Dexmedetomidine Attenuates Hippocampal Damage and Improves Cognition by Up-Regulating Glyoxalase1 in APP/PS1 Mice

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Research Article

Keywords: Dexmedetomidine, Alzheimer's disease, GLO-1, methylglyoxal, apoptosis

Posted Date: May 25th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-512431/v1>

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Abstract

Background: Dexmedetomidine (DEX), an α_2 -adrenoceptor agonist, has been reported to possess neuroprotective effects against postoperative cognitive impairment. GLO-1 plays a key role in the pathogenesis of Alzheimer's disease (AD). Here, the primary goal was to assess whether DEX affect GLO-1 and protect cognition impairment in APP/PS1 transgenic mice.

Methods: After DEX was intraperitoneally injected in APP/PS1 mice, behavior was tested by Water Maze to illustrate whether DEX treatment has a significantly positive effect on ameliorating the cognition deficits in AD. We assessed the effect of DEX on the expression of GLO-1 and the production of other oxidative stress factors by ELISA and Western blot. To determine whether DEX play roles in the A β induced neuron apoptosis, flow cytometry was used.

Results: DEX treatment significantly ameliorated cognition deficits in APP/PS1 mice. DEX increased GLO-1 expression and decreased MG activity in the hippocampus. In addition, DEX increased activity of SOD, GSH and reduced the activity of MDA. In vitro, DEX could protect the neuron apoptosis induced by A β . GLO-1 inhibitor could block the protective role of DEX.

Conclusion: Taken together, our findings suggest that DEX prevents progression of AD-like pathology through upregulating GLO-1.

1 Introduction

Alzheimer's disease (AD) is characterized by a gradual deterioration of cognitive function compared to healthy patients, which may be associated with a significant reduction in brain volume in AD patients(1,2). The causes of atrophy are synaptic degeneration and neuronal death, especially in the hippocampus, which plays a role in memory and spatial orientation (3). Age is the highest risk factor for AD and peoples over 85 have a 50 per cent risk the disease (4,5).

A number of evidences show that oxidative stress plays an important role in AD pathogenesis (6,7). The brain is particularly vulnerable to oxidative damage because it has:1) a large number of easily oxidized polyunsaturated fatty acids, 2) a high level of reactive oxygen species (ROS) and catalyst iron,3) a relatively lack of antioxidant capacity(8,9). Oxidative stress is thought to be a common factor for AD(10). Glyoxalase-1 (Glo1) is a key driver in oxidative stress mediators. Glo1 is a cytosolic protein that forms the acetaldehyde enzyme system together with acetaldehydease 2 and glutathione(11). The major function of the system is the detoxification of active diethyls, especially methylglyoxal (MG)(12). MG is a highly active metabolite of diethylglycolysis. MG is degraded by the acetaldehydease system, which is an efficient enzymatic detoxification system in which Glo1 is a rate-limiting enzyme(13). It was reported that Glo1 overexpression protected lifespan reduction, neurostructural damage and neurofunctional damage. Glo1 down-regulation also occurred in oxidative stress-induced anxiety and memory impairment in rats(14).

Dexmedetomidine (DEX) is a highly selective $\alpha 2$ -adrenoceptor agonist used as an off-label medication for pediatric sedation and analgesia(15). DEX was reported to exhibit neuroprotective efficacy in several brain injury models (16). In neonatal rats, DEX (20 μ g/kg) injection enhances spatial learning and memory in 36 days old (17). In mice, DEX ameliorated sleep deprivation-induced deterioration of short-term memory and spatial learning ability(18). In the study, we investigated whether DEX can counteract cognition impairment and regulate Glo1 expression in APP/PS1 transgenic AD mouse model.

2 Materials And Methods

2.1 Materials

DEX was purchased from Selleck. Annexin V-FITC Apoptosis Detection Kit and MTT were purchased from Sigma-Aldrich. GLO-1 inhibitor was purchased from MCE. GLO-1 and β -actin primary antibodies were purchased from Abcam. SOD, GSH, MDA, GLO-1 and MG ELISA kits were purchased from Nanjing Jiancheng Biotechnology.

2.2 Animal

6 months old male APP/PS1 mice were purchased from Beijing Zhongke Zisheng Biotechnology Co., Ltd. 6 months old male C57/BL6 mice were set as Con group. These mice were feed with free access to water and food. The procedures followed were assessed and approved by the Committee on the Ethics of the affiliated hospital of Inner Mongolia medical university.

2.3 DEX administration

When mice were feed to 7 months old, APP/PS1transgenic mice were randomly assigned to two groups: (1) APP/PS1 group were treated with 0.9% saline by intraperitoneal injection once daily for 28 days (n = 10). (2) DEX group were treated with 20ug/kg DEX by intraperitoneal injection once daily for 28 days (n = 10). 7 months old C57/BL6 male mice served as Con group for APP/PS1 transgenic mice (n = 10).

2.4 Water maze

Water maze assess cognitive function by training mice to use spatial cues in a room to navigate to a hidden escape platform. The water maze apparatus was composed of a circular pool (100 cm diameter, 50 cm high) filled with water and divided into four imaginary quadrants. At the beginning of the swim, one mouse which faced the wall was placed into the pool from the quadrant which is opposite to the platform and ended once the animal had found the platform; if the mouse had not found the platform within 60 sec, it was guided there by hand. This process will continue 5 days. On day 6, each mouse was placed into the pool to find the platform in 60s. A video camera connected with a trail analysis system was set above the center of the pool.

2.5 Western blotting

Brain hippocampal tissues were homogenized and Western blotting performed using rabbit polyclonal antibodies GLO-1 (Abcam, 1:500) and β -actin (Abcam, 1:2000). Blots were scanned and measured using LiCor Odyssey software.

2.6 ELISA test

GLO-1, MG, SOD, GSH and MDA in hippocampus homogenates and cells were determined using ELISA kit.

2.7 Cell culture

SH-SY5Y human neuroblastoma cell line was used for in vitro experiments. The cell line was purchased from ATCC. Cells were cultured in Dulbecco's Modified Eagle's Medium supplemented with 10% fetal calf serum. When indicated, the cells were treated with 25uM A β 25–35 for 24h.

2.8 MTT assay

MTT[3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] method is based on the ability of mitochondrial dehydrogenase in living cells to cut the tetrazolium ring of yellowish MTT and form dark blue methyl nitrogen crystals. MTT was operated according to the instructions.

2.8 Flow cytometry

Cell death was assessed using an annexin V-FITC and PI apoptosis detection kit. Cells were harvested using trypsin and incubated for 5 min at room temperature in the dark with Annexin V-FITC and propidium iodide (PI) according to the manufacturer's instructions. The fluorescence of FITC and PI was analyzed by flow cytometry.

2.9 Statistical evaluation

One-way ANOVA was used. A value of $p < 0.05$ was considered significant.

3 Results

3.1 DEX prevents cognitive decline in APP/PS1 mice

The cognition was detected by Water Maze. APP/PS1 mice shows increased escape latency time and distance compared to Con group. Administration of 20ug/kg DEX for 28 days prevented the cognitive decline. As shown in Fig. 1A-B, DEX significantly decreased the escape latency time and distance in APP/PS1 mice.

3.2 DEX increases Glo-1 activity and decreases MG activity in hippocampus and serum

To find out whether DEX regulate Glo-1 system, we measured the Glo-1 activity and the protein expression. As shown in Fig. 2A-C, much less expression of Glo1 in hippocampus and serum was observed in APP/PS1 mice than in the Con group. DEX treatment could significantly increase the Glo-1

activity and the protein expression. Subsequently, we examined MG levels in serum. Normally, MG can be catalyzed into lactic acid by Glo-1. MG itself has cytotoxic effects. As shown in Fig. 2D, the level of serum MG was significantly higher in APP/PS1 mice than in the Con group. After DEX treatment, the serum MG level was decreased. These data suggested that DEX could regulate Glo-1 system.

3.3 DEX increases SOD, GSH and decreases MDA levels in APP/PS1 mice

APP/PS1 mice exhibited decreased levels of SOD, GSH and increased level of MDA in hippocampus and serum compared with Con group. DEX treatment significantly reversed these changes (Fig. 3).

3.4 To determine the role of GLO-1 downregulation in A β induced cell viability decline

A β 25–35 is the fragment obtained by hydrolysis of A β protein in vitro. It does not exist in the body, but its neurotoxicity is almost equal to that of endogenous A β . We first developed a SY5Y cell model of A β 25–35 damage. Exposure SY5Y cells to A β for 24 h caused cell viability decline (Fig. 4A). Then we detected the GLO-1 and MG levels in the cells. The results showed that A β exposure to SY5Y cells decreased GLO-1 and increased MG levels (Fig. 4B-C). It suggested that GLO-1 downregulation is involved in A β induced cell viability decline. To further characterize the function of GLO-1 in A β induced cell viability decline, we used GLO-1 inhibition and MG to assess their effects on cell viability. MTT analysis showed that both GLO-1 inhibition and MG decreased cell viability (Fig. 4D). These results identified that GLO-1 participated in A β induced SY5Y cell viability decline.

3.5 DEX inhibited cell apoptosis through upregulating GLO-1

Cell apoptosis was increased after incubation with A β . GLO-1 inhibitor also increased the cell apoptosis. Treatment with DEX at 1 μ M significantly decreased the cell apoptotic rate. The protective effect of DEX was blocked in the cell model of A β damage when incubating GLO-1 inhibitor for DEX 2 hours in advance (Fig. 5A-B). Furthermore, DEX increased the GLO-1 level and GLO-1 inhibitor can inhibit the up-regulation of GLO1 by DEX (Fig. 5C).

3.6 DEX treatment increases SOD, GSH and decreases MDA levels in neurons exposed to A β

The levels of SOD and GSH in A β group were markedly lower than those in Con group. After DEX treatment for 24 h, the levels of SOD and GSH were significantly higher than those in the A β group. Meanwhile, the MDA level in A β group was markedly higher than that in Con group. After DEX treatment for 24 h, the MDA level was significantly lower than that in the A β group (Fig. 6).

4 Discussions

AD pathological features are mainly progressive exacerbation of cognitive impairment (19). AD is mostly diagnosed later when neuronal cell death is irreversible. Furthermore, there are no therapeutic drugs that can effectively halt AD progress (20). The APP/PS1 mouse model has been widely used to study cognitive deficits related to AD (21). Here, we report that (i) DEX alleviates cognitive impairment in APP/PS1 mice. (ii) DEX blocks A β -induced neuron apoptosis. (iii) DEX plays its role through regulating GLO-1.

In this study, we propose DEX regulate multiple pathological changes that are important in AD and suggest repositioning the DEX to regulate lots of aspects of the AD. Dex is an efficacious, safe drug used to sedate patients in the ICU or during procedural sedation(22). We found that DEX enhance AD cognitive deficits which upregulating GLO-1 to block MG-mediated neurotoxicity. DEX can also regulate the activities of oxidative stress related enzymes such as SOD, GSH and MDA.

Oxidative stress has been proposed as a common factor for AD. Among all oxidative stress mediators, GLO-1 plays an important role(23). GLO-1 is an enzyme that detoxifies MG. MG is an effective precursor of advanced glycation end products and is considered to be a key factor in neuronal injury(24,25). DEX administration halts AD progression in APP/PS1 mice, it may be through regulating GLO-1. In the study, we observed that DEX reversed the changes of GLO-1 and MG in APP/PS1 mice model. Interaction between GLO-1 and MG might provide A β -related cell death pathology in AD and also provide a potential drug target for the disease.

Then, we identified the role of GLO-1 in cell model mediated by A β injury. We selected A β 25–35 to injure SHSY5Y cells. A β 25–35 is a fragment between 25–35 A β peptide which showing neurotoxic activity in cultured cells(26). SH-SY5Y cell is a human neuroblastoma cells with sustainable cell morphology and biochemistry of mature human neurons(27). In the SH-SY5Y cell model injured by A β 25–35, we found A β led to cell viability decline. A β also decreased GLO-1 and MG levels. GLO-1 inhibition and MG decreased cell viability. It suggested that GLO-1 down-regulation is involved in A β induced cell viability decline. DEX significantly decreased the cell apoptotic rate. GLO-1 inhibitor could block the protective effect of DEX. DEX increased the GLO-1 level in the cell model too.

It has been reported that bilateral microinjection of MG is sufficient to induce changes in anxiety-like behavior(28). The function of GLO-1, the AGE/RAGE signaling pathway and the generation of reactive oxygen species were all abnormal in MG-treated HUVECs(29). Considerable evidence and our work, it has shown that the expression of Glo1 can be up-regulated by EDX. Although the mechanisms still remain unclear, the role of GLO-1 has been increasingly acknowledged.

In summary, we presented evidence that 28 days administration of EDX relieved oxidative stress, elevated the protein level of GLO-1 to reduce MG accumulation and ameliorated memory deficits in APP/PS1 transgenic mice. All of these benefits were related to reduce neuron apoptosis in AD process. Although the molecule mechanism requires further exploration, DEX may serve as a potential anti dementia drug.

Declarations

Ethics approval and consent to participate All experimental protocols were approved by Ethics Committee of the Affiliated Hospital of Inner Mongolia Medical University. All methods were carried out in accordance with relevant guidelines and regulations. All methods are reported in accordance with ARRIVE guidelines for the reporting of animal experiments.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests: There were no competing interests.

Funding: Science and Technology Million Project of Inner Mongolia Medical University (YKD2015KJBW022).

Authors' contributions: Chunyan Guo, Lei Zhang and Yaoxing Gao performed the experiment. Junzhi Sun, Lingling Fan and Yuguang Bai contributed to data analysis. Jing Zhang and Gaowa Naren helped perform the data analyses and wrote the original manuscript. Jiwen Yang and Libiao Li contributed to the conception of the study and approved the final manuscript.

Acknowledgements: Not applicable.

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Figures

Fig1

A

B

Figure 1

Examination of cognition using Water maze test. DEX prevents the decrement in distance (A) and escape latency time (B) in Water Maze in APP/PS1 mice. APP/PS1 mice were administered DEX at the dose of 20ug/kg by intraperitoneal injection for 28 days. Data are expressed as means $\pm$ SD. **p < 0.01 vs Con. #p < 0.05; ##p < 0.01 vs APP/PS1. n=10.

Fig2

Figure 2

Western blot and ELISA analyses of Glo-1 and MG activity measurements in hippocampus and serum in APP/PS1 mice after 28 days DEX treatment. DEX increased the Glo1 level and decreased the MG level in APP/PS1 mice. (A) The activity of Glo1 in hippocampus homogenate determined by ELISA. (B) The expression of Glo1 in hippocampus determined by western blot. (C) The activity of Glo1 in serum determined by ELISA. (D) The activity of MG in serum determined by ELISA. * $p < 0.05$, ** $p < 0.01$ vs Con. # $p < 0.05$; ## $p < 0.01$ vs APP/PS1. $n = 10$.

Fig3

Figure 3

Examination of SOD(A,D), GSH(B,E), and MDA(C,F) level in hippocampus and serum in APP/PS1 mice. APP/PS1 mice showed marked decrease in the activity of SOD and GSH with following by increase in the activity of MDA, which were reversed with DEX treatment. * $p < 0.05$, ** $p < 0.01$ vs Con. # $p < 0.05$; ## $p < 0.01$ vs APP/PS1. $n = 10$.

Fig4

Figure 4

Identification of GLO-1 participating in Aβ-induced SHSY5Y cell viability decline. (A) Aβ treatment induced SHSY5Y cell viability decline. The cell viability was determined by MTT assay. (B) The activity of Glo1 in SHSY5Y cell. (C) The activity of MG in SHSY5Y cell. (D) MG and GLO-1 inhibitor caused cell viability decline. * $p < 0.05$, ** $p < 0.01$ vs Con. # $p < 0.05$; ## $p < 0.01$ vs Aβ. $n = 6$.

Fig5

A

B

C

Figure 5

Electronic gating strategy for flow cytometric analysis of cell apoptosis. DEX reduced the apoptosis induced by Aβ. GLO-1 inhibitor could block the protective role of DEX *p < 0.05; **p < 0.01 versus Con. #p < 0.05; ##p < 0.01 versus Aβ.n=6.

Fig6

Figure 6

The activity of SOD(A),GSH(B) and MDA(C) in SHSY5Y cells. Aβ decreased the activity of SOD,GSH and increased the activity of MDA. DEX could reverse these damages. *p < 0.05; **p < 0.01 versus Con. #p < 0.05; ##p < 0.01 versus Aβ.n=8.