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*Agnieszka Baranowska-Bik[1, 2], Małgorzata Waszkiewicz-Hanke[2]

Adiponectin as a neuropeptide

Adiponektyna jako neuropeptyd

[1]Department of Endocrinology, Centre Bielański Hospital of Postgraduate Medical Education, Warsaw
Head of Department: Professor Wojciech Zgliczyński, MD, PhD
[2]Department of Endocrinology, Bielanski Hospital, Warsaw
Head of Department: Professor Wojciech Zgliczyński, MD, PhD

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Summary

Adipose tissue is able to secrete many biologically active substances, named adipokines. Adiponectin, an adipokine, possesses a wide spectrum of properties including anti-inflammatory and anti-apoptotic activity that could also be present within the central nervous system.

Neuropeptide could be defined as a biologically active substance secreted from the neuronal cells of different types that influences the activity of the brain. Although adiponectin is not a classical neuropeptide, there is some evidence that this peptide acts as a modulator of selected brain functions.

In this paper we present a general knowledge considering interactions between adiponectin and the central nervous system. Moreover, we discuss the role of adiponectin in selected neurological diseases.

Data from experimental and clinical studies indicate that adiponectin may play an important role in the modification of the central nervous activity and function, and may change neurological diseases course. Possibly, therapeutic agent based on adiponectin might be a promising treatment method of neurological diseases. Adiponectin could also be considered as a link between peripheral adipose tissue and the brain.

Streszczenie

Tkanka tłuszczowa wydziela wiele biologicznie czynnych substancji, nazywanych adipokinami. Adiponektyna, jedna z adipokin, posiada szerokie spektrum funkcji. Między innymi może wykazywać aktywność przeciwzapalną i antyapoptotyczną również w obrębie centralnego układu nerwowego.

Neuropeptyd może być zdefiniowany jako biologicznie czynna substancja wydzielana przez różnego typu komórki nerwowe, która wpływa na aktywność mózgu.

Pomimo że adiponektyna nie jest klasycznym neuropeptydem, to istnieją dowody na to, że może ona działać jako modulator niektórych funkcji mózgu.

W pracy prezentujemy aktualną wiedzę na temat interakcji pomiędzy adiponektyną a centralnym układem nerwowym. Poza tym omawiamy rolę adiponektyny w wybranych chorobach neurologicznych.

Wyniki badań eksperymentalnych i klinicznych wskazują, że adiponektyna może odgrywać istotną rolę w modyfikacji aktywności i funkcji centralnego układu nerwowego, jak również może wpływać na przebieg chorób neurologicznych. Niewykluczone, że lek oparty na adiponektynie może stać się obiecującą metodą terapeutyczną w chorobach neurologicznych.

Adiponektyna może stanowić również ogniwo łączące obwodową tkankę tłuszczową i centralny układ nerwowy.

Conflict of interest
Konflikt interesów

None
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Address/adres:

*Agnieszka Baranowska-Bik
Klinika Endokrynologii
Centrum Medyczne
Kształcenia Podyplomowego
Szpital Bielański
ul. Cegłowska 80, 01-809 Warszawa
tel. +48 (22) 834-31-31
klinendo@cmkp.edu.pl

INTRODUCTION

Adipose tissue was originally recognized as an energy storage reservoir. Since the 1990s its endocrine activity has been evaluated as it is able to secrete many biologically active substances, named adipokines (1). Adipokines represent a wide spectrum of polypeptides and small molecules with different activity.

Adiponectin (ADPN) is an adipose-derived peptide that was discovered in 1995. Adiponectin is a 30 kD protein representing 0.01% of total serum proteins in

humans (2). It circulates in the blood as complexes of trimers (low molecular weight – LMW), hexamers (medium molecular weight – MMW) or multimers (high molecular weight – HMW) or globular form (gADPN). It has been reported that HMW adiponectin is the most metabolically active form in the periphery. The presence of adiponectin has been also confirmed in the cerebrospinal fluid with concentrations much lower than in the periphery (2).

Adiponectin possesses insulin-sensitizing, anti-inflammatory, anti-apoptotic and anti-atherosclerotic properties. Therefore, this peptide promotes beneficial metabolic effects, including enhanced insulin sensitivity and decreased inflammation. It has ability to increase insulin sensitivity in the liver, resulting in decreased hepatic glucose production (3). Interestingly, adiponectin levels inversely correlate with adiposity and are decreased in obesity and diabetes mellitus type 2. It is widely accepted that adipose tissue secretes pro-inflammatory mediators to the periphery causing a systemic chronic low-grade inflammation (4). It is known that ADPN is systemic anti-inflammatory adipokine, with ability to macrophage polarization towards an anti-inflammatory M2 phenotype by inhibiting tumor necrosis factor (TNF) α, INFγ, monocyte chemoattractant protein 1 (MCP-1) and IL-6 production as well as increasing anti-inflammatory cytokine production (e.g. IL-10, IL-1Ra) (5).

Moreover, ADPN possesses anti-apoptotic ability which is carried out by the activation of the enzyme ceramidase (6).

Furthermore, it has been reported that decreased concentration of circulating adiponectin is associated with episodes of cardiovascular disease including cerebrovascular disease caused by atherosclerosis. Increased mortality rate after ischemic stroke was also correlated with low ADPN levels.

Neuropeptide could be defined as a biologically active substance secreted from the neuronal cells of different types that influences the activity of the brain. Although adiponectin is not a classical neuropeptide, there is some evidence that this peptide acts as a modulator of selected brain functions.

Herein, we aimed to present a general knowledge considering interactions between adiponectin and the central nervous system. Moreover, we discuss the role of adiponectin in selected neurological diseases.

ADIPONECTIN IN THE CENTRAL NERVOUS SYSTEM

Despite the fact that adiponectin in CSF is 1000 x lower in comparison of the results in serum or plasma, it has been established that these concentrations correlate with each other (7-9). It is worth to notice that LMW adiponectin have been found in the CSF of both humans and mice and LMW adiponectin might be the most active form of adiponectin in the CNS (2).

To date, the exact source of adiponectin in CSF has not been specified. However, it has been suggested that adiponectin is able to cross the blood brain barrier (BBB). The results of experimental studies may confirm this hypothesis. In details, Kadowaki et al. reported that peripheral administration of adiponectin caused a stimulation of AMPK in the mice hypothalamus being responsible for an increase of food intake and a decrease in energy expenditure (10). Nevertheless, the local synthesis within the central nervous system cannot be also excluded. Indeed, adiponectin mRNA has been detected in chicken and murine brain extracts (11, 12), but not in human brain extracts. However, an expression of ADPN mRNA has been reported in human pituitary gland. In the pituitary gland, adiponectin plays a putative role in the autocrine/paracrine control and regulation of the release of somatotrophs and gonadotrophs (13).

ADIPONECTIN RECEPTORS

According to the literature, three ADPN receptors have been identified so far: AdipoR1, AdipoR2 and T-cadherin (T-cad). The first two receptors are highly structurally related and ubiquitously expressed, though they differ between each other with affinity to different isoforms and variable predominance in some tissues. Receptors for adiponectin (AdipoRs) are widely expressed with AdipoR1 expression being more pronounced. In the human brain, AdipoRs have been localized in the hypothalamus, pituitary gland, the nucleus basalis of Meynert and in the hippocampus (14). In mice, AdipoRs expressions have been detected in the hypothalamus, brainstem and endothelial cells, as well as in the whole brain and pituitary extracts (2, 12, 13) Moreover, mouse cortical neurons also express both AdipoR1 and AdipoR2, with AdipoR1 expression being more pronounced than AdipoR2 (14). The effect of adiponectin is mediated by ceramidase activity (6). Therefore, interaction between adiponectin and the receptor results in decreased intracellular ceramide concentrations. Subsequently, it has been reported that adiponectin receptors themselves may have ceramidase activity (15).

ADIPONECTIN AND ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a progressive central nervous system disease with clinical hallmark of dementia. From histopathological point of view, Alzheimer's disease is characterized by deposition within the brain of pathological β-amyloid (Aβ) and tau hyperphosphorylation leading to neurodegeneration, neuroinflammation and apoptosis. Although all processes take place in the CNS, there is a growing evidence supporting the thesis that this neurodegenerative disorder coexists with metabolic dysfunction (16, 17). AD is characterized by cerebral glucose hypometabolism caused by insulin receptor impairment, insufficiency and/or resistance to insulin and insulin-like growth factor (IGF) (17, 18).

Adiponectin may influence neuropathological processes seen in AD in several ways. Firstly, ADPN due to its insulin-sensitizing, anti-inflammatory, anti-apop-

totic and anti-atherosclerotic properties can indirectly modulate a course of disease (2). ADPN is regarded as systemic anti-inflammatory adipokine that can inhibit synthesis and secretion of pro-inflammatory cytokines, and it has ability to enhance production of anti-inflammatory factors. Secondly, ADPN anti-apoptotic properties include activation of the enzyme ceramidase, and enhancement of its metabolite, sphingosine-1-phosphate (S1p) (6). It has been found that S1p is involved in survival pathways (19). Moreover, growing evidence indicates that ADPN modulates the expression of endothelial adhesion molecules, stimulates eNOS phosphorylation and nitric oxide (NO) production, and regulates angiogenesis potentially protecting the brain against Aβ-induced vascular impairment (2).

Experimental study on APP transfected-neuroblastoma cells revealed that adiponectin protected cells against Aβ neurotoxicity. Therefore, it has been suggested that chronic ADPN deficiency may cause AD-like pathology (20). The group of Ng used ADPN-knockout mice model to assess how adiponectin deficiency influences cerebral insulin resistance, cognitive decline and Alzheimer's-like pathology. Their study resulted in conclusion that chronic ADPN deficiency inactivated AMPK causing insulin desensitization and elicited AD-like pathogenesis in aged mice which also developed significant cognitive impairments and psychiatric symptoms (21).

Other authors reported diminished hippocampal neurogenesis in ADPN-haploinsufficient and/or ADPN-deficient mice. This process was reversed with intracerebroventricular ADPN administration (2).

The findings of clinical studies concerning adiponectin concentration in plasma/serum of patients with Alzheimer's disease are inconsistent. The majority of researchers found enhanced levels of ADPN in the course of AD in comparison with the results of non-demented individuals (9, 22, 23). It should be highlighted that there is only one meta-analysis analyzing adiponectin levels in AD. This meta-analysis also confirmed higher peripheral levels of ADPN in AD individuals with respect to the controls (24).

However, there are also reports with opposing findings. These studies failed to observe significant differences in total adiponectin levels between AD individuals and cognitively normal controls (25-27). Finally, Teixeira and colleagues revealed decreased adiponectin levels in AD Alzheimer's disease when compared to normally cognitive counterparts (28).

Discrepancies in the results of peripheral ADPN concentration in AD could be explained by heterogeneity of groups included in the studies. Indeed, BMI variances, metabolic status or gender were not included in the study assumptions. A sample size could also influence on obtained findings.

Remarkably, the results of Framingham Heart Study indicate that circulating ADPN influences the risk of progression of dementia. Interestingly, women but no men in whom increased total adiponectin levels were observed had an increased risk of AD and all-cause dementia when compared with those females with adiponectin values less than the median (29).

PARKINSON'S DISEASE

Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by motor symptoms including a resting tremor, bradykinesia and rigidity. These symptoms are caused by degeneration of dopaminergic neurons in the substantia nigra. Pathologically, PD brains show accumulation of α-synuclein in structures termed 'Lewy bodies' and loss of dopaminergic neurons in the substantia nigra (30). Growing evidence suggests that neurodegeneration is associated with metabolic abnormalities, but the mechanisms are still unclear. Investigation of this issue might provide a new strategy for treatment of neurodegenerative diseases (31).

It's widely known that patients with PD experience unintended weight loss that appears to involve mainly adipose tissue. Rocha et al. measured circulating levels of adiponectin, leptin and resistin in a group of 40 PD patients and 25 age-, gender- and body mass index-matched controls. There was no significant difference between PD patients and controls regarding plasma levels of the evaluated adipokines. Although adipokines play important roles in inflammation, it seems that they are not implicated particularly in the inflammatory response associated with PD (32).

In 2011 Cassani et al. published the results of the first study that showed that PD patients have elevated serum adiponectin concentrations, comparable to the levels of young normal-weight subjects with absence of cardiovascular risk factors. Moreover, adiponectin concentrations were related to HDL cholesterol levels. PD patients with HDL cholesterol $\geq$ 50 mg/dL had better metabolic protection (and higher adiponectin levels) as well as normal BMI and fasting glucose levels. It's well known that high-density lipoprotein (HDL) cholesterol is a common and independent protective cardiovascular risk factor. The conclusion from this study was that adiponectin might play a role of protective factor against cardiovascular disease also in PD patients (33).

It's of note that adiponectin may have potential for implementation in novel therapies against PD. Li et al. investigated the role of adiponectin in L166P mutant DJ-1 that has been linked with a genetic form of the disease. Their results demonstrated that adiponectin treatment could prevent against neurotoxicity by attenuating increased levels of reactive oxygen species and nitric oxide induced by the DJ-1L166P mutation. In addition, adiponectin could rescue impaired mitochondrial membrane potential induced by DJ-1L166P (34).

Sekiyama et al. investigated autopsy brain with α-synucleinopathies including PD and dementia with Lewy bodies (DLB), and analyzed the effects of adiponectin in cellular and in mouse models of α-synucleinopathies. The main objective of this study was to determine whether adiponectin is protective against α-synucleinopathies such as PD. It was

observed that adiponectin is localized in Lewy bodies derived from α-synucleinopathies like Parkinson's disease and dementia with Lewy bodies. Moreover, study showed that intranasal treatment with a short peptide derived from adiponectin (e.g. gADPN) may suppress disease progression in mice models of α-synucleinopathies – in neuronal cells expressing α-synuclein (αS), aggregation of αS was suppressed in an AdipoRI-AMP kinase pathway-dependent manner. Concomitantly, phosphorylation and release of αS were significantly decreased by adiponectin suggesting that adiponectin may play anti-neurodegenerative roles. In transgenic mice expressing αS both histopathology and movement disorder were significantly improved by intranasal treatment with globular ADPN when the treatment was initiated in the early stage of the disease. In a mouse model, reduced levels of guanosine- and inosine-monophosphates, potential stimulators of aggregation of αS, might partly contribute to suppression of aggregation of αS by adiponectin. Given that ADPN is systemically involved in protection in various tissues and organs, it is likely that reinforcement of ADPN in human brain would not be associated with severe side effects. Thus, noninvasive treatment presented by authors using gADPN could be a candidate for therapy for α-synucleinopathies and possibly for other neurodegenerative diseases (31).

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system that affects 2.3 million people worldwide (35). Clinical and experimental data, together with epidemiological studies, have suggested that the pathogenesis of MS might involve factors that link the immune system with the metabolic status (36). There is a general consensus, that obesity, especially in adolescence, is associated with MS susceptibility, but also negatively influences disease progress and treatment response in patients with diagnosed MS.

The role of adipokines in the pathogenesis of MS has been widely investigated. Some studies have reported increased levels of leptin, resistin (37) and visfatin, and decreased levels of adiponectin in patients with relapsing-remitting MS (RRMS) in comparison with healthy controls (38), a profile also observed among subjects with obesity (39).

Piccio et al. proved the hypothesis that adiponectin has a protective role in EAE (experimental autoimmune encephalitis being a mouse model for MS). Adiponectin deficient (AdKO) mice developed greater CNS inflammation, demyelination and axon injury, proliferation of lymphocytes with producing larger amounts of TNF-α, IFN-γ, IL-17, and IL-6 and a decreased Treg number and function. Furthermore, treatment with globular adiponectin *in vivo* ameliorated EAE, and was associated with an increase in Treg cells. These data indicate that adiponectin is an important regulator of T-cell functions during EAE, suggesting a new potential way of MS treatment (40). Zhang et al. demonstrated that adiponectin could inhibit Th1 and Th17 but not Th2 cells differentiation *in vitro*. In the *in vivo* study they found that adiponectin deficiency promoted CNS inflammation, demyelination and exacerbated EAE. Adiponectin deficiency increased Th1 and Th17 cell cytokines of both the peripheral immune system and CNS in mice suffering from EAE, predominantly promoting the antigen-specific Th17 cells response in autoimmune encephalomyelitis. In addition, adiponectin upregulated sirtuin 1 (SIRT1) and peroxisome proliferator-activated receptor γ (PPARγ) and inhibited retinoid-related orphan receptor-γt (RORγt), the key transcription factor during Th17 cell differentiation (41).

Negrotto et al. reported data from a prospective cohort study which was conducted among 50 obese patients with MS who also developed metabolic syndrome (20 patients received pioglitazone-PPAR-γ activator, 20 patients metformin, 20 untreated patients served as controls) and demonstrated that treatment with metformin and pioglitazone has beneficial anti-inflammatory effects in patients with MS and metabolic syndrome. Compared with the controls, both treatments led to a decrease in mean leptin levels, and increase in mean adiponectin serum levels (42).

Kraszula et al. evaluated selected adipocytokines and nTreg cells and assessed their relationship with relapsing-remitting MS. The study was conducted among 25 patients with RRMS and 25 healthy individuals. Significantly lower adiponectin levels were found in patients with RRMS in comparison with control group; however, adiponectin level was not correlated with nTreg (37). Musabak et al. compared 57 patients with MS and 34 healthy controls and also demonstrated decreased adiponectin levels in individuals with MS compared to the healthy controls. Furthermore, these levels were higher in female than in male patients with MS. Thus, it is a proof that adiponectin is gender dependent, because the same behavior is observed in healthy controls (43). In contrast, Penesova et al. did not find any difference in adiponectin (as well as resistin, leptin, TNF and IL-6) levels between 2 groups: 19 newly diagnosed MS patients and 19 age-, gender- and body mass-index (BMI) matched healthy controls (44).

Hietaharju et al. assessed a difference in the adipocytokine levels in CSF and sera of twins discordant for MS and revealed a significant difference in the adipocytokine levels in CSF samples. Individuals suffering from MS had higher concentrations of adiponectin and adipsin than their asymptomatic co-twins. The conclusion was that there was no correlation between serum and CSF concentration of adiponectin (and also adipsin) and there could be a secondary intrathecal synthesis of those adipocytokines in MS (7).

Coban et al. analyzed the value of serum adipokines levels as biomarker in determining the clinical progression of MS. The levels of adiponectin were measured in 40 healthy individuals, 24 subjects with classical clinical course of MS (C-MS) and 26 individuals with benign MS (B-MS). Concentrations of adiponectin were

significantly higher in C-MS patients compared with B-MS patients and healthy controls. These findings suggest the potential role of adiponectin as prognostic biomarker in MS (45).

Devorak et al. evaluated whether genetically increased adiponectin level influence risk of MS. Using genome-wide significant single nucleotide polymorphisms (SNPs) for adiponectin, they undertook a Mendelian randomisation study to estimate the effect of adiponectin on MS. The authors made a conclusion that lifelong genetically increased adiponectin levels have no clear effect on MS risk (46).

CONCLUSIONS

We conclude that adiponectin may act as a neuropeptide. This adipokine has a modulatory effect on the central nervous activity and function. Data from experimental and clinical studies indicate that adiponectin may play an important role in the modification of neurological diseases course. Possibly, therapeutic agent based on adiponectin might be a promising treatment method of neurological diseases. Furthermore, adiponectin could be considered as a link between peripheral adipose tissue and the brain.

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