRs appear to be complex and are governed by numerous factors. Physiologically, a circadian expression profile of these receptors is seen in adipose tissue (Berner *et al.*, 2004) that appears to be regulated by feeding states (Ding *et al.*, 2004; Liu *et al.*, 2008a), levels of free fatty acids and insulin (Tsuchida *et al.*, 2004; Beylot *et al.*, 2006; Bullen *et al.*, 2007; Bonnard *et al.*, 2008; Liu *et al.*, 2008b). Growth hormone has been shown to selectively up-regulate AdipoR2 (Fasshauer *et al.*, 2004; Liu *et al.*, 2008b), while long-term exercise can specifically up-regulate AdipoR1 expression (Chang *et al.*, 2006; Zeng *et al.*, 2007; Christiansen *et al.*, 2009). Additionally, various nuclear receptors like liver X receptor (LXR), PPAR α and drugs such as PPAR γ agonists, metformin and fibrates may alter expression levels of AdipoRs (Chinetti *et al.*, 2004; Ding *et al.*, 2007; Shimizu *et al.*, 2007; Liu *et al.*, 2008b). The AdipoRs display differential binding affinities for the various adiponectin multimers. While AdipoR1 binds to gAd with high affinity, AdipoR2 has an intermediate binding affinity for both gAd and full-length adiponectin. On the other hand, T-cadherin only has a putative interaction with hexameric and HMW multimeric forms (Yamauchi *et al.*, 2003).

AdipoR signalling

Signalling molecules activated by adiponectin include AMPK, p38-MAPK and PPAR α (Matsuzawa, 2005) (Figure 3). Of these, AMPK acts as a major downstream component of adiponectin signalling. AMPK generally acts as the cellular energy sensor in the body and is normally activated when there is an increase in the intracellular AMP/ATP ratio (Snehalatha *et al.*, 2003; Wang *et al.*, 2005a). Numerous studies have shown that metabolic effects mediated by adiponectin in the liver and muscle are due to the activation of AMPK (Yamauchi *et al.*, 2002; Civitarese *et al.*, 2005; 2006; Kola *et al.*, 2006; Viollet *et al.*, 2006). AMPK activation is also involved in adiponectin-mediated actions in vascular endothelial cells and the heart, in a manner that is reported to be beneficial in protection against cardiovascular diseases (Kobayashi *et al.*, 2004; Ouchi *et al.*, 2004). For example, adiponectin-mediated activation of AMPK in endothelial cells stimulates production of NO, and

it reduces myocardial infarct size and apoptosis in a mouse model of heart ischaemia-reperfusion (Chen *et al.*, 2003; Shibata *et al.*, 2005; Guerre-Millo, 2008). Thus, there is evidence that adiponectin-dependent AMPK signalling may mediate beneficial metabolic and cardiovascular effects of adiponectin (Kahn *et al.*, 2005).

Recently, an adaptor protein containing a pleckstrin homology domain, a phosphotyrosine domain and a leucine zipper motif (APPL1) has been shown to both bind to AdipoRs and acts as a link between the receptors and its downstream signalling molecules (Mao *et al.*, 2006; Cheng *et al.*, 2007). APPL1 is required for adiponectin-induced activation of AMPK, p38-MAPK and ERK 1/2-MAPK pathways. APPL1 has been shown to mediate adiponectin-regulated insulin, sensitizing actions in the periphery and modulating endothelial NOS (eNOS) function in endothelial cells (Deepa and Dong, 2009). In addition, Chandrasekar *et al.* (2008) reported that the anti-inflammatory and cytoprotective effects of adiponectin are mediated, at least in part, through APPL1-dependent AMPK activation of the phosphatidylinositol 3-kinase (PI3K)-v-akt (Akt) signalling pathway. Hence, until recently, APPL1 was the only AdipoR-interacting protein identified, through which AdipoR activation could modulate and possibly integrate its downstream signalling responses (Mao *et al.*, 2006). However, over the past two to three years, various interacting and adapter proteins for AdipoRs have been discovered. These include the regulatory subunit of the protein kinase casein kinase (CK) 2 that binds to the AdipoR1 N-terminus and appears to be vital in mediating the crucial step of acetyl-CoA carboxylase (ACC) phosphorylation in adiponectin-mediated fatty acid oxidation (Heiker *et al.*, 2009). In addition, the receptors for activated C-kinase-I (RACK-I) and the endoplasmic reticulum protein 46 (ERp46) have been reported as two other potential binding partners for AdipoR1. While RACK-I appeared to act as a scaffold protein in mediating adiponectin-induced glucose uptake in hepatocytes, the ER chaperone ERp46 appears to be vital in adiponectin-mediated AMPK- and p38-MAPK signalling, through AdipoR1 (Xu *et al.*, 2009; Charlton *et al.*, 2010). Another important facet of AdipoR signalling is its arrangement at the cell surface during adiponectin-mediated signalling because of the possibility of its dimerization and internalization. It has been shown that AdipoR1 and AdipoR2 are capable of forming homo- and hetero-oligomeric complexes *in vitro* (Yamauchi *et al.*, 2003), with homodimerization more common with AdipoR1 than AdipoR2. In addition, AdipoR1 can internalize constitutively and in an agonist-dependent manner (Kosel *et al.*, 2010), whereas little information is available regarding these processes in AdipoR2 (Ding *et al.*, 2009). Since information regarding the oligomerization, internalization and desensitization of cell surface receptors during downstream signal modulation are vital to ascertain the receptor accessibility and the prospects of its use as therapeutic targets (Dalrymple *et al.*, 2008; Hanyaloglu and von Zastrow, 2008), the presence of such features in AdipoR-mediated signalling could be instrumental in exploring their therapeutic potentials.

While adiponectin seems to exert several positive effects via multiple signalling mechanisms, it seems possible that adiponectin may also exert many unfavourable effects. For example, the view that adiponectin may be an

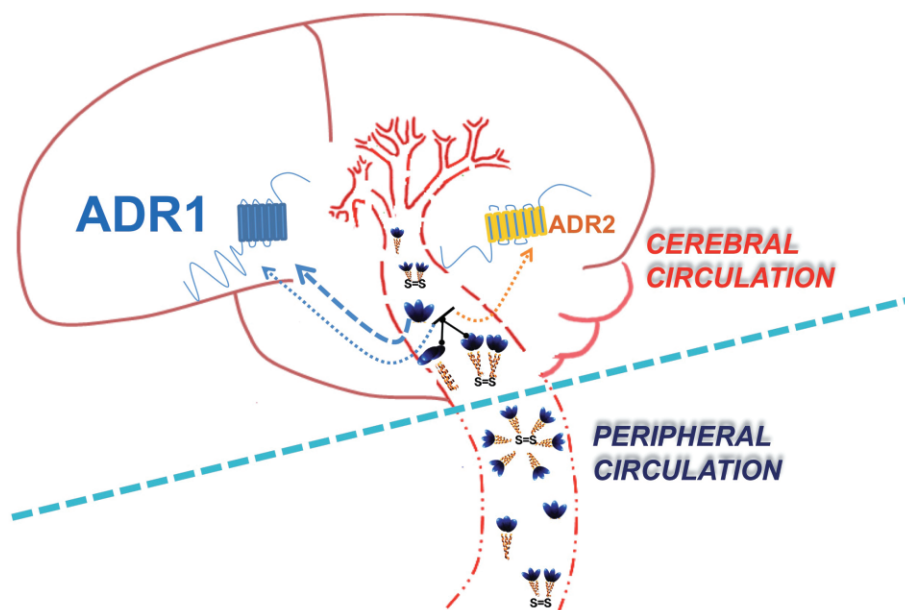


Figure 4

Differences between the peripheral and cerebral circulations regarding adiponectin signalling. The tight regulated membrane permeability of the cerebral blood vessels, as compared with their peripheral counterparts, permits the selective passage of only the trimers, hexamers and possibly globular forms of adiponectin into the CNS. Both AdipoR1 and AdipoR2 are present in the brain, with AdipoR1 being more pronounced. Different adiponectin isomers bind to the AdipoRs with different binding affinities, as demonstrated by the thickness of the arrows.

anti-inflammatory cytokine could be challenged in light of recent reports of elevated levels of this protein in various inflammatory disease states. Adiponectin has been shown to be elevated in arthritis, preeclampsia and end-stage renal diseases (Shoji *et al.*, 2005; D'Anna *et al.*, 2006; Haugen *et al.*, 2006; Otero *et al.*, 2006; Senolt *et al.*, 2006; Haugen and Drevon, 2007). Also, it was shown that adiponectin induces production of the pro-inflammatory mediator IL-6 and activation of NF- κ B in human synovial fibroblasts and adhesion molecule expression in endothelial cells (Hattori *et al.*, 2006; Tomizawa *et al.*, 2008; Smith *et al.*, 2009; Liao *et al.*, 2010). One plausible explanation for this pleiotropy of effects demonstrated by adiponectin could be the presence of various circulating oligomers of adiponectin. Although HMW multimers appear to be the most bioactive form of adiponectin in the circulation, which mediate the actions of adiponectin on liver, muscle and the vasculature, other isomeric forms of adiponectin like hexamers and gAd could modulate different signalling molecules at various other sites in the body and exert quite different effects (Wang *et al.*, 2005b; Hada *et al.*, 2007; Palanivel *et al.*, 2007; Hattori *et al.*, 2008). Thus, the question of whether or not adiponectin has an overall anti- or pro-inflammatory role still needs to be clarified, as this may be dependent on the specific tissue it acts on and the presence or absence of a disease state.

Adiponectin in the brain

In stark contrast to available information regarding adiponectin and its actions in the periphery, still very little is known

about the effects of adiponectin in the CNS. The presence of adiponectin and its role in the brain still remains controversial and a matter of debate. It had been initially suggested that adiponectin was not present in the brain, as it was unable to cross the blood–brain barrier (BBB). These conclusions were based on the results of some studies that could not detect adiponectin in the CSF (Pan *et al.*, 2006; Spranger *et al.*, 2006). However, this initial view conflicted with a report that CSF adiponectin was detectable after an i.v. injection of full-length adiponectin in C57Bl/6J mice, and that both systemic and i.c.v. administration of adiponectin reduced serum glucose and lipid levels and decreased body weight (Qi *et al.*, 2004). This latter study was therefore instrumental for suggesting that adiponectin could be a centrally acting signalling molecule. This proposition was further substantiated by Kubota *et al.* (2007), who showed that peripherally administered adiponectin stimulated AMPK in the hypothalamus of mice to increase food intake and decrease energy expenditure. However, whether endogenous adiponectin might have a similar effect in humans is not clear. This is because the physiological levels of adiponectin in human CSF is 1000-fold lower than its concentration in serum (Pan *et al.*, 2006; Kos *et al.*, 2007; Kusminski *et al.*, 2007) (Figure 4). In mice too, the CSF adiponectin corresponds to only 1–4% of plasma adiponectin in mice (Ahima *et al.*, 2006). As regards the presence of endogenous adiponectin in the brain in addition to CSF, adiponectin mRNA has been detected in chicken and murine brain extracts (Maddineni *et al.*, 2005; Hoyda *et al.*, 2007). Adiponectin mRNA was not detected in human brain extract, but it has been reported to be expressed in human pituitary gland (Rodriguez-Pacheco *et al.*, 2007; Wilkinson

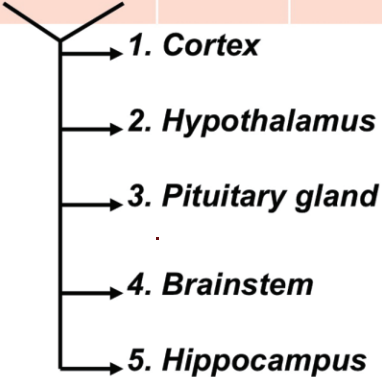
Cell types	ADR1	ADR2	Brain regions and pathologies involved	Receptor activated	Signalling pathways activated	Outcome on functions
Microglia 	??	??	Physiological conditions <i>Hypothalamus/ Brainstem</i>	ADR1	AMPK	↑Food intake ↓Energy expenditure
Astrocyte 	✓	✓	<i>Cortex</i>	ADR2	Unknown	Controls cellular and behavioural actions of alcohol
Neurons 	✓✓✓	✓	<i>Pituitary gland</i>	ADR1	Unknown	May be involved in regulation of somatotrophins
			Pathological conditions <i>Ischaemic Stroke</i>	ADR1 Unknown	↑AMPK/P-38 MAPK ↑enos ↑AMPK	Cell death Protective Protective
			<i>Kainate - induced neurotoxicity</i>	ADR1		
			<i>Epilepsy</i>	??	??	Protective
			<i>Alzheimer's diseases</i>	??	??	Pro- inflammatory

Figure 5

The CNS distribution of adiponectin receptors and their roles in adiponectin-mediated signalling in normal and disease states. Table A indicates the different cells of the CNS and their AdipoR receptor expression patterns. Expression of AdipoRs in isolated microglia is yet to be ascertained. The neuronal expression of both AdipoR1 and AdipoR2 has been demonstrated in different brain regions as indicated in the figure. Table B indicates the roles of adiponectin-mediated signalling.

et al., 2007). In the pituitary gland, adiponectin seems to assume a putative role in the autocrine/paracrine control and regulation of the release of somatotrophs and gonadotrophs (Qi *et al.*, 2004; Malagon *et al.*, 2006; Pan *et al.*, 2006; Psilopanagiotti *et al.*, 2009).

There is substantial evidence to suggest that AdipoRs are expressed widely in the brain. Their expressions have been detected in regions of the mouse hypothalamus (area postrema and paraventricular nuclei), brainstem and endothelial cells, as well as in whole brain and pituitary extracts (Yamauchi *et al.*, 2003; Fry *et al.*, 2006; Spranger *et al.*, 2006; Hoyda *et al.*, 2007; Neumeier *et al.*, 2007; Rodriguez-Pacheco *et al.*, 2007; Wilkinson *et al.*, 2007) (Figures 4 and 5). We recently showed that mouse cortical neurons also express both AdipoR1 and AdipoR2, with AdipoR1 expression being more pronounced than AdipoR2 (Thundyil *et al.*, 2010). Our results

were consistent with those of another study that mapped the distribution of AdipoR2 mRNA to various cortical and sub-cortical regions of the rat brain (Repunte-Canonigo *et al.*, 2010). In addition to the expression in the murine nervous system, moderate to strong expressions of AdipoR1 and AdipoR2 have been shown in the pars distalis area of the pituitary gland, and in humans, AdipoR1 expression was localized to neurons in the lateral hypothalamic area and nucleus basalis of Meynert (Psilopanagiotti *et al.*, 2009). Although there is still some ambiguity regarding the bioactive oligomer of adiponectin in the brain, growing evidence suggests that LMW multimers, particularly trimers, may be the active forms. LMW multimers have been detected in the CSF of both humans and mice (Escobar-Morreale *et al.*, 2006; Aroda *et al.*, 2008; Glintborg *et al.*, 2008). Hence, it appears that while adiponectin's peripheral effects are mediated

predominantly by HMW forms, LMW multimers may be responsible for its central effects.

Contrary to its counterpart leptin, the role of adiponectin in the brain has not yet been well elucidated (Schulz *et al.*, 2010). However, the discovery of leptin in the brain and its precise roles in food intake and regulating energy expenditure prompted more researchers to explore the potential cross-talk between brain and adipose tissue. In addition, the inverse co-relations of plasma leptin and adiponectin levels with that of body weight led to hypotheses that adiponectin could exert a central control of energy homeostasis. This speculation led to various studies that suggested that adiponectin does indeed exert central actions, especially as regards regulating energy homeostasis. One such study has showed that an i.c.v. injection of adiponectin increased energy expenditure, without any effect on food intake (Qi *et al.*, 2004). Contrary to this result, other publications showed that adiponectin reduced food intake (Shklyav *et al.*, 2003; Coope *et al.*, 2008) via AdipoR1-mediated activation of IRS1/2, ERK, Akt, FOXO1, JAK2 and STAT3. Peripheral administration of adiponectin was shown to decrease body weight by enhancing fatty acid oxidation, without any apparent change in food intake (Berg *et al.*, 2001; Yamauchi *et al.*, 2001; Tomas *et al.*, 2002). However, Kubota *et al.* (2007) reported that peripherally administered adiponectin rather exerted an orexigenic effect and decreased energy expenditure. These findings strongly suggest that this adipose-derived hormone plays a vital role in the physiological neuromodulation of food intake, energy expenditure and possibly even neuroendocrine and autonomic functions in the brain. While there is now considerable evidence for the presence of adiponectin and its receptors in the brain, the precise molecular and signalling mechanisms activated during the neural regulation of food intake and energy homeostasis still remain unclear. Moreover, given the broad distribution of AdipoRs in different regions of the brain, the role of adiponectin may not be limited to regulation of energy homeostasis, but this important adipokine could perhaps also be a major contributor to 'adipocyte-brain cross-talk'.

Although its anti-inflammatory properties have been questioned by some (Garaulet *et al.*, 2007; Fantuzzi, 2008), the anti-diabetic and anti-atherosclerotic effects of adiponectin in various *in vitro* and *in vivo* studies have prompted researchers to explore its use, or the targeting of its receptors, for therapy in these disease conditions (Iwaki *et al.*, 2003; Shimada *et al.*, 2004; Axelsson *et al.*, 2005; Mendez-Sanchez *et al.*, 2006). Another facet of adiponectin actions that has attracted attention in recent years is its effect on apoptosis. Physiological apoptosis is well known to regulate many pivotal biological processes like organ development and differentiation. However, dysfunction or dysregulation of apoptosis under pathological conditions like cancer, ischaemia-reperfusion injury and cardiovascular and cerebrovascular conditions is detrimental (Kockx and Herman, 2000; Ghavami *et al.*, 2009; Guo and Wang, 2010). A few studies have reported anti-apoptotic effects of adiponectin (Lin *et al.*, 2004; Masaki *et al.*, 2004; Rakatzi *et al.*, 2004; Shibata *et al.*, 2005; 2007), whereas many others have found adiponectin to promote apoptosis under both *in vitro* and *in vivo* conditions (Yokota *et al.*, 2000; Brakenhielm *et al.*, 2004; Kang *et al.*, 2005; Dieudonne *et al.*, 2006; Wang *et al.*, 2006b;

Cong *et al.*, 2007; Ishikawa *et al.*, 2007; Korner *et al.*, 2007; Akifusa *et al.*, 2008; Dos Santos *et al.*, 2008; Kawai *et al.*, 2008; Konturek *et al.*, 2008; Thundyil *et al.*, 2010). Hence, caution must be exercised in characterizing the role of adiponectin on apoptosis in different organ systems. This may be particularly important in the case of the brain, and since adiponectin and its receptors have been shown to be present in the brain, its role in mediating apoptosis in brain cells is of considerable interest for physiology and especially in disease.

Adiponectin in CNS pathologies

A few studies have investigated the role of adiponectin in cerebrovascular diseases. The objectives of these studies ranged from establishing whether hypoadiponectinaemia is a predictor of cerebrovascular disease to ascertaining if adiponectin has a neuroprotective function during stroke. The results from these studies have so far been conflicting with no clear correlation between serum adiponectin levels and stroke onset (Soderberg *et al.*, 2004; Chen *et al.*, 2005). Recently, Nishimura *et al.* (2008) reported that adiponectin has a cerebroprotective action mediated through the eNOS signalling pathway. They showed that adiponectin-KO mice developed larger brain infarction and exhibited greater neurological deficits after ischaemia-reperfusion compared with wild-type (WT) mice. Moreover, systemic administration of adenoviral vectors expressing full-length murine adiponectin significantly reduced cerebral infarct size in WT and adiponectin-KO mice (Nishimura *et al.*, 2008). However, that study did not investigate the effect of gAD, which has a higher binding affinity towards AdipoR1. We recently published that mouse cortical neurons express AdipoR1 and AdipoR2, and that the levels of AdipoR1 increase in response to ischaemic conditions *in vitro* or *in vivo* (Thundyil *et al.*, 2010). Furthermore, we observed that neurons treated with either globular or trimeric adiponectin exhibited increased vulnerability to oxygen and glucose deprivation, which was associated with increased activation of a pro-apoptotic signalling cascade involving p38-MAPK and AMPK. We propose an underlying mechanism initiated by the complex pathophysiological processes that disrupt the BBB in stroke (Arumugam *et al.*, 2005), whereby the microvasculature assumes an inflammatory phenotype characterized by leukocyte-endothelial cell adhesion, leukocyte capillary plugging, endothelial barrier dysfunction and activation of resident leukocytes including neutrophils (Ishikawa *et al.*, 2005). Although the brain is normally isolated from the immune system by the BBB, activated leukocytes can readily infiltrate the brain once the BBB is disrupted during ischaemic stroke. This disruption could also facilitate the penetration of full-length adiponectin into injured brain tissues, which could then be further cleaved into gAD by leukocyte elastase at the site of injury (Waki *et al.*, 2005).

The pathophysiological importance of adiponectin cleavage by leukocyte elastase *in vivo* and especially during stroke still remains unclear. However, various studies in different cell types have reported a pro-inflammatory role for gAD (Haugen and Drevon, 2007; Hattori *et al.*, 2008; Tomizawa *et al.*, 2008). These studies showed gAD to be a potent stimulator of NF- κ B and other pro-inflammatory genes, which could be

detrimental during an inflammatory pathology such as ischaemic stroke. Since physiological levels of adiponectin in both human and mouse serum have been reported to range from 2 to 17 $\mu\text{g}\cdot\text{mL}^{-1}$, and that they are elevated during inflammatory disease conditions such as preeclampsia and arthritis (Senolt *et al.*, 2006; Toussirost *et al.*, 2007; Fantuzzi, 2008; Brochu-Gaudreau *et al.*, 2010), the concentration of adiponectin used in our study (10 $\mu\text{g}\cdot\text{mL}^{-1}$) was well within the physiological range.

A recent study by Une *et al.* (2010) demonstrated the presence of adiponectin in mild cognitive impairment and Alzheimer's disease (AD) patients. They analysed adiponectin in plasma and CSF from cognitively normal controls (NC), subjects with mild cognitive impairment (MCI) and patients with AD. They found that plasma adiponectin was significantly higher in MCI and AD compared with NC, whereas CSF adiponectin was significantly higher in MCI compared to NC. These higher adiponectin levels in plasma and CSF in MCI and AD patients is intriguing and could suggest that this molecule plays a role in the onset of AD. The authors also suggested that the weight loss and lower body mass index seen in elderly AD patients, and the correspondingly high level of adiponectin during the same period, could point to a role for adiponectin during the pro-dromal state of AD by altering the CNS control of energy homeostasis and body weight (Aziz *et al.*, 2008; Luchsinger, 2008; Luchsinger and Gustafson, 2009a,b) (Figure 5).

From observations obtained so far regarding its proapoptotic role, it could be that adiponectin promotes neuronal apoptosis even in conditions such as stroke and AD. Furthermore, an epidemiological study by Hietaharju *et al.* (2010) showed that multiple sclerosis (MS) patients had elevated adiponectin levels in CSF that could be related to immune reactions responsible for inciting MS relapses. In another study published by Jeon *et al.* (2009), they showed that adiponectin treatment protected hippocampal neurons against kainic acid (KA)-induced neurotoxicity and thus had neuroprotective effects in an animal model of seizures. The decreased serum adiponectin levels and increased hippocampal AdipoR1 expression levels in KA-treated mice were shown to be protected by adiponectin pretreatment. The up-regulation of hippocampal VEGF, eNOS and NF- κ B levels in the seizure mice were reduced following adiponectin treatment. Although that study shows a beneficial effect of adiponectin and is in stark contrast to our studies, the up-regulation of AdipoR1 in this model, too, suggests the possibility that adiponectin and its receptors may not be mere spectators in neuronal regulation during physiological and pathological processes, but they may have a larger and more definitive role in the functioning and maintenance of the brain.

Although it is now established that that adiponectin is present in the CSF, further investigations will be needed to clarify where CSF adiponectin is produced and how it circulates in the brain. The issue of adiponectin transport from the periphery into the CNS and how this occurs is still a matter of contention (Qi *et al.*, 2004; Pan *et al.*, 2006; Spranger *et al.*, 2006). One plausible explanation is that adiponectin enters the brain via receptor-mediated transcytosis (Kos *et al.*, 2007). Another potential site of entry is via the circumventricular organs (CVOs) (Ahima *et al.*, 2006; Fry *et al.*, 2006). However,

this view has been challenged because the low surface area of the CVOs cannot account for the levels of adiponectin detectable in CSF (Begley, 1994). Also, an intrathecal synthesis of adiponectin is possible because the level of adiponectin in CSF does not appear to correlate with the level in plasma (Hietaharju *et al.*, 2010). This capacity for endogenous production of adiponectin within the CNS has been shown in rodents and chicken (Maddineni *et al.*, 2005; Wilkinson *et al.*, 2007). Hence, more work is required to clarify whether adiponectin is synthesized intrathecally or whether it flows into the intrathecal space from plasma passing through BBB. Second, it will be important to define the role(s) of AdipoR-mediated signalling in the brain in normal physiology and in disease states. It appears that the confounding findings have arisen at least partly from the fact that adiponectin circulates as different oligomers. Although, recently developed ELISAs are more sensitive for detecting adiponectin in the CSF, their large-scale use has been curtailed primarily due to the high costs involved. Furthermore, the complications arising from the measurement of different adiponectin oligomers versus total adiponectin, together with its pleiotropic roles, has limited the usefulness of adiponectin as a biomarker of human diseases. Hence, the prospect of devising a co-relation of adiponectin between peripheral and CNS is still premature and requires much deliberation.

Concluding remarks

It has become evident in recent years that AdipoR expression and functionality extends to the CNS. Neurons express different subsets of AdipoRs, and it is not surprising, therefore, that AdipoRs play important roles in neurodegenerative processes. AdipoRs appear to be intimately involved in several neurodegenerative disorders including AD, MS, epilepsy and ischaemic stroke, which implies a broad functionality of these receptors in neurological disease. We predict that AdipoRs may emerge as a target for intervention in the relentless efforts to find new therapies for neurodegenerative disorders.

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Conflict of Interest

On behalf of all the named authors, I declare that there is no conflict of interest.

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