

Effect of agmatine on impairment of hippocampal neurogenesis and neuroinflammation in streptozotocin-induced diabetes in rats

H. Zortul¹, F. Aricioglu¹, G. Hafez², Y. Yazir³, T. Utkan⁴

¹Marmara University- Faculty of Pharmacy, Department of Pharmacology and Psychopharmacology Research Unit, Istanbul, Turkey

²Altinbas University- Faculty of Pharmacy, Department of Pharmacology, Istanbul, Turkey

³Kocaeli University- School of Medicine, Department of Department of Histology Embryology, Kocaeli, Turkey

⁴Kocaeli University- School of Medicine, Department of Pharmacology, Kocaeli, Turkey

BACKGROUND

Diabetes mellitus (DM) is associated with modest impairments in cognition. Common molecular pathways to cellular and metabolic dysfunction have been implicated in both DM and cognitive dysfunctions. It has been shown in rodent models that cognitive impairment might be an adverse effect of diabetes. These models are being increasingly used to study pathogenesis and to develop new treatments [1,2]. Agmatine is an endogenous guanidoamine produced from L-arginine in many organs, including brain. Studies suggest that agmatine could be regarded as a neurotransmitter and shown to facilitate memory and learning in rats, in scopolamine-induced amnesia, streptozotocin (STZ)-induced Alzheimer model and chronic stress-induced depression [3]. Hence, the present study was conducted to examine the effect of agmatine as a possible antidiabetic agent in STZ-induced diabetes mellitus (DM) model in rats by evaluating cognitive functions, molecular mechanisms of neuroinflammation and neuroplasticity besides histological changes due to astrocyte/microglial activation.

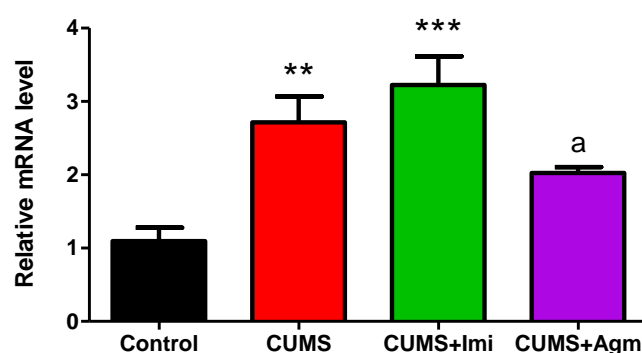
METHODS

Male Wistar rats were divided into three groups (6 rats in each): Control, DM and DM+Agmatine (40 mg/kg i.p for 4 weeks). DM was induced by STZ (50 mg/kg dissolved in 0.1 M sodium citrate buffer (pH 4.4); ip). STZ-treated rats received 5% glucose solution instead of water for the next 24 h in order to reduce the death risk due to hypoglycemic shock. Blood glucose levels were measured in samples, which were collected from the tail vein 48 h after STZ injection. Animals with fasting blood glucose levels >200 mg/dl were considered to have DM. At the end of the agmatine treatment schedule, rats were tested in Morris water maze (MWM) and passive avoidance (PA). Blood glucose levels were recorded weekly. Then rats were decapitated and blood samples were used to analyze IL-1 β , IL-6, TNF- α and brains were either examined immunohistochemically for BDNF, Iba-1 and GFAP or used for molecular analysis of member of pattern recognition receptors of the natural immune system such as nod-like protein (NLRP)-1, NLRP-3, caspase-1 and ASC in hippocampus.

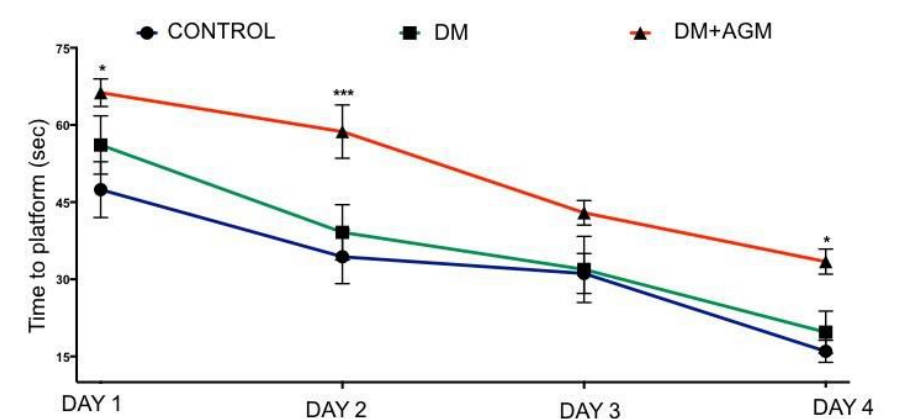
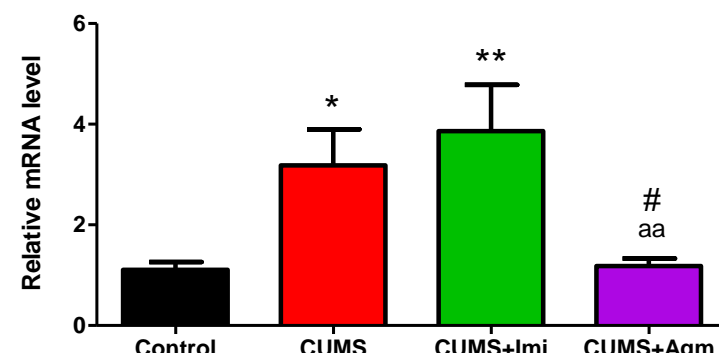
RESULTS

The swimming time in platform area in MWM and retention time in PA tests were decreased in DM while latencies to platform finding in MWM was increased. These effects were reversed with agmatine treatment. DM caused significant elevations in mRNA levels of NLRP1, NLRP3, caspase-1 and ASC in hippocampus. Levels of mRNA gene expression of these parameters were reduced with agmatine treatment. BDNF, Iba-1 and GFAP immunoreactivity elevated in DM in hippocampus, which were significantly reduced by agmatine treatment.

PFC NLRP1

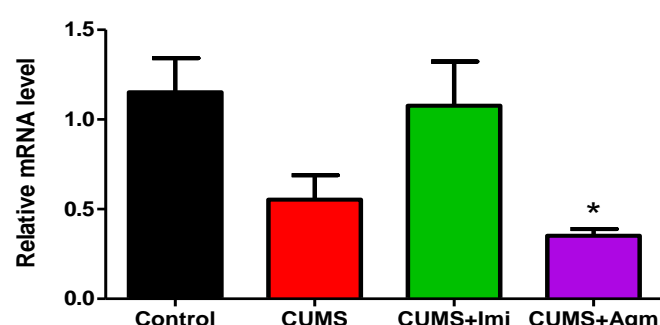


PFC Caspase-1

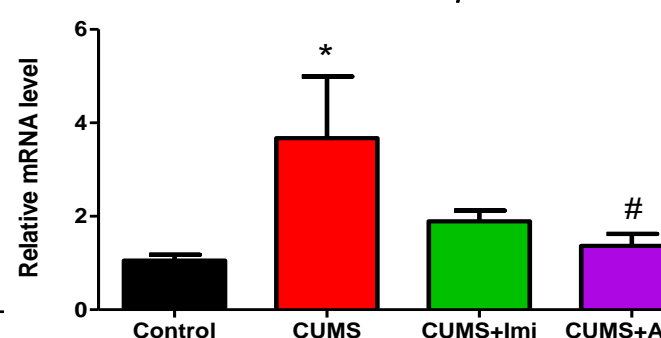


The effect of STZ-induced DM and agmatine (AGM) treatment on learning in MWM test.

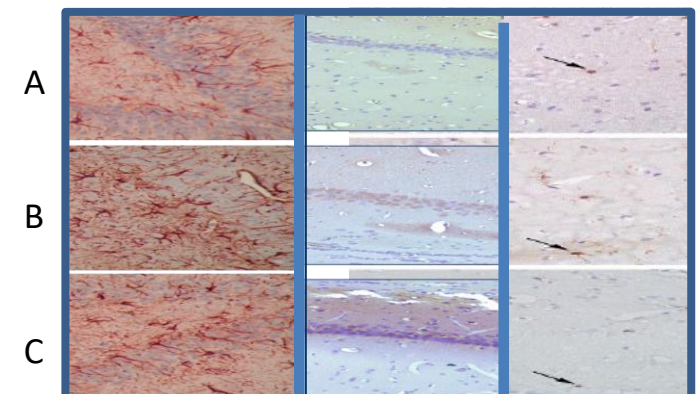
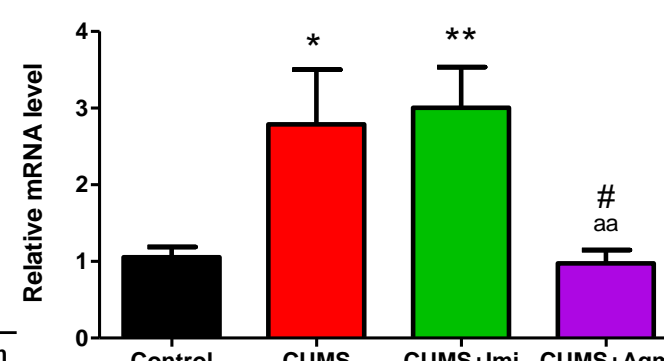
PFC NLRP3



PFC IL-1 β



PFC IL-6



The effect of DM and agmatine treatment of GFAP, Iba-1 and BDNF immunoreactivity in hippocampus of rats. (A) Control, (B) DM, (C) DM+Agmatine

The effect of STZ-induced DM and treatments of relative mRNA levels of inflammatory mediators in PFC of rats. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ versus control, # $p < 0.05$ versus CUMS, $^a p < 0.05$, $^{aa} p < 0.01$ versus CUMS+Imi. All data are expressed as mean \pm S.E.M. and represented as fold change relative to control. One-way ANOVA followed by Tukey's post-hoc test was used for statistical analysis.

CONCLUSIONS

Considerable overlapping mechanisms has been identified in the pathophysiological mechanisms of cognitive disorders and DM. By expanding our understanding of these conditions, we can accelerate rational development of disease-modifying and symptomatic treatments for cognitive dysfunction in DM. Therefore the results of the study suggest that agmatine, as an endogenous molecule, which has antidiabetic and cognitive enhancing effects through modulating microglial/astrocyte activation and neuroinflammation pathway might be worth for further investigation.

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