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Use of Antidiabetic Drugs in Prevention of Dementia among Elderly

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Abstract

Cognitive impairment, including memory problems or pathologies related to thought processes, can be caused by mental, neurodegenerative, and somatic diseases. Parkinson's disease, Alzheimer's disease and vascular disease are common in elderly people who are burdened with chronic diseases such as diabetes and can contribute to the deterioration of cognitive functions. Research indicates a possible neuroprotective effect of antidiabetic drugs used in the treatment of type 2 diabetes. Therefore, the use of incretin drugs and fluids in order to improve cognitive functions seems to be very promising.

Key words: *Alzheimer's disease (AD), Parkinson's disease (PD), Neuroinflammation, Glucagon-like peptide-1 (GLP-1), DPP-4 inhibitors*

Cognitive functions in elderly – introduction

Cognitive functions are activities that serve a person in obtaining spatial orientation, information about themselves and their own body, analyzing the situation, formulating conclusions, making appropriate decisions and acting [1]. These include perceptual, attention, memory, thought, language, learning, and executive functions [1].

The quality of cognitive functions declines with age. It manifests itself through deterioration of memory, reaction, focus, reasoning, and accidents from structural changes, and aging [2]. According to some authors [3], the deterioration of cognitive functions contributes to the increased risk of Alzheimer's disease.

The incidence of dementia increases with age: in people aged 60–64 it is 1–2%, aged 75–79 years – 6–8%, over 90 years – over 35% [4]. Also, earlier occurrence of mild cognitive impairment (MDI; cognitive impairment that is greater than expected for a given age but does not significantly affect daily functioning) increases the risk of future dementia [5].

Many mechanisms can lead to the development of cognitive dysfunction. J. Dzierzewski et al. [2] mention, among others, deposition of amyloid-β and Tau protein, increased neurodegenerative processes, hypoxia, vascular changes, low physical activity, and sleep problems.

One of the risk factors of cognitive impairment is type 2 diabetes (T2D) [12]. It is associated with an increased risk of mild dementia, compared to the general population [13], and a faster transition of MDI to dementia [14]. In diabetic patients, the aging process begins earlier and progresses faster – this also applies to cognitive functions [1]. People over 60 years of age, 4 years after the diagnosis of diabetes, showed a significant deterioration of cognitive functions compared to healthy people. At the same time, it occurs more often than in people of the same age without disturbances in carbohydrate metabolism [1]. In a meta-analysis involving over a million patients, the risk of dementia in people with diabetes was almost twice as high as in people without diabetes. It concerned both Alzheimer's disease and vascular dementia [15].

This disease is associated with an increased risk of vascular pathologies in a more significant way than with atherosclerosis and neurofibrillary tangles characteristic of Alzheimer's disease [16]. Endocrine system disorders may cause degenerative-atrophic changes in the CNS [1]. Also, episodes of hypoglycemia occurring in the course of diabetes increase the risk of developing dementia [14].

Cognitive impairment in patients with diabetes mellitus is associated with worse self-control, glycemic control, and greater incidence of hospitalizations, episodes of severe hypoglycemia, and cardiovascular events [14].

Although the subject is not new, the question of the influence of diabetes on cognitive functions has not been well researched [1]. The society gets older, that is why the problem of dementia is current and we found the possibility of stopping it using antidiabetic drugs very interesting. The life expectancy prolongs, and it is important to provide a good quality of the life for the elderly people. Antidiabetic drugs, which connection with cognitive functions we researched, are supposed to be a good prophylaxis of dementia in elderly patients.

Influence of incretin drugs on cognitive functions in Alzheimer's Disease:

Alzheimer's disease (AD) is a neurodegenerative disease that is the most common cause of dementia in the world [17]. Most often it appears after the age of 65, while in the case of a genetically determined form, the disease emerges around the age of 45 [17]. The disease affects about 3% of people aged 65–75, 17% aged 75–84 and 32% of people over 84 years of age. This number is expected to increase to 13.8 million by 2050 [34].

The background of the disease includes deposition of β-amyloid (Aβ) plaques as well as hyperphosphorylated tau protein in neurofibrillary neuron tangles (NFT), which results in decreased function or loss of synapses and neurodegeneration [17, 34]. The lesions attack the areas of the cerebral cortex and the hippocampus, most often starting from the frontal and temporal lobes, where senile plaques and neurofibrillary tangles are initially detected [17, 18].

Aβ is a natural product of the cleavage of amyloid precursor protein (APP) into peptides of different lengths in healthy individuals, Aβ is rapidly broken

down. In patients with AD, the main aggregation is the Aβ42 isoform with amyloidogenic properties, which increases the plasma Aβ42/ Aβ40 isoform ratio. Abnormal amyloid plaque (Aβ) contributes to the hyperphosphorylation of the tau protein, which spreads to neighboring neurons causing their death [18]. Dysfunction of the APO-E gene on chromosome 19, which encodes the apolipoprotein E (APOE) protein involved in the catabolism of lipoproteins, also contributes to the development of the disease [17, 18]. APOE exists in 3 isoforms: APOE2, APOE3 and APOE4. Studies have shown that APOE4 is associated with an increased risk of AD and a reduced risk of developing the disease associated with APOE2 [17].

AD proceeds from cognitive and functional deterioration [34]. Episodic memory disorders, i.e. the ability to encode new information and create memories, occur in the early stages of the disease [18, 19]. Then there are topographic difficulties, problems with multitasking and loss of self-confidence. As the disease progresses, the disorders worsen and become more and more burdensome in everyday life. Later in the disease, cognitive disorders may be accompanied by behavioral changes, impaired mobility, hallucinations and convulsions [35].

One of the risk factors for AD in addition to age is diabetes mellitus (DM). Evidence suggests a 2-fold higher risk of AD in people with DM compared to healthy people [28]. One of the common features of both AD and DM is the presence of aberrant insulin signaling [29]. Research has shown that insulin signaling influences neuronal function, the disturbance of which leads to Alzheimer's disease. Additionally, in diabetics, disturbances in insulin signaling may contribute to the progression of AD [36]. Chronic peripheral hyperglycemia is responsible for cognitive impairment in DM, additionally, patients suffer from chronic peripheral hyperinsulinemia and insulin resistance [24]. Hyperinsulinemia can cause insulin resistance in the nerve tissues that build the brain, which interferes with the activity of the insulin receptor and results in defective transport to the brain [25]. In the brains of AD patients, decreased insulin sensitivity was observed despite the lack of concomitant diabetes [24, 25]. The presence of insulin resistance reduced Aβ degradation by the insulin-degrading enzyme (IDE), while the resulting amyloid plaque

accumulation caused the destruction of insulin receptors from the cell surface. Additionally, a decrease in insulin signaling results in an increase in the activity of glycogen synthase 3 kinase (GSK-3β) and leads to abnormal phosphorylation of the tau protein [27]. Impairment of insulin signaling may affect cognitive functions in both DM and AD [19–21]. Both in the course of DM and PD, mitochondrial function disorders, increased inflammation, amyloid plaque deposition and excessive oxidative stress also occur [26].

Glucagon-1-like peptide (GLP-1) is a hormone secreted in the small intestine in response to the food it receives, but it can also be synthesized in the central nervous system by cells of the solitary nucleus (NTS) [32]. A study using a GLP-1 receptor agonist showed increased proliferation and decreased degradation of pancreatic β cells, decreased gluconeogenesis, and increased insulin production, and may also provide protection against oxidative damage [33, 34]. Liraglutide and exenatide, which are GLP-1 agonists, inhibit AD progression and neurodegenerative processes, reducing the level of Aβ [34]. GLP-1, after crossing the blood-brain barrier, binds to its receptor, which results in the activation of signaling pathways, facilitating insulin signaling. Additionally, GLP-1 may act as a growth factor in the brain, causing synaptogenesis and neurogenesis [34].

Dipeptidyl peptidase-4 (DPP-4) inhibitors are currently used in the treatment of type II diabetes (T2DM). Studies show their possible effectiveness in the treatment of AD [26]. Linagliptin and sitagliptin belong to the group of DPP-4 inhibitors [26]. Linagliptin enhances insulin signaling, thereby reducing tau protein hyperphosphorylation by preventing GSK3β activation [26, 27]. In a mouse study on the use of Linagliptin in AD, a reduction in the Aβ42/Aβ40 ratio was also noticed, which resulted in reduced formation of senile plaques in the extracellular space and reduced NFT deposition, which in turn improved cognitive functions [27].

Research confirms that sitagliptin also reduces the accumulation of Aβ in the brain structures by about 60%, which may be related to the stromal cell-derived factor 1α (SDF-1α) [31]. DPP-4 inhibitors inhibit DPP-4, which reduces the activity of the SDF-1α/CXCR4 axis. The probable cause of CNS neurogenesis in adults may be the proliferation of neuronal stem cells (NSCs)

and hemopoietic stem cells (HSCs) stimulated by the SDF-1α/CXCR4 Axis and the migration of NSCs and HSCs to pathologically altered areas [30]. Blocking DPP-4 with DDP-4 inhibitors enables the action of the SDF-1α/CXCR4 axis and thus promotes neurogenesis also that the SDF-1α/CXCR4 axis regulates synaptic transmission, neuron excitability, which promotes the regeneration of lost neurons in the diseased brain. Neurogenesis, on the other hand, influences learning and memory processes that are disturbed in AD [30]. It has been proven that signal propagation in glial networks and reduces Aβ accumulation (Bezzi et al., 2001, Wang et al., 2012b). CXCL12/CXCR4 signaling promotes synaptic integration and reduces beta amyloid deposition through astrocyte-mediated glutamate release in CA1 [14]. Additionally, DPP-4 inhibitors slow down the enzymatic degradation of GLP-1, extending its half-life in the blood and enhancing its effect [30, 31]. Moreover, sitagliptin reduces the level of markers of inflammation and oxidative stress and improves cognitive functions in the elderly [31].

Influence on the course of Parkinson's disease

Parkinson's disease (PD) is one of the most common neurodegenerative disorders in which there is a loss of dopaminergic (DA) neurons in the substantia nigra of the midbrain [37]. PD is characterized by the presence of the Lewy bodies, formed by fibril proteins, mainly α-synuclein [37]. A-synuclein is a protein involved in inter-vesicular transport. Its erroneous folding leads to a change in the conformation into a β-sheet and aggregation into larger structures that may have neurotoxic effects, e.g. by impaired axonal transport or synaptic dysfunction [37]. Neurological deficits are visible in the area of motor functions (e.g. ataxia), but there are also problems with memory, unexplained pain, mood and sleep disturbances [38].

In the aging global population, we can observe an increase in the incidence of Parkinson's disease [39]. According to data from 2017, about 1 million people are struggling with this disease, most often they are elderly people around the age of 60, although the disease is more and more often diagnosed in much younger patients, even around the age of 40 [40]. It is

estimated that by 2030 the number of people with PD will increase by over 50% [41]. Metabolic diseases are one of the risk factors for neurodegenerative disorders [42], therefore diabetics are approximately twice as likely to develop dementia [43].

Diabetic patients are more prone to PD [44]. It is associated with the participation of insulin resistance and chronic microglial inflammation in the pathogenesis of PD [44]. The study shows [45] that α-synuclein reduces the activity of the insulin signaling pathway by abnormal activation of P13 K, AKT, mTORC1 pathways, and also due to activation of JNK [45]. This causes, for instance reduction of tissue sensitivity to insulin and loss of homeostasis [45]. Insulin resistance, initiated by aggregation of alpha-synuclein, enhances its accumulation, which is the self-propelling mechanism of PD [46].

Incretin drugs used in the treatment of diabetes, i.e. glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), can find their application in the treatment of Parkinson's disease by influencing the mechanisms causing it [47]. The positive effect of incretin drugs in patients with PD is indicated by a study [48] involving 45 patients with non-coexisting diabetes who were administered exendin-4 for 12 months, a significant improvement in physical activity and cognitive parameters was observed by an average of 2.7 points on the MDS-UPDRS. Moreover, 12 months after the end of drug administration, these parameters did not change. Phase II double-blind studies confirmed the previous findings [48]. GLP-1 may help not only in the treatment of Parkinson's disease, but also in other neurodegenerative diseases due to its positive effect on cognitive-motor function [49]. Stimulation of the GLP-1 receptor increases the expression of complex I, formed in the basal cytoplasm from cytochrome c and the Apaf-1 protein, and Bcl-2, and also reduces the activation of caspase-3, which allows the maintenance of mitochondrial function in dopaminergic neurons and translates into improved levels of striatal dopamine in diabetics with PD [50].

GLP-1 analogs are capable of crossing the blood-brain barrier. They show neuroprotective effects of GLP-1 receptor stimulation and improvement in both motor and non-motor disorders [51]. A study conducted with the use of a GLP-1 receptor agonist showed increased proliferation and decreased

degradation of pancreatic β cells, decreased gluconeogenesis and increased insulin production [52]. Exendin-4 protects pancreatic β cells by improving mitochondrial function and inactivating FOX01. Reversal of biochemical and behavioral deficits after the use of GLP-1 analogues has also been reported [52].

The same is true of the sister hormone GIP, which as a growth hormone is important in resuming the body's use of energy (this drops significantly with PD). GIP analogues reduce the inflammation of cells of the immune system. Improvement in motor activities and exploratory behavior was also noted [53]. It is very important for the function of nerve cells and the connections between them that both hormones are growth hormones – thus the number of synapses is maintained [54].

After many studies showing the positive effect of incretin drugs on the course of PD, other therapies have been explored. Rosiglitazone, a thiazolidinedione drug, lowers glucose levels by improving the insulin sensitivity of cells. Its main task is to regulate the formation of new cells that build adipose tissue together with glucose and metabolism [55]. In the experiment from 2016, the degeneration of dopaminergic cells in rodents was achieved (so that, similarly to Parkinson's disease, cytoplasmic Lewy bodies, oxidative stress and characteristic stiffness were produced). Thanks to these actions, it has been proven that therapy with a drug from the thiazolidinedione group responds to inflammation in the body, with the weakening of the activity of central nervous system cells, with pro-inflammatory cytokines, oxidative stress and astrocytic gliosis. Additionally, it inhibits a very important enzyme in the metabolism of dopamine [45].

The data from the United Kingdom Clinical Practice Research Datalink (CPRD) database on the incidence of PD in diabetics depending on the medications taken was also analyzed. In people taking rosiglitazone, the incidence of PD was 28% lower than in people taking other drugs for diabetes [21].

Influence on vascular diseases of central nervous system

Worldwide, stroke is the second leading cause of death and the third leading cause of disability [56]. Currently, early reperfusion is the only FDA-approved

therapy proven to be highly effective and to reduce disability in patients undergoing intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT) [58–60].

Due to the high number of deaths, more and more researchers are trying to develop complementary treatment strategies that would reduce damage to nerve cells or even help renew them. Drugs used in the treatment of diabetes mellitus type 2 (DM2) are also of great interest, especially GLP-1 analogs (glucagon like peptide-1), with liraglutide being a representative of which. Many data suggest that it may have neuroprotective effects [59]. Liraglutide is widely used in the treatment of diabetes mellitus type 2, administered subcutaneously once a day and in obesity [61]. The mechanism of action leads to binding GLP-1 to the glucagon-like peptide-1 receptor (GLP-1R) and secrete insulin in a glucose-dependent manner, and cause lowers of glucose level. Activation of GLP-1R also leads to the induction of proliferation and increased resistance to apoptosis of beta cells. It exerts glucoregulatory effect via slowing of gastric emptying and glucose-dependent inhibition of glucagon secretion [62]. For potentially and neurological benefits, it is important that it crosses the blood brain barrier (BBB) [63] and it is also dipeptidyl peptidase-IV (DPP-4) resistant analogues of human GLP-1 [64].

The result of ischemia, in particular late reperfusion, is the production of reactive oxygen metabolite, which in turn contribute to the activation of processes leading to cell death [65]. Clinical research suggests that liraglutide is a neuroprotective agent, it may prevent apoptosis and reduce oxidative stress [66] and also has antioxidant effects and increases the level of vascular endothelial growth factor (VEGF). On the report of Steven P Marso et al. [67] liraglutide reduced the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus. According to Zhu et al. [68] liraglutide reduced infarct volume caused by the occlusion of middle cerebral artery occlusion (MCAO), decreased neurological deficits and decreased stress-induced hyperglycemia. Liraglutide inhibited cell apoptosis by reducing reactive oxygen stages (ROS) as well, increased the expression level of the anti-apoptotic Bcl-2 and Bcl-xl proteins, while it decreased the expression

level of the pro-apoptotic Bax and Bad proteins. As stated by Briyal S et al. [69] the administration of liraglutide for 14 days before induction of MCAO markedly attenuated infarct volumes, neurological deficit and the reduction of oxidative stress markers. Terminal deoxynucleotidyl transferase (TdT) dUTP Nick-End Labeling (TUNEL) assay has been designed to detect apoptotic cells that undergo extensive DNA degradation during the late stages of apoptosis [70]. As a result of the TUNEL analysis of cells, the number of TUNEL-positive cells was significantly reduced. In many publications based on preclinical studies, GLP-1 mimetics influence the acute inflammatory response secondary to ischemia by reducing the release of proinflammatory cytokines and biomarkers of oxidative stress [71] Jin et al. [72] introduced that exenatide significantly reduced the expression of hypoxia-inducible factor-1α (HIF-1α), which stimulates the expression of inflammatory cytokines, influencing cell apoptosis after ischemic stroke [74]. High doses of exenatide (50 μg/kg) delivered 1.5 and 3 hours after the ischemic episode has shown neuroprotective effects, but the effect disappeared when the drug was administered later [75]. Experimental studies by Basalay et al. [76] compared the effects of two GLP-1 analogues, liraglutide and semaglutide. The functional neuroprotective effects of liraglutide in a rat model of acute ischemic stroke have been shown to be dose-dependent, and both drugs reduce infarct size. It should be noted that this effect was observed when liraglutide was administered 90 minutes of middle cerebral artery occlusion (MCAO), but not in the 120 and 180 minutes ischaemia. It is related to the difference in infarct progression in the brain of rats vs. humans [77, 78]. Therefore, more research is needed in order to draw conclusions about the effectiveness of liraglutide in acute cerebral ischemia of humans.

Conclusion

Cognitive functions deteriorate among older people [2]. Some factors of these processes are unknown [3], others relate to DM [12]. As DM is connected with higher risk of Alzheimer's disease [28] and Parkinson's disease [44], the more important is appropriate treatment. This article shows the

results of the research, which suggest positive role of anti-diabetic drugs in the therapy of neurological diseases [26, 47, 60], not only DM. Some results also indicate the influence of GLP-1 on neurogenesis [34], what can mean that these medicines have improving effect on the cognitive function also among patients without DM but suffering from dementia. The use of anti-diabetic drugs can be a base for the new way of dementia treatment, but further research is needed.

References

1. Talarowska M, Florkowski, Gałecki P, Orzechowska A, Janiak M, Zboralski K. Cognitive impairments among diabetic patients. Pol Merkur Lek 2008 Oct; 25(148): 349–355.

2. Dzierzewski JM, Dautovich N, Ravyts S. Sleep and Cognition in Older Adults. Sleep Medicine Clinics 2018 Mar; 13(1): 93–106. https://doi.org/10.1016/j.jsmc.2017.09.009.

3. Weinstein G, Elran Barak R, Schnaider Beeri M, Ravona-Springer R. Personality traits and cognitive function in old-adults with type – 2 diabetes. Aging Ment Heal 2019 Oct; 23(10): 1317–1325. https://doi.org/10.1080/13607863.2018.1493720.

4. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: A systematic review and metaanalysis. Alzheimer's and Dementia 2013 Jan; 9(1): 63–75.e2. https://doi.org/10.1016/j.jalz.2012.11.007.

5. Nilsson H, Berglund JS, Renvert S. Periodontitis, tooth loss and cognitive functions among older adults. Clin Oral Investig 2018 Jun; 22(5): 2103––2109. https://doi.org/10.1007/s00784-017-2307-8.

6. Kronholm E, Sallinen M, Suutama T, Sulkava R, Era P, Partonen T. Self-reported sleep duration and cognitive functioning in the general population. J Sleep Res 2009 Dec; 18(4): 436–446. https://doi.org/10.1111/j.1365-2869.2009.00765.x.

7. Tworoger SS, Lee S, Schernhammer ES, Grodstein F. The association of self-reported sleep duration, difficulty sleeping, and snoring with cognitive function in older women. Alzheimer Dis Assoc Disord 2006 Jan–Mar; 20(1): 41–48. https://doi.org/10.1097/01.wad.0000201850.52707.80.

8. Paraskevas S, Huizinga JD, Loos BG. A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. J. Clin Periodontol 2008 Apr; 35(4): 277–290. https://doi.org/10.1111/j.1600-051X.2007.01173.x.

9. Schmidt R, Schmidt H, Curb JD, Masaki K, White LR, Launer LJ. Early inflammation and dementia: A 25-year follow-up of the Honolulu-Asia Aging Study. Ann Neurol 2002 Aug; 52(2): 168–174. https://doi.org/10.1002/ana.10265.

10. Noble JN, Scarmeas N, Celenti RS, Elkind MSV, Wright CB, Schupf N, Papapanou PN. Serum IgG antibody levels to periodontal microbiota are associated with incident Alzheimer disease. PLoS One 2014 Dec 18; 9(12): e114959.

11. McGeer PL, Schulzer M, McGeer EG. Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: A review of 17 epidemiologic studies. Neurology 1996 Aug; 47(2): 425–432. https://doi.org/10.1212/WNL.47.2.425.

12. Strachan MWJ, Reynolds RM, Marioni RE, Price JF. Cognitive function, dementia and type 2 diabetes mellitus in the elderly. Nat Rev Endocrinol 2011 Feb; 7(2): 108–114. https://doi.org/10.1038/nrendo.2010.228.

13. Whitmer RA. Type 2 diabetes and risk of cognitive impairment and dementia. Current Neurology and Neuroscience Reports 2007 Sep; 7(5): 373–380. https://doi.org/10.1007/s11910-007-0058-7.

14. LeRoith D, Biessels GJ, Braithwaite SS, Casanueva FF et al. Treatment of Diabetes in Older Adults: An Endocrine Society* Clinical Practice Guideline. J Clin Endocrinol Metab 2019 May 1; 104(5): 1520–1574. https://doi.org/10.1210/jc.2019-00198.

15. Gudala K, Bansal D, Schifano F, Bhansali A. Diabetes mellitus and risk of dementia: A meta-analysis of prospective observational studies. J. Diabetes Investig 2013 Nov 27; 4(6): 640–450. https://doi.org/10.1111/jdi.12087.

16. Abner EL, EL, Nelson PT, Kryscio RJ, Schmitt FA et al. Diabetes is associated with cerebrovascular but not Alzheimer's disease neuropathology. Alzheimer's Dement 2016 Aug; 12(8): 882–889. https://doi.org/10.1016/j.jalz.2015.12.006.

17. Colin LM, Randall B, Kaj B, Christopher CR et al. Alzheimer's disease. Nat Rev Dis Primers 2015 Oct 15; 1: 15056. https://doi.org/10.1038/nrdp.2015.56.

18. Jason W, Andrew B, Current understanding of Alzheimer's disease diagnosis and treatment. F1000Res 2018 Jul 31; 7: F1000 Faculty Rev-1161. https://doi.org/10.12688/f1000research.14506.1. eCollection 2018.

19. Xu W, Yang Y, Yuan G, Zhu W, Ma D, Hu S. Exendin-4, a glucagon-like peptide-1 receptor agonist, reduces Alzheimer disease-associated tau hyperphosphorylation in the hippocampus of rats with type 2 diabetes. J Investig Med 2015; 63(2): 267–272.

20. Barone E, Di Domenico F, Cassano T, Arena A, Tramutola A, Lavecchia MA, Coccia R, Butterfield DA, Perluigi M. Impairment of biliverdin reductase-A promotes brain insulin resistance in Alzheimer disease: A new paradigm. Free Radic Biol Med 2016 Feb; 91: 127–142. https://doi.org/10.1016/j.freeradbiomed.2015.12.012.

21. Talbot K1, Wang HY, Kazi H, Han LY, Bakshi KP, Stucky A, Fuino RL, Kawaguchi KR, Samoyedny AJ, Wilson RS, Arvanitakis Z, Schneider JA, Wolf BA, Bennett DA, Trojanowski JQ, Arnold SE. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance,

IRS-1 dysregulation, and cognitive decline. J Clin Invest 2012 Apr; 122(4): 1316–1338. https://doi.org/10.1172/JCI59903.

22. Steen E, Terry BM, Rivera E, Cannon JL, Neely TR, Tavares R et al: Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease – is this type 3 diabetes? J Alzheimers Dis 2005; 7(1): 63–80.

23. Lester-Coll N, Rivera EJ, Soscia SJ, Doiron K, Wands JR, de la Monte SM: Intracerebral streptozotocin model of type 3 diabetes: relevance to sporadic Alzheimer's disease. J Alzheimers Dis 2006; 9(1): 13–33.

24. Maggi S, Limongi F, Noale M, Romanato G, Tonin P, Rozzini R et al: ILSA Study Group. Diabetes as a risk factor for cognitive decline in older patients. Dement Geriatr Cogn Disord 2009; 27(1): 24–33.

25. Moreira PI. Alzheimer's disease and diabetes: an integrative view of the role of mitochondria, oxidative stress, and insulin. J Alzheimers Dis 2012; 30 (Suppl 2): S199YS215.

26. Efthalia A, Christina P.DPP-4 inhibitors: a promising therapeutic approach against Alzheimer's disease. Ann Transl Med 2018 Jun; 6(12): 255. https://doi.org/10.21037/atm.2018.04.41.

27. Michał W, Karol G, Maciej W, Eryk W et al. Neuroprotective Properties of Linagliptin: Focus on Biochemical Mechanisms in Cerebral Ischemia, Vascular Dysfunction and Certain Neurodegenerative Diseases. Int J Mol Sci 2019 Aug; 20(16): 4052. https://doi.org/10.3390/ijms20164052.

28. Moreira RO, Campos SC, Soldera AL. Type 2 Diabetes Mellitus and Alzheimer's Disease: from physiopathology to treatment implications. Diabetes Metab Res Rev 2013. https://doi.org/10.1002/dmrr.2442.

29. Duarte AI, Moreira, Oliveira CR. Insulin in central nervous system: more than just a peripheral hormone. J Aging Res 2012; 384017–384038.

30. Nehru S Ch, Pindiprolu S SK, Duraiswamy B, Possible role of DPP4 inhibitors to promote hippocampal neurogenesis in Alzheimer's disease. J Drug Target 2018 Sep; 26(8): 670–675. https://doi.org/10.1080/1061186X.2018.1433682. Epub 2018 Mar 2. https://pubmed.ncbi.nlm.nih.gov/29378454/.

31. Michał W, Eryk W, Maciej S, Maciej W et al., Neuroprotective Activity of Sitagliptin via Reduction of Neuroinflammation beyond the Incretin Effect: Focus on Alzheimer's Disease. Biomed Res Int 2018; 6091014. https://doi.org/10.1155/2018/6091014 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6116461/.

32. Ilgin YS, Utku ES, Sevki C. Glucagon like peptide-1 (GLP-1) likes Alzheimer's disease. Diabetes Metab Syndr 2018 May; 12(3): 469–475. https://doi.org/10.1016/j.dsx.2018.03.002. Epub 2018 Mar 16.

33. EA Elbassuoni, RF Ahmed, Mechanism of the neuroprotective effect of GLP-1 in a rat model of Parkinson's with pre-existing diabetes. Neurochem Int 2019 Dec; 131: 104583. https://doi.org/10.1016/ j.neuint.2019.104583. Epub 2019 Oct 22.

34. Jose ASL, Hector MG, Gabriel CL. Alzheimer's disease. Handb Clin Neurol 2019; 167: 231–255. https://doi.org/10.1016/B978-0-12-804766-8.00013-3.

35. Lane CA, Hardy J, Schott JM. Alzheimer's disease. Eur J Neurol 2018 Jan; 25(1): 59–70. https://doi.org/10.1111/ene.13439. Epub 2017 Oct 19.

36. Shuko T, Naoyuki S, Hiromi R, Ryuichi M. Molecular mechanisms linking diabetes mellitus and Alzheimer disease: beta-amyloid peptide, insulin

signaling, and neuronal function. Mol Biosyst 2011 Jun; 7(6): 1822–1827. https://doi.org/10.1039/c0mb00302f. Epub 2011 Mar 24.

37. Heller J, Dogan I, Schulz JB, Reetz K. Evidence for gender differences in cognition, emotion and quality of life in Parkinson's disease? Aging Dis 2013 Oct 22; 5(1): 63–75. https://doi.org/10.14366/AD.2014.050063.

38. Cacabelos R. Parkinson's disease: from pathogenesis to pharmacogenomics. Int J Mol Sci 2017 Mar 4; 18(3): 551. https://doi.org/10.4103/0028-3886.226451.

39. Zhang ZQ, Hölscher C. GIP has a neuroprotective effect in models of Alzheimer's and Parkinson's disease. Peptides November 2020 Mar; 125: 170184. https://doi.org/10.1016/ j.peptides.2019.170184.

40. Hölscher C. Novel double GLP-1/GIP receptor agonists show neuroprotective effects in models of Alzheimer's and Parkinson's disease. Neuropharmacology January 2018 136(Pt B). https://doi.org/10.1016/j.neuropharm.2018.01.040.

41. Kupryjaniuk A, Sobstyl M, Pietras T. Jakość życia, deficyty funkcji poznawczych i depresja w chorobie Parkinsona: Quality of life, cognitive deficits, and depression in Parkinson's disease. Fides et Ratio 2020 December 19; 44(4). https://doi.org/10.34766/fetr.v44i4.434.

42. Rhee SY, Ha K-D, H. Kwon, Park S-E, Park Y-G, Kimet Y-H et al. Association Between Glycemic Status and the Risk of Parkinson Disease: A Nationwide Population-Based Study. Diabetes Care 2020 Sep; 43(9): 2169–2175. https://doi.org/10.2337/dc19-0760.

43. C. Hierro-Bujalance, C. Infante-Garcia, A. Del Marco, M. Herrera, M. J. Carranza-Naval, J. Suarez et al. Empagliflozin reduces vascular damage and cognitive impairment in a mixed mouse model of Alzheimer's disease

and type 2 diabetes. Alzheimers Res Ther 2020 Apr 7; 12(1): 40. https://doi.org/10.1186/s13195-020-00607-4.

44. Lima MMS, Targa ADS, Noseda ACD, Rodrigues LS, Delattre AM, dos Santos FV et al. Does Parkinson's disease and type – 2 diabetes mellitus present common pathophysiological mechanisms and treatments? CNS Neurol Disord Drug Targets 2014 Apr; 13(3): 418–428. https://doi.org/10.2174/18715273113126660155.

45. Bosco D, Plastino M, Cristiano D, Colica C, Ermio C, Bartolo MD et al. Dementia is associated with insulin resistance in patients with Parkinson's disease. J Neurol Sci 2012 Apr 15; 315(1–2): 39–43. https://doi.org/10.1016/j.jns.2011.12.008. Epub 2012 Jan 21.

46. Normando EM, Davis BM, De Groef L, Nizari S, Turner LA, Ravindran N. Retina as an early biomarker of neurodegeneration in a model of rotenone-induced Parkinson's disease: evidence of neuroprotective effects of rosiglitazone in the eye and brain. Acta Neuropathologica Communications 2016 August 18. https://doi.org/10.1186/s40478-016-0346-z.

47. Capriotti T, Terzakis K. Parkinson Disease. Home Healthc Now 2016 Jun; 34(6): 300–307. https://doi.org/10.1097/NHH.0000000000000398.

48. Hölscher Ch. Novel dual GLP-1/GIP receptor agonists show neuroprotective effects in Alzheimer's and Parkinson's disease models. Neuropharmacology 2018 Jul 1; 136(Pt B): 251–259. https://doi.org/10.1016/j.neuropharm.2018.01.040. Epub 2018 Jan 31.

49. Glotfelty EJ, Olson L, Karlsson TE, Li Y, Greig NH. Glucagon – like peptide – 1 (GLP – 1) receptor agonists in the treatment of Parkinson's disease. Expert Opin Investig Drugs 2020 Jun; 29(6): 595–602. https://doi.org/10.1080/13543784.2020.1764534.

50. Athauda D, Foltynie T. Protective effects of the GLP – 1 mimetic exendin – 4 in Parkinson's disease. Neuropharmacology 2018 Jul 1; 136(Pt B): 260–270. https://doi.org/10.1016/j.neuropharm.2017.09.023.

51. Ashraghi MR, Pagano G, Polychronis S, Niccolini F, Politis M. Parkinson's Disease, Diabetes and Cognitive Impairment. Recent Pat Endocr Metab Immune Drug Discov 2016; 10(1): 11–21. https://doi.org/10.2174/1872214810999160628105549.

52. Elbassuoni EA, Ahmed RF. Mechanism of the neuroprotective effect of GLP – 1 in a rat model of Parkinson's with pre-existing diabetes. Neurochem Int 2019 Dec; 131: 104583. https://doi.org/10.1016/j.neuint.2019.104583.

53. Trist BG, Hare DJ, Double KL. Oxidative stress in aging substantia nigra and the etiology of Parkinson's disease. Aging Cell 2019 Dec; 18(6): e13031. https://doi.org/10.1111/acel.13031.

54. Quintanilla BSR, Correa R. Rosiglitazone. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan.

55. Brauer R, Bhaskaran K, Chaturvedi N, Dexter DT, Smeeth L, Douglas I. Glitazone treatment and Parkinson's disease in people with diabetes: a retrospective cohort study. PLoS Med 2015 July 21; 12(7): e1001854. https://doi.org/10.1371/journal.pmed.1001854.

56. Walter J, Oyere O, Mayowa O, Sonal S. Stroke: a global response is needed. Bulletin of the World Health Organization 2016 Sep 1; 94(9): 634–634A. https://doi.org/10.2471/BLT.16.181636.

57. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ et al. A randomized trial of intraarterial treatment for acute ischemic stroke. Clinical Trial N Engl J Med 2015 Jan 1; 372(1): 11–20. https://doi.org/10.1056/NEJMoa1411587. Epub 2014 Dec 17.

58. Campbell BCV, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi NF et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. Randomized Controlled Trial N Engl J Med 2015 Mar 12; 372(11): 1009–1018. https://doi.org/10.1056/NEJMoa1414792. Epub 2015 Feb 11.

59. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. Randomized Controlled Trial N Engl J Med 2015 Mar 12; 372(11): 1019–1030. https://doi.org/10.1056/NEJMoa1414905. Epub 2015 Feb 11.

60. Wiciński M, Socha MJ, Malinowski B, Wódkiewicz E, Walczak M, Górski K et al., Liraglutide and its Neuroprotective Properties-Focus on Possible Biochemical Mechanisms in Alzheimer's Disease and Cerebral Ischemic Events. Int J Mol Sci 2019 Mar; 20(5): 1050.

61. Sfairopoulos D, Liatis S, Tigas S, Liberopoulos E. Clinical pharmacology of glucagon-like peptide-1 receptor agonists. Hormones (Athens) 2018 Sep; 17(3): 333–350. https://doi.org/10.1007/s42000-018-0038-0. Epub 2018 Jun 12.

62. Baggio L, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology 2007 May; 132(6): 2131–2157. https://doi.org/10.1053/j.gastro.2007.03.054.

63. Hunter K, Hölscher C. Drugs developed to treat diabetes, liraglutide and lixisenatide, cross the blood brain barrier and enhance neurogenesis. BMC Neurosci 2012 Mar 23; 13: 33. https://doi.org/10.1186/1471-2202-13-33.

64. Stephens JW. The incretin system in the management of type 2 diabetes mellitus. Clin Med (Lond) 2010 Oct; 10(5): 491–495. https://doi.org/10.7861/clinmedicine.10-5-491.

65. Rejdak K, Słowik A. Patogeneza udaru niedokrwiennego mózgu – możliwości neuroprotekcji i stymulowania plastyczności mózgu. Polski Przegląd Neurologiczny 2018; 14(4): 230–239.

66. Sato K, Kameda M, Yasuhara T et al. Neuroprotective effects of liraglutide for stroke model of rats. Int J Mol Sci 2013; 14(11): 21513–21524. Published 2013 Oct 30. https://doi.org/10.3390/ijms141121513.

67. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2016 Jul 28; 375(4): 311–322. https://doi.org/10.1056/NEJMoa1603827. Epub 2016 Jun 13.

68. Zhu H, Zhang Y, Shi Z, Lu D, Li T, Ding Y, Ruan Y, Xu A. The neuroprotection of liraglutide against ischaemia – induced apoptosis through the activation of the PI3K/AKT and MAPK pathways. Sci Rep 2016; 6: 26859. https://doi.org/10.1038/srep26859.

69. Briyal S, Shah S, Gulati A. Neuroprotective and anti-apoptotic effects of liraglutide in the rat brain following focal cerebral ischemia. Neuroscience 2014; 281: 269–281. https://doi.org/10.1016/j.neuroscience.2014.09.064.

70. Kyrylkova K, Kyryachenko S, Leid M, Kioussi C. Detection of apoptosis by TUNEL assay. Methods Mol Biol 2012; 887: 841–847. https://doi.org/10.1007/978-1-61779-860-3_5.

71. Kuroki T, Tanaka R, Shimada Y, Yamashiro K, Ueno Y, Shimura H. Exendin-4 Inhibits Matrix Metalloproteinase – 9 Activation and Reduces Infarct Growth After Focal Cerebral Ischemia in Hyperglycemic Mice. Stroke 2016 May; 47(5): 1328–1335. https://doi.org/10.1161/STROKEAHA.116.012934. Epub 2016 Mar 15.

72. J. Jin , H. Kang, J. Jung, J. Jeong, C. Park Related expressional change of HIF – 1α to the neuroprotective activity of exendin – 4 in transient global ischemia. Neuroreport 2014 Jan 8; 25(1): 65–70. https://doi.org/10.1097/WNR.0000000000000046.

73. Jiang Q, Geng X, Warren J, E. Eugene Paul Cosky , S. Kaura , C.Stone et al. Hypoxia Inducible Factor – 1α (HIF – 1α) Mediates NLRP3 Inflammasome – Dependent – Pyroptotic and Apoptotic Cell Death Following Ischemic Stroke Neuroscience 2020 Nov 10; 448: 126–139. https://doi.org/10.1016/j.neuroscience.2020.09.036. Epub 2020 Sep 22.

74. Darsalia V, Hua S, Larsson M, Mallard C, Nathanson D, Nyström T et al. Exendin-4 reduces ischemic brain injury in normal and aged type 2 diabetic mice and promotes microglial M2 polarization PLoS One 2014 Aug 7; 9(8): e103114. https://doi.org/10.1371/journal.pone.0103114. eCollection 2014.

75. Basalay MV, Davidson SM, Yellon DM. Neuroprotection in Rats Following Ischaemia-Reperfusion Injury by GLP – 1 Analogues – Liraglutide and Semaglutide, Cardiovasc Drugs Ther 2019; 33(6): 661–667. https://doi.org/10.1007/s10557-019-06915-8.

76. Memezawa H, Smith ML, Siesjö BK. Penumbral tissues salvaged by reperfusion following middle cerebral artery occlusion in rats. Stroke 1992 Apr; 23(4): 552–559. https://doi.org/10.1161/01.str.23.4.552.

77. Powers WJ, Rabinstein AA, Ackerson T et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2018; 49: e46–110. https://doi.org/10.1161/STR.0000000000000158.