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Human Dental Pulp Stem Cells Transplantation Improves Passive Avoidance Memory, Neuroinflammation and Hippocampal Histopathology in Trimethyltin-Induced Alzheimer's Disease Rat Model

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Abstract

Background: According to the increasing incidence of Alzheimer's disease (AD), this study aimed to investigate the effect of human dental pulp stem cells (hDPSCs) transplantation on passive avoidance memory, neuroinflammation, and hippocampal histopathology in trimethyltin (TMT)-induced AD rat model. **Materials and Methods:** In this experimental study, 18 male Wistar rats were randomly divided into three groups: Control, TMT+PBS (rats received 8 mg/kg TMT+0.5 ml phosphate-buffered saline (PBS)), and TMT+DPSCs (TMT + 1×106 cells/ml DPSC in 0.5 ml PBS) groups. Then, after one month, a passive avoidance test was performed. Also measured the Nuclear Factor Kappa-β (NF-Kβ) serum level and the percentage of damaged neurons in the hippocampus were determined. **Results:** hDPSCs transplantation showed significantly increased step-through latency to the dark compartment compared to control and TMT+PBS groups in 24 hours after shock (P=0.01). Also, time spent in the dark compartment of TMT+DPSCs significantly decreased compared to control and TMT+PBS groups in 24 and 48 hours after shock (P=0; P=0.002, respectively). Furthermore, hDPSCs transplantation significantly decreased the NF-Kβ serum level (P=0) and improved 20% of damaged pyramidal neurons of CA1 compared with TMT+PBS (P=0). **Conclusion:** hDPSCs transplantation improved memory and learning, regulated NF-Kβ serum level, and decreased damage neurons of CA1 hippocampus in TMT-induced AD rat model. **[GMJ.2021;10:e2254|DOI:10.31661/gmj.v10i0.2254**

Keywords: Stem Cells; Memory; Alzheimer's Disease; Cognitive Dysfunction; Trimethyltin

Introduction

Alzheimer's disease (AD) is a severe neurological disorder in which memory impairment and cognitive impairment are the main symptoms. It is then caused by the destruction of nerve cells in essential brain areas (forehead and other areas of the brain). Some risk factors are known to increase the prevalence of AD in the population,

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such as genetic factors (e.g., APP, PS1, and PS2 genetic mutations in familial AD, and genetic susceptibility polymorphisms in sporadic cases), biological factors (e.g., age, gender, bodyweight, etc.), and environmental factors (e.g., lifestyle, brain damage, toxins, etc.); These factors cause the production of reactive oxygen species (ROS) and lead to mitochondrial dysfunction as well as the aggregation of Aβ plaques [1]. Trimethyltin (TMT) is a potent neurotoxin that acts in the hippocampus.

Also, TMT injection (intraperitoneal; i.p) increased ROS production in mice in sensitive areas such as the hippocampus and frontal cortex [2].

After injecting TMT, animals show behavioral changes such as seizures, aggressive behavior, self-biting, impaired working memory, and hyperactivity. Studies show that TMT poisoning causes cognitive and behavioral dysfunction in experimental animals and humans [3]. Nuclear factor-kappa b (NF-kb) plays an active role in AD progression.

Disruption of this signaling also causes phenotypic changes such as oxidative stress, neuroinflammation, microglial activation, and apoptotic cell death. It, therefore, leads to hemostatic abnormalities in the brain that essentially produce normal neurons in the degeneration process under AD conditions [4]. Gronthos et al. 2000 were the first to isolate Dental Pulp Stem Cells (DPSCs) from adult human dental pulp [5]. DPSCs have many properties such as fibroblast-like morphology, high clonal capacity, and high proliferation rate; also, DPSCs expressed all specific markers of undifferentiated embryonic stem cells. In comparison with human Bone Marrow-Mesenchymal Stem Cells (BM-MSCs), human DPSCs (hDPSCs) demonstrate approximately three times higher proliferation rate in vitro. Also, they possess multipotency and could differentiate into cartilage, muscle, bone, and other cell types [6].nThe hDPSCs are a promising source for regenerative medicine, especially in neurological disorders treatment; also, they could be obtained non-invasively and easily from extracted teeth without ethical problems. hDPSCs are neural crest-derived stem cells within the dental pulp perivascular niche.

Furthermore, the immunosuppressive properties of DPSCs make them interesting for allogeneic transplantation manner [7,8]. Also, DPSCs demonstrated both neural stem cells and MSCs properties. Studies showed stem cells to be helpful for the treatment of AD. Human NSCs transplanted into fimbria fornix enhance behavioral and pathological phenotypes in the AD transgenic murine model [9]. Also, another study showed transplantation of Neural Stem Cells (NSCs) decreased Aβ peptide levels at an early stage of AD disease in mice [10]. Transplantation of placenta-derived mesenchymal stem cells regulated neurogenesis, neuronal death, and glial cell activation in the hippocampus and improved memory dysfunction in a mouse model of AD [11].

Furthermore, transplantation of neural stem cells into the hippocampus improves short-term memory on a spatial task in an inducible neuronal loss of mouse model [12]. One study reported conditioned medium from the stem cells of human dental pulp improves memory and cognitive function in a mouse model of AD following injection (intracerebroventricular; icv) of Amyloid β1−40 (Aβ1−40) into the hippocampus [13]. The present study induced AD with an injection of TMT chloride into male rats as a chemical drug. Then memory and learning were assessed through the Passive Avoidance task, the amount of NF-Kβ serum level, and the percentage of damaged neural cells in Dentate Gyrus (DG) and Cornu Ammonis 1-3 (CA1, CA2, and CA3) regions as subfields of the hippocampus after DPSCs transplantation. This study aimed to investigate the effect of human dental pulp stem cells transplantation on passive avoidance memory, neuroinflammation, and hippocampal histopathology in TMT- induced AD rat model.

Materials and Methods

Ethics

All animal experimentation protocols were performed under the supervision of the Local Ethics Committee of Islamic Azad University, Shiraz Branch. All endeavors made to

minimize the number of animals used and animal suffering in this study.

Animals

This study was performed on 18 male Wistar rats weighing 220±20g and two months of age. The animals were kept at controlled temperature (24±2ºC) and 12-h light/dark cycle. Also, Food and water were available ad libitum. Rats were held in the animal houses of the Animal Science Research Laboratory of Shiraz University.

Experimental Design

The animals were randomly categorized into three groups of 6 rats: control, TMT+PBS (injected TMT 8 mg/kg, ip+0.5 ml PBS; phosphate-buffered saline), and TMT+DPSCs (Receiving 8 mg/kg body weight of TMT and one million human dental pulp in 0.5 ml PBS).

AD Induction

TMT chloride (Sigma-Aldrich, USA) was purchased from Sigma-Aldrich company. TMT (8 mg/kg of body weight) was dissolved in saline (NaCl 0.9%) and then was injected (intraperitoneal; ip) to the TMT+PBS and TMT+DPSCs groups. Also, 48 hours after TMT injection, the DPSCs were transplanted into the TMT+DPSCs group.

Extraction and Cultured of Dental Pulp Stem Cells

Third molar teeth without decay were obtained and maintained in Hanks (HBSS) medium. Dental pulp extracted mechanically and then washed in phosphate-buffered saline (PBS; Gibco, USA); after that collagenase type I enzyme (Invitrogen, USA) was added into Dental pulp cells and incubated for 30 min at 37ºC. Furthermore, in T25 culture flasks were added Dulbecco's Modified Eagle Medium (DMEM; Gibco, USA), 10% Fetal Bovine Serum (FBS; Gibco, USA), 1% penicillin and streptomycin, 1% L-glutamine (Sigma, USA) and finally added dental pulps (Figure-1:I: A). Then flask contents cells were transferred in a CO2 incubator at 37ºC with 5% CO2. Every two days, the medium was changed. Cells were passaged at 75-85% of confluence.

MSCs Confirmation

For confirmation of the osteogenic potential, 2×104 cells of DPSCs were added into osteogenic medium containing DMEM-F12 (Bio West, France) with 10% FBS (FBS, BioIdea, Iran), 1% penicillin/streptomycin, 1% L-glutamine (BioIdea, Iran), 50 µg/ml L-ascorbic acid, 10 mM β-glycerophosphate (Sigma, USA) and dexamethasone (Sigma, USA). Then, was transferred to a CO2 incubator at 37ºC with 5% CO2; also the medium was changed every 3-4 days. After 21 days, cells were fixed in 70% ethanol for 15 min and stained with 2% Alizarin Red (Sigma Aldrich). Also, the cell was observed under a light microscope. In addition, the flow cytometry analysis was performed against Cluster of Differentiation 34, 44, and 90 (CD34, CD44, and CD90) antigens.

Intravenous Injection of DPSCs

hDPSCs were digested with trypsin and were washed with PBS. After that 1×106 cells/cm2 of hDPSCs suspended in 0.5 ml PBS. For hDPSCs infusion in rats, animals were anesthetized with a mixture of 100 mg/kg ketamine and 50 mg/kg xylazine drugs. hDPSCs suspension (1×106 cells/ml in 0.5 ml PBS) was slowly injected through the jugular vein (Figure-1: II: A).

Passive Avoidance Memory

Passive Avoidance is one of the behavioral tests used in learning and memory in short-term or long-term condition studies in small laboratory animals such as rats and mice. In this task, animals learned to avoid an environment that previously received a foot shock. The shuttle box consisted of light and dark compartments (20×80×20 cm) separated by a guillotine sliding door in the middle of the box. The floor of the dark chamber includes stainless steel with electric shock potential. Tamburella's protocol was used for this test with minor modification [14]. This test consists of three steps: habituation (to familiarise with instruments), shock (0.2 mA, 3 seconds; about 50 HZ intensity), and tests (24 and 48 hours after shock for short and long-term memory, respectively). In the test step, 24 hours after the shock, the rats were

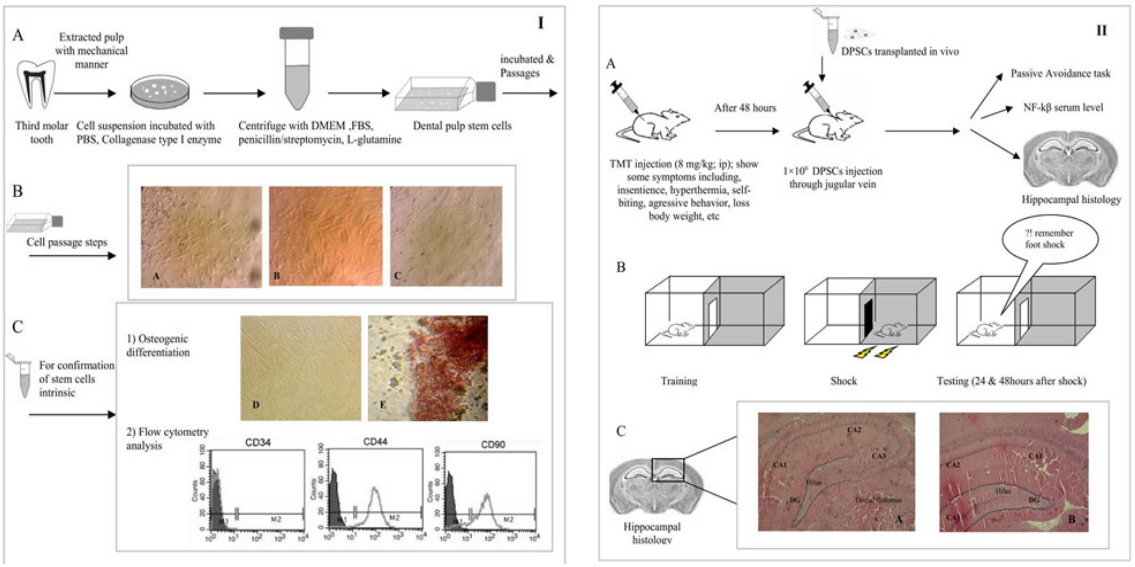

Figure 1. I :Schematic of dental pulp extraction, culture (**A**), passages (**B**) and MSCs intrinsic confirmation (**C**). **II:** Also, schematic of dental pulp stem cells transplantation (**A**) and assessment of memory, cognitive function (**B**), and hippocampus histology (**C**). When see 75-85% confluency of cells performed cell passages; cells derived from dental pulp in the different passages (**I :B: A-C**; zero, first and third passages, repectively). For confirmation of stem cells intrinsic of dental pulp (**I:C**) assessed osteogenic differentiation ability (**I: C- 1**) and performed Flow cytometry analysis against CD 34, 44, 90 antigenes (**I: C- 2**). Calcium nodules which positively stained confimed MSCs intrinsic with red color affected of Alzarin Red observed under a microscope (**I :C:1:E**) in compare with fourth passage of dental cells (**I :C:1:D**). In addition, positive expression of CD 44, 90 (Mesenchymal markers) and negative expression of CD34 (hematopoietic marker) observed with Flow cytometry analysis (**I :C:2**); which confirmed SCs intrinsic of dental pulp. Then, DPSCs transplanted into rats that received i.p injection of TMT (8 mg/kg, bw) about 48 hours before DPSCs transplantation (**II: A**). After one month from DPSCs transplantation performed Passive Avoidance memory task (**II: B**); this task performed in four consecutive days. also, it includes three steps: training (just for familiarising with instruments), shock (0.2 mA, 3 seconds), and testing that is repeated two times 24 & 48 hours after shock. Also, after six weeks from DPSCs transplantation, rats were sacrificed and brain removed for histopathological study (**II: C**); Photomicrograph of rat hippocampus regions (DG, CA1, CA2, and CA3) in Control (**II: C: A**) and TMT+DPSCs (**II: C: B**) groups (H&E; 10x).

placed into the light compartment, and after 30 seconds, the sliding door was raised for 300 seconds, and all data were recorded (like Step- through latency to a dark compartment; and TSDC: whole times of spent in the dark compartment). Also, 48 hours after the shock, this test was repeated (Figure-1:II: B). During testing, the Step- through latency to the dark compartment is used as an index of the animal memory and learning ability; the relationship between the aversive stimulus and the learn and remember ability is shown. After 300 seconds during the test step, the refusal to spend time in the dark compartment is considered completely learned.

Determination of Serum NF-Kβ Level

At the end of the study, blood samples were

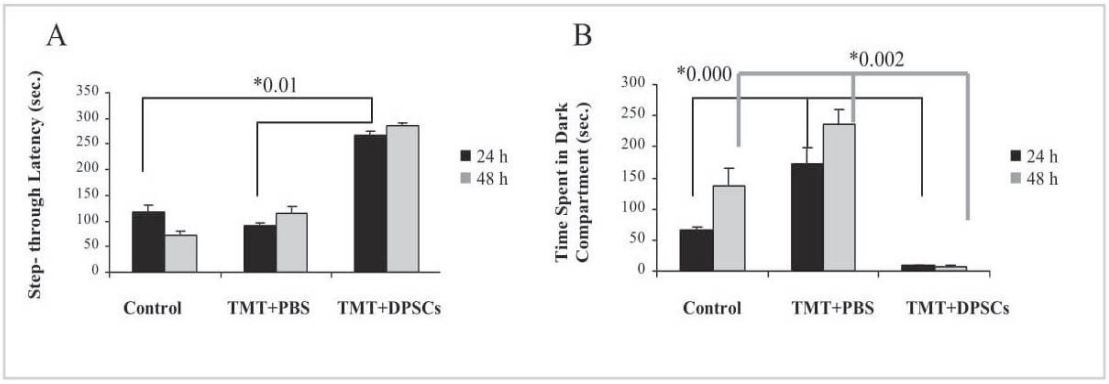

Figure 2. Comparison of latency time (A) and Time Spent in Dark Compartment (TSDC); (B) after 24 & 48 hours after shock between different groups (*p<0.05). The Tukey analysis was used for comparing groups to each other. Data expressed as Mean±SD of 6 rats in each group.

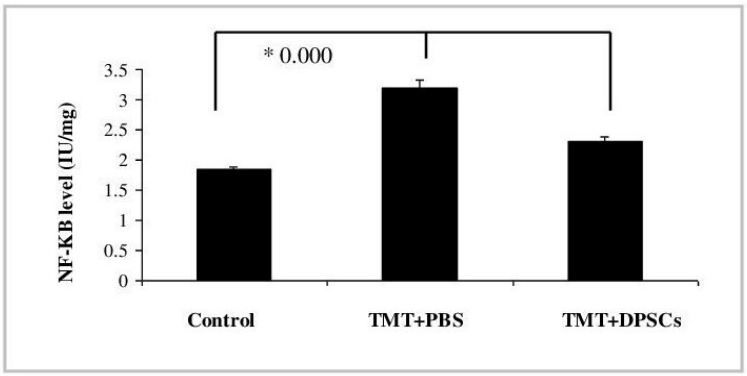

Figure 3. Comparison of NF-Kβ serum level between different groups (*p<0.05). The Tukey analysis was used for comparing the group to each other. Data expressed as Mean±SD of 6 rats in each group

collected from the heart, and then plasma was separated with centrifugation at 1500 rpm for 10 min. The level of serum NF-Kβ was measured by ELISA according to the procedures provided in the kits.

Histopathology of Hippocampus

After the rats were anesthetized and sacrificed, the brains were removed (in a perfusion manner) and placed into a 4% paraformaldehyde solution. Specimen-produced serial coronal sections were cut at 5 µm thicknesses in a rotary microtome. The sections were mounted on glass slides and stained with Hematoxylin and Eosin (H&E). All sections were studied under a light microscope. The damaged neural cells of DG, CA1, CA2, and CA3 were evaluated in all groups (Figure-1:II: C). Also, ten sections of each group were counted, and then data was expressed with percent.

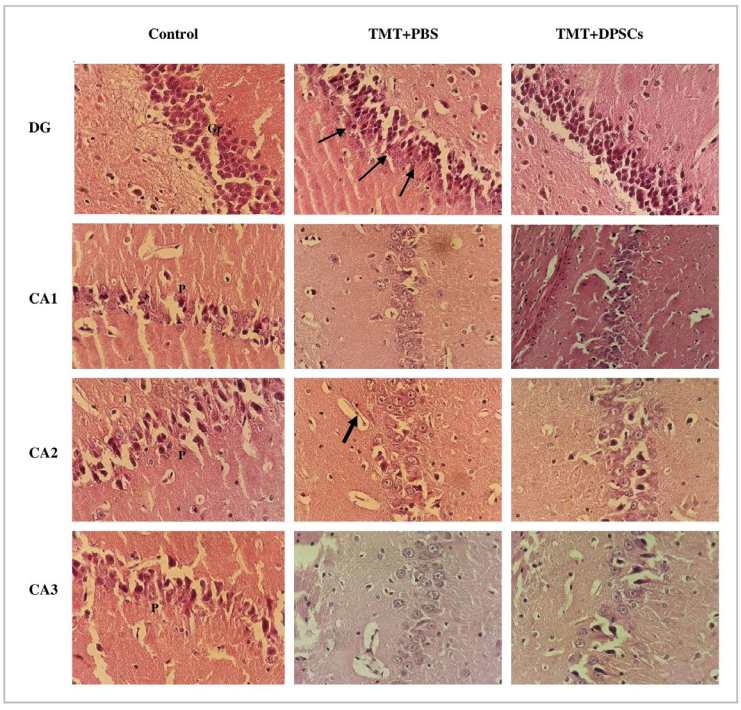

Figure 4. The photomicrographs of rat hippocampal DG, CA1, CA2, and CA3 regions from different groups (H&E; 40x). (Gr: Granular layer cells; P: Pyramidal cells). Sections were obtained from rat hippocampus after TMT toxicity (TMT+PBS) and treatment with DPSCs followed by neurotoxicity (TMT+DPSCs) compared to the control group. Look at the 5-6 compact cell layer of DG and CA1 in the control group compared to necrotic cells (thin arrow) in TMT+PBS. Also, wide blood capillaries (arrow) showed in TMT+PBS. The TMT+DPSCs cells staining showed improvement of damage neuron cells compared to TMT+PBS.

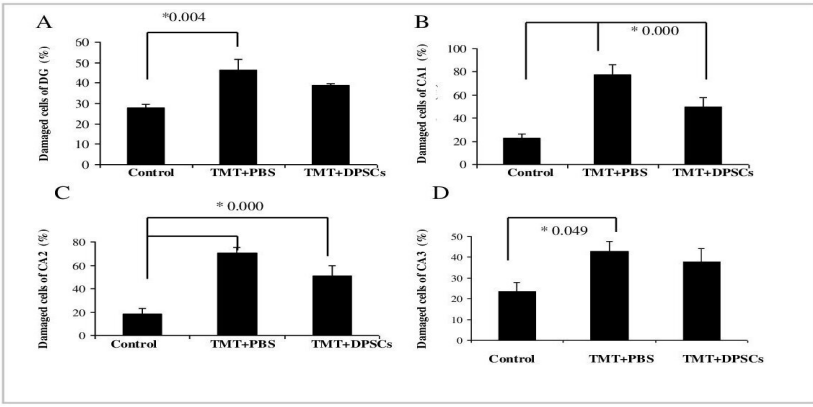

Figure 5. Comparison of the percentage of damaged hippocampus DG (A), CA1 (B), CA2 (C), and CA3 (D) cell numbers between groups (*p<0.05). The Tukey analysis was used for comparing the group to each other. Data expressed as Mean±SD of 6 rats in each group.

Statistical Analysis

The data were analyzed by one-way ANOVA followed by Tukey analysis with SPSS (IBM SPSS Statistics V23 Core System; Armonk, N.Y., USA) software. Statistically significant were considered with P<0.05; Also, data were expressed as Mean±SD.

Results

MSCs Confirmation

Some characterizations of stem cells were displayed in third and fourth passages, like a long spindle shape fibroblastic morphology and plastic-adherent confirmed MSCs characterizations. The osteogenic differentiation of DPCs was confirmed the MSCs lineage of DP (Figure-1:I: B). The surface marker expression was identified MSCs intrinsic. The flow cytometry analysis was showed negative expression of CD34 and positive expression of CD44 and CD90 confirmed MSCs intrinsic of DPCs (Figure 1:I: C).

Passive Avoidance Memory

This study showed that the Step- through latency in the TMT+DPSCs group (267.92±14.89) significantly increased in comparison with the control and TMT+PBS group (116.24±37.93) in 24 hours after shock (p=0.01). Also, the Time Spent in Dark Compartment (TSDC) in the TMT+PBS group (172.2±65.15; 236.26±56.83) significantly increased compared to the control group (65.58±12.93; 135.84±74.78) 24 & 48 hours after shock, respectively. Also, TSDC in the TMT+DPSCs group (9.27±2.83; 6.38±5.62) significantly decreased compared to control and TMT+PBS groups (172.2±65.15; 236.26±56.83) in 24 & 48 hours after shock (p=0.002, Figure 2).

Determination of Serum NF-Kβ Level

The results showed that NF-Kβ serum level significantly increased in the TMT+PBS group compared to the control group. Also, the NF-Kβ serum level significantly decreased in the TMT+DPSCs group compared to the TMT+PBS group (p<0.05, Figure 3).

Histopathology of Hippocampus

The results showed that the number of DG, CA1, CA2, and CA3 cells significantly decreased in the TMT+PBS group compared to the control group. Also, the number of percentage damage CA1 cells significantly decreased in the TMT+DPSCs group (%50±17.95) compared to the TMT+PBS group (%77.12±22.23); also this amount in control group is %22.94 ± 8.9; p=0, Figure-5 and Figure-4). In addition, the percentage of damage CA2 cells of TMT+DPSCs group (%51.01±20.54) showed significant differences in compared to control group (%18.58 ± 11.60; p=0.000) but not significant with TMT+PBS group (%70.19± 12.61).

Discussion

The present study constructed the AD rat model with TMT injection (i.p); this model is commonly used to establish an AD model in animals [15, 16] and makes it helpful in studying the pathological changes in the hippocampus or behavioral assessments in the AD rat model. DPSCs have a neural crest origin with great ability to the treatment of neurological disorders in comparison with other MSCs types. One study showed DPSCs transplantation improves behavioral and cognitive function in Aβ- induced AD in a rat model [17]. Geloso et al. (2007) showed transplantation of fetal neural stem cells into the rat hippocampus differentiated into neurons and astrocytes in TMT- induced neurodegeneration rat model [18]. In addition, the study showed DPSCs repair degree of demyelination and promoted recovery in peripheral nerve injury rat model [19].

The passive avoidance task is a model for learning and memory studies. This model is based on the inherent priority of rodents for dark compartments and then repression of this inherent priority by shock exposure. The task's base is an adaptive reaction to a stressful experience that recognizes the learning and memory level. This study showed that 8 mg/kg injection of TMT causes memory impairment and hippocampus neurons loss in rats.

On the other hand, systemic hDPSCs transplantation significantly decreased the TSDC over the control group in the short-term and long-term through passive avoidance tasks. Also, following DPSCs transplantation showed significantly increased step-through latency to enter the dark compartment (24 h; short-term) compared to control and TMT+PBS groups. The hDPSCs transplantation improved memory function and significantly decreased the percentage of damaged CA1 pyramidal neurons compared to the TMT+PBS group. However, it should be noted that the present study was performed in six weeks, and the problems and complications of stem cell transplantation have not been studied in the long term. Systemic injection of stem cells is a new paradigm of stem cell therapy for disease treatment and tissue regeneration. This model has advantages such as regulating immune response and enhancing endogenous regeneration.

Studies have shown that low-level TMT exposure damaged cerebellar granule cells, although a high level of TMT causes necrosis and both low and high levels of TMT produced ROS. Also, one study reported blocking ERK activation protected SH-SY5Y cells from TMT-induced apoptosis; that suggested that ERK contributed to TMT-induced apoptosis [20].

In our previously published we demonstrated transplantation of the human dental pulp stem cells improve anxiety and memory impairment that measured with Elevated plus and Y Maze task in a rat model. Also, we showed, following administration of DPSCs, significantly decreased nuclear factor kappa (NF-k) levels assessed by the ELIZA method compared to the TMT+PBS group. There is a contradictory relation between the NF-kb signaling pathway and normal brain function. This pathway plays a crucial role in synaptic plasticity, maintaining and balancing learning and memory. Therefore, impairment of NF-kb signaling causes altered neuronal dynamics [21].

NF-kb regulated the transcriptional activity of proinflammatory transcription factors, cytokines, adhesion molecules, chemokines, and moderated neuronal survival. NF-kb members are abundantly present in the glial cells and cerebral blood vessels. Also, NF-kb dimer formation subunits could regulate neurotoxicity or neuroinflammation [22]. NF-kb is a risk factor in the incidence of AD that is associated with neurodegeneration. NF-kb plays as an innate immunity key regulator in genetic and environmental risk factors in cellular, vertebrate, invertebrate models of AD [23]. In addition, activated NF-kb is mainly found in glial cells and neurons in Ab plaque surrounding areas in AD patients [24]. Intraperitoneally injection of mesenchymal stem cell-conditioned medium (MSC-CM) significantly increased anti-inflammatory responses and down-regulation of inflammatory reactions in a mouse model of inflammatory bowel disease (IBD) autoimmune/inflammatory responses. Also, FoxP (Forkhead Box P) has an essential

role in the immune reaction of inflammatory conditions [25]. Dental Pulp Stem Cell Conditioned Media (DPSC-CM) had an immunomodulatory effect on the proliferation of allogeneic cells. Also, DPSC-CM could inhibit stimulated and non-stimulated PBMCs (Peripheral Blood Mononuclear Cells) proliferation after 48 and 72 hours [26].

Generally, the hippocampus is a very vulnerable region, and many neural disorders are associated with the loss of hippocampal neurons. Studies demonstrated CA3 is an essential region for remembering sequences of spatial events [27]. The administration of TMT damaged hippocampus neurons and showed the pyramidal cell loss in the CA1 area in a dose-dependent manner. The experimental lesion of cholinergic nuclei suppressed the hippocampus neurogenesis. In contrast, activating the cholinergic system improved hippocampus neurogenesis and cognitive function [28]. Intrahippocampal (IHP) injection of Aβ decreased learning in the passive avoidance task within 2 weeks [29]. Also, intracerebroventricular (icv) injections of Aβ induced learning impairment, cognitive dysfunction, and decreased choline acetyltransferase activity in the medial septum, cortex, and hippocampus, but not basal forebrain [30]. Bilateral injection of Aβ in nucleus basalis cause learning impairment in passive avoidance tasks [31]. Our results are consistent with the above studies; we demonstrate TMT injection causes dementia, cognitive-behavioral disorders, and severe damage of the rat hippocampus neuronal cells. Also, immediately (up to 24 hours) after injection of TMT observed some apparent symptoms such as numbness, seizure, and increased body temperature; other symptoms such as aggression, loss of appetite, and weight loss are seen in the next few days. Generally, TMT is a strong toxic that can be used to understand better AD's mechanisms and subsequent treatment of this disease.

In this study, according to the spindle morphology, the cells' adhesion to the flask floor and the osteogenic differentiation capacity were proved the cells extracted from dental pulp are mesenchymal stem cells. Our flow cytometry analysis was confirmed the stem cell source of dental pulp; data was showed negative expression of CD34 and positive expression of CD44 and CD90 that confirmed MSCs intrinsic of hDPCs. Studies showed bone marrow transplantation improved pathological and behavioral alteration in the AD mice model. APOE3-expressing cells derived from bone marrow transplantation possess a higher neuropathological and behavioral alteration ability than APOE4 in AD [32]. Interestingly, studies showed AD in vulnerable young adults brain regions (carrying apoE4 allele) with abnormally low rates of glucose metabolism in several decades before the possible onset of dementia [33]. A study showed a decrease in CA1 neurons in the AD rat model [34]. They showed that after transplantation, the cells not only survived and migrated to the host tissue but also expressed neuronal-like cells, cholinergic cells, and Glial fibrillary acidic protein (GFAP) through the Double staining immunohistochemistry method; which suggested that the epidermal-neural crest stem cells were very similar to glial and neuronal-like differentiation cells in the AD model in vivo. Investigated the effect of BDNF and Adipose tissue-derived stem cell transplantation on cognitive impairment in the AD animal model in two months after transplantation [35]. In addition, they showed that induction of BDNF expression improved dementia within14 days. Our results are consistent with the above studies, that we demonstrated human DPSCs transplantation significantly improved memory and learning in Passive Avoidance memory task in comparison with the control group; also significantly decreased the percentage of damage pyramidal neurons of CA1 in TMT-induced AD rat model following DPSCs administration in compare with TMT+PBS group. One study showed a significant decrease in neural density in CA1 and CA3 hippocampal regions in AD patients [36]. Also, the a significant association between CA2 hippocampal pathology and cognitive decline in Parkinson's Disease (PD) patients [37]. Human neural stem cells transplantation enhanced synaptic plasticity and improved cognitive function in a mouse model of AD [38]. Also, one study reported

that injection of BMSCs (1×106 in 20 µl PBS) into the cerebrospinal fluid (CSF) significantly decrease the number of hippocampus dark neurons [39]. In addition, one study showed that transplantation of stem cells from human exfoliated deciduous teeth decreases cognitive impairment in a chronic cerebral ischemia rat model. Also, they reported transplantation of SHED inhibited neuronal apoptosis in the hippocampus of the CA1 region. Furthermore, hippocampal infusion (2×105) or injection into tail vein (2×106) of SHED transplantation improved the spatial memory in the Morris Water Maze (MWM) task on chronic cerebral ischemia rats [40].

Our study is consistent with these results as shown hDPSCs transplantation (1×106) significantly increased memory and learning in the Passive Avoidance task, significantly decreased the NF-Kβ serum level, and significantly decreased the hippocampus pyramidal neurons damage CA1 (approximately 20%) in comparison with TMT+PBS group in TMT- induced AD rat model.

Conclusion

According to the present study, hDPSCs transplantation significantly increased step-through latency to enter the dark compartment (short term; 24 h aftershock) and significantly decreased the time spent in the dark compartment (short and long term; 24 and 48 hours after the shock, respectively) in compare with TMT+PBS groups in passive avoidance task. So, hDPSCs improved memory and learning; also, hDPSCs significantly decreased the amount of NF-kβ serum level in comparison with the TMT+PBS group. In addition, hDPSCs transplantation significantly decreased the damage of CA1 pyramidal neurons compared with the TMT+PBS group in an AD rat model. Transplantation of human DPSCs into rats promises the use of cell and tissue transplantation among various species. Although, according to possible side effects of this transplantation, further studies seem necessary, especially in the long term.

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Conflict of Interest

The authors declare no conflict of interests.

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