The gut microbiota affects the severity of Alzheimer's disease

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Current treatment methods and modern medicines keep people alive ever longer, however the longer we live, the more age-related diseases we can face to. A typical disease of such type is dementia. The most common cause of dementia is Alzheimer's disease (AD) a multifactorial disease, thus environmental factors, in addition to genetics, have a significant impact on its development. Several studies suggest, that one of such factors is the gut microbiome. In this review we discuss the potential impact of gut microbiota in the development of AD and the mechanisms of bacteria-related neurodegenerative processes.
Keywords: Alzheimer's disease, microbiome, neurodegenerative processes

Črevný mikrobióm ovplyvňuje závažnosť Alzheimerovej choroby
Súčasné metódy liečby a moderné liečivá udržujú ľudí nažive čoraz dlhšie, s tým však prichádzajú aj ďalšie s vekom spojené ochorenia. Typickým ochorením tohto typu je demencia. Najčastejšou príčinou demencie je Alzheimerova choroba (AD), multifaktoriálne ochorenie, takže okrem genetiky majú významný vplyv na jej vývoj faktory životného prostredia. Viaceré štúdie naznačujú, že jedným z týchto faktorov je črevný mikrobióm. V tomto prehľade sa zameriame na potenciálny vplyv črevného mikrobiómu pri rozvoji AD a mechanizmy, ktorými môžu baktérie iniciovať neurodegeneratívne procesy.
Kľúčové slová: Alzheimerova choroba, mikrobióm, neurodegeneratívne procesy

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Introduction

Neurological disorders are the third most common cause of death in the Slovakia accounting for nearly 3600 deaths in 2017. According to GHDx database Alzheimer's disease (AD) and other dementias are responsible for 83,5% of this mortality. In 2017 there were approximately 45 million patients with Alzheimer's dementia worldwide[(1)]. It is estimated, there is a new case in the world every three seconds[(2)]. Most of caregivers for AD patients come from family members suffering significant emotional and physical difficulties which has a devastating effect on these persons. Moreover, health care for AD patients is very expensive, therefore it is one of the most expensive diseases in the world[(3)].

AD is a neurodegenerative disease with a multifactorial etiology, based on genetic and environmental risk factors, that affects the brain. Many epidemiological studies suggest that one of the factors that significantly increases the risk of AD is obesity[(4)]. Obese patients have deficits in learning, memory and cognitive perception compared to patients who are not obese[(5)]. Although, there are several studies that controvert these findings[(6)], the most publications suggest, that obesity has a negative impact on neurodegenerative diseases.

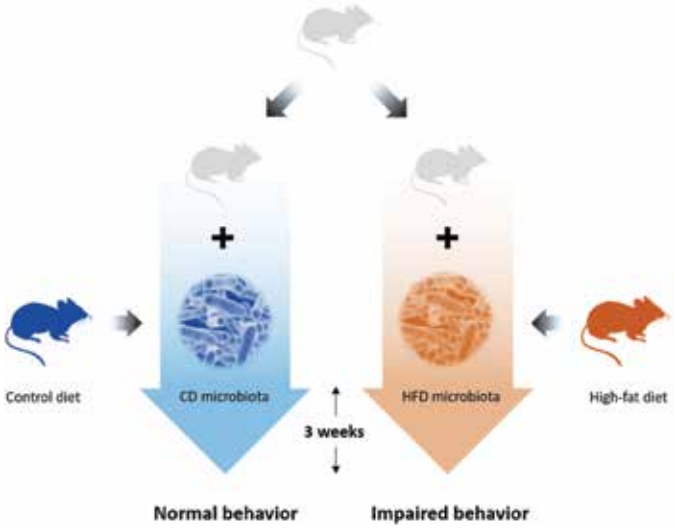
Effect of gut microbiota on the central nervous system

There are findings that obesity increases the risk of AD independently of its accompanying phenomena such as hypertension, dyslipidemia, diabetes and others[(4)]. It suggests the existence of other mechanism by which obesity affects the development of the disease. It is known, that a specific type of intestinal microbiome is associated with the obesity, and number of emerging studies exploring the potential effect of gut microbiome on the central nervous system (CNS) is increasing[(7)]. Animal studies have shown that germ-free (GF) mice had increased motor activity and reduced anxiety behavior compared to mice with normal intestinal microbiome. In addition, this phenotype was normalized after colonization of GF mice with normal microbes. After colonization of GF mice, their behavior was more similar to mice with normal microbiome. This experiment confirms that the intestinal microflora can influence the development of mammalian brain, and consequently their adult behavior[(8)].

Study by Bruce-Keller et al. provide a clearer answer, if the intestinal microbes associated with obesity damages the CNS ***(Figure 1)***. Two groups of mice of the same origin were prepared. One group of mice was colonized with intestinal microbiota from High-Fat Diet (HFD) subjects. The second group consisted of mice colonized with microbiome obtained from subjects on a control diet. After 3 weeks, phenotypic differences were observed between the two groups. Mice colonized with HFD-associated microbiota have been shown to have significantly impaired exploratory, cognitive, and stereotypical behaviors. This is the first experiment that demonstrates that intestinal microbiota associated with a fat diet damages the physiology and function of the brain independently of obesity. Mice were not altered in any way and there was no adiposity or metabolic syndrome[(9)].

Although it has been confirmed that the gut microbiome affects the CNS, the mechanism by which bacteria affect the behavior of the host is still unclear. Several theories have been described in this connection, but further studies are needed to verify them.

Figure 1. Scheme of experiment by Bruce-Keller et al. Transplantation of microbiota shaped by high fat diet (HFD), but not control diet (CD), caused significant disruptions in exploratory, cognitive, and stereotypical behavior in mice.



Direct interaction with CNS

There is theory about a direct interaction of the intestinal microbiota with the CNS of the host through the vagus nerve, which directly connects the intestine with the brain. Bacteria have been found to synthesize neuroactive agents such as catecholamines, histamine, and other components that can stimulate host neurophysiology. However, bacteria can not only produce but also recognize these substances, suggesting that there may be two-way communication between the host and the microbiome. In other words, the microbiota affects the host, and the host may affect the microbiota[10].

Extracellular amyloid proteins

Amyloids are protein aggregates, with a β-sheet structure, formed by amyloid fibers produced by incorrect protein folding or misfolding. More than 60 proteins that produce amyloid fibers have been described[11]. Several of them have been shown to have some function in the human body, such as protecting melanocytes from toxicity. Also, some peptide hormones have amyloid-like structure during their storage in secretory granules[12]. In several studies, accumulation of amyloid fibers in some organs has been associated with neurodegenerative disorders, including AD[12-14]. Bacteria that occur in the human digestive tract have also been found to produce extracellular amyloid proteins that are biochemically similar to amyloid structures associated with neurodegenerative diseases. Amyloids have been detected in naturally occurring bacterial populations of Proteobacteria, Bacteriodetes, Chloroflexi, Actinobacteria and Firmicutes[13]. In bacteria, these proteins serve as molecular scaffolds that hold bacteria together and play a role in biofilm formation, e.g. the extracellular amyloid protein called Curli, produced in *Escherichia coli*[15].

It seems that bacterial amyloids may induce neurodegeneration in the human body by multiple mechanisms. One of them is the so-called cross-seeding[16]. It is the ability of amyloids to produce seeds that can spread to new tissues and then multiply. In this way, amyloids could induce misfolding of neural proteins and consequently the development of AD[17].

Inflammation

Immune activation and inflammation are associated with almost the all neurodegenerative diseases. Many studies even suggest, inflammation has a causal role in the pathogenesis of AD(18). Bruce-Keller et al. showed that HFD-associated microbiota increases systemic and brain inflammation in mice. They found Toll-Like Receptor 2 (TLR2) overexpression in lymphocytes[9]. TLR plays an important role in protection of the host from invading microbes. Studies suggest that the TLR2/TLR1 complex can recognize amyloids produced by Firmicutes, Bacteroidetes, and Proteobacteria. Activation of microglial TLR2 induces cytokine production, inflammation, phagocytosis and innate immune defense responses that directly impact CNS homoeostasis and drive neuropathology[19]. It is remarkable that microbial amyloids induce pro-inflammatory cytokines IL-17 A and IL-22, the same cytokines that are often associated with AD[20].

Protective effect of diet in the prevention of Alzheimer's disease

It is now well known that diet has an important role in shaping the intestinal microbiota. Different dietary habits and/or access to food cause significant differences in the taxonomic composition of the intestinal microbiota between some populations[21]. Several epidemiological studies suggest that certain types of diet have a protective effect on cognitive perception and reduce the risk of dementia. Dietary Approaches to Stop Hypertension (DASH) and a Mediterranean diet (MD) were found to have been associated with a slower rate of cognitive decline in elderly[22]. Subsequently, the hybrid Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet, combining a MD and a DASH diet, was created. The MIND diet emphasizes the dietary components associated with neuroprotection and prevention of dementia. It was shown, such diet significantly reduced the incidence of cognitive disorders and the risk of AD[23]. The microbiota associated with the MIND diet has not been described yet, but several studies focuses on the MD, which was also associated with a lower risk of Alzheimer's disease. These studies suggest, the MD promotes the microbiota with a health benefit for the human body[21]. Based on these results, we assume that the MIND diet should also promotes the composition of the microbiota reducing the risk of AD.

Conclusions

AD is a relatively common disease that brings many complications not only for the patients themselves, but also for family members and the financial budget. Therefore, the disease is being given great attention and scientists are attempting to devise new therapeutic approaches. This review suggests that certain types of diet are associated with a particular gut microbiota that can affect the CNS. Several mechanisms, how bacteria may drive neuropathology e.g. direct interaction with hosts CNS, amyloid proteins production or stimulation of inflammation, have been described. Based on these findings, modulation of gut microbiota through dietary approaches, probiotics or antibiotics intervention and fecal microbiota transplantation could reduce the prevalence and severity of AD.

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