sciforum
IECBS 2021 The 2nd International Electronic Conference on Brain Sciences
15–30 JULY 2021 | ONLINE
Cognitive Neuroscience
sciforum-045637
brain sciences MDPI

Reversal of cognitive dysfunction and oxidative brain damage induced by chronic D-gal treatment in mice by Calcium dobesilate, a vasoactive and angioprotective drug with antioxidant properties

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INTRODUCTION

- Calcium dobesilate (CaD) is an established vasoactive and angioprotective drug commonly used for the clinical treatment of diabetic retinopathy and chronic venous insufficiency, reducing vascular permeability [1,2].
- Previous studies also reported the antioxidant properties of CaD [3,4]. It is a potent free radical scavenger in the retina and reduces the level of malondialdehyde (MDA), inhibiting lipid peroxidation [4]. Moreover, CaD increases the activity of antioxidant enzymes [3,5].
- D-galactose (D-gal) long-term treatment in mice, used as an 'accelerated aging model' [6] induces the overproduction of reactive oxygen species (ROS) [7,8] and is a well-accepted experimental model of oxidative stress-linked cognitive disorders in physiological aging [9,10].

AIMS

To study the possible role of CaD against Cognitive dysfunction and Anxiety, and as well as against Oxidative brain damage induced by D-gal treatment in mice

METHODS

CaD was administered (50 and 100 mg/kg/day p.o.) in male mice treated with D-gal (500 mg/kg/day p.o.) for six weeks. Thereafter, animals were behaviorally assessed in elevated plus-maze , Y-maze, and shuttle box tests, and brains were dissected for further oxidative stress biochemical analysis of malondialdehyde (MDA) levels and increasing superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) enzyme activities.

Data were presented as mean ± SEM. For parametric variables, the differences between the groups were analyzed by one-way analysis of variance (ANOVA), Antioxidants 2021, 10, 649 4 of 11 followed by the Tukey post hoc test. For non-parametric variables, the groups' differences were analyzed with Kruskal–Wallis followed by the Dunn post hoc test. A two-way repeated-measures ANOVA (RMA) was used for comparison of body weight changes among experimental groups. Differences were considered statistically significant when $p < 0.05$.

The Guide for the Care and Use of Laboratory Animals (Institute for Laboratory Animal Research, National Research Council,Washington, DC, National Academy Press, no. 85-23, revised 1996) was followed. The Animal Ethics Committee of the Rafsanjan University of Medical Sciences approved this study protocol (Approval ID : IR.RUMS.REC.1397.108).

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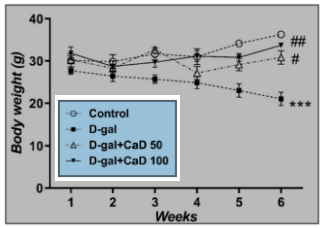
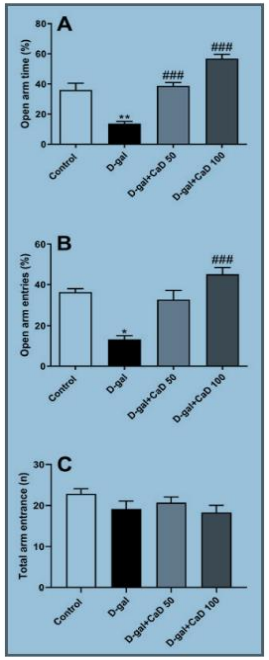
RESULTS

1 CaD inhibited the Body weight loss induced by D-Gal treatment

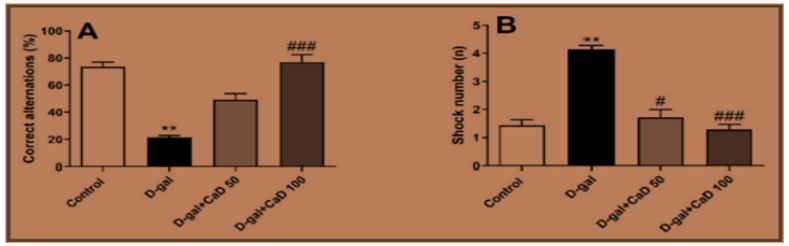


Figures 1.2.3 and 4.
Effect of calcium dobesilate (50 and 100 mg/kg, p.o.) on
[1] Body weight loss,
[2] Anxiety-like behavior in the elevated plus maze,
[3] Cognitive impairment in the (A) Y-maze and (B) Shuttle box, and
[4] Oxidative stress, in D-galactose (500 mg/kg, p.o.) mice.
Values are mean ± SEM (n = 7 in each group). *** $p < 0.001$ compared to control group; # $p < 0.05$ and ## $p < 0.01$ compared to D-gal treated group.

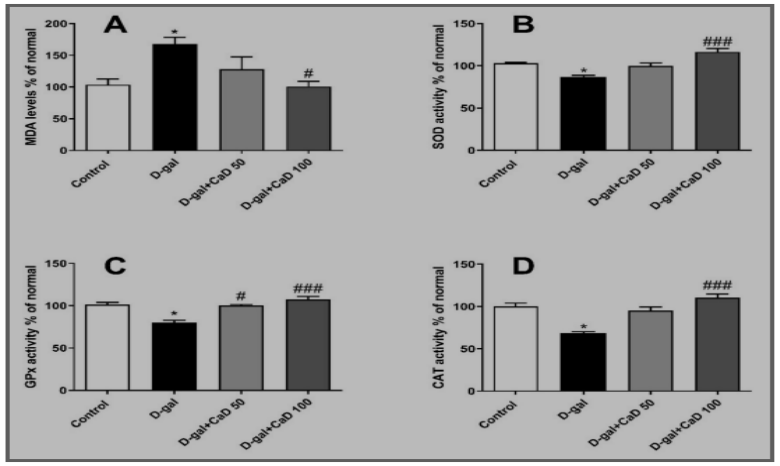
2 CaD decreased the Anxiety-like behavior in D-Gal treated mice



3 CaD attenuated the Cognitive Impairments in D-Gal tr. mice



4 CaD reduced the Oxidative Stress in D-Gal treated mice



CONCLUSIONS

- ✓ Results demonstrated that bodyweight loss and cognitive impairments of D-gal-treated animals were reversed by CaD administration as evaluated by the measurement of mice performance. Future studies should include female sex.
- ✓ CaD treatment also inhibited brain oxidative stress in aging mouse by decreasing malondialdehyde (MDA) levels and increasing superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) enzyme activities.
- ✓ With the animal model's limitation, our results suggest that CaD, which is already approved for clinical use and safe, could be an interesting pharmacological tool to reduce or prevent age-related behavioral and brain oxidative stress conditions.
- ✓ These results could open new perspectives for the clinical use of CaD in counteracting brain oxidative stress and preventing cognitive impairment in aging.