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Anxiolytic and cognition enhancing effects of the novel 1,4-dihydropyridine derivative in transgenic Alzheimer's disease model-mice

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Our previous studies have shown the ability of 1,4-dihydropyridine (DHP) derivatives to produce neuroprotective (Klusa V, 1995), anti-inflammatory (Klegeris A et al., 2002; Pupure J et al., 2008) and mitochondria-regulating (Velena A et al., 1997) activities. These features are considered as essential to prevent/treat the neurodegenerative processes in Alzheimer's disease. The present study investigated the novel cationic amphiphilic DHP derivative ESF-M1, suggesting its ability to penetrate easily the blood-brain barrier, and thus produce a long-term improvement of behaviour, particularly cognitive responses.

Methods. ESF-M1 was administered (1mg/kg, i.p.) daily for three weeks in three months old male (n=9) and female (n=10) transgenic Alzheimer's disease APP_{SweDI} model-mice (Davis et al., 2004). Saline was injected in control animals. The assessment of the anxiety levels and cognitive performances was carried out from the beginning of the third week using elevated plus-maze, light-dark box, sociability apparatus and water maze. All behavioral tests were done 3h after injection. After the termination of the behavioural procedures, the animals were anesthetized and perfused transcardially with a cold saline solution, followed by 4% buffered paraformaldehyde solution. The brains were cut on freezing sliding microtome in 30 µm thin sections, and were stained with antibodies against amyloid β, GFAP (glial fibrillary acidic protein), Iba-1 (ionized calcium binding adaptor molecule 1), GAD67 (glutamate decarboxylase 67) and VGAT (vesicular GABA transporter). The intensity of staining was quantified with densitometric analysis.

Results. DHP derivative ESF-M1 significantly increased the time spent in open arms of the elevated plus-maze in both female and male mice, whereas the time spent in the light compartment of the light-dark box was significantly increased only in male animals. In the social recognition test, no changes were observed between groups. ESF-M1 treatment considerably improved the spatial learning performance in Morris water maze test in mice of both sexes.

Immunohistochemical assessment showed that ESF-M1 significantly increased GAD67 and VGAT immunoreactivity in the *cingulate cortex* and *hippocampus*. However ESF-M1 administration did not significantly change the amyloid beta load and inflammation levels (GFAP and Iba-1) in the brain of these mice compared with saline treated-animals.

Statistics. For the statistical analysis, GraphPad Prism 5 software was used. The results are expressed as the mean ± SEM, and the level of significance for the behavioural and immunohistochemical studies was $*p < 0.05$ vs saline control group (unpaired t-test). Male mice (n=9) and female mice (n=10).

Conclusion: These data show that the novel cationic amphiphilic DHP derivative ESF-M1 induces the anxiolytic effect and enhances cognitive behaviour probably through the increasing GABAergic transmission in the brains of transgenic Alzheimer's disease APP_{SweDI} model-mice. One may suggest ESF-M1 as molecule comprising pharmacophores that can be beneficially used for the design of novel drugs useful for the therapy of mild cognitive impairment, a typical early syndrome of Alzheimer's disease.

References. Davis J et al., (2004) J Biol Chem 279: 20296-20306; Klegeris A et al., (2002) Eur J Pharmacol 441: 203-208; Klusa V (1995) Drugs of the Future 20: 135-138; Pupure J et al., (2008) Basic Clinical Pharmacology & Toxicology 26: 620-631; Velena A et al., (1997) Cell Biochem Function 15: 211-220.

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