The influence of dimethyl fumarate on the spatial memory and neurogenesis in the rat model of Alzheimer's disease

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The sporadic form of Alzheimer's disease (sAD) affects over 95% of AD patients, it is nonhereditary and mainly related to environmental factors. One of the earliest symptoms of AD include disturbances in orientation and spatial memory, as well as olfactory deficits. Disruption of the postnatal neurogenesis in the hippocampus and olfactory bulb (OB) may be the main mechanism underlying these abnormalities. The animal model of an intracerebroventricular injection of streptozotocin (STZ-ICV) which reflects behavioural and neurochemical changes occurring in patients with sAD, is commonly used for studying sAD pathophysiological mechanisms and testing new therapeutic approaches. Currently, there are only 6 approved drugs for AD treatments, but none of them is able to effectively modify the course of the disease or stop its development. **The main aim of my study was to evaluate the effectiveness of dimethyl fumarate (DMF) in alleviating spatial memory and neurogenesis disorders in the rat model of sAD evoked by STZ-ICV.** DMF has antioxidant, anti-inflammatory and neuroprotective properties, and its effectiveness has been confirmed in the treatment of another neurodegenerative disease - multiple sclerosis. Changes associated with aging are one of the main risk factors for AD development, therefore **the next aim of this study was to verify the hypothesis that the age of animals has significant impact on the activity of both - STZ and DMF.**

Study was performed on young (n=28) and aged (n=28) male Wistar rats, divided into 4 experimental groups: STZ (n=7) – subjected to STZ-ICV (3 mg/b.w.), STZ+DMF (n=7) – subjected to STZ-ICV and 26-day DMF therapy (0.4% in feed), Sham+DMF (n=7) – subjected to ICV of the citrate buffer and DMF therapy, Sham (n=7) – subjected to ICV of the citrate buffer. Spatial cognitive processes, including the acquisition and functioning of long-term reference memory, and the performance of short-term working memory in animals were assessed in the Morris water maze test. The level of postnatal neurogenesis processes in the dentate gyrus of the hippocampus (DG) and in the OB, including new nerve cells ($BrdU^+$) proliferation, immature neurons (DCX^+) survival, as well as the differentiation and survival of immature neurons newly formed during the experiment ($BrdU+DCX^+$) were assessed on brain sections in animals previously subjected to behavioural procedures using immunohistochemistry methods and fluorescent microscopy.

I demonstrated that STZ-ICV caused severe impairments in the acquisition and functioning of spatial reference and working memory. Postnatal neurogenesis disorders may be the neuronal basis of these cognitive abnormalities. I observed deficits in the proliferation of new nerve cells, and a reduction in immature neurons differentiation and survival in the DG and OB of rats subjected to STZ-ICV. The obtained results indicate that DMF therapy significantly alleviated the effects induced by the central activity of STZ in the context of spatial cognitive processes. DMF therapy also contributed to the attenuation of STZ-ICV-induced disorders of postnatal neurogenesis in the DG and OB. In this study, I showed a significant impact of age on STZ activity - aged rats subjected to STZ-ICV were characterized by a higher

level of disturbances in spatial orientation and memory, and stronger disorders of postnatal neurogenesis than younger rats. DMF therapy was effective in reducing STZ-induced deficits in both age groups of rats, however, the obtained results suggest that age can modify the therapeutic potential of DMF - young rodents were characterized by significantly higher levels of the examined parameters in the DG and OB compared to aged rats subjected to STZ-ICV and DMF therapy.

The results of this study demonstrate the important role of postnatal neurogenesis disorders in AD pathogenesis, especially in the context of deficits in cognitive functions - spatial learning and memory, which may be an early diagnostic marker of AD development in humans. The obtained results may also contribute to better understanding of the modifying effect of age on the effects induced by STZ-ICV in the animal model of sAD, as well as on the therapeutic potential of DMF. The therapeutic effectiveness of DMF in alleviating cognitive disorders and disruption of postnatal neurogenesis, which was confirmed in this study, suggests that this substance may be a new promising therapeutic agent in limiting the development of AD and/or delaying the onset of symptoms in patients affected by this disease.