Chronic magnesium supplementation increases hippocampal neurogenesis and decreases proliferation in myocardium in ACTH-treated rats

**Background:** Major depressive disorder (MDD) is a devastating psychiatric syndrome, characterized by several molecular and neuroendocrine changes, including impaired neurogenesis in hippocampal dentate gyrus that is reversed by antidepressants. Further, MDD was recognized as an important risk factor, that contributes, per se, to development of cardiovascular disease. Animal studies have shown that chronic stress and depressive phenotype are accompanied by changes in myocardial structure: altered proliferation and enhanced fibrosis. On the other hand, magnesium ion (Mg) is essential for proper functioning of cardiovascular and nervous system.

**Materials and Methods:**
Male, Wistar rats (n=20) were used in this study. Immunohistochemical analysis was performed and parameters of proliferation were assessed: Ki-67 in hippocampal dentate gyrus (DG), while proliferating cell nuclear antigen (PCNA) was measured in cardiomyocytes and cells of myocardial interstitium. Finally, Ki-67 immunopositive cardiomyocytes were counted as well. Number of immunopositive cells was counted in 10 non-overlapping fields in myocardium and in hippocampus entire DG was analyzed. Results were processed in SPSS, statistical significance was ascertained by one-way ANOVA, post hoc test was LSD and p<0.05 was considered significant.

**Results:**
![Figure 1](image1.png)

**Figure 1.** Experimental design and timeline; animals were assigned into 4 experimental groups: ACTH group received adrenocorticotrophic hormone (10 μg/day s.c., 21 days), Mg group received magnesium (300 mg/L via drinking water, 28 days), ACTH/Mg group received respective combination that included ACTH administration for the last 21 days of Mg supplementation and Control group received saline. On the 28th day from the onset of experiment, rats were anesthetized, brain and myocardial tissue were extracted and immunohistochemistry (IHC) was performed.

![Figure 2](image2.png)

**Figure 2.** Representative hippocampal dentate gyrus photomicrographs of adult male Wistar rats treated with adrenocorticotrophic hormone (ACTH), magnesium (Mg), respective combination (ACTH/Mg) and saline (Control). The sections are presented at 100× total magnification. Effects of different treatments on density of Ki-67 immunopositive neurons are shown. Values present mean number of immunopositive cells in granular and subgranular zone of hippocampal dentate gyrus per section. Results are shown as means ± SEM. *p<0.05, **p<0.01, ***p<0.001.

![Figure 3](image3.png)

**Figure 3.** The effects of different treatments of adult male Wistar rats on number of Ki-67 immunopositive cardiomyocytes (A), level of PCNA expressed as PCNA index in myocardial interstitium (B) and PCNA index in cardiomyocytes (C). PCNA index presents number of immunopositive cells divided by total number of cells counted, per 0.07 mm². Values are shown as means ± SEM. *p<0.05, **p<0.01, ***p<0.001.

**Conclusions:** Our study demonstrated, for the first time, that in vivo magnesium supplementation increased cell proliferation and number of newborn neurons in hippocampal dentate gyrus and that neurogenesis remained enhanced even in rats chronically exposed to both ACTH and Mg. Further, in ACTH model of depression resistant to tricyclic antidepressants, magnesium was efficient in abolishing an increase in cardiomyocyte proliferation.

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We declare that we have no potential conflict of interest. Contact information: jellena@pharmacy.bg.ac.rs