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Metformin as an adjuvant therapeutic agent in central nervous system disorders

Zamira M. Muruzheva[1, 2, 3], Anna V. Vasilieva[2], Daria A. Obukhova[1], Oleg N. Ergashev[1], Marina N. Karpenko[1], Tatiana M. Alekseeva[4]

[1] Institute of Experimental Medicine, 12 Akademika Pavlova str., Saint Petersburg, 197022, Russian Federation
[2] Leningrad Regional Clinical Hospital, 2 Zaozernaya str., urban settlement Kuzmolovsky, Leningrad Region, 188663, Russian Federation
[3] North-Western State Medical University named after I.I. Mechnikov, 41 Kirochnaya str., Saint Petersburg, 191015, Russian Federation
[4] Almazov National Medical Research Center, 2 Akkuratova str., Saint Petersburg, 197341, Russian Federation

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Corresponding author:
Zamira M. Muruzheva
E-mail:
zamira.muruzheva@mail.ru

ABSTRACT. The article reviews current evidence on the neuroprotective properties of metformin in central nervous system disorders, focusing on its mechanisms of action mediated by 5'AMP-activated protein kinase (AMPK) activation, which regulates energy metabolism, autophagy, neuroinflammation, and oxidative stress. Preclinical studies demonstrate reduced α-synuclein pathology in Parkinson's disease, decreased β-amyloid accumulation in Alzheimer's disease, and immunomodulatory effects in multiple sclerosis. Clinical data reveal conflicting evidence: some studies report improvements in cognitive/motor functions, while others show no significant benefits. The authors emphasize the necessity of large-scale randomized trials to evaluate metformin's efficacy as an adjuvant therapy, given dose-dependent effects, treatment duration variability, and population-specific responses.

Keywords: metformin, cognitive impairment, Parkinson's disease, Alzheimer's disease, multiple sclerosis

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Метформин как препарат для адъювантной терапии заболеваний центральной нервной системы

Замира Магомедовна Муружева[1, 2, 3], Анна Валерьевна Васильева[2], Дарья Алексеевна Обухова[1], Олег Николаевич Эргашев[1], Марина Николаевна Карпенко[1], Татьяна Михайловна Алексеева[4]

[1] Институт экспериментальной медицины, 197022, г. Санкт-Петербург, ул. Академика Павлова, д. 12, Российская Федерация
[2] Ленинградская областная клиническая больница, 188663, Ленинградская область, г.п. Кузьмоловский, ул. Заозерная, д. 2, Российская Федерация
[3] Северо-Западный государственный медицинский университет имени И.И. Мечникова, 191015, г. Санкт-Петербург, ул. Кирочная, д. 41, Российская Федерация
[4] Национальный медицинский исследовательский центр имени В.А. Алмазова, 197341, г. Санкт-Петербург, ул. Аккуратова, д. 2, Российская Федерация

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Автор для корреспонденции:
Замира Магомедовна Муружева
E-mail: zamira.muruzheva@mail.ru

РЕЗЮМЕ. В статье обобщены современные данные о нейропротекторных свойствах метформина при заболеваниях центральной нервной системы. Основное внимание уделено механизмам действия через активацию 5'АМФ-активируемой протеинкиназы (AMPK), модулирующей энергетический метаболизм, аутофагию, нейровоспаление и окислительный стресс. Рассмотрены доклинические исследования, демонстрирующие снижение патологии α-синуклеина при болезни Паркинсона, уменьшение накопления β-амилоида при болезни Альцгеймера и иммуномодуляцию при рассеянном склерозе. Клинические данные демонстрируют противоречивые результаты — часть работ указывает на улучшение когнитивных/двигательных функций, другие не подтверждают значимых эффектов. Подчеркивается необходимость масштабных рандомизированных исследований для оценки роли метформина как адъювантной терапии, учитывая зависимость эффектов от дозы, длительности лечения и популяционных особенностей.

Ключевые слова: метформин, когнитивные нарушения, болезнь Паркинсона, болезнь Альцгеймера, рассеянный склероз

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INTRODUCTION

Metformin is a biguanide that has become one of the most commonly used hypoglycemic agents due to its affordability, high safety profile, and effectiveness. The mechanisms of metformin's antidiabetic action are primarily associated with the inhibition of gluconeogenesis in the liver, increased glucose utilization by muscles, increased tissue sensitivity to insulin, and reduced insulin inactivation [1, 2]. A new wave of interest in the drug has been sparked by recent data showing that metformin crosses the blood-brain barrier (BBB) and can therefore directly affect cells in the central nervous system (CNS) [3, 4]. This hypothesis is confirmed by the results of a number of studies on animal models of various diseases of the nervous system, including multiple sclerosis, Alzheimer's disease, Parkinson's disease, epilepsy, stroke, etc. [5–8].

AIM

The aim of this review is to summarize the results of studies on the mechanism of action and efficacy of metformin in the treatment of CNS diseases.

METFORMIN AND PARKINSON'S DISEASE

Parkinson's disease (PD) is a progressive neurodegenerative disorder that develops as a result of the death of dopaminergic neurons in the substantia nigra and striatum and is characterized by the development of rigidity, bradykinesia, resting tremor, postural instability, and a wide range of non-motor symptoms [9, 10]. PD remains an incurable disease; all currently available therapeutic approaches are aimed at symptomatic correction and do not prevent the progression of the disease, which is why the search for new treatments that alter the course of the disease is one of the main tasks. Current data confirm a direct link between type 2 diabetes mellitus (T2DM) and an increased likelihood of developing PD, suggesting common molecular mechanisms underlying these diseases [11–13]. In this regard, metformin has been proposed as a promising drug for the treatment of PD. Studies in animal models of PD have shown that the neuroprotective effect of metformin is achieved through a complex effect on energy metabolism, oxidative stress, inflammation, and autophagy. The most studied mechanisms of metformin's action are mediated by the activation of 5'AMP-activated protein kinase (AMPK), which is an ubiquitously expressed kinase that is considered a “sensor” of cellular metabolic status. AMPK has been shown to coordinate key cellular processes such as autophagy, cell growth, and mitochondrial quality control [14]. In a study using a PD model (administration of rotenone to rats), it was shown that an 18-day course of metformin activates the AMPK-FOXO3 pathway (transcription factor) pathway, reduces vascular endothelial growth factor production, caspase-3/9 activation, and cytoplasmic cytochrome C levels [15]. Young-Kyoung Ryu et al. (2020) studied the effect of metformin on motor function in a mouse model of PD induced by 6-hydroxydopamine (6-OHDA). The authors showed that oral administration of metformin at a dose of 100–200 mg/kg for 4 weeks activates AMPK signaling pathways, stimulates the production of the neurotrophic factor BDNF, suppresses microglial activation, and significantly improves motor function in mice with 6-OHDA-induced PD [16]. In another study investigating the neuroprotective potential and main mechanisms of action of metformin in a rotenone-induced mouse model of PD, it was shown that 10 days of metformin administration (300 mg/kg per day, intraperitoneally) attenuated the loss of dopaminergic neurons by suppressing lipid peroxidation and significantly reduced the rotenone-induced increase in cleaved caspase-3 and α-synuclein accumulation in the substantia nigra [17]. N. Katila et al. (2017) also demonstrated that metformin administration led to a decrease in the level of serine 129 phosphorylated α-synuclein (α-synuclein pSer129) through the activation of protein phosphatase 2A (PP2A), which is known to mediate the dephosphorylation of α-synuclein. According to the authors, the activation of PP2A by metformin can occur through both AMPK-dependent and AMPK-independent pathways [18]. Similar results were obtained when metformin (at a dose of 200 mg/kg per day) was administered to mice in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of PD: a significant decrease in α-synuclein pSer129 levels was observed, due to PP2A activation. In this study, the metformin-mediated decrease in pathological

α-synuclein levels, together with autophagy activation, increased production of neurotrophic factors (BDNF, GDNF), and regulation of downstream signaling pathways (Akt, Erk1/2) contributed to the restoration of dopamine content in the striatum and improvement of motor functions in mice [19]. In addition, metformin attenuates lipopolysaccharide (LPS)-induced neuroinflammation, which may be due to the drug's inhibitory effect on the translocation of the transcription factor NF- κB (nuclear factor kappa B) to the nucleus and suppression of proinflammatory cytokine production in various cell types [20, 21]. This is an important fact, since there is a model of PD in which a number of links in the pathogenesis of PD are modeled by administering high doses of LPS to laboratory animals [22]. However, despite the impressive number of studies demonstrating the positive effects of metformin in PD, there are studies showing the opposite results. For example, a 2016 study showed that metformin exacerbated damage to dopaminergic neurons in mice with an MFTP model of PD [23]. The clinical data currently available on the effect of metformin on the course of PD are also ambiguous. According to a study by M.L. Wahlqvist et al. (2012), patients with T2DM had a twofold increase in the risk of developing PD, which decreased to 1.3 with the use of hypoglycemic drugs; the confidence interval (CI) for the odds ratio (OR) was 0.77–2.19. However, the use of metformin as monotherapy did not reduce the risk of developing PD, while the combined use of metformin and sulfonylurea reduced the risk of developing PD to 0.78 (0.61–1.01) [13]. A 2019 US analysis of a 5-year follow-up of 5,528 patients with T2DM (mean age 63.2±10.9 years) showed that long-term metformin therapy (more than 4 years) significantly reduced the risk of developing PD among patients with T2DM (OR 0.19; 95% CI 0.12–0.31) [24]. Conversely, according to a systematic review published in 2020, which analyzed 19 studies involving more than 250,000 people, no positive effects associated with the use of metformin for the treatment of PD were identified. Moreover, the review showed that metformin use may even increase the risk of developing PD [25]. At the same time, a meta-analysis published in 2023 covering 15 studies involving a total of 2,910,405 patients with T2DM found no significant association between hypoglycemic drugs, including metformin, sulfonylureas, glucagon-like peptide-1 (GLP-1) receptor agonists, and glitazones with the risk of developing PD [26].

It is noteworthy that a recent randomized, double-blind, placebo-controlled clinical trial showed that exenatide, a GLP-1 receptor agonist, improves motor function in patients with PD [27]. These data suggest that increasing GLP-1 with metformin may be another potential molecular mechanism contributing to its neuroprotective effect in PD [28]. Furthermore, it is interesting to note that metformin does not affect the pharmacotherapeutic effects of levodopa, suggesting that the combination of both drugs may be useful in the treatment of levodopa-induced dyskinesias in PD without compromising the efficacy of levodopa [29]. These data support the need for further study of metformin as a drug that potentiates the action of antiparkinsonian agents.

METFORMIN AND ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a neurodegenerative disease characterized by a gradual, subtle onset in presenile or senile age, steady progression of memory and higher brain function disorders leading to dementia with the formation of a characteristic complex of neuropathological, neuroimaging, and biochemical features. The main histopathological feature of AD is the deposition of β-amyloid (Aβ) in the brain parenchyma and in the walls of blood vessels (with the formation of senile plaques), which has neurotoxic properties, leading to damage and death of neurons. There is ample evidence that the molecular mechanisms of T2DM and AD have points of contact, and one of the common features linking the two diseases is insulin resistance. In particular, it has been shown that insulin resistance in brain cells (especially in the hippocampus and cortex) is associated with the accumulation of Aβ and tau pathology [30]. Insulin signaling in the brain, which is crucial for neuronal function, involves the activation of insulin receptors (IR) and IGF-1R, leading to the phosphorylation of IRS protein and subsequent activation of PI3K/ Akt and MAPK pathways, which regulates glucose metabolism, synaptic plasticity, and cell survival. In insulin resistance, this cascade is disrupted due to increased phosphorylation of serine/threonine in IRS proteins, decreased tyrosine phosphorylation, and reduced activation of this path-

way [31, 32]. In this regard, one of the main areas of research into the mechanisms of metformin action in AD is the analysis of its effect on insulin resistance and insulin signaling in the brain.

Metformin has been shown to increase insulin sensitivity in the CNS by activating AMPK and enhancing the insulin/IGF-1 signaling pathway [33]. In a study by K.A. DiTacchio (2015) on transgenic AβPP mice showed that administration of metformin (at a dose of 350 mg/kg per day) for 14–16 months increases insulin sensitivity in males, increases lifespan, and slows down the degradation of the estrous cycle in females [34]. Metformin also improved cognitive function in APP/PS1 transgenic mice (an animal model of AD) and contributed to a reduction in the deposition of pathological Aβ and tau proteins in the hippocampus and cerebral cortex [35]. S.A. Farr et al. showed that metformin reduces the expression of APPc99 and p-tau proteins in SAMP8 mice (animals characterized by accelerated aging; they spontaneously develop signs of aging as early as 6–8 months instead of 18–24 months in normal mice, making them a convenient model for research). Thus, the use of metformin in SAMP8 mice significantly reduced the hyperphosphorylation of tau and APPc99 proteins, which led to improved learning and memory processes [36].

The mechanisms by which metformin reduces the accumulation of Aβ and tau protein are associated with the activation of AMPK, which in turn activates MARK1 kinase, which regulates the processing of amyloid precursor protein (APP). In addition, AMPK enhances autophagy by inhibiting mTOR, promoting Aβ clearance [37]. However, in some studies, long-term use of metformin increased Aβ levels due to the suppression of insulin degradase (IDE), which is involved in the destruction of Aβ [38].

Another mechanism of metformin's neuroprotective action in AD is mediated by its anti-inflammatory effects. It is known that in AD, as in PD, activated microglia intensify the process of neuroinflammation by secreting pro-inflammatory cytokines. Metformin inhibits NF-κB activation via AMPK, reducing cytokine production. Thus, in rodent models, metformin reduced microglial activation and astrogliosis, improving neuronal survival [37]. In addition, metformin has been shown to activate AMPK/PGC-1α-dependent mitochondrial biogenesis, increasing energy metabolism [39]. However, at high doses, metformin can inhibit complex I of the respiratory chain, increasing oxidative stress (a paradoxical effect) [40].

In addition to preclinical studies, there are currently many studies demonstrating the effectiveness of metformin in clinical practice for AD. A study by Tseng Chin-Hsiao (2019) showed that metformin stops or slows the onset of dementia in adult patients with T2DM [41]. From 2008 to 2012, Columbia University (New York) conducted a pilot study of 80 patients with amnestic mild cognitive impairment. The participants were overweight, but none of them had diabetes. Patients received either metformin at a daily dose of 2000 mg or a placebo for one year. Cognitive function was assessed using the Systemic Reasoning Test (SRT) and the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog). Secondary endpoints were glucose uptake by 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) in the posterior cingulate cortex and plasma levels of Aβ42, the most toxic form of the Aβ peptide. The metformin group showed slightly higher SRT scores than the placebo group (9.7±8.5 vs. 5.3±8.5; p=0.02). No differences in ADAS-Cog scores, glucose uptake, or plasma Aβ42 levels were found between the groups [42]. A.M. Koenig et al. (2017) conducted a similar study, but in addition to assessing cognitive function and neuroimaging in patients, they measured the concentration of metformin in cerebrospinal fluid (CSF). The results of the study showed that metformin use improves executive function, learning, and attention. The researchers also noted that metformin was safe, well tolerated, and measurable in CSF at a mean steady-state concentration of 95.6 ng/mL [43]. An interesting study was conducted based on data from the Alzheimer's Disease Neuroimaging Initiative (ADNI[1]) in 2022. In addition to cognitive functions, the assessment included levels of Aβ, tau, and phosphorylated tau in CSF, as well as neuroimaging data (hippocampal volume and cortical thickness were assessed). It turned out that patients with T2DM who received metformin treatment in the early stages of AD had better cognitive performance and lower levels of tau and phosphorylated tau in the CSF than patients who did not receive metformin. Patients receiving metformin also had less severe atrophy in the hippocampus and

[1] Available at: https://adni.loni.usc.edu/ (accessed: 10.09.2025).

cortex according to neuroimaging data [44]. However, despite numerous studies demonstrating the positive effects of metformin on cognitive function, there are studies that cast doubt on the available results. Thus, a recent meta-analysis found no significant association between metformin use and the risk of developing AD (OR 1.17; 95% CI 0.88–1.56; p=0.291). Moreover, subgroup analysis showed that among Asians, the risk of developing AD was significantly higher in patients taking metformin than in those who did not take it (OR 1.71; 95% CI 1.24–2.37; p=0.001) [45].

A randomized controlled trial (MET-FINGER, phase IIb) is currently underway to evaluate a new multimodal approach to the prevention of cognitive impairment and disability, combining lifestyle modification (diet, physical activity, cognitive training, monitoring of cardiovascular/metabolic risk factors, social interaction) with metformin in older adults at increased risk of dementia who do not have diabetes. The study is expected to provide decisive evidence for the implementation of innovative combined strategies for the prevention of AD [46].

Since 2021, a multicenter randomized controlled trial of metformin in the prevention of dementia in AB, phase 2/3 (MAP), has been underway. This study involves 326 people aged 55 to 90 who are overweight or obese, without diabetes, and with early or late mild cognitive impairment. Study participants receive 2000 mg of extended-release metformin per day or placebo (1:1). In addition to neuropsychological testing, the study assesses changes in hippocampal volume and white matter hyperintensity in the brain based on neuroimaging data, changes in the standardized uptake value ratio (SUVR) Aβ, changes in SUVR tau in the medial and inferior lateral temporal cortex, as well as changes in plasma AD biomarkers. The study is expected to continue until 2027 [47].

Thus, metformin demonstrates the potential to modulate key mechanisms of AD (Aβ and tau pathology, neuroinflammation, insulin resistance), but its effects depend on dose, age, duration of use, and time of initiation of therapy. Further preclinical studies are needed to optimize treatment regimens and clarify risks.

METFORMIN AND MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic demyelinating disease characterized by a complex of autoimmune inflammatory and neurodegenerative processes leading to multiple focal and diffuse lesions of the central nervous system, resulting in disability and a significant reduction in quality of life.

The role of the immune system and neuroinflammation in the development of this disease is now beyond doubt and is confirmed by the high efficacy of modern immunomodulatory drugs used to treat MS. However, despite the effectiveness of the drugs used, the disease steadily progresses, transitioning to a secondary progressive form that develops as a result of the inevitable degeneration of neurons, which requires the search for new pharmacological agents that affect not only the inflammatory but also the neurodegenerative process in MS. Metformin has become a promising candidate for the treatment of MS due to its diverse mechanisms of action and well-established safety profile. Recent studies have shown that metformin affects key immunopathological mechanisms underlying the development of systemic autoimmune diseases, such as the balance between T helper 17 (Th17) and regulatory T lymphocytes (Tregs), autoantibody production, macrophage polarization, and cytokine synthesis [48]. Thus, W. Duan et al. (2019) showed that metformin, through AMPK activation, suppresses T-cell proliferation and Th17 cell differentiation, while promoting Treg development *in vitro*. The authors demonstrated that administration of metformin to NOD mice (mice with spontaneously developing type 1 autoimmune diabetes) at a dose of 200 mg/kg alleviates the course of autoimmune insulin syndrome and significantly reduces the amount of interferon-γ (IFN-γ) and CD4 (+) interleukin-17 (IL-17) (+) T cells [49]. N. Nath et al. (2010) showed that metformin (20–100 mg/kg) successfully slowed disease progression, reduced immune cell infiltration, and decreased the expression of proinflammatory cytokines (IFN-γ, TNFα, IL-1β, IL-6, and IL-17) and proinflammatory mediators such as matrix metalloproteinase 9 (MMP-9) and chemokine RANTES/CCL5 in the CNS of animals with experimental autoimmune encephalitis (EAE). The authors demonstrated that metformin activated AMPK in macrophages, thereby inhibiting the biosynthesis of phospholipids and neutral lipids, as well as suppressing the expression of proinflammatory cytokines induced by endotoxin (LPS) and their mediators (iNOS and cyclooxygenase) [50].

The effects of metformin on B cells include modulation of activation and differentiation processes, reduction of antibody production, and influence on B cell-mediated inflammation, which plays a key role in the pathogenesis of MS [51]. The effect of metformin on the mTOR pathway contributes to a reduction in the proliferation of inflammatory cells and regulated differentiation of immune cells. In addition, this modulation affects myelin regeneration processes and neuronal survival mechanisms. In a recent study, N. Sanadgol et al. (2020) showed that metformin (50 mg/kg body weight per day) induces remyelination in mice with cuprizone-induced demyelination through direct activation of AMPK and indirect regulation of the AMPK/Nrf2/mTOR pathway in oligodendrocytes. Metformin also reduced brain apoptosis markers (cleaved caspase-3/α-tubulin and Bax/Bcl-2 ratios) and improved motor activity in mice in the Open Field test [52]. Another study investigated the effect of metformin on remyelination in the "acute" and "delayed" periods of EAE. Metformin contributed to a reduction in demyelination and improvement in motor function in mice with EAE in the "acute" period, but did not show its effectiveness in the "delayed" period [53].

Unlike the many promising fundamental studies of metformin's effects on animal models of MS-EAE, the number of studies investigating the effects of metformin on patients with MS is limited. A cohort study conducted by L. Negrotto et al. on MS patients receiving metformin (850–1500 mg/day) demonstrated a significant reduction in the total number of new T2 lesions and contrast-enhancing lesions in the brain and spinal cord according to neuroimaging data. The effect was observed after 6 months of therapy and persisted for up to 24 months. In addition, the study showed increased AMPK expression, decreased IFN-γ and IL-17 production, and an increased percentage of Tregs in MS patients receiving metformin [54]. In 2024, the results of a prospective, open-label, randomized controlled trial were published, which aimed to study the efficacy and safety of metformin as an adjuvant therapy to interferon beta 1a (IFNβ-1a) in patients with relapsing-remitting multiple sclerosis (RRMS). Patients were assessed for IL-17, IL-22, malondialdehyde (MDA), T2 lesions on magnetic resonance imaging (MRI), and expanded disability status scale (EDSS) at baseline and after 6 months. The study showed that adding metformin to IFNβ-1a contributed to a decrease in the oxidative stress marker malondialdehyde, but no statistically significant effect on immunological, neuroimaging, and clinical parameters was found [55].

Several clinical trials (Phase I and IIa) are currently underway to study the efficacy of metformin in MS. These studies are investigating the effect of metformin on remyelination processes, modulation of immune responses, and the impact on neurodegeneration in various subtypes of MS. The results of the studies have not yet been published, which does not allow conclusions to be drawn about the success of the clinical trials.

Thus, the available data support the efficacy of metformin in MS, but larger clinical trials are needed to definitively establish the therapeutic value of metformin, particularly its potential to improve existing MS treatments and provide a neuroprotective effect.

CONCLUSION

In neurology, drug repurposing programs include the search for drugs with neuroprotective activity or those that potentiate the action of neuroprotectors among known and widely used drugs. The basis for searching for neuroprotective properties in drugs intended for other purposes is the fact that signaling pathways in cells are characterized by a large number of cross-interactions, and some of them may be involved in the process of stimulating/intensifying neuron survival. Finding such intersections is possible thanks to advances in genomics, proteomics, bioinformatics, and the emergence of powerful analytical systems. Analysis of the current literature has shown that hypoglycemic agents, in particular metformin, have high neuroprotective potential. Currently, the preventive and therapeutic significance of metformin in diseases of the nervous system has been widely studied. According to the literature, metformin can modify the process of autophagy, prevent mitochondrial dysfunction, reduce neuroinflammation, and have a neuroprotective effect. However, there are studies that have not identified the neuroprotective effects of metformin. This may be due to differences in animal models and varying

Table 1

Effects of metformin in diseases of the central nervous system (compiled by the authors)

Таблица 1

Эффекты метформина при заболеваниях центральной нервной системы (составлено авторами)

Заболевание Disease	**Животная модель или клинические испытания** Animal model or clinical trials	**Доза препарата / способ введения** Dosage of the drug / route of administration	**Механизмы, эффекты** Mechanisms, effects	**Ссылки на литературу** References to literature
Болезнь Паркинсона Parkinson's disease	Мыши, МФТП-модель Mice, MPTP model	200 мг/кг, внутрибрюшинно 200 mg/kg, intraperitoneally	• улучшение двигательных функций; • improvement of motor functions; • повышение уровня дофамина в полосатом теле; • increased dopamine levels in the striatum; • снижение каспазы-3 и ингибирование апоптоза; • decreased levels of caspase-3 and inhibition of apoptosis; • снижение активации астроглии; • attenuation of astroglial activation; • активация AMPK и ингибирование mTOR; • AMPK activation and mTOR inhibition; • активация PP2A и снижение α-син pSer129; • activation of PP2A and reduction of pS129-α-syn; • повышение уровня нейротрофических факторов (BDNF, GDNF) и активация нисходящих сигнальных путей (Akt, Erk1/2); • increased levels of neurotrophic factors (BDNF, GDNF) and activation of downstream signaling pathways (Akt, Erk1/2)	[19]
	Мыши, ротеноновая модель Mice, rotenone model	300 мг/кг, внутрибрюшинно 300 mg/kg, intraperitoneally	• предотвращение дегенерации дофаминергических нейронов в черной субстанции; • prevention of degeneration of dopaminergic neurons in the substantia nigra; • снижение апоптоза, опосредованного каспазой-3; • attenuation of caspase-3-mediated apoptosis; • снижение накопления α-синуклеина; • decreased α-synuclein accumulation; • снижение уровня продуктов перекисного окисления липидов (4-HNE, MDA); • decreased levels of lipid peroxidation products (4-HNE, MDA)	[17]
	Мыши, модель 6-гидроксидотамина (6-OHDA) Mice, 6-hydroxydotamine (6-OHDA) model	100–200 мг/кг, перорально 100–200 mg/kg, orally	• улучшение двигательных функций; • improvement of motor functions; • активация сигнальных путей AMPK, стимуляция продукции нейротрофического фактора BDNF; • activation of AMPK signaling pathway, stimulation of BDNF production; • подавление активации микроглии; • suppression of microglial activation	[16]
	Крысы, ЛПС-индуцированная модель Rats, LPS-induced model	150 мг/кг 2 раза в день, перорально 150 mg/kg 2 times a day, orally	• уменьшение количества активированных микроглиальных клеток; • decreased number of activated microglial cells; • снижение уровня провоспалительных цитокинов (ФНО, ИЛ-1β, ИЛ-6) и микроглиальных провоспалительных фенотипов; • decreased levels of proinflammatory cytokines (TNF, IL-1β, IL-6) and microglial proinflammatory phenotypes; • снижение выработки активных форм кислорода; • decreased production of reactive oxygen species	[56]

Continuation of the Table 1 / Продолжение табл. 1

Заболевание Disease	**Животная модель или клинические испытания** Animal model or clinical trials	**Доза препарата / способ введения** Dosage of the drug / route of administration	**Механизмы, эффекты** Mechanisms, effects	**Ссылки на литературу** References to literature
Болезнь Альцгеймера Alzheimer's disease	Трансгенные мыши АβPP АβPP transgenic mice	350 мг/кг, перорально 350 mg/kg, orally	• повышение чувствительности к инсулину у самцов; • increased insulin sensitivity in males; • увеличение продолжительности жизни у самок; • extended lifespan in females	[34]
	Мыши SAMP8 SAMP8 mice	20–200 мг/кг, подкожно 20–200 mg/kg, subcutaneously	• улучшение обучения и памяти; • improvement of learning and memory; • снижение гиперфосфорилирования белков тау и APPc99; • reduction of hyperphosphorylation of tau and APPc99 proteins	[36]
	Крысы, скополамин-индуцированные когнитивные нарушения Rats, scopolamine-induced cognitive impairment	50, 100–200 мг/кг, через зонд 50, 100–200 mg/kg, via tube	• улучшение обучения и памяти; • improvement of learning and memory; • повышение уровня фосфорилированной AMPK; • increased levels of phosphorylated AMPK; • снижение уровня малонового диальдегида (MDA); • decreased levels of malondialdehyde (MDA); • повышение активности супероксиддисмутазы (SOD) в гиппокампе; • increased superoxide dismutase (SOD) activity in the hippocampus	[39]
	Трансгенные мыши APP/PS1 APP/PS1 transgenic mice	4 мг/мл в питьевой воде 4 mg/ml in drinking water	• способствование фагоцитозу белков Aβ и тау за счет усиления способности микроглиальной аутофагии • promotion of the phagocytosis of Aβ and tau proteins due to enhanced microglial autophagy capability	[35]
	Клинические данные Clinical data	2000 мг/день 2000 mg/day	• снижение риска развития деменции у пациентов с сахарным диабетом 2-го типа; • reduced risk of developing dementia in patients with type 2 diabetes mellitus; • улучшение результатов селективного теста на память у пациентов с легкими когнитивными нарушениями без диабета; • iimproved selective reminding test performance in patients with mild cognitive impairment without diabetes; • снижение уровней тау и фосфорилированного тау в СМЖ; • decreased levels of tau and phosphorylated tau in CSF	[42–44]
Рассеянный склероз Multiple sclerosis	Мыши C57BL/6 и SJL, экспериментальный аутоиммунный энцефаломиелит C57BL/6 and SJL mice, experimental autoimmune encephalomyelitis	20–100 мг/кг, через зонд 20–100 mg/kg, via tube	• замедление прогрессирования заболевания; • attenuation of the disease progression; • ограничение инфильтрации мононуклеарных клеток в ЦНС; • restriction of mononuclear cell infiltration into the central nervous system; • снижение экспрессии провоспалительных цитокинов (ИЛ-1β, ИЛ-6, ИЛ-17, ИФН-γ и ФНО-α) в ЦНС; • down-regulation of the expression of proinflammatory cytokines (IL-1β, IL-6, IL-17, IFN-γ and TNF-α) in the central nervous system; • подавление экспрессии матриксной металлопротеиназы 9 и хемокина (RANTES); • suppression of matrix metalloproteinase 9 and chemokine (RANTES) expression	[50]

Ending of the Table 1 / Окончание табл. 1

Заболевание Disease	**Животная модель или клинические испытания** Animal model or clinical trials	**Доза препарата / способ введения** Dosage of the drug / route of administration	**Механизмы, эффекты** Mechanisms, effects	**Ссылки на литературу** References to literature
	Мыши C57BL/6, экспериментальный аутоиммунный энцефаломиелит C57BL/6 mice, experimental autoimmune encephalomyelitis	100 мг/кг, через зонд 100 mg/kg, via tube	• снижение уровня Th17 и способствование пролиферации Tregs; • decreased Th17 levels and promotion of Tregs proliferation; • повышение уровней противовоспалительных цитокинов, трансформирующего фактора роста-β (TGF-β) и ИЛ-10; • increased levels of anti-inflammatory cytokines, transforming growth factor-β (TGF-β) and IL-10; • подавление активации пути мишени рапамицина у млекопитающих (mTOR); • suppression of activation of the mammalian target of rapamycin (mTOR) pathway	[48]
	Крысы, экспериментальный аутоиммунный энцефаломиелит Rats, experimental autoimmune encephalomyelitis	150 мг/кг, через зонд 150 mg/kg, via tube	• ослабление клинических симптомов; • alleviation of clinical symptoms; • повышение уровней Tregs и снижение уровней Th1 и Th17 в периферической нервной системе (ПНС) и ЦНС; • increased levels of Tregs and decreased levels of Th1 and Th17 in the peripheral nervous system (PNS) and CNS; • снижение демиелинизации и потери аксонов; • attenuation of demyelination and axonal loss; • ослабление воспалительных реакций и повышение экспрессии нейротрофических факторов, посредством активации AMPK; • attenuation of inflammatory responses and increased expression of neurotrophic factors via AMPK activation; • подавление окислительного стресса; • suppression of oxidative stress	[57, 58]
	Пациенты с ремиттирующим РС, когортное исследование Patients with relapsing-remitting MS, cohort study	850–1500 мг/день 850–1500 mg/day	• снижение общего количества новых Т2-очагов и очагов, накапливающих контраст, в головном и спинном мозге; • decrease in the total number of new T2 lesions and contrast-enhancing lesions in the brain and spinal cord; • повышение экспрессии мРНК AMPK; • increased AMPK mRNA expression; • снижение выработки ИФН-γ и ИЛ-17 и повышение процента Tregs; • decreased production of IFN-γ and IL-17 and an increase in the percentage of Tregs	[54]
	Пациенты с ремиттирующим РС, клиническое исследование Patients with relapsing-remitting MS, clinical trial	2000 мг/день 2000 mg/day	• снижение уровня малонового диальдегида (MDA) • decreased levels of malondialdehyde (MDA)	[55]

doses of the drug. Clinical studies of metformin in the treatment of nervous system diseases are progressing slowly, with most of them being prospective or retrospective clinical studies; there is still a lack of large multicenter randomized controlled trials. The data are summarized in Table 1.

Thus, this literature review confirms that metformin can be considered a potential drug for the prevention and treatment of CNS diseases, but large-scale randomized controlled clinical trials are needed to provide more adequate clinical evidence.

ADDITIONAL INFORMATION

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Authors' info

* **Zamira M. Muruzheva** — Cand. Sci. (Med.), Head of the neurological department of the Leningrad Clinical Hospital; researcher at the Laboratory of Neurochemistry of the Physiological Department named after Academician I.P. Pavlov, Institute of Experimental Medicine; Associate Professor of the Department of Normal Physiology of North-Western State Medical University named after I.I. Mechnikov. E-mail: zamira.muruzheva@mail.ru; https://orcid.org/0000-0003-2789-8431; SPIN: 9248-3689
Anna V. Vasilieva — Neurologist of the Neurological Department of the State Budgetary Institution of Healthcare of the Leningrad Regional Clinical Hospital; graduate student N.P. Bechtereva Institute of the Human Brain, RAS. E-mail: ann.valeryevna@mail.ru; https://orcid.org/0009-0008-6187-623X
Daria A. Obukhova — Junior Researcher, Laboratory of Neurochemistry of the Physiological Department named after Academician I.P. Pavlov, Institute of Experimental Medicine. E-mail: obuhowadaria@gmail.com; https://orcid.org/0009-0002-4287-0808; SPIN: 3164-3927
Oleg N. Ergashev — Dr. Sci. (Med.), Professor, Acting Director, Institute of Experimental Medicine. E-mail: ergashew@mail.ru; https://orcid.org/0009-0003-5188-8900; SPIN: 2970-2672
Marina N. Karpenko — Dr. Sci. (Med.), Head of the Laboratory of Neurochemistry of the Physiological Department named after Academician I.P. Pavlov, Institute of Experimental Medicine. E-mail: mnkarpenko@mail.ru; https://orcid.org/0000-0002-1082-0059; SPIN: 6098-2715
Tatiana M. Alekseeva — Dr. Sci. (Med.), Professor, Head of the Department of Neurology with the Clinic of the IMO. E-mail: atmspb@mail.ru; https://orcid.org/0000-0002-4441-1165; SPIN: 3219-2846

* Corresponding author.
Автор, ответственный за переписку.

Об авторах

* **Замира Магомедовна Муружева** — к.м.н., заведующая неврологическим отделением ЛОКБ; научный сотрудник лаборатории нейрохимии Физиологического отдела им. И.П. Павлова, ФГБНУ ИЭМ; доцент кафедры нормальной физиологии СЗГМУ им. И.И. Мечникова. E-mail: zamira.muruzheva@mail.ru; https://orcid.org/0000-0003-2789-8431; SPIN: 9248-3689

Анна Валерьевна Васильева — врач-невролог неврологического отделения ГБУЗ ЛОКБ, аспирант ИМЧ РАН. E-mail: ann.valeryevna@mail.ru; https://orcid.org/0009-0008-6187-623X

Дарья Алексеевна Обухова — младший научный сотрудник лаборатории нейрохимии физиологического отдела им. И.П. Павлова, ФГБНУ ИЭМ. E-mail: obuhowadaria@gmail.com; https://orcid.org/0009-0002-4287-0808; SPIN: 3164-3927

Олег Николаевич Эргашев — д.м.н., профессор, ИО директора ФГБНУ ИЭМ. E-mail: ergashew@mail.ru; https://orcid.org/0009-0003-5188-8900; SPIN: 2970-2672
Марина Николаевна Карпенко — д.б.н., заведующая лабораторией нейрохимии Физиологического отдела им. И.П. Павлова, ФГБНУ ИЭМ. E-mail: mnkarpenko@mail.ru; https://orcid.org/0000-0002-1082-0059; SPIN: 6098-2715
Татьяна Михайловна Алексеева — д.м.н., профессор, заведующая кафедрой неврологии с клиникой ИМО. E-mail: atmspb@mail.ru; https://orcid.org/0000-0002-4441-1165; SPIN: 3219-2846