Alzheimer's disease (AD) is characterized by a progressive decline of cognitive functions. Comparative studies identified that there are no detectable signs of drug-induced changes in cognitive functions in healthy animals brain versus diseased brain, therefore, to see decreased behavioral manner of AD suffered animals needs to mimic all specific features of the disease [1]. More evidence suggests the early role of reactive oxygen species in AD major source of which is the mitochondria [2]. The mitochondrial poisoning hypothesis of AD underlying is based on the fact that in human post-mortem AD brains the complex IV activity declines [3]. Inhibition of this complex could be evoked by chronic subcutaneous sodium azide (NaN₃) treatment via implanted osmotic minipumps in animals [4]. For screening, however, minipumps are not ideal tools due to high cost, one-time usability and long treatment time. We developed a new method to produce AD-like dementia by selective inhibition of cytochrome c complex using intraperitoneally (ip.) injected NaN₃ for 5 days with a subsequent reduction to 10 mg/kg/day in rats. These results show that treatment regime of 12.5 mg/kg/day NaN₃ than reduced to 10 mg/kg/day had significantly longer escape latency. To investigate NaN₃-induced interactions we measured the animals’ spontaneous locomotor activity (SMA), and the weight of their body and adrenal glands.

Results and Discussion

According to swimming velocity results the observed effects developed without the loss of movement ability. 24 hours after the last NaN₃ treatment SMA, body and adrenal glands weights of animals in any of the NaN₃-treated group did not differ from the control, indicating the lack of any non-specific effect (e.g. stress). Measurement of corticosteron-regulated immunological markers (IL-8, IL-10) is in progress. Detailed histopathology of the different regions of brain was performed at the termination of the study. Neuronal degeneration and necrosis were seen in the cortical and hippocampal areas in the treated rats. Pathological changes in the ultrastructure of mitochondria and glial cells were detected in NaN₃-treated animals suggesting some degree of disruption of blood–brain barrier. Significant loss of neurons was detected in the hippocampal CA1 and CA3 regions. Ki67 immunohistochemistry to evaluate neurogenesis demonstrated decreased rate of cellular proliferation in the dentate gyrus of the treated rats.

These results show that treatment regime of 12.5 mg/kg/day ip. NaN₃ for 5 days with a subsequent reduction to 10 mg/kg/day for the following 9 days is a suitable method to produce dementia in rats.

We confirmed that with the ip. injection method of NaN₃ for 15 days produces comparable level of dementia caused by 31 days infusion of NaN₃ using implanted osmotic minipumps in rats. In summary, our developed new treatment regime seems to be an improved method for pharmacological screening of neuroprotective compounds, where low cost, reproducibility and short experiment time are required.

References.