

# Adipose-derived mesenchymal stem cells (ASCs) transplantation restored olfactory function in anosmic rats

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## Summary

Olfactory dysfunction is a major challenge in medicine and there is no absolute treatment for anosmic patients. Adipose-derived mesenchymal stem cells (ASCs) are multipotent cells capable of differentiating into several cell lineages. The aim of present study was to assess effects of ASCs upon restoration of the olfactory function in anosmic rats.

## Materials and methods

ASCs were isolated from the periuterine fat tissue of rats using collagenase type I. Anosmia was induced by intraperitoneal injection of 3-methylindole. Further on,  $5 \times 10^5$  ASCs were transnasally transferred into the case group one day after the induction of anosmia. The control group included anosmic rats that were injected with culture media without ASCs. The olfactory function was evaluated weekly by a food-finding test. Olfactory neuroepithelium and bulb were harvested for histopathologic study at 4 and 8 weeks.

## Results

Injection of ASCs caused about seven- and six-fold statistically significant reduction in the food-finding time in the case group of rats when compared to the control group tested, respectively, 4 and 8 weeks after injection of ASCs (P-value= 0.00 and =0.035, respectively). Histopathological findings showed reconstruction of olfac-

tory neuroepithelium in 93% of the cases while it was detected in 50% of control rats. The olfactory bulb was detectable in 60% of the case group rats, compared with 20% of the control rats.

## Conclusion

Our present results show that regeneration of olfactory epithelium may be accelerated using local ASCs treatment. These data suggest that ASCs might be a promising source for the treatment of olfactory dysfunction in the future.

## Keywords

Anosmia, experimental, mesenchymal stem cells, adipose-derived, differentiation, neural cells.

## Introduction

Anosmia is a Greek word meaning the inability to perceive odor or loss of the sense of smell. It is a major olfactory disorder that greatly impairs an individual's quality of life. Several etiologies such as sinonasal disorders, including inflammatory disease like rhinosinusitis, nasal fracture, obstructive conditions of the upper respiratory tract, viral infections, brain trauma, and congenital and neurologic diseases may induce an olfactory dysfunction [1, 2]. Olfactory disorders are also caused by reduction of olfactory receptor neurons in neuroepithelium and olfactory bulb area. The olfactory neuroepithelium covers the ethmoturbinate structure that contains the olfactory receptor neurons and is located in posterior region of the nasal cavity. Olfactory neuronal damage is mainly caused by loss of olfactory receptor neurons [3, 4, 5], and regeneration of these receptors is associated with the function and presence of neural stem cells. Therefore, application of stem cells may have benefits for the treatment of olfactory dysfunction. In previous animal model studies, the olfactory function of anosmic mice was improved after transplantation of stem cells [4, 6]. Such studies suggested a correlation between olfactory dysfunction and a decrease in the neuronal olfactory population, which can be replaced or repaired by using neural stem cells.

Mesenchymal stem cells (MSCs) are among the most interesting types of adult stem cells that could be isolated from different tissues, such as bone marrow, adipose tissue, umbilical cord blood, placental and amniotic fluid, and menstrual blood. These cells can be *ex vivo* manipulated and successfully applied for treatment clinical conditions, like coronary artery disease and vascular ischemia, bone and cartilage defects, and graft versus host disease (GVHD) [7, 8]. These effects are caused by the immunomodulatory properties of MSCs [8, 9], or differentiation ability of these cells into various mesodermal cell lineages [10-12]. Previous reports have also demonstrated the transdifferentiation ability of MSCs into endodermal and ectodermal lineages [13-15], including neural, epithelial, and islet-like cells. Adipose tissue is one of the most prominent sources of MSCs owing to the fact that this tissue is the most available and easy to harvest for extracting MSCs.

Hence, the aim of present study was to see how adipose-derived mesenchymal stem cells (ASCs) can contribute to the improvement of anosmia in rats.

## Materials and methods

### Adipose-derived mesenchymal stem cells (ASCs) isolation, culture and characterization

This case-control study in animal model was approved by the Research Animal Care Committee of Laboratory Animals of Shiraz University of Medical Sciences. Twenty-five Sprague Dawley female rats weighing 200 g each were divided into the case (N=15, 10 rats for autologous and 5 rats for allogenic transplantation) and control (N=10) groups. ASCs were isolated from periuterine fat tissue of the case group, washed with phosphate-buffered saline (PBS), sliced into small pieces, and then incubated with 0.2% collagenase

type I (Gibco, USA) at 37°C in a shaker for two hours. Following routine cell centrifugation, the resulting pellet was incubated for 10 minutes in RBC lysis buffer and centrifuged again. The cell pellet was obtained for the separation of the stromal vascular fraction (SVF) using Ficoll-Paque density gradient (Biosera, UK). The SVF pellet was re-suspended in DMEM culture medium (Gibco, USA) containing 10% fetal bovine serum (FBS, Gibco, USA) and 1% penicillin/streptomycin (Biosera, UK). Non-adherent cells were discarded and adherent cells were cultured by changing the medium every three to four days and harvested on passage 3 for further experiments.

The third-passaged rat ASCs were examined by flow cytometry. Briefly,  $5 \times 10^5$  trypsinized cells were separately stained with allophycocyanin (APC)-conjugated anti-rat CD90 or CD73 (BD Biosciences, USA) and fluorescein isothiocyanate (FITC)-conjugated anti-rat CD14 (BD Biosciences, USA). Isotype-matched irrelevant monoclonal antibodies (BD Biosciences, USA) were used to exclude non-specific staining of the cells (BD Biosciences, USA). Flow cytometric analysis was performed using FlowJo software version 7.6.

### Standard functional olfactory ability evaluation

Before starting the experiments, olfactory function of the rats was evaluated, and then all the animals were put in the new environment, Maze apparatus (Suppl. Fig. 1), for adapting them to find food for 2 weeks. All the rats were fed routinely before the test, and then underwent fasting, except for water, for three days. Each rat was evaluated every 20 minutes for one hour to find the food, using the standard Maze test (food-finding test) [16]. The average time taken to find the food was between 12 and 19 seconds for all rats. Anosmia was induced by intraperitoneal injection of 3-methylindole (Sigma, USA) (30 µg/kg) which was applied elsewhere for induction of anosmia [17, 18]. On the next day, 500000 ASCs/100µl culture media were injected intranasally five times, 10 µl in each nasal cavity every time. Autologous cells were used in 10 rats, and allogeneic, in five other rats. For the control group, culture medium without ASCs was similarly used for 10 rats. Evaluation of anosmia and the effects of injected ASCs were examined at four and eight weeks after induction of anosmia by means of standard Maze test and immunohistochemistry for olfactory bulb and olfactory neuroepithelium specimens.

### Histological study

Rats were sacrificed with high dose of ketamine followed by harvesting of olfactory bulb and olfactory neuroepithelium and formalin fixation. The samples were then embedded in paraffin. Tissue sections were prepared, the slides were generated, and evaluation of the slides was done histologically using Hematoxylin staining.

### Statistical evaluation

The data were analyzed with a Statistical Package for Social Science (SPSS) version 17 for windows (IBM, USA) using Student's t test to determine statistical significance between the control and case groups. Results were expressed as mean  $\pm$  SD and a p-value <0.05 was considered significant.

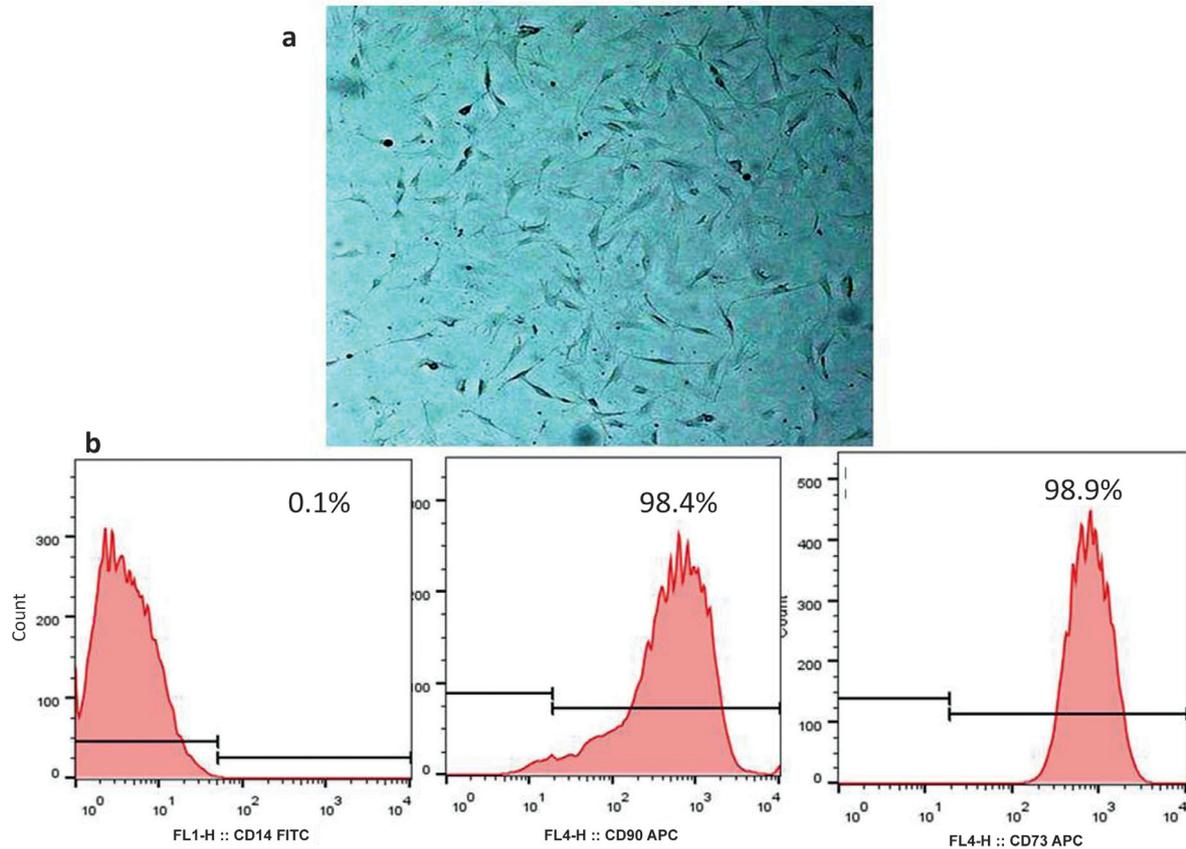


Figure 1. (a) Microscopic appearance of ASCs in culture in passage 3. Cultured ASCs were observed as spindle-shaped cell population. (b) Flow cytometric analysis of MSC-specific markers. Expression of CD73 and CD90 and absence of CD14 were shown on the surface of ASCs

## Results

### The average time for food finding was significantly different between the case and control groups

Adipose-derived mesenchymal stem cells were recognized by their spindle-shaped appearance in culture (Fig. 1a). These cells were positive for the expression of MSC specific markers, CD73 and CD90, but were negative for CD14 expression (Fig. 1b).

Olfactory function of rats was evaluated using the food-finding test. After four weeks, the mean  $\pm$  SD of the food-finding time were 13.8 $\pm$ 4.1 sec., 14.6 $\pm$ 8.6 sec., and 99.2 $\pm$ 44.6 sec. in the rats after autologous injections, in rats subjected to allogeneic injections, and in anomic controls, respectively. Thus, the injection of ASCs caused about a seven-fold statistically significant reduction in food-finding time in our case group of rats (P-value=0.00, Fig. 2). A six-fold statistically significant reduction in the food-finding time was observed in the case group of rats compared to the control group eight weeks after injection of ASCs. Accordingly, the food-finding time was 12.25 $\pm$ 1.7 sec. in the case group, comparing with 73.6 $\pm$ 29.3 sec. in the control group (P-value=0.035, Fig. 2). The mean food-finding time was not statistically different between the groups with autologous and allogeneic transplants (P-value >0.05).

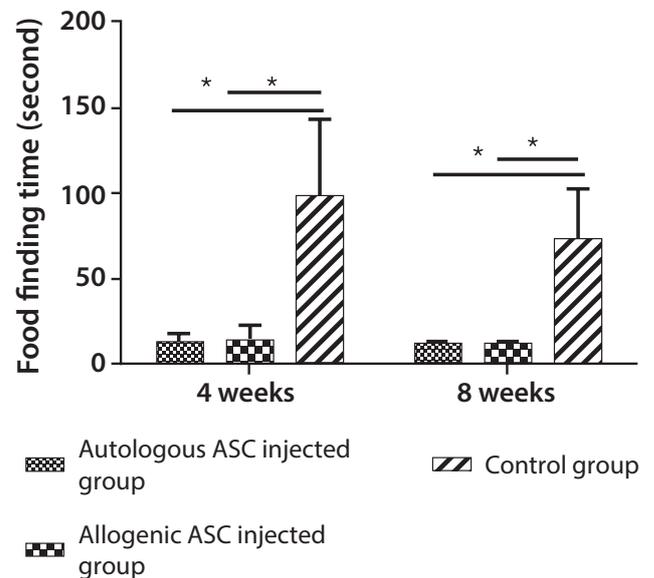


Figure 2. Comparison of the food finding mean time between the rats injected with autologous and allogeneic ASC (case group) and control group by 4 and 8 weeks after evaluation of olfactory function using the food-finding test. The differences between case and control groups were statistically significant. \*: P-value <0.05 means a significant difference.

### Histological evaluation

Histological evaluations of the brain and ethmoturbinate of the stem-cell transplanted rats showed that olfactory neuroepithelium and olfactory bulbs were revealed, respectively, in 14 rats (93%) (Fig. 3b) and nine rats (60%) (Fig. 4b) out of 15 ASC-treated animals. No significant difference was found between autologous and allogeneic ASC-injected groups. In the control group, olfactory epithelium (Fig. 3a) and olfactory bulb (Fig. 4a) were seen in five rats (50%) and two rats (20%) of all 10 control rats, respectively. As depicted in Fig. 3a, olfactory epithelium in the control group showed severe infiltration with lymphocytes and neutrophils that penetrated the surface layers.

### Discussion

MSCs are renowned mostly because of their unparalleled effects in regenerative medicine, which is caused by their outstanding ability to differentiate into various cell types, such as chondrocytes, osteocytes, and neural cells [7, 8, 14]. Recently, MSCs have been reported as promising therapeutic cell sources for restoring the function of neurons in neuro-

degenerative disorders, including stroke, Batten disease, Parkinson's, Alzheimer's disease, and spinal cord injury [19,20].

Olfactory disorders represent a common health problem, and their incidence has recently increased by 4-25% [21]. Impairment of sensory neural system is the main cause of olfactory dysfunction. Despite several therapeutic options, including medical and surgical procedures, the patients still suffer from recurrent anosmia. Since anosmia can be caused by degeneration of olfactory neuron receptors, Lee and colleagues suggested that transplantation of the neural stem cells stimulates regeneration of damaged olfactory cells [4]. Previous studies have demonstrated that other types of stem cells may effectively restore olfactory functions in various olfactory disorders. Jo et al. reported that the bone marrow mesenchymal stem cell (BMSCs) transplantation influences regeneration of olfactory epithelium and olfaction by expression of the nerve growth factor (NGF) and the brain-derived neurotrophic factor (BDNF) [22]. Ochi et al. reported migration of BMSCs to olfactory epithelium and higher engraftment rates in mice, and showed differentiation of these cells to premature olfactory receptor neurons in mice [23]. Human cord blood stem cells also showed promising results

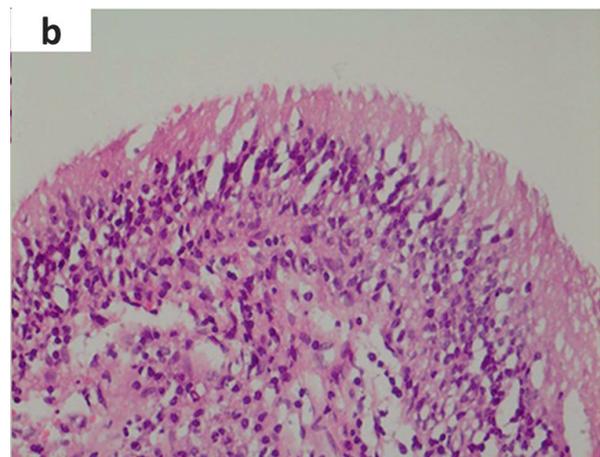
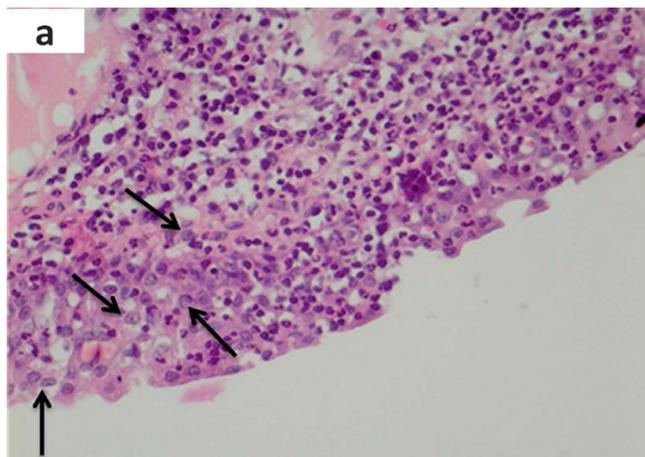


Figure 3. Olfactory epithelium in the non ASC-injected (control) and ASC-injected (case) groups. a: Olfactory epithelium in the control group with severe infiltration of lymphocytes and neutrophils penetrating surface layers. H&E X250. b: Olfactory epithelium in the case group without inflammation. H&E X250.

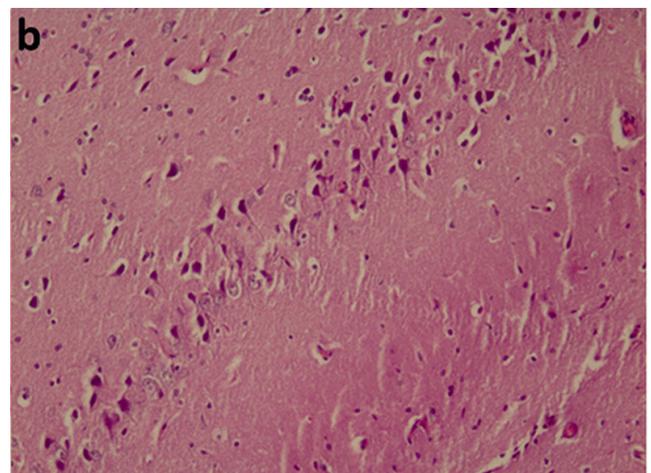
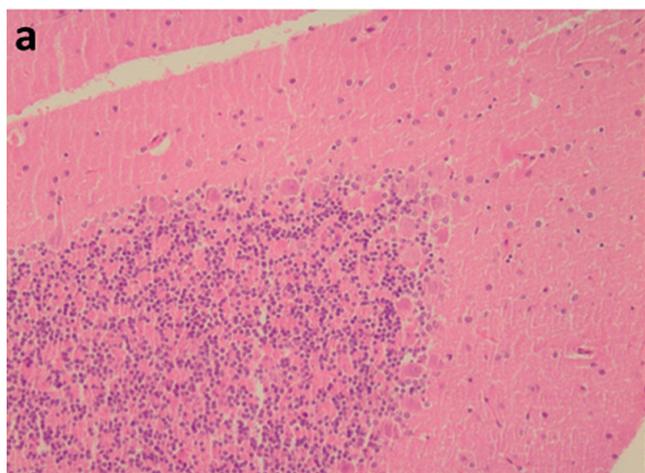


Figure 4. Olfactory bulb in the control group (a), and case group (b) with intact architecture and cells, however, without inflammation after ASC injection. H&E X100.

because it has been previously shown that BDNF-expressing hUCB-MSCs have great ability to differentiate into astrocytes and olfactory bulb in mice [24]. Furthermore, adipose tissue, an important source for stem cells, can be considered for differentiation towards a neuronal lineage and olfactory restoration [25-28]. As shown by Kokai and colleagues, ASCs may differentiate into different cell types, like neural stem cells [25]. Transplantation of ASCs in mice showed convincing results for restoration of neuroepithelium in the damaged olfactory region [29]. In the present study, anosmia was induced in a group of rats using 3-methylindole; then olfactory function of the anosmic rats was evaluated after injection of ASCs. The transplantation was performed either with allogeneic, or autologous ASCs, in order to compare any possible difference between the results, and to show whether autologous source of ASCs have any preference to allogeneic ones. Based on our results, a statistically significant reduction was observed in the food-finding time in anosmia-induced rats by four and eight weeks post injection of ASCs. Histological evaluation confirmed the effects of ASCs, since olfactory neuroepithelium and olfactory bulb of the brain and ethmoturbinate were detected in the stem cell-transplanted rats but not in the control group. No difference between autologous and allogeneic groups was found either in the mean duration of food-finding, or in histological evaluation. Accordingly, our findings are consistent with other reports showing the effects of stem cell transplantation in the recovery from anosmia, because the rats transplanted with ASCs after anosmia induction and destruction of the olfactory region, could find the food more rapidly than the animals from control group. This finding showed a faster functional recovery of olfactory system following ASCs treatment. Compared to other studies, the present survey was more preferential, due to safer and less invasive way for isolating stem cells and minimizing probable differentiation of the stem cells to other lineages by transnasal delivery of ASCs.

## Conclusion

In summary, the present study provides the *in vivo* experimental evidence indicating that the administration of ASCs obtained from periuterine fat tissue may improve olfactory function. Studies with larger numbers of animals over longer periods of time can provide more confirmation of the efficacy of this approach as a therapeutic intervention for anosmic patients in the future. Adipose tissue represents an abundant and easily available cell source from which stem cells can be obtained by a less invasive method. Accordingly, this tissue may be considered the most promising alternative to the other sources of stem cells to these purposes.

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The authors declare that they have no conflict of interest concerning this article.

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# Трансплантация жировых мезенхимальных стволовых клеток (жМСК) восстанавливает обонятельную функцию у крыс с аносмией

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## Резюме

Нарушения обонятельной функции являются большой проблемой медицины, и нет радикального лечения больных с аносмией. Мезенхимные стволовые клетки, полученные из жировой ткани (АМСК) являются мультипотентными клетками, способными к дифференцировке в несколько клеточных ростков. Целью настоящего исследования была оценка эффектов АМСК на восстановление обонятельной функции у крыс с аносмией.

## Материалы и методы

АМСК изолировали из околоматочной жировой ткани крыс с применением коллагеназы типа 1. Аносмию индуцировали путем интраперитонеального введения 3-метилендола. Затем через 1 сут. после индукции аносмии, вводили  $5 \times 10^5$  АМСК трансназально животным опытной группы. В контрольной группе были крысы с аносмией, которым вводили культуральную среду без АМСК. Обонятельную функцию оценивали еженедельно с помощью теста нахождения пищи. Обонятельный нейроэпителий и луковицу забирали для гистопатологического исследования в сроки 4 и 8 недель.

## Результаты

После инъекции АМСК наблюдалось примерно 6-7 кратное снижение времени нахождения пищи в опытной группе крыс по сравнению с контрольной группой. Различия были достоверными при  $P=0,00$  и  $P=0,035$ , соответственно, через 4 и 8 недель после инъекции АМСК. Результаты гистопатологического исследования показали реконструкцию обонятельного нейроэпителия в 93% случаев в опытной группе, и в 50% – у контрольных крыс. Обонятельная луковица выявлялась у 60% крыс в опыте, по сравнению с 20% в контроле.

## Выводы

Полученные нами результаты показывают, что регенерация обонятельного эпителия может быть ускорена при использовании локального введения АМСК. Эти данные предполагают, что АМСК в будущем могут быть перспективным источником лечения дисфункции обоняния.

## Ключевые слова

Аносмия, экспериментальная, мезенхимные стволовые клетки, жировая ткань, дифференцировка, нейрональные клетки.