

Research Number 6:

Evaluation of nootropic activity of telmisartan and metformin on diazepam-induced cognitive dysfunction in mice through AMPK pathway and amelioration of hippocampal morphological alterations

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Abstract

Cognitive impairments such as dementia are considered the biggest challenges for public health. Benzodiazepines are often prescribed for treatment of anxiety disorder but they are associated with elevated risk of dementia. The present study has been designed to evaluate the neuroprotective effect of telmisartan and metformin on diazepam-induced cognitive dysfunction in mice. Piracetam was used as an established nootropic agent. Mice were divided into 8 groups, group1; control group which received normal saline. groups 2, 3 and 4 were received telmisartan 0.3mg/kg/day, metformin 100 mg/kg/day and piracetam 200mg/kg/day respectively. group 5; DZP group that injected with diazepam 2.5 mg/kg, groups 6, 7 and 8 were received diazepam 2.5 mg/kg+telmisartan 0.3mg/kg/day, metformin 100 mg/kg/day and piracetam 200mg/kg/day respectively. All drugs were administrated for 15 successive days. Cognitive skills of the animals were examined with Elevated plus maze and Passive Shock Avoidance tests. Investigations of oxidative stress markers were performed. Gene expression levels of TNF- α , NF κ B, Caspase 3 and AMPK were analyzed using RT-PCR. Histological and immunohistochemical techniques were performed in hippocampus using H&E, cresyl violet stain, anti GFAP and anti COX-2 immunostain. The study revealed that administration of diazepam increased initial and retention transfer latency as well as it decreased step down latency that means it caused memory impairment. There was a significant increase in hippocampal expression levels of TNF- α , NF κ B, and Caspase 3 and downregulation of AMPK expression levels associated with increased neurodegeneration, astrocytes activation and COX-2 immunohistochemical staining. This study indicates that diazepam caused a decline in cognitive function depending on hippocampal activity. Telmisartan, a common antihypertensive agent and metformin, a traditional antidiabetic drug improved this cognitive dysfunction through their anti-oxidant and anti-inflammatory effect as they decreased initial and retention transfer latency as well as it increased step down latency. Also they decreased TNF- α , NF κ B, and Caspase 3 and upregulated AMPK expression, moreover they ameliorated the hippocampal morphological alterations, GFAP and COX-2 immunoexpression.

Keywords: Diazepam; Telmisartan; Metformin; Piracetam; hippocampus; Cognitive dysfunction