Available online at www.sciencedirect.com
ScienceDirect
Journal of Nutritional Biochemistry 20 (2009) 831 – 839
Journal of Nutritional Biochemistry

REVIEWS: CURRENT TOPICS

Adiponectin and energy homeostasis: consensus and controversy

Sami Dridi[a,*], Mohammed Taouis[b]

[a]Department of Ophthalmology & Visual Sciences, Ocular Angiogenesis Research Laboratory, University of Kentucky, Lexington, KY 40506, USA
[b]NOPA, UMR 1197, University Paris sud, bat 447, 91405 Orsay Cedex, France

Received 12 February 2009; received in revised form 27 April 2009; accepted 2 June 2009

Abstract

Adiponectin regulates energy homeostasis through the modulation of glucose and fatty acid metabolism in peripheral tissues. However, its central effect on energy balance remains unclear and controversial. Despite the disparate data, recent advances in our understanding of the signal transduction mechanisms used by adiponectin in the periphery and in the hypothalamus suggest that intracellular cross-talk between adiponectin, leptin and insulin may occur at several levels. The present review will summarize recent reports describing the peripheral and central effects of adiponectin and discuss progress concerning its molecular mechanisms. We will also particularly focus on apparent controversies and related mechanisms associated with the central effects of adiponectin on energy homeostasis.

Keywords: Adiponectin; Energy homeostasis; Periphery; Hypothalamus

1. Introduction

Obesity currently qualifies as a worldwide health epidemic [1,2]. It is associated with increased risk of diabetes, cardiovascular disease, obstructive sleep apnea, nonalcoholic fatty liver disease, malignancies, gall bladder disease, arthritis and various complications [1]. It also increases mortality [3]. Obesity is fundamentally a problem of energy balance in that self-evidently it can develop when energy intake exceeds energy expenditure, resulting in fat accumulation and excessive adipose tissue mass.

Adipose tissue, in addition to its function as the major storage depot for triglycerides, is an active endocrine tissue sensing metabolic signals and secreting hormones called adipocytokines/adipokines that affect whole-body energy homeostasis [4–6].

The list of adipocytokines keeps growing [7,8]. Adiponectin is the most abundant adipocytokine [9]. Unlike leptin and other adipose tissue-derived hormones which circulate at picograms or nanograms per milliliter, adiponectin circulates at very high levels (micrograms per milliliter). It circulates as several multimeric species, including a high-molecular-weight (HMW) form thought to be the most clinically relevant.

Adiponectin is decreased in obesity, is inversely related to glucose and insulin and increases during fasting [9]. Adiponectin deficiency results in insulin resistance, glucose intolerance, dyslipidemia and increased susceptibility to vascular injury and atherosclerosis [10–12]. Adiponectin treatment reverses these abnormalities [11,12].

Recently, adiponectin was shown to be present in the cerebrospinal fluid (CSF) of rodents and humans [12–14] and to enter the CSF from the circulation [15]. Additionally, adiponectin receptors (Adip-R1 and Adip-R2) were found to be abundantly expressed in the hypothalamus [14], the center

Abbreviations: ACC, acetyl-coenzyme-A carboxylase; ACO, Acyl-coenzyme A oxidase; Adip-R1/Adip-R2, adiponectin receptor 1/2; Acrp30, adipocyte complement related protein30; AGRP, agouti related protein; Akt, protein kinase B; AMPK, adenosine monophosphate-activated protein kinase; APPL1, Adaptor protein containing PH domain, PTB domain and leucine zipper motif; ARC, arcuate nucleus; CART, cocaine- and amphetamine-regulated transcript; CD36, cluster of differentiation 36; CSF, cerebrospinal fluid; CRH, corticotropin releasing hormone; FOXO1, forkhead transcription factor 1; GFP, green fluorescent protein; JAK2, janus kinase 2; LHA, lateral hypothalamus; MAPK, mitogen activated protein kinase; NPY, neuropeptide Y; PA, area postrema; POMC, pro-opiomelanocortin; PPARα, peroxisome proliferator-activated receptor α; PVN, paraventricular nucleus; STAT3, signal transducer and activator of transcription 3; TRH, thyrotropin releasing hormone; VMH, ventromedial nucleus of the hypothalamus.

* Corresponding author. Tel.: +1 859 257 3902; fax: +1 859 257 2317.
E-mail address: sami.dridi@uky.edu (S. Dridi).

0955-2863/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.jnutbio.2009.06.003

of hunger and satiety [16]. Furthermore, we recently showed that Adip-R1 and Adip-R2 are present in proopiomelanocortin (POMC) and neuropeptide Y (NPY) neurons in the arcuate nucleus (ARC) [17], suggesting a potential role for adiponectin in the central regulation of energy intake and expenditure. However, various studies investigating the effect of adiponectin on energy balance in rodents have yielded conflicting data. They showed either a lack of an effect on food intake [18] or reduced [19] or increased [15] food intake. Similarly, adiponectin has been shown to either increase [18] or reduce [15] energy expenditure. This review discusses these disparate data and presents possible alternative and/or complementary explanations.

1.1. Adiponectin and its receptors

Adiponectin, also named gelatin-binding protein 28, adipocyte complement related protein 30 (Acrp30), adipose most abundant gene transcript 1 (apM1), or adipoQ [20–23] is a 30-kDa adipocytokine hormone of 244 amino acids mainly secreted from the adipose tissue in mammals. Structurally, adiponectin belongs to the complement 1q family. Adiponectin monomer consists of an *N*-terminal collagenous domain and a C-terminal globular domain [20] that generates low-molecular-weight dimers or trimers, medium (hexamers) and high-molecular-weight complexes (HMW, dodecamers and 18 mers) in mammalian plasma [24]. The three multimeric forms are found in the circulation, associated with several serum proteins [25,26]. The globular fragment was also detected in the trimeric form in human and mouse plasmas and was shown to be generated by proteolytic cleavage [27]. Adding to this complexity, a family of seven proteins homologous to adiponectin has been identified [28] that might exhibit partial functional redundancy with adiponectin. It has not yet been clearly established which adiponectin form(s) is (are) biologically active. Based on clinical observations, the current consensus is that the HMW form is the most clinically relevant. Interestingly, a mutant adiponectin with a substitution of Cys by Ser at codon 39 (C39S), which formed a trimer and readily underwent proteolytic cleavage, showed much more potent bioactivity compared with the HMW adiponectin [29]. In vivo, globular adiponectin protected ob/ob mice from diabetes and apolipoprotein E-deficient mice from atherosclerosis [30], indicating that globular adiponectin is also efficient as the full-length. Overall, not only the total concentrations but also the multimer forms distribution should be considered when interpreting plasma adiponectin levels in normal and pathophysiological conditions.

The signaling mechanisms responsible for the action of adiponectin are not completely understood. Two adiponectin receptors, Adipo-R1 and Adipo-R2, have been identified [31]. These receptors contain seven transmembrane domains and are structurally and functionally distinct from G-protein-coupled receptors (GPCR). Indeed, unlike GPCRs, the amino (*N*)-termini of Adipo-R1 and Adipo-R2 are intracellular, and the C termini are extracellular. Adipo-R1 and Adipo-R2 may form both homo- and heteromultimers. Scatchard plot analysis revealed that Adipo-R1 is a receptor for globular adiponectin, whereas Adipo-R2 is a receptor for full-length adiponectin [31]. Additionally, suppression of Adipo-R1 or Adipo-R2 with small interfering RNA (siRNA) reduced the increase in fatty acid oxidation by globular or full-length adiponectin, respectively.

Other investigators have demonstrated binding of adiponectin to T-cadherin but not to Adipo-R1 and R2 and have proposed that T-cadherin affects the bioavailability of adiponectin [32]. Most recently, an adaptor protein containing PH domain, PTB domain and leucine zipper motif (APPL1) was shown to interact with adiponectin receptors in mammalian cells and the interaction is stimulated by adiponectin [33]. Overexpression of APPL1 increases, whereas suppression of APPL1 reduces, adiponectin signaling and adiponectin-mediated downstream events [33].

1.2. Mechanisms of adiponectin function in peripheral tissues

It is well established that adiponectin plays a key role in the control of energy homeostasis through the regulation of glucose and fatty acid metabolism in peripheral tissues such as muscle and liver [34]. Indeed, in skeletal muscle, adiponectin up-regulated cluster of differentiation 36 (CD36, molecule involved in fatty acid transport), Acyl-coenzyme A oxidase (ACO, molecule involved in fatty acid combustion) and uncoupling protein 2 (UCP2, molecules involved in energy dissipation) leading to enhanced lipid catabolism and reduced triglyceride content and thereby improved insulin sensitivity [35]. Most of the adiponectin effects in muscle are mediated by globular adiponectin, since globular adiponectin has higher affinity for Adip-R1, and Adip-R1 is the most abundantly expressed adiponectin receptor in skeletal muscle [31]. These effects of adiponectin are mediated through peroxisome proliferator activated receptor (PPAR)α (transcription factor that regulate CD36, ACO and UCP2). Indeed, adiponectin treatment increased PPARα gene expression in vivo and in vitro by using C2C12 myocytes [30,35]. Furthermore, both globular and full-length adiponectin stimulated β-oxidation and glucose uptake in skeletal muscle via phosphorylation and activation of adenosine monophosphate-activated protein kinase (AMPK) during a short-period treatment (<6 h) [36]. In parallel with its activation of AMPK, adiponectin stimulated phosphorylation of acetyl-coenzyme-A carboxylase (ACC), fatty acid combustion, glucose uptake and lactate production in myocytes [36]. A dominant negative mutant of AMPK inhibited these effects, indicating that stimulation of glucose utilization and fatty-acid oxidation by adiponectin occurs, at least partly, through activation of AMPK [37]. The effects of adiponectin are also mediated through p38 mitogen activated protein kinase (MAPK) activation [31]. Yoon and coworkers [38] showed that adiponectin increases fatty acid oxidation in skeletal muscle by sequential activation of AMPK, p38 MAPK

and PPARα. It has been shown that p38 MAPK phosphorylate and activate PPAR and its co-activator peroxisome proliferator-activated receptor gamma coactivator 1α [39].

Skeletal muscle has also a relatively high expression of APPL1. Overexpression of APPL1 in C2C12 myocytes significantly increases phophorylation levels of AMPK, p38 MAPK, ACC and fatty acid oxidation. On the contrary, suppression of APPL1 attenuated these effects, indicating the key role of APPL1 in mediating adiponectin-regulated lipid metabolism in skeletal muscle [33]. Overexpression of APPL1 enhances also GLUT4 membrane translocation in L6 cells [33]. Adiponectin stimulated the interaction between APPL1 and Rab5, and the disruption of APPL1-Rab5 interaction blocked adiponectin-mediated translocation of GLUT4 to the membrane [33]. Overexpression of a dominant negative form of Rab5 inhibited the adiponectin-stimulated p38 MAPK activation, suggesting that the activation of p38 MAPK by adiponectin is partly through APPL1-Rab5 association [33].

In liver, adiponectin decreased gluconeogenesis by attenuating the expression levels of phosphoenolpyruvate carboxykinase and glucose 6-phosphatase, leading to reduced levels of glucose [36]. The acute glucose-lowering effects of adiponectin is mediated via activation of AMPK and transducer of regulated CREB activity-2, and only the full-length adiponectin activates AMPK and increases phosphorylation of ACC and fatty acid oxidation in liver. Adiponectin activated also PPARα, thereby stimulating fatty acid oxidation and decreasing TG content in the liver [9]. Overexpression of Adip-R1–activated AMPK in hepatocytes reduced hepatic glucose production and increased fatty acid oxidation; however, overexpression of Adip-R2 activated PPARα pathway leading to increased fatty acid oxidation and decreased inflammation and oxidative stress, indicating that hepatic Adip-R1 and Adip-R2 differ in their signaling pathways [40]. Moreover, overexpression of APPL1 in mouse hepatocytes activated p38 MAPK and adiponectin treatment could further enhanced this effect, suggesting that APPL1 plays a crucial role in adiponectin signaling in liver [33].

In adipocytes, AMPK was reported to be involved in glucose uptake stimulated by the globular domain of adiponectin [41]. Overexpression of adiponectin in 3T3-L1 adipocytes promoted adipocyte differentiation, increased lipid content, and enhanced insulin sensitivity [42]. Adip-R1 knockout mice have increased total body fat mass which is due to decreased energy expenditure [43].

1.3. Role and mechanism of adiponectin in central energy homeostasis

1.3.1. Adiponectin and its receptors in the central nervous system

The hypothalamus is the major regulatory center for food intake and whole body energy homeostasis. Specific hypothalamic nuclei have been described as satiety or hunger centers such as the ventromedial hypothalamus or the lateral hypothalamus (LHA), respectively [44]. In addition, the characterization of feeding-related hypothalamic neuropeptides and their regulation has furthered our knowledge about the key role of the hypothalamus in the control of energy balance.

It is likely that adiponectin contributes to the cross-talk between peripheral tissues and the brain and, specifically, in brain energy sensing processes. Indeed, adiponectin plays pleiotropic functions in several peripheral tissues through different mechanisms (see previous part) and may be a key messenger to central energy homeostasis.

It has been shown that CSF contains lower levels of adiponectin compared with serum in rodents [18,45], and this level increases after intravenous injection of adiponectin [18] confirming its ability to enter the brain from the circulation. In human, these data are controversial. Indeed, Spranger et al. [46] and Pan et al. [47] reported that adiponectin does not cross the blood-brain barrier (BBB); however, Kos et al. [14] detected a low level of adiponectin in CSF with the same ratio that has been noted in rats. These results suggest a species-specific variation of adiponectin in CSF. In addition, the discrepancies between these studies may be due to the sensitivity of method used to detect adiponectin in CSF.

The forms of adiponectin found in the CSF of the wild-type mice are restricted to the trimeric and hexameric forms and not the HMW. In adiponectin knockout mice, after intravenous administration of full-length adiponectin, all three forms (trimers, hexamers and HMW multimers) were found in the serum, whereas only trimers and hexamers, and not HMW multimers, were found in the CSF [15]. These data indicate that the distribution of the multimeric forms of adiponectin in the CSF differs from that in the serum, and due to its large size (>500 KDa), the HMW is unlikely to pass through the BBB. It is likely that adiponectin is transported from blood to CSF by receptor-mediated transcytosis. It is also possible that adiponectin enter the brain via the circumventricular organs such as the area postrema (PA) [48]. Adiponectin may be also locally expressed in the brain as it has been shown in chicken and mice [49,50].

Both Adip-R1 and Adip-R2 are located throughout the central nervous system, notably in regions of the hypothalamus and brainstem important in controlling autonomic function and feeding behavior, including the PA [48], ARC [15] and the paraventricular nucleus (PVN) [50]. Immunohistochemical analysis revealed colocalization of Adip-R1 and the leptin receptor in the ARC of mice [15]. Recently, by using homozygous transgenic POMC- or NPY-green fluorescent protein (GFP) mice, we showed that Adip-R1 and Adip-R2 are present in POMC and NPY neurons in the ARC (Fig. 1) [17]. Taken together, these data reinforced a potential role for adiponectin and its receptors in the central regulation of energy intake and expenditure. Furthermore, in wild-type mice, serum and CSF adiponectin levels and Adip-

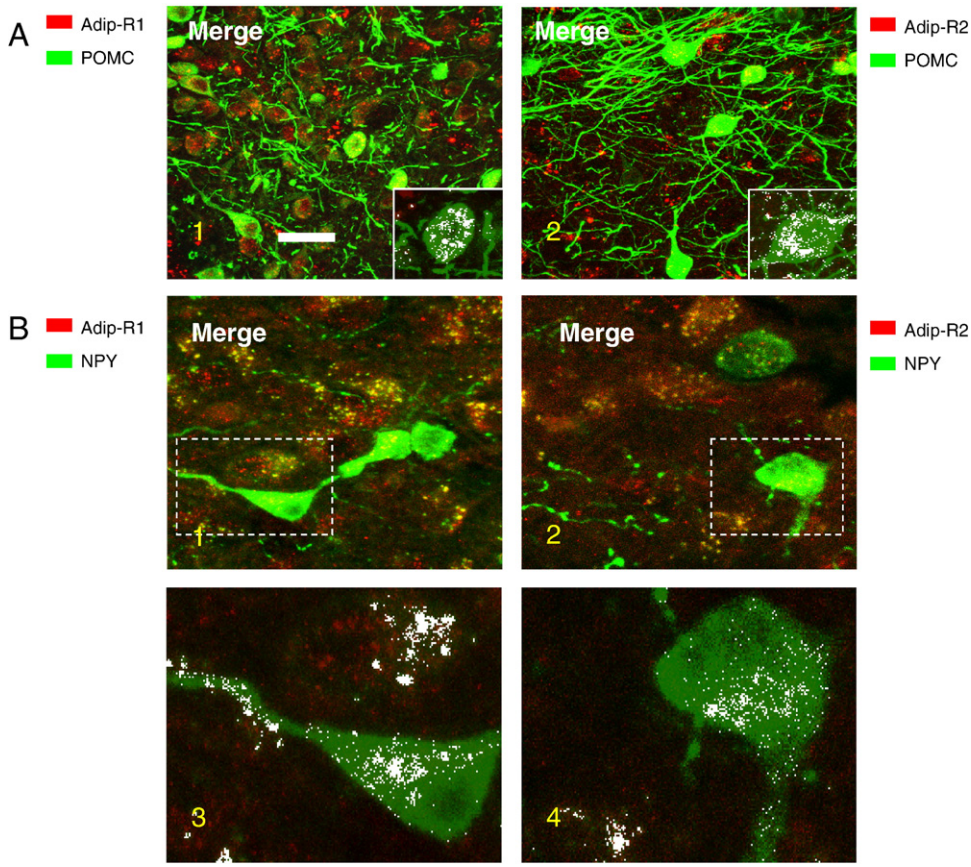

Fig. 1. Fluorescent immunohistochemical detection of adip-R1 or Adip-R2 in the ARC of POMC (A)- and NPY-GFP (B) mice by confocal laser scanning microscopy. Colocalization of Adip-R1 and Adip-R2 with POMC or NPY appears as yellow on the projection of 1-μm-thick optical section (A1 and 2 or B1 and 2), or as white pixels in detailed optical section (insets A1 and 2 or B3 and 4). For more details, see Ref. [17].

R1 expression in the ARC increased under fasting conditions and decreased after refeeding, whereas Adip-R2 remained unchanged. These data indicate that central adiponectin system is sensitive to energy status and that central Adip-R1 and Adip-R2 most likely involve different signaling pathways. In addition, a previous study has shown the expression of Adip-R1 and Adip-R2 in the human endothelial cells of the choroid plexus [46], which is relevant to the controlled entry of proteins through the BBB. Moreover, adiponectin protects human neuroblastoma SH-SY5Y cells from apoptosis induced by the mitochondrial complex I inhibitor, 1-methyl-4-phenylpyridinium, indicating a direct action of adiponectin on neurons [51].

1.3.2. Does adiponectin affects energy intake and expenditure?

Whether adiponectin affects energy intake and expenditure is controversial. Peripheral adiponectin administration has been reported to reduce body weight by enhancing fatty acid oxidation and energy expenditure [35,37,52], without apparent effects on food intake. However, sustained peripheral expression of transgene adiponectin through a viral vector reduces food intake and body weight, concomitantly with improved insulin sensitivity and decreased lipid levels in diet-induced obese rats [19].

Recently, Coope et al. [53] demonstrated that intracerebroventricular (ICV) injection of recombinant rat adiponectin promoted anorexigenic condition in rats with a 40% reduction in food intake and activates signal transduction through the classical insulin and leptin signaling pathways. Indeed adiponectin increases phosphorylation levels of insulin receptor substrate (IRS) 1/2, AKt/PKB, extracellular signal-regulated kinase (ERK), forkhead transcription factor 1, janus kinase 2 (JAK2) and signal transducer and activator of transcription 3 (STAT3). These actions were mediated by Adip-R1 and not Adip-R2. As in peripheral tissues and in isolated cell systems, adiponectin induces also the association of both receptors with APPL1 in the hypothalamus indicating a key role of APPL1 in mediating the central anorexigenic effect of adiponectin. The activation of the canonical insulin and leptin signaling pathways by adiponectin suggest a cross-talk between these hormones in the hypothalamus (Fig. 2). Similar results concerning the activation of the insulin signaling pathway were observed in the peripheral tissues [54]; however, the opposite effect on STAT3 was observed in DU145 and HepG2 cells [55].

In another study performed by Qi et al. [18], ICV administration of recombinant adiponectin decreases body weight and fat by increasing energy expenditure without

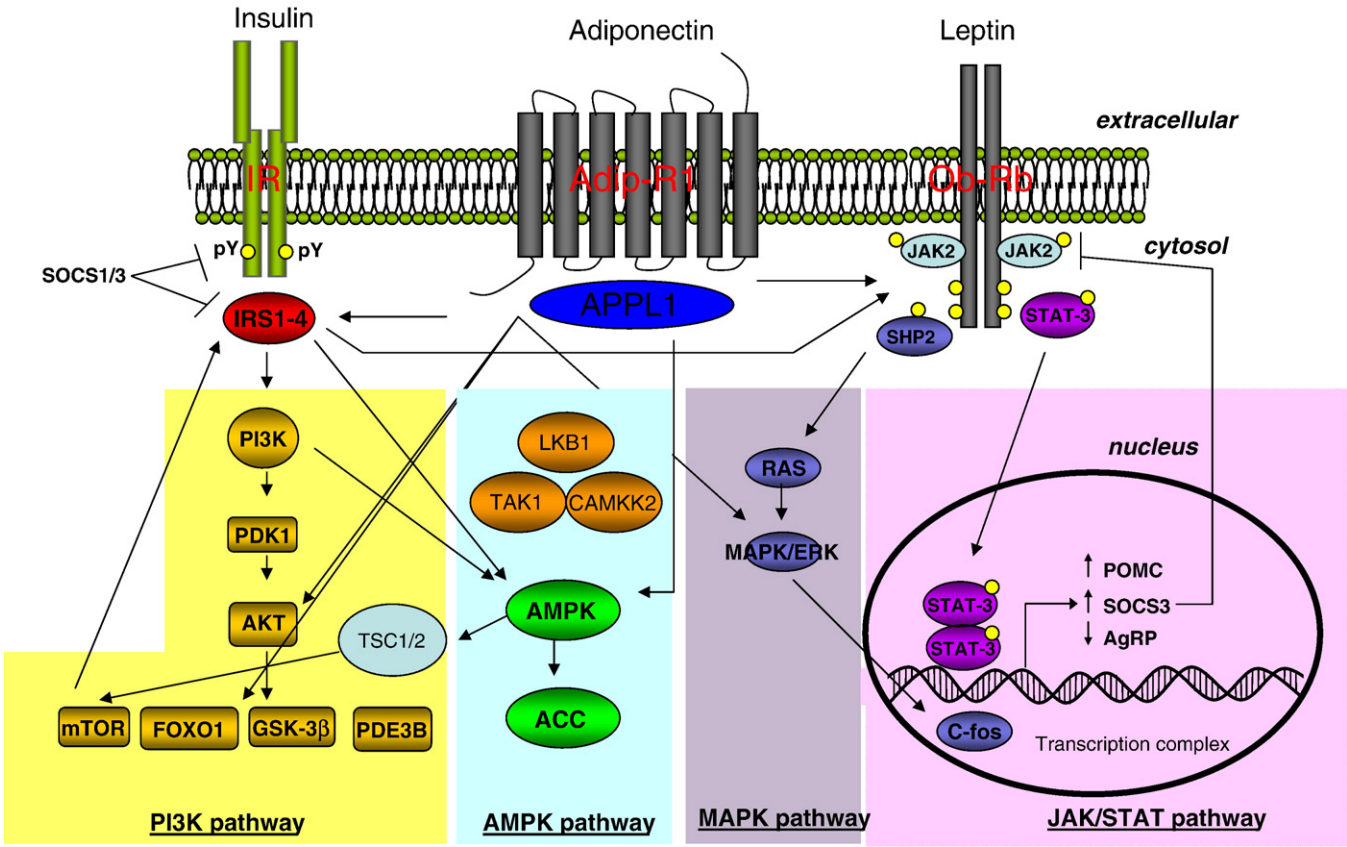

Fig. 2. Possible cross-talk between adiponectin, leptin and insulin in the hypothalamus. Insulin binds to its receptor and activates an intrinsic tyrosine kinase, leading to phosphorylation of the intracellular domain of the insulin receptor. IRS proteins bind to the phosphorylated residues on the IR, become activated by tyrosine phosphorylation and, in turn, initiate downstream signals such as the activation of the Ras-Raf-MAPK cascade or activation of PI3K pathway including PDK1, GSK3β and PKB/Akt. Leptin binds to its receptor, which dimerizes and through the activation of JAK2, phosphorylates STAT3 that translocate to the nucleus and modulate transcription of several neuropeptide genes including NPY, SOCS3 and POMC. Leptin also acts through components of the insulin signaling cascade since JAK2 phosphorylates IRS proteins and activates PI3K and MAPK signaling pathways. MAPK pathway is also activated by leptin via Ob-Rb-mediated recruitment of SHP2. Adiponectin binds to the extracellular C-terminus of Adip-R1 and recruits APPL1 to the intracellular N-terminus of Adip-R1 and activates leptin/insulin signaling pathways. It is also possible that activation of the AMPK pathway by adiponectin lead to the activation of TSC1/2 signaling that reduce mTOR/S6K-mdiated serine phosphorylation of IRS proteins. This results in the enhancement of IRS tyrosine phosphorylation and insulin signaling. Adip-R, adiponectin receptor; AgRP, agouti-related peptide; Akt, protein kinase B; CAMKK2, Ca(2+)/calmodulin-dependent protein kinase kinases 2; *FOXO*, forkhead transcription factor O; GSK3, glycogen synthase kinase 3; IR, insulin receptor; JAK, janus kinase; LKB, serine/threonine kinase 11, MAPK, mitogen activated protein kinase; mTOR, mammalian target of rapamycin; Ob-Rb, leptin receptor; PDE3B, phosphodiesterase 3B; PDK, protein-dependent kinase; PI3K, phosphatidylinositol 3 kinase; Ras, Ras small GTPase, SHP2, SH2-domain-containing cytoplasmic tyrosine phosphatase; SOCS, suppressor of cytokine signaling; STAT, signal transducer and activator of transcription; TAK, TGFβ activated kinase; TSC, tuberous sclerosis.

affecting food intake in mice. Furthermore, the full-length, the globular and a mutant (C39S) adiponectin were all effective, whereas the collagenous tail was not. In contrast to leptin, adiponectin did not affect the mRNA expression of both orexigenic [NPY/agouti related protein (AGRP)] and anorexigenic [cocaine- and amphetamine-regulated transcript (CART)/POMC] hypothalamic neuropeptides [18]. However, both hormones increased corticotropin-releasing hormone (CRH) mRNA abundance in the PVN (Fig. 3). Additionally, adiponectin controls the excitability of specific groups of neurons in the parvocellular region of the PVN, depolarizing neuroendocrine CRH and pre-autonomic thyrotropin releasing hormone (TRH) neurons [56]. Further analyses revealed that adiponectin depolarized PA neurons expressing both receptors Adip-R1 and adip-R2, whereas AP neurons expressing only one receptor were insensitive indicating different roles of adiponectin and different pathways of its receptors in controlling excitability of AP neurons [56].

CRH is an endogenous anorectic and thermogenic agent [57]. CRH secretion modulates food intake in the absence of stress by exerting an inhibitory tone on appetite. Injection of CRH into the hypothalamic PVN decreases spontaneous feeding or fasting-induced feeding in mammals [58]. Chronic administration of CRH causes sustained anorexia and progressive body weight loss [59]. PVN TRH neurons also control feeding behavior, participate in the stress response and control metabolic function [60]. Although the differential effects of adiponectin and leptin on the common feeding-related hypothalamic neuropeptides (NPY/AGRP and

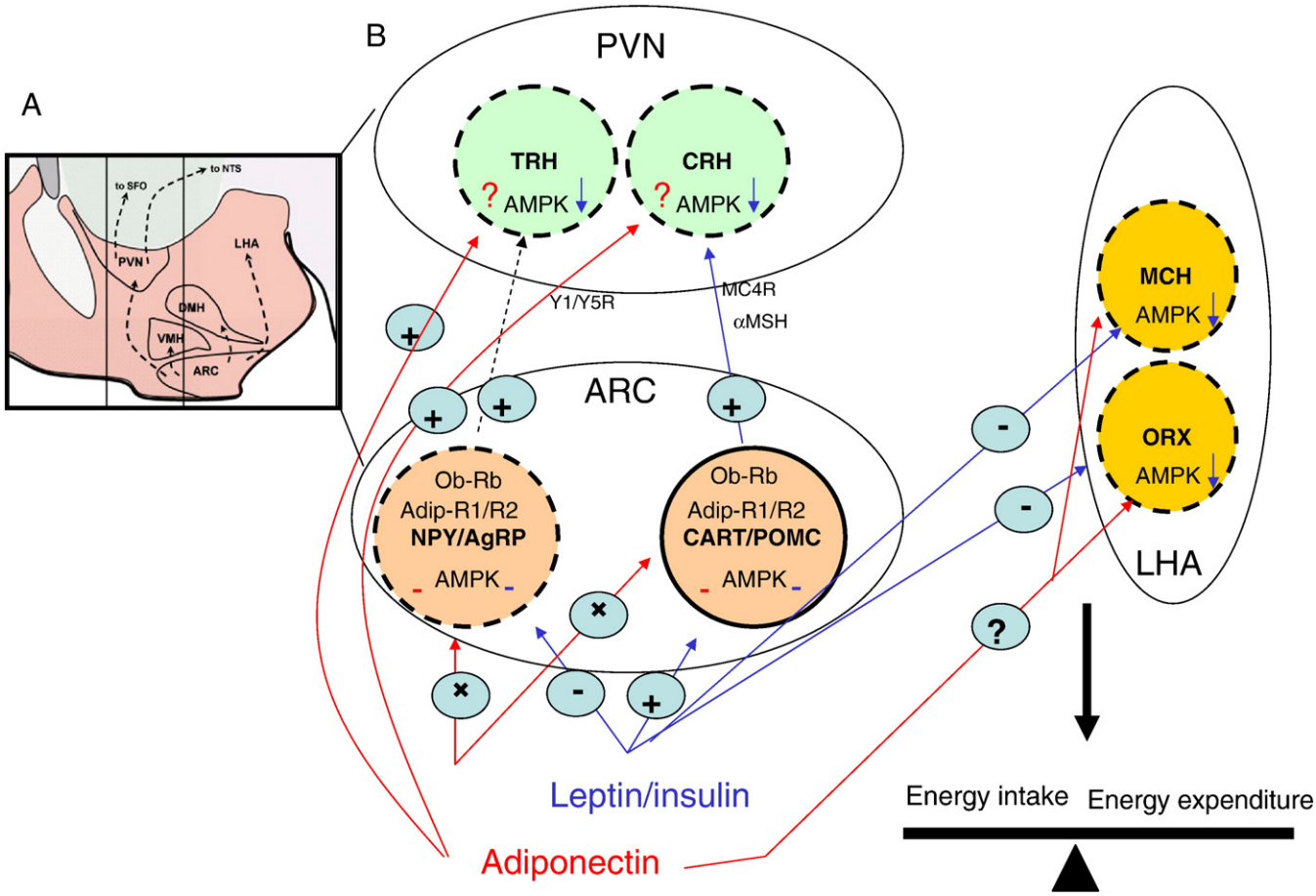

Fig. 3. Neuronal targets of adiponectin, leptin and insulin in the hypothalamus. (A) Sagittal view of the hypothalamus outlines the major anatomical projections of the hypothalamic circuitry involved in the control of energy balance (adapted from [16]). (B) Leptin acts directly in the ARC to increase POMC/CART and reduce NPY/AgRP through reduction of AMPK activity. Arcuate neurons project to the LHA and PVN, where leptin decreases feeding through CRH and ORX. In contrast to leptin, adiponectin increases AMPK activity in the ARC and thereby stimulates food intake and decreases energy expenditure without affecting the expression of both orexigenic (NPY/AgRP) and anorexigenic (POMC/CART) hypothalamic neuropeptides. However, both hormones increased CRH in the PVN. As for leptin, the melanocortin system is necessary for the action of adiponectin, since agouti ($A^{y/a}$) mice are not responsive to ICV injection of leptin and adiponectin. +, increase; −, decrease; x, no effect; ?, unknown. Adip-R, adiponectin receptor; αMSH, alpha melanocyte-stimulating hormone; AgRP, agouti related peptide; MCH, melanin concentration hormone; MC4R, melanocortin-4 receptor; NTS, nucleus tractus solitarius; Ob-Rb, leptin receptor; ORX, orexin; SFO, subfornical organ.

CART/POMC), these two adipokines may share a common pathway via CRH to control energy intake and expenditure.

Another possible central mechanism by which leptin and adiponectin control the energy homeostasis is the melanocortin system, since agouti ($A^{y/a}$) mice are not responsive to ICV administration of leptin and adiponectin [18]. It has been shown that adiponectin potentiate the thermogenic, lipolytic and glucose-lowering actions of leptin [18] reinforcing again a possible crosstalk between the two adipocytokines. However, there was no synergic effect of the two hormones on food intake reflecting a specific action of leptin on feeding behavior [18].

Interestingly, Kubota et al. [15] have shown that peripheral injection of adiponectin increased AMPK phosphorylation levels and its downstream target ACC in the hypothalamic ARC of mice via Adip-R1 but not Adip-R2, and this resulted in stimulation of food intake. Increased AMPK activity in the ARC has been shown to stimulate food intake [61,62].

To rule out the possibility that the action of adiponectin in peripheral organs (after the peripheral administration) participate in the activation of the hypothalamic AMPK, Kubota et al. [15] administered the hexameric form of adiponectin, the predominant form in the CSF, directly in the lateral cerebral ventricles. They showed that ICV administration of the hexameric form of adiponectin also increased food intake after refeeding, along with enhancing the AMPK and ACC phosphorylation levels. These effects were blunted following the ablation of Adip-R1 by siRNA or AMPK signaling by AMPK dominant negative [15]. These data demonstrate that adiponectin directly regulates food intake in the hypothalamus through its receptor Adip-R1 and the activation of AMPK and ACC (Fig. 4). Consistent with their electrophysiological data, Kubota et al. showed that

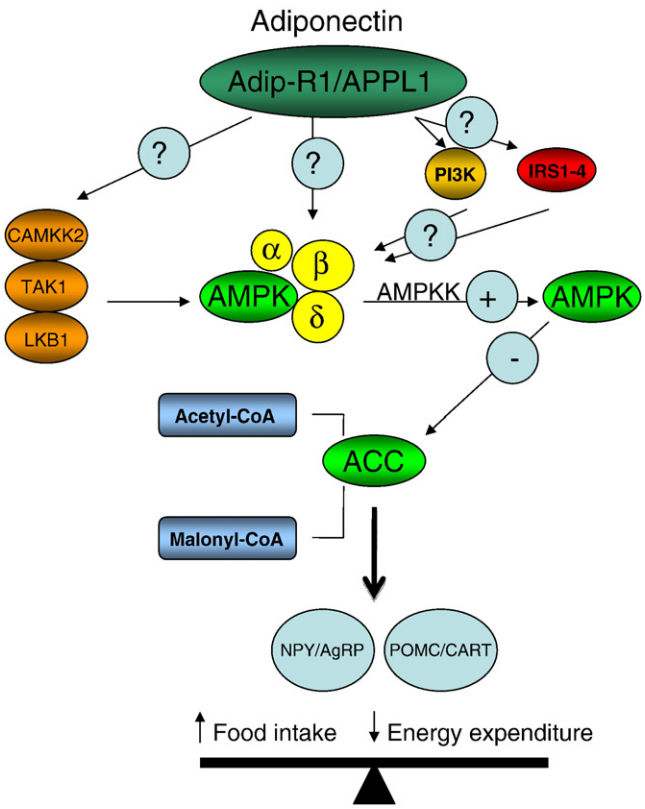

Fig. 4. Putative signaling pathway of adiponectin through hypothalamic AMPK to regulate the energy homeostasis. Kubota's study [15] showed that activation of AMPK by adiponectin/Adip-R1 is associated with increased phosphorylation of ACC, leading to stimulation of food intake and reduction of energy expenditure. These results suggest that the increase in ACC phosphorylation may decrease ACC activity and decrease in cellular malonyl-CoA levels. A decrease in malonyl-CoA levels would stimulate mitochondrial CPT-1 and fatty acid oxidation. The upstream signals of AMPK and the downstream pathways of ACC that are mediated by adiponectin to regulate energy intake and expenditure are still unclear. It is known that AMPK activity is regulated by changes in nucleotides and is covalently regulated by protein phosphatase 2C and at least three upstream kinases, LKB1, CAMKK2 and TAK1 [75], with CAMKK2 most likely dominant in the brain [76]. Further studies are warranted to clarify these pathways. Adip-R, adiponectin receptor; ADP, adenosine diphosphate; AgRP, agouti related peptide; ATP, adenosine triphosphate; CAMKK, Ca(2+)/calmodulin-dependent protein kinase kinases 2; CPT-1, carnitine palmitoyltransferase 1; ETC, electron transport chain; FAS, fatty acid synthase; LKB, serine/threonine kinase 11; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3 kinase; SCD, stearoyl CoA desaturase; SREBP, sterol regulatory element binding protein; TAK, TGFβ-activated kinase; TCA, tricarboxylic acid cycle.

hypothalamic AMPK and ACC phosphorylation levels were suppressed in adiponectin knockout mice after fasting. Concomitantly, daily food intake was reduced however both receptors Adip-R1 and Adip-R2 remained unchanged. Expression of NPY in the ARC was lower, and POMC was higher in adiponectin knockout mice after fasting compared with the wild-type mice. In addition, adiponectin knockout mice have much higher sensitivity to chronic low dose of leptin [15], and adiponectin administration reverses the suppressive effect of leptin on AMPK activity. These results suggest that adiponectin and leptin have an opposing central action to maintain the energy balance.

The decrease of adiponectin levels after fasting and its orexigenic effect led Kubota et al. [15] to consider adiponectin as a starvation signal, opposite to the satiety signal leptin. They hypothesized that during fasting conditions, adiponectin in the ARC increases, leading to activation of AMPK and thereby stimulated food intake. After food consumption, leptin signal in the ARC increases, consequently decreased the AMPK activity and thereby inhibited food intake. In obese condition, serum adiponectin levels are reduced in human and mice (ob/ob) which would be expected to reduce appetite, but these ob/ob mice are hyperphagic. This implies that in obesity, loss of appetite control occurs by the relatively stable or low levels of adiponectin in the CSF combined with hyperleptinemia and hypothalamic leptin resistance.

Similar to these disparate data on food intake, the central effect of adiponectin on energy expenditure was also controversial. Indeed, Qi et al. [18] showed that adiponectin stimulate energy expenditure in rodents when administered centrally; however, Kubota et al. [15] showed that adiponectin decrease energy expenditure as manifested by lower body temperature, lower oxygen consumption and lower uncoupling protein 1 gene expression in brown adipose tissue.

In-depth analysis of these discrepant studies was carried out in an attempt to explain this seemingly disparate data raised several points of considerations. Firstly, the models used by these groups were different. Kubota et al. [15] and Qi et al. [18] used mice; however, Coope et al. [52] used rats. Secondly, when the same model was used, the age of animal was different. Thirdly, the experimental protocols were different between these groups, including the preparation of recombinant adiponectin (mammalian cells vs. bacteria or virus), the dose injected (from 6 pg to 1 mg), the way of injection (Kubota et al. [15] injected adiponectin through a catheter placed in the jugular vein, whereas Qi et al. [18] and Coope et al. [52] administered adiponectin via a cannula placed in the lateral cerebral ventricle). Finally, the physiological and nutritional states of the animals were different. Indeed, in Kubota's study, fed instead of fasting mice were compared; however, the other groups used fasting animals. These differences may have profound implications in the final results.

2. Conclusion

Overall, adiponectin is clearly an important peripheral hormone pertinent to determining levels of insulin sensitivity through multiple mechanisms including AMPK and leptin/insulin signaling, but further work is required to resolve actions of this adipokine within the brain. Several crucial questions still remain to be clarified: how adiponectin is transported across the BBB in the cerebral endothelium and/

or the blood-CSF barrier in the choroids plexus? What form of adiponectin reaches the hypothalamus? What's its accurate signaling pathway in the brain? Would adiponectin systems in human behave like those of the rodents? If adiponectin is a starvation signal which is increased with fasting and reduced in fed state, could reduction of CSF adiponectin levels in obese individuals be a therapeutic approach to switch off appetite?

Acknowledgments

We thank Dr. Romulo Albuquerque (Department of Physiology and Department of Ophthalmology and Visual Sciences, University of Kentucky) for valuable discussions.

References

[1] Kopelman PG. Obesity as a medical problem. Nature 2000;404: 635–43.
[2] Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the United States. JAMA 2001;286:1195–200.
[3] Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. JAMA 2005; 293:1861–7.
[4] Mohamed-Ali V, Pinkney JH, Coppack SW. Adipose tissue as an endocrine and paracrine organ. Int J Obes Relat Metab Disord 1998;22: 1145–58.
[5] Havel PJ. Role of adipose tissue in body-weight regulation: mechanisms regulating leptin production and energy balance. Proc Nutr Soc 2000;59:359–71.
[6] Ahima RS, Flier JS. Adipose tissue as an endocrine organ. Trends Endocrinol Metab 2000;11:327–32.
[7] Trayhurn P, Wood IS. Adipokines: inflammation and the pleiotropic role of white adipose tissue. Br J Nutr 2004;92:347–55.
[8] Vettor R, Milan G, Rossato M, Federspil G. Review article: adipocytokines and insulin resistance. Aliment Pharmacol Ther 2005;22:3–10.
[9] Kadowaki T, Yamauch T. Adiponectin and adiponectin receptors. Endocr Rev 2005;26:439–51.
[10] Nawrocki AR, Rajala MW, Tomas E, Pajvani UB, Saha AK, Trumbauer ME, et al. Mice lacking adiponectin show decreased hepatic insulin sensitivity and reduced responsiveness to peroxisome proliferator-activated receptor gamma agonists. J Biol Chem 2006;281:2654–60.
[11] Maeda N, Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H, et al. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. Nat Med 2002;8:731–7.
[12] Kubota N, Yasuo Y, Yamauchi T, Kubota T, Moroi M, Matsui J, et al. Disruption of adiponectin causes insulin resistance and neointimal formation. J Biol Chem 2002;277:25863–6.
[13] Kubota N, Terauchi Y, Kubota T, Kumagai H, Itoh S, Satoh H, et al. Pioglitazone ameliorates insulin resistance and diabetes by both adiponectin-dependent and -independent pathways. J Biol Chem 2006;281:8748–55.
[14] Kos K, Harte AL, Da Silva NF, Tonchev A, Chaldakov G, James S, et al. Adiponectin and resistin in human cerebrospinal fluid and expression of adiponectin receptors in the human hypothalamus. J Clin Endocrinol Metab 2007;92:1129–36.
[15] Kubota N, Yano W, Kubota T, Yamauchi T, Itoh S, Kumagai H, et al. Adiponectin stimulates AMP-activated protein kinase in the hypothalamus and increases food intake. Cell Metab 2007;6:55–68.
[16] Smith PM, Ferguson AV. Neurophysiology of hunger and satiety. Dev Disabil Res Rev 2008;14:96–104.
[17] Guillod-Maximin E, Roy AF, Vacher CM, Aubourg A, Bailleux V, Lorsignol A, et al. Adiponectin receptors are expressed in hypothalamus and colocalized with proopiomelanocortin and neuropeptide Y in rodent arcuate neurons. J Endocrinol 2009;200:93–105.
[18] Qi Y, Takahashi N, Hileman SM, Patel HR, Berg AH, Pajvani UB, et al. Adiponectin acts in the brain to decrease body weight. Nat Med 2004;10:524–9.
[19] Shklyaev S, Aslanidi G, Tennant M, Prima V, Kohlbrenner E, Kroutov V, et al. Sustained peripheral expression of transgene adiponectin offsets the development of diet-induced obesity in rats. Proc Natl Acad Sci U S A 2003;100:14217–22.
[20] Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to C1Q, produced exclusively in adipocytes. J Biol Chem 1995;270:26746–9.
[21] Nakano Y, Tobe T, Choi-Miura NH, Mazda T, Tomita M. Isolation and characterization of GBP28, a novel gelatin-binding protein purified from human plasma. J Biochem (Tokyo) 1996;120:803–12.
[22] Maeda K, Okubo K, Shimomura I, Funahashi T, Matsuzawa Y, Matsubara K. cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (adipose most abundant gene transcript 1). Biochem Biophys Res Commun 1996;221:286–9.
[23] Hu E, Liang P, Spiegelman BM. AdipoQ is a novel adipose-specific gene dysregulated in obesity. J Biol Chem 1996;271:10697–703.
[24] Waki H, Yamauchi T, Kamon J, Ito Y, Uchida S, Kita S, et al. Impaired multimerization of human adiponectin mutants associated with diabetes. Molecular structure and multimer formation of adiponectin. J Biol Chem 2003;278:40352–63.
[25] Fruebis J, Tsao TS, Javorschi S, Ebbets-Reed D, Erickson MR, Yen FT, et al. Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. Proc Natl Acad Sci U S A 2001;98:2005–10.
[26] Wang Y, Xu LY, Lam KS, Lu G, Cooper GJ, Xu A. Proteomic characterization of human serum proteins associated with the fat-derived hormone adiponectin. Proteomics 2006;6:3862–70.
[27] Waki H, Yamauchi T, Kamon J, Kita S, Ito Y, Hada Y, et al. Generation of globular fragment of adiponectin by leukocyte elastase secreted by monocytic cell line THP-1. Endocrinology 2005;146:790–6.
[28] Wong GW, Wang J, Hug C, Tsao TS, Lodish HF. A family of Acrp30/adiponectin structural and functional paralogs. Proc Natl Acad Sci U S A 2004;101:10302–7.
[29] Pajvani UB, Du X, Combs TP, Berg AH, Rajala MW, Schulthess T, et al. Structure-function studies of the adipocyte-secreted hormone Acrp30/adiponectin. Implications for metabolic regulation and bioactivity. J Biol Chem 2003;278:9073–85.
[30] Yamauchi T, Kamon J, Waki H, Imai Y, Shimozawa N, Hioki K, et al. Globular adiponectin protected ob/ob mice from diabetes and ApoE-deficient mice from atherosclerosis. J Biol Chem 2003;278:2461–8.
[31] Yamauchi T, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, et al. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature 2003;423:762–9.
[32] Hug C, Wang J, Ahmad NS, Bogan JS, Tsao TS, Lodish HF. T-cadherin is a receptor for hexameric and high-molecular-weight forms of Acrp30/adiponectin. Proc Natl Acad Sci U S A 2004;101: 10308–13.
[33] Mao X, Kikani CK, Riojas RA, Langlais P, Wang L, Ramos FJ, et al. APPL1 binds to adiponectin receptors and mediates adiponectin signalling and function. Nat Cell Biol 2006;8:516–23.
[34] Berg AH, Combs TP, Scherer PE. ACRP30/adiponectin: an adipokine regulating glucose and lipid metabolism. Trends Endocrinol Metab 2002;13:84–9.
[35] Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med 2001;7:941–6.
[36] Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med 2002;8:1288–95.
[37] Tomas E, Tsao TS, Saha AK, Murrey HE, Zhang Cc C, Itani SI, et al. Enhanced muscle fat oxidation and glucose transport by ACRP30 globular domain: acetyl-CoA carboxylase inhibition and AMP-

activated protein kinase activation. Proc Natl Acad Sci USA 2002;99: 16309–13.
[38] Yoon MJ, Lee GY, Chung JJ, Ahn YH, Hong SH, Kim JB. Adiponectin increases fatty acid oxidation in skeletal muscle cells by sequential activation of AMP-activated protein kinase, p38 mitogen-activated protein kinase, and peroxisome proliferator-activated receptor. Diabetes 2006;55:2562–70.
[39] Puigserver P, Rhee J, Lin J, Wu Z, Yoon JC, Zhang CY, et al. Cytokine stimulation of energy expenditure through p38 MAP kinase activation of PPARγ coactivator-1. Mol Cell 2001;8:971–82.
[40] Yamauchi T, Nio Y, Maki T, Kobayashi M, Takazawa T, Iwabu M, et al. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic action. Nat Med 2007;13:332–9.
[41] Wu X, Motoshima H, Mahadev K, Stalker TJ, Scalia R, Goldstein BJ. Involvement of AMP-activated protein kinase in glucose uptake stimulated by the globular domain of adiponectin in primary rat adipocytes. Diabetes 2003;52:1355–63.
[42] Fu Y, Luo N, Klein RL, Garvey WT. Adiponectin promotes adipocyte differentiation, insulin sensitivity, and lipid accumulation. J Lipid Res 2005;46:1369–79.
[43] Bjursell M, Ahnmark A, Bohlooly YM, William-Olsson L, Rhedin M, Peng XR, et al. Opposing effects of adiponectin receptors 1 and 2 on energy metabolism. Diabetes 2007;56:583–93.
[44] Bray GA, Inoue S, Nishizawa Y. Hypothalamic obesity. The autonomic hypothesis and the lateral hypothalamus. Diabetologia 1981;20 (Suppl):366–77.
[45] Caja S, Torrente M, Martinez I, Abelenda M, Puerta M. Adiponectin values are unchanged during pregnancy in rats. J Endocrinol Invest 2005;28:609–15.
[46] Spranger J, Verma S, Gohring I, Bobbert T, Seifert J, Sindler AL, et al. Adiponectin does not cross the blood-brain barrier but modifies cytokine expression of brain endothelial cells. Diabetes 2006;55:141–7.
[47] Pan W, Tu H, Kastin AJ. Differential BBB interactions of three ingestive peptides: obestatin, ghrelin, and adiponectin. Peptides 2006;27:911–6.
[48] Fry M, Smith PM, Hoyda TD, Duncan M, Ahima RS, Sharkey KA, et al. Area postrema neurons are modulated by the adipocyte hormone adiponectin. J Neurosci 2006;26:9695–702.
[49] Maddineni S, Metzger S, Ocon O, Hendricks G, Ramachandran R. Adiponectin gene is expressed in multiple tissues in the chicken: food deprivation influences adiponectin Messenger ribonucleic acid expression. Endocrinology 2005;146:4250–6.
[50] Wilkinson M, Brown R, Imran SA, Ur E. Adipokine gene expression in brain and pituitary gland. Neuroendocrinology 2007;86:191–209.
[51] Jung TW, Lee JY, Shim WS, Kang ES, Kim JS, Ahn CW, et al. Adiponectin protects human neuroblastoma SH-SY5Y cells against MPP(+)-induced cytotoxicity. Biochem Biophys Res Commun 2006; 343:564–70.
[52] Berg AH, Combs TP, Du X, Brownlee M, Scherer PE. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. Nat Med 2001;7:947–53.
[53] Coope A, Milanski M, Araujo EP, Tambascia M, Saad MJA, Geloneze B, et al. AdipR1 mediates the anorexigenic and insulin/leptin-like actions of adiponectin in the hypothalamus. FEBS Lett 2008;582: 1471–6.
[54] Wang C, Mao X, Wang L, Liu M, Wetzel MD, Guan KL, et al. Adiponectin sensitizes insulin signaling by reducing p70 S6 kinase-mediated serine phosphorylation of IRS-1. J Biol Chem 2007;282: 7991–6.
[55] Miyazaki T, Bub JD, Uzuki M, Iwamoto Y. Adiponectin activates c-Jun NH2-terminal kinase and inhibits signal transducer and activator of transcription 3. Biochem Biophys Res Commun 2005; 333:79–87.
[56] Hoyda D, Samson WK, Ferguson AV. Adiponectin depolarizes parvocellular paraventricular nucleus neurons controlling neuroendocrine and autonomic function. Endocrinology 2009;150:832–40.
[57] Rothwell NJ. Central effects of CRF on metabolism and energy balance. Neurosci Biobehav Rev 1990;14:263–71.
[58] Hulsey MG, Pless CM, Martin RJ. ICV administration of anti-corticotropin-releasing factor antisense oligonucleotide: effects on feeding behavior and body weight. Regul Pept 1995;59:241–6.
[59] Heinrichs SC, Klaassen A, Koob GF, Schulteis G, Ahmed S, De Souza EB. Corticotropin-releasing factor receptor blockade enhances conditioned aversive properties of cocaine in rats. Psychopharmacology 1998;136:247–55.
[60] Lechan RM, Fekete C. The TRH neuron: a hypothalamic integrator of energy metabolism. Prog Brain Res 2006;153:209–35.
[61] Andersson U, Filipsson K, Abbott CR, Woods A, Smith K, Bloom SR, et al. AMP-activated protein kinase plays a role in the control of food intake. J Biol Chem 2004;279:12005–8.
[62] Minokoshi Y, Alquier T, Furukawa N, Kim YB, Lee A, Xue B, et al. AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus. Nature 2004;428:569–74.