Neuroinflammation and acetylcholinesterase overexpression as the main targets for low doses of GABA-A receptor agonists in Alzheimer's disease rat model

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Background. Deficiency in GABAergic signalling potentiates neuroinflammation, one of the key factors in the early stages of Alzheimer’s disease (AD) (Crowley et al., 2016). Previously, it was reported that relatively high doses (about 1-10 mg/kg) of the GABA-A receptor agonists muscimol (GABA site agonist) and diazepam (bezodiazepine site agonist) impair cognitive responses (Castellano and McGaugh, 1990). In the present study, we investigate for the first time the effects of these drugs at low doses, which do not produce any tranquilizing action, on spatial memory, expression of cortical and hippocampal proteins related to neuroinflammation and neurotransmitter synthesis in a rat model of AD.

Methods. A non-transgenic rat model of AD was obtained by intracerebroventricular injection of streptozocin (STZ, 750 microgram/10 microliter) in male Wistar rats. Animals were pre-treated intraperitoneally with saline (control), muscimol (0.01 and 0.05 mg/kg) and diazepam (0.05 and 1 mg/kg) for three days and for four consecutive days during water maze training. Two weeks after STZ administration, spatial learning/memory performance was assessed. Ex vivo, astrocyte marker glial fibrillary acidic protein (GFAP) and GABA synthesizing glutamate decarboxylase-67 (GAD67) expression in the hippocampus and cortex, and the expression of dopamine synthesizing tyrosine hydroxylase (TH) in the substantia nigra were assessed immunohistochemically, and acetylcholinesterase (AChE) expression was detected histochemically.

Results. At the tested doses, both muscimol and diazepam protected against STZ-induced spatial memory impairment, prevented STZ-induced neuroinflammation by decreasing GFAP, and normalizing AChE expression. Neither STZ nor drugs did not significantly alter TH and GAD67 expression.

Conclusions. We suggest that memory-enhancing effect of low doses of both GABA-A receptor site agonists muscimol and diazepam is based on their anti-inflammatory action and intensification of the cholinergic system, probably mediated via non-specific regulatory pathways. Obtained results indicate the usefulness of low doses of GABA-A receptor agonists for the treatment of AD in the early stages.

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