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Fursa G.A., Fedorov A.V., Stepanova O.V., Chekhonin V.P., 2026

DOI: 10.31088/CEM2026.15.3.48-57

Survival, migration, and differentiation of neural stem/progenitor cells in experimental Alzheimer's disease

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Abstract. *Introduction.* Alzheimer's disease is a severe neurodegenerative disorder characterized by neuronal loss and brain atrophy. Cell therapy utilizing neural stem/progenitor cells represents a promising approach for its treatment, as these cells may facilitate the regeneration of neural tissue by replacing damaged neurons and glial cells *in vivo*. This study aimed to evaluate the survival, migration, and differentiation of neural stem/progenitor cells derived from the olfactory mucosa in an experimental model.

Materials and methods. Alzheimer's disease was modeled in female rats via stereotaxic injection of β -amyloid 1–42 into the hippocampus. The model was validated using the Morris water maze test. Rat olfactory mucosa neural stem/progenitor cells, labeled with PKH26, were transplanted bilaterally into the CA1 region of the hippocampus.

Results. The cells were shown to survive for up to 4 weeks post-transplantation within the hippocampal region and migrate into the corpus callosum and cerebral cortex. Moreover, the grafted cells exhibited the capacity for glial and neuronal differentiation, as evidenced by the expression of GFAP and β -III-tubulin, respectively.

Conclusion. The survival, migration, and *in vivo* differentiation potential of olfactory mucosa-derived neural stem/progenitor cells support further investigation as a promising tool for personalized cell-based therapies in patients with Alzheimer's disease.

Keywords: neural stem/progenitor cells, olfactory mucosa, β -amyloid 1–42, Alzheimer's disease, cell therapy

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For citation: Karsuntseva E.K., Voronova A.D., Pokidko V.Yu., Mukhina A.I., Shishkina V.S., Chadin A.V., Fursa G.A., Fedorov A.V., Stepanova O.V., Chekhonin V.P. Survival, migration, and differentiation of neural stem/progenitor cells in experimental Alzheimer's disease. Clin. exp. morphology. 2026;15(3)48–57. DOI: 10.31088/CEM2026.15.3.48-57.

Funding. The study was supported by the Russian Science Foundation, grant № 22-15-00141-P.

Received 24.03.2026. **Received in revised form** 31.03.2026. **Accepted** 14.05.2026.

УДК: 57.084.1

Выживаемость, миграция и дифференцировка нейральных стволовых/прогениторных клеток при экспериментальной болезни Альцгеймера

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Резюме. *Введение.* Болезнь Альцгеймера – крайне тяжелое нейродегенеративное заболевание, характеризующееся гибелью нейронов и атрофией головного мозга. Перспективным подходом при данной патологии может быть клеточная терапия на основе трансплантации нейральных стволовых/

прогениторных клеток. Они способны стимулировать регенерацию нервной ткани головного мозга, в частности замещать погибшие нейроны и клетки глии *in vivo*. Цель исследования – изучить выживаемость, миграцию и дифференцировку нейральных стволовых/прогениторных клеток обонятельной выстилки при экспериментальной болезни Альцгеймера.

Материалы и методы. Болезнь Альцгеймера моделировали на самках крыс путем стереотаксического введения β -амилоида 1–42 в зону гиппокампа. Валидацию метода проводили с помощью поведенческого теста «водный лабиринт Морриса». Затем меченные витальным красителем РКН26 нейральные стволовые/прогениторные клетки обонятельной выстилки крыс трансплантировали билатерально в зону СА1 гиппокампа.

Результаты. Установлено, что трансплантированные клетки сохраняют жизнеспособность в течение 4 недель после введения в гиппокамп, а также мигрируют в мозолистое тело и кору больших полушарий. Кроме того, выявлена их способность к дифференцировке в глиальном и нейральном направлении, что подтверждается положительной иммуногистохимической реакцией на маркеры GFAP и β -III-тубулин.

Заключение. Полученные данные о выживаемости, миграции и дифференцировке нейральных стволовых/прогениторных клеток обонятельной выстилки *in vivo* открывают перспективы их использования в персонализированной терапии у пациентов с болезнью Альцгеймера.

Ключевые слова: нейральные стволовые/прогениторные клетки, обонятельная выстилка, β -амилоид 1–42, болезнь Альцгеймера, клеточная терапия

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Для цитирования: Карсунцева Е.К., Воронова А.Д., Покидько В.Ю., Мухина А.И., Шишкина В.С., Чадин А.В., Фурса Г.А., Федоров А.В., Степанова О.В., Чехонин В.П. Выживаемость, миграция и дифференцировка нейральных стволовых/прогениторных клеток при экспериментальной болезни Альцгеймера. Клин. экп. морфология. 2026;15(3):48–57. DOI: 10.31088/CEM2026.15.3.48-57.

Финансирование. Исследование выполнено при поддержке Российского научного фонда (грант № 22-15-00141-П).

Статья поступила 24.03.2026. Получена после рецензирования 31.03.2026. Принята в печать 14.05.2026.

Introduction

Alzheimer's disease (AD) is a severe neurodegenerative disorder that primarily affects individuals over the age of 65 years and is characterized by progressive memory impairment, cognitive decline, and behavioral disturbances [1]. The key distinction between AD and physiological aging lies in the pathological accumulation of β -amyloid plaques in the brain along with the aggregation of hyperphosphorylated tau protein which forms neurofibrillary tangles within neurons [2]. These pathological deposits are considered principal drivers of neuronal loss and synaptic dysfunction [2] and they also trigger neuroinflammatory responses mediated by reactive astrocytes and microglial cells [3]. Collectively, these neurodegenerative processes ultimately result in severe cerebral atrophy.

To date, AD remains incurable. Conventional pharmacological approaches targeting only symptomatic manifestations, as well as recently developed next-generation therapeutics, including anti- β -amyloid antibodies, have failed to restore damaged neural tissue [1, 4]. In this context, cell-based therapy has emerged as a promising avenue for the development of effective AD treatments [5]. Transplanted cells may exert beneficial effects on the local microenvironment through the secretion of neurotrophic factors and anti-inflammatory cytokines *in vivo*, thereby potentially initiating regenerative processes within neural tissue [6].

Neural stem/progenitor cells (NSPCs) are among the most extensively studied cell types for the treatment of neurodegenerative disorders. NSPCs represent multipotent stem cells predominantly localized in the olfactory mucosa, olfactory bulb, subventricular zone, and subgranular zone of the hippocampus [7]. NSPCs have been demonstrated to differentiate into neurons and glial cells, restore the balance of neurotrophic factors, promote neural tissue regeneration, and influence axonal growth and remyelination both *in vitro* and *in vivo*. These cells can be obtained from embryonic, fetal, and postnatal neural tissue, as well as through cellular reprogramming techniques. Numerous preclinical studies using animal models of AD have demonstrated the therapeutic potential of NSPCs [8, 9]. Specifically, NSPC transplantation has been shown to reduce β -amyloid deposition and hyperphosphorylated tau protein levels, enhance synaptic plasticity, and significantly improve cognitive functions in experimental animals [10]. Nevertheless, clinical data on the application of NSPCs in patients with AD remain unavailable.

The olfactory epithelium of the olfactory mucosa (OM) represents a particularly attractive source of NSPCs. OM-derived NSPCs are responsible for the lifelong renewal of olfactory neurons. The pronounced neuroregenerative capacity of these cells provides a strong rationale for their potential application in AD therapy. At the Department of Fundamental and Applied Neurobiology, V.P. Serbsky

National Medical Research Centre for Psychiatry and Narcology, we have developed a protocol for obtaining adhesive NSPC cultures from the OM, which enables the isolation of highly enriched NSPC populations [11]. The clinical application of NSPCs obtained from adult donors, in contrast to those derived from embryonic or fetal tissues, is not associated with bioethical concerns or legislative restrictions [12, 13]. However, experimental and clinical data regarding the application of OM-derived NSPCs in AD remain scarce; particularly, the survival, migration, and differentiation of these cells following intracerebral transplantation have not yet been investigated.

Therefore, we aimed to evaluate the survival, migration, and differentiation of OM-derived NSPCs in an experimental AD model.

Materials and methods

The study employed analytical-grade plasticware and reagents from Corning (USA), NEST Biotechnology (China), PanEco (Russia), Thermo Fisher Scientific (USA), HyClone (USA), Abcam (Great Britain), and Sigma (USA). The overall experimental design is presented in Figure 1. All procedures were approved by the Local Ethics Committee of the V.P. Serbsky National Medical Research Centre for Psychiatry and Narcology (protocol dated May 22, 2025)

and performed in accordance with the European Union Directive 2010/63/EU on the protection of animals used for scientific purposes.

NSPCs were isolated from the olfactory epithelium of adult female Wistar rats ($n=4$). Animals were housed under controlled environmental conditions (21–24°C, 50–70% humidity, a 12-hour light/dark cycle) with ad libitum access to food and water. Adhesive NSPC cultures were obtained according to the protocol developed at the Department of Fundamental and Applied Neurobiology of the V.P. Serbsky National Medical Research Centre for Psychiatry and Narcology [11].

Cells were cultured in Neurobasal medium supplemented with 2.5% fetal bovine serum, 2% B-27 supplement, 1% penicillin-streptomycin, 1% L-glutamine, 0.1% epidermal growth factor (EGF), and 0.1% fibroblast growth factor (FGF). Phenotypic characterization of cell population was performed by immunocytochemical detection of the principal NSPC markers Sox-2 (a nuclear transcription factor associated with stemness) and nestin (a marker of early neural differentiation), with representative data not shown. NSPCs from passages 1–2 were used for subsequent transplantation into the brains of animals with experimental AD.

Experimental AD was induced in rats ($n=6$) by stereotaxic bilateral injection of synthetic β -amyloid pep-

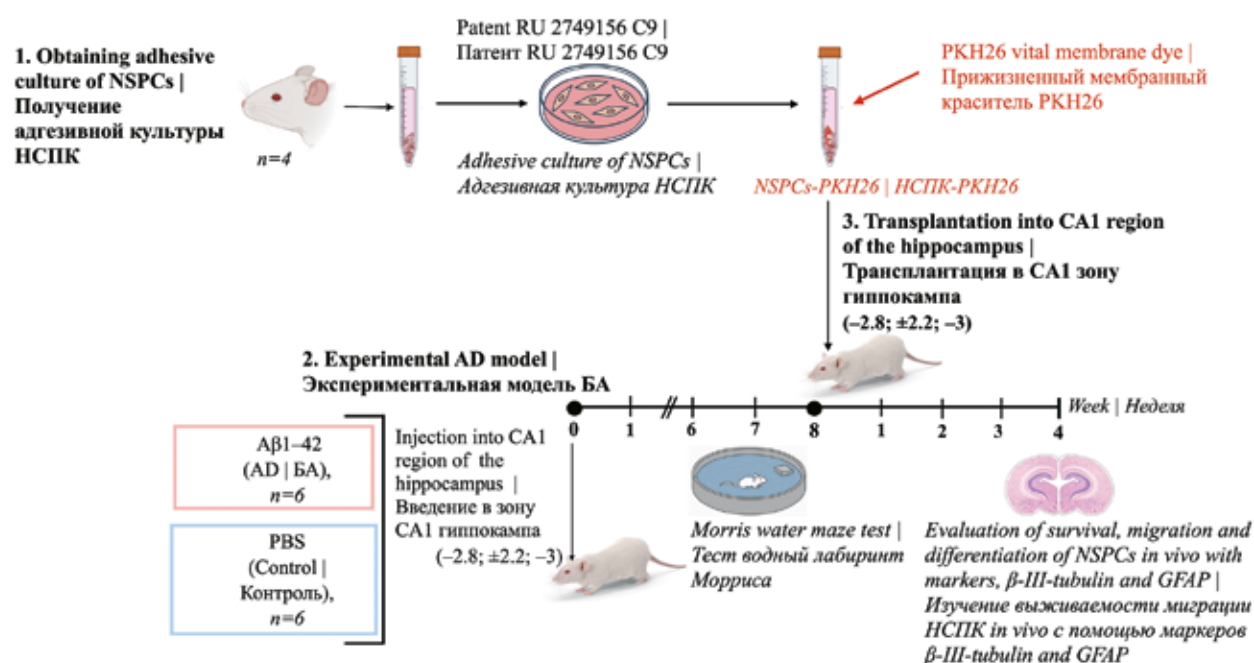


Fig. 1. Experimental design.

1 – obtaining adhesive culture of neural stem progenitor cells (NSPCs). 2 – stereotaxic AD modeling with bilateral Aβ1-42 injection into the hippocampus and validation with Morris water maze test. 3 – transplantation of NSPCs staining with PKH26 (NSPCs-PKH26) into the hippocampus and evaluation of their survival, migration, and differentiation *in vivo*

Рис. 1. Схема эксперимента.

1 – получение адгезивной культуры нейральных стволовых/прогениторных клеток – НСПК. 2 – стереотаксическое моделирование болезни Альцгеймера (БА) путем билатерального введения Aβ1-42 в гиппокамп и валидация модели с помощью поведенческого теста «водный лабиринт Морриса». 3 – трансплантация НСПК, меченных PKH26 (НСПК-PKH26), в гиппокамп и оценка их выживаемости, миграции и дифференцировки *in vivo*

tide 1–42 (A β 1–42; Elabscience Biotechnology, China) into the CA1 region of the hippocampus using the following coordinates: $-3, \pm 2.2, -3.2$ [14]. Control animals ($n=6$) received phosphate-buffered saline (PBS; PanEco, Russia). Animals were randomly assigned to experimental groups.

Prior to surgery, animals were anesthetized by intraperitoneal injection of a mixture of vesitol (40 mg/kg; Vetstem, Russia) and xylazine (5 mg/kg; Alfasan International B.V., Netherlands). After skull exposure and craniotomy at the specified coordinates, A β 1–42 peptide (1 mg/mL) was injected at a volume of 5 μ L with an infusion rate of 1 μ L/min. Postoperatively, rats received cefazolin (375 mg/kg) as an antibiotic and ketoprofen (5 mg/kg) as an analgesic.

To validate the experimental AD model, we assessed cognitive functions of subjects using the Morris water maze test 8 weeks after A β 1–42 administration. This behavioral paradigm evaluates spatial learning and memory by measuring the ability of animals to locate a submerged platform following a training course [15]. Testing was conducted 48 hours after the final training session. Each rat was allowed 60 seconds to locate the platform.

To evaluate NSPC survival, migration, and differentiation following transplantation into the brains of rats with experimental AD, cells were labeled with the fluorescent membrane dye PKH26 (Invitrogen, USA). PKH26-labeled NSPCs were prepared according to the manufacturer's instructions.

Cells were bilaterally transplanted into the CA1 region of the hippocampus using the same stereotaxic coordinates as those used for A β 1–42 injection during AD modeling ($-3, \pm 2.2, -3.2$). A total of 100,000 cells in 5 μ L were injected at a rate of 1 μ L/min.

We assessed NSPCs survival by immunofluorescence analysis 4 weeks after transplantation. For brain tissue collection, animals were deeply anesthetized by intraperitoneal anesthetic injection, followed by decapitation. The brains were then extracted, fixed in 10% formalin for 24 hours, and subsequently rinsed in PBS. Tissue samples were sectioned using a vibrating microtome (HM650V, Thermo Fisher Scientific, USA) to obtain 30- μ m-thick sections, which were then washed in PBS supplemented with Tween-20 (1 μ L/mL).

For immunofluorescence staining, we used primary antibodies against the neuronal marker β -III-tubulin (1:100; Abcam, UK) and the astrocytic marker GFAP (1:100; Abcam, UK), followed by Alexa Fluor 488- and Alexa Fluor 633-conjugated secondary antibodies (1:500; Thermo Fisher Scientific, USA). Nuclei was counterstained with DAPI (Invitrogen, USA). Samples were examined using a Nikon A1R MP+ laser scanning confocal microscope equipped with a multiphoton module (Nikon, Japan).

Statistical analysis was performed using GraphPad Prism 10 (GraphPad Software, Dotmatics, USA). Data normality was assessed using the Shapiro–Wilk test, whereas between-group differences were evaluated using Student's t-test for independent samples. The data are presented as

median and interquartile range (IQR). Differences were considered statistically significant at $p<0.05$.

Results

The experimental AD model was validated 8 weeks after A β 1–42 administration into the CA1 region of the hippocampus using the Morris water maze test.

Animals that received A β 1–42 injections exhibited a significantly longer latency to locate the submerged platform (mean: 35 s; Fig. 2) compared to control animals injected with PBS (mean: 8 s). Statistical analysis revealed a highly significant difference between the groups ($p<0.0001$). Thus, these findings confirm that the developed AD model reproduces cognitive impairments characteristic of AD in human patients [3, 14, 16].

The validated model was subsequently used for NSPC transplantation to investigate cell survival, migration, and differentiation *in vivo*, which represent key parameters for evaluating therapeutic efficacy in AD-associated neuropathology.

To the best of our knowledge, this is the first study when OM-derived NSPCs were transplanted into the hippocampus of control animals and those with experimental AD. Four weeks after transplantation, we detected pronounced accumulations of PKH26-labeled cells in the brains of AD animals (Fig. 3). Moreover, we observed migration of transplanted cells to adjacent brain regions, including the corpus callosum and cerebral cortex. Thus, transplanted NSPCs

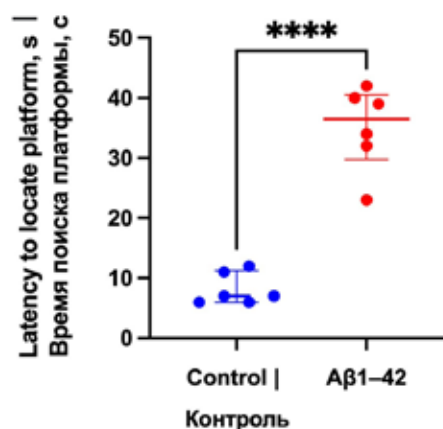


Fig. 2. Validation of the experimental AD model in the Morris water maze test. Control – PBS-injected animals, A β 1–42 – animals with experimental AD. The data are presented as median and interquartile range (IQR)

**** – $p<0.0001$, t-test (parametric one-way ANOVA), normality – Shapiro–Wilk test

Рис. 2. Валидация экспериментальной модели БА в тесте «водный лабиринт Морриса». Контроль – группа животных с введением PBS, A β 1–42 – животные с экспериментальной БА. Данные представлены в виде медианы и интерквартильного размаха **** – $p<0,0001$, t-тест (параметрический однофакторный дисперсионный анализ), нормальность – тест Шапиро–Уилка

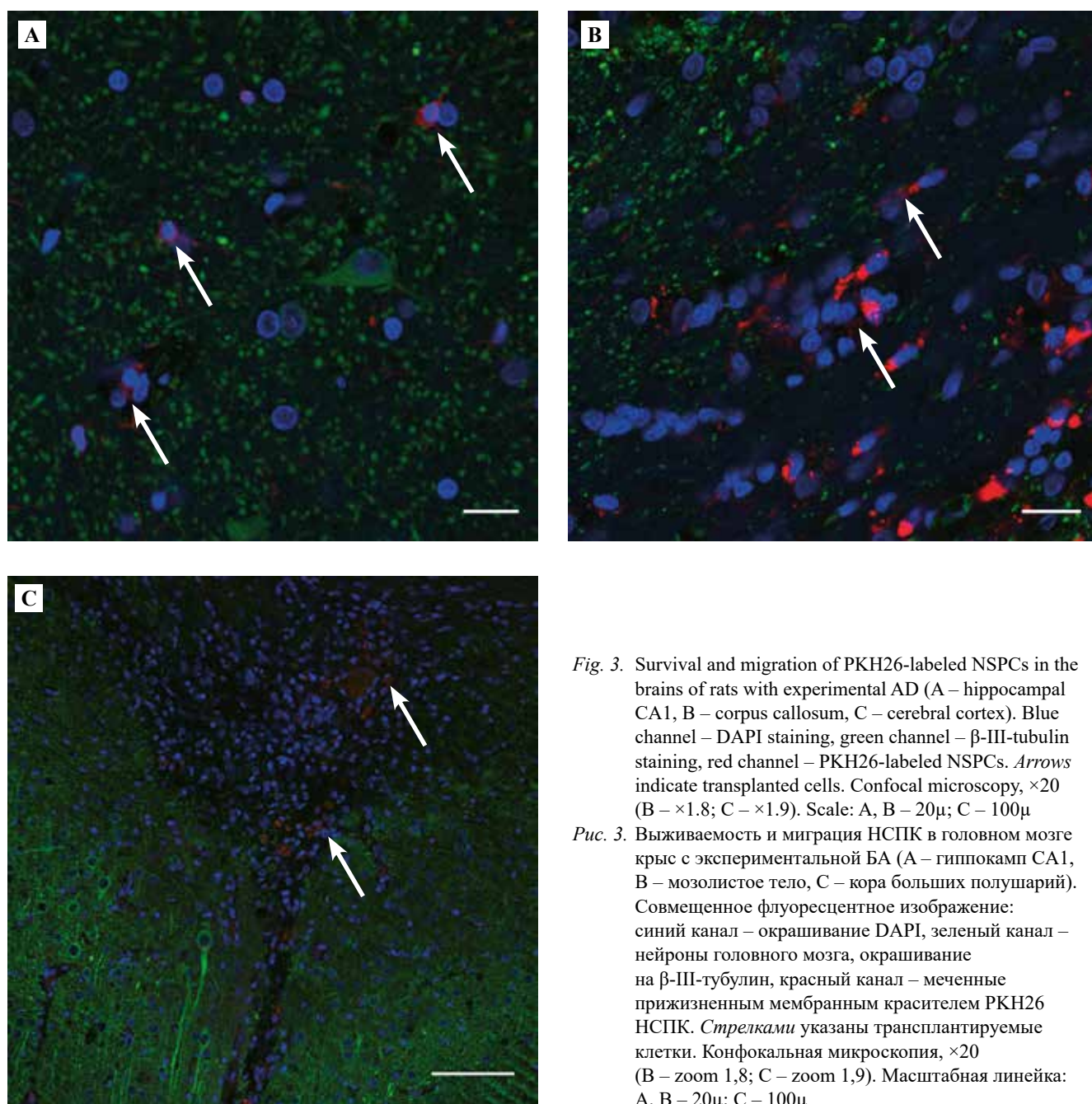


Fig. 3. Survival and migration of PKH26-labeled NSPCs in the brains of rats with experimental AD (A – hippocampal CA1, B – corpus callosum, C – cerebral cortex). Blue channel – DAPI staining, green channel – β -III-tubulin staining, red channel – PKH26-labeled NSPCs. Arrows indicate transplanted cells. Confocal microscopy, $\times 20$ (B – $\times 1.8$; C – $\times 1.9$). Scale: A, B – 20μ ; C – 100μ

Рис. 3. Выживаемость и миграция НСПК в головном мозге крыс с экспериментальной БА (А – гиппокамп CA1, В – мозолистое тело, С – кора больших полушарий). Совмещенное флуоресцентное изображение: синий канал – окрашивание DAPI, зеленый канал – нейроны головного мозга, окрашивание на β -III-тубулин, красный канал – меченные прижизненным мембранным красителем РКН26 НСПК. Стрелками указаны трансплантируемые клетки. Конфокальная микроскопия, $\times 20$ (В – zoom 1,8; С – zoom 1,9). Масштабная линейка: А, В – 20μ ; С – 100μ

demonstrated survival and migration across three distinct brain regions at 4 weeks post-transplantation. NSPC survival within the hippocampus and migration to the cerebral cortex and corpus callosum represents a particularly significant finding, as damage to these brain regions substantially contributes to cognitive deficits in AD [17, 18]. Viable transplanted cells identified within these regions may subsequently exert neuroprotective effects, promote neuroregeneration, and ultimately contribute to the restoration of cognitive functions [19].

We also investigated the ability of transplanted OM-derived NSPCs to differentiate toward neuronal and glial lineages *in vivo*. A subset of PKH26-labeled transplanted

NSPCs was shown to express β -III-tubulin within the rat hippocampus (Fig. 4), suggesting incipient differentiation of transplanted NSPCs toward a hippocampal neuronal phenotype. Notably, at 4 weeks post-transplantation, we did not detect the expression of mature neuronal markers (MAP2, NSE) by transplanted cells, which is likely to indicate a longer time period required for complete neuronal differentiation, which has been reported to range from 8 to 12 weeks [20]. Additionally, we observed expression of the astrocytic marker GFAP in individual NSPCs located within the corpus callosum (Fig. 5), which demonstrates the ability of transplanted NSPCs to undergo glial differentiation.

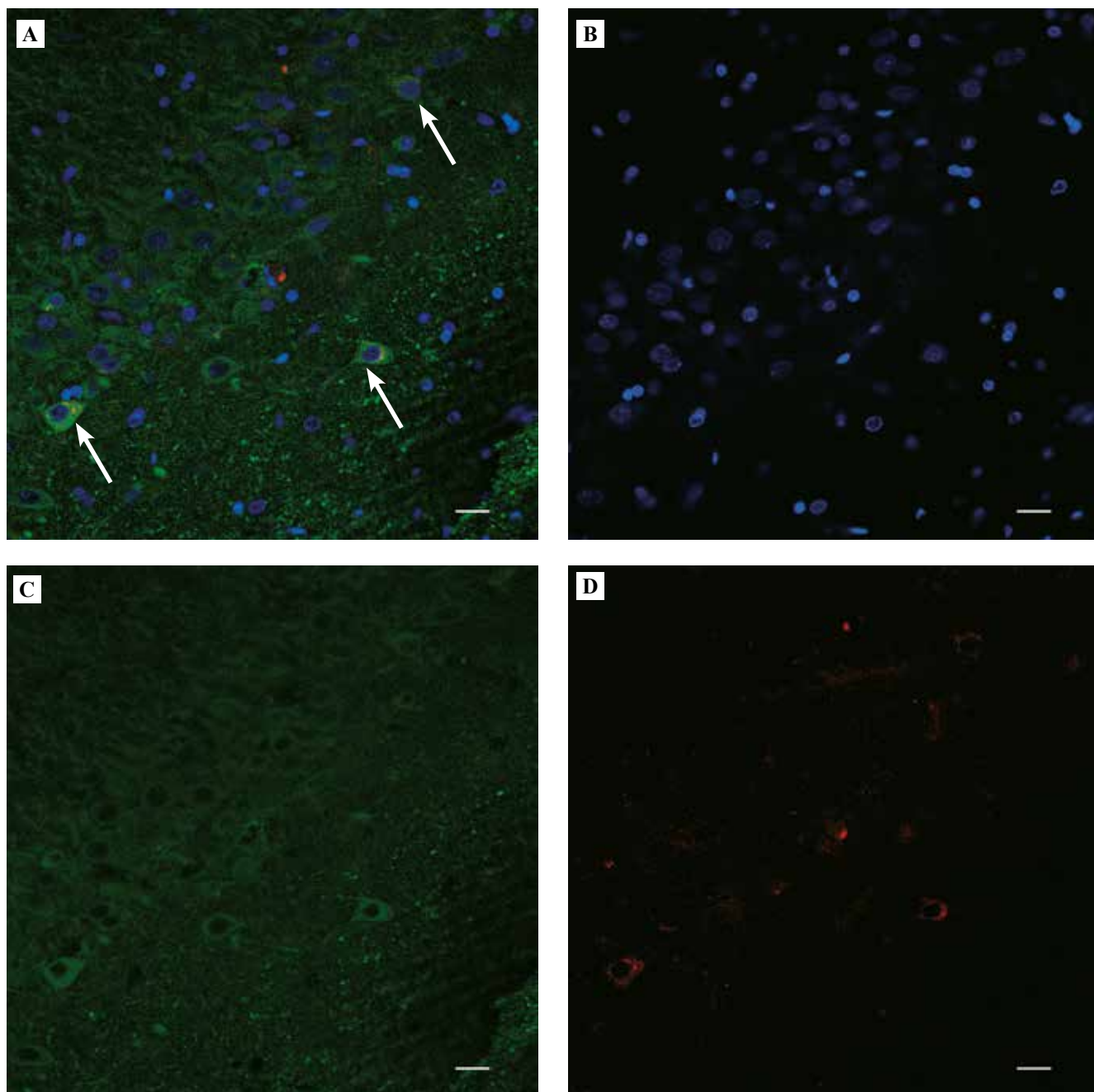


Fig. 4. Differentiation of PKH26-labeled NSPCs (arrows) into immature neurons in the hippocampal region of rats with experimental AD. A – merged image, B – DAPI nuclear staining, C – β -III-tubulin staining, D – PKH26-labeled NSPCs. Confocal microscopy, $\times 20$. Scale – 25μ

Рис. 4. Дифференцировка НСПК (стрелки), меченных прижизненным мембранным красителем РКН26, в головном мозге крыс с экспериментальной БА в незрелые нейроны зоны гиппокампа.

А – совмещенное изображение, В – окрашивание ядер на DAPI, С – окрашивание на β -III-тубулин, D – меченные прижизненным мембранным красителем РКН26 НСПК. Конфокальная микроскопия, $\times 20$. Масштабная линейка – 25μ

Discussion

Our findings on NSPCs survival, migration, and differentiation after intracerebral transplantation are consistent with the existing results demonstrating differentiation toward neuronal and glial lineages using lineage-specific markers [21]. Specifically, mouse ESC-derived NSPCs were demonstrated to survive for 8 weeks, migrate within

the hippocampus, and differentiate into astrocytes (GFAP+) and neuronal precursors (DCX+) after transplantation into the brains of transgenic APdE9 mice with experimental AD [22]. In another study employing the APP/PS1 mouse model of AD, mouse ESC-derived NSCs exhibited migration to the cerebral cortex and differentiation into neurons (Map2+), astrocytes (GFAP+), and oligodendrocytes

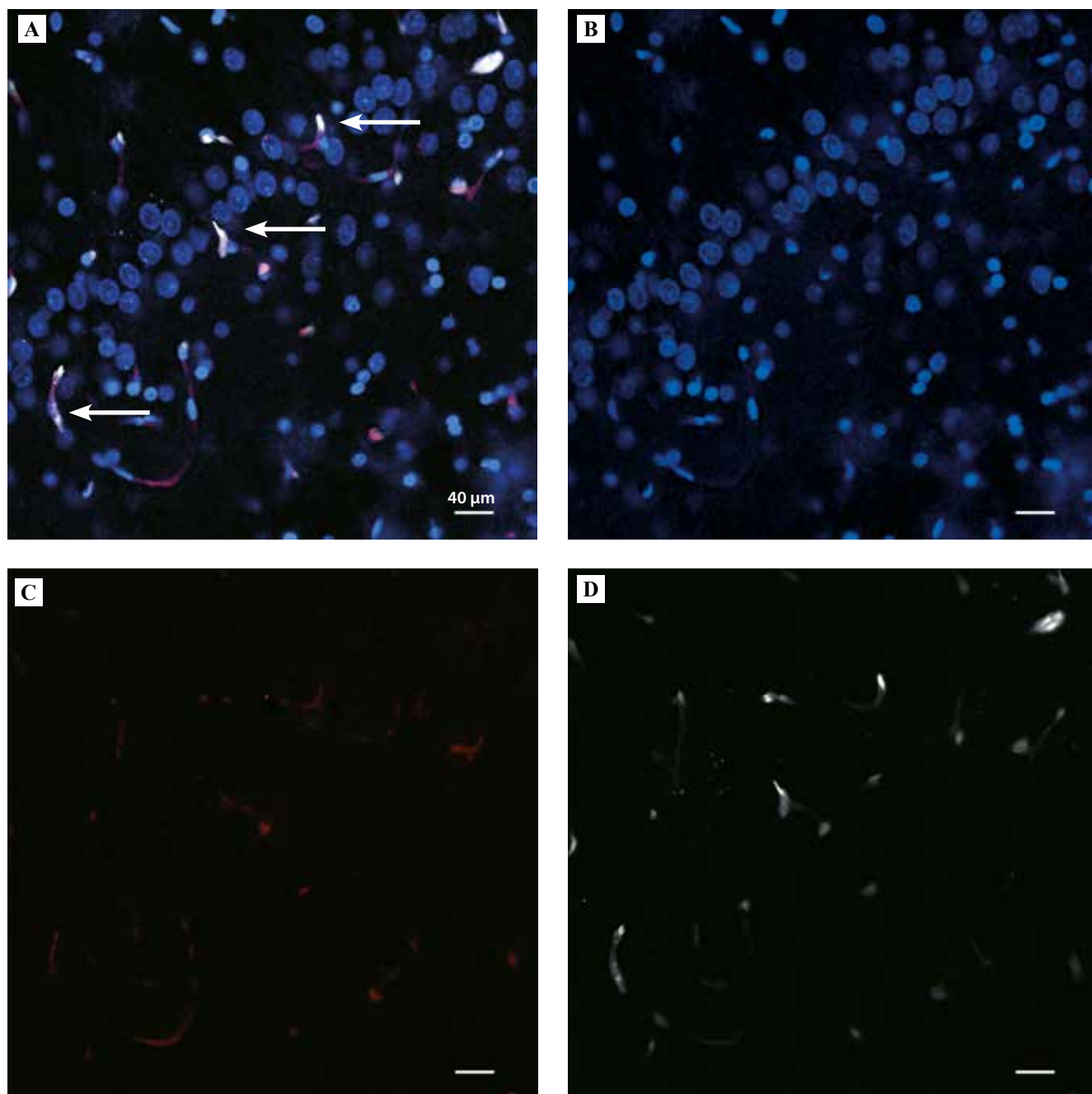


Fig. 5. Differentiation of PKH26-labeled NSPCs (arrows) into the glial lineage in the corpus callosum of rats with experimental AD. A – merged image, B – DAPI nuclear staining, C – PKH-labeled NSPCs, D – astrocyte staining for GFAP. Confocal microscopy, $\times 20$. Scale – 40μ

Рис. 5. Дифференцировка НСПК (стрелки), меченных прижизненным мембранным красителем РКН26, в мозолистом теле головного мозга крыс с экспериментальной БА в глиальную линию. А – совмещенное изображение, В – окрашивание ядер на DAPI, С – трансплантируемые НСПК, меченные РКН26, D – окрашивание астроцитов на GFAP. Конфокальная микроскопия, $\times 20$. Масштабная линейка – 40μ

(GalC+), with a predominant differentiation bias toward glial lineages [23].

NSPCs have low immunogenicity, which may contribute to improved survival after transplantation compared to other cell types [24]. Additionally, NSPCs are capable of regulating neuroinflammation by secreting anti-inflammatory cytokines, thereby reducing microglial activation and

inducing T-cell apoptosis [19, 25, 26]. This may attenuate the immune response to NSPC transplantation and promote neural tissue repair. Having been transplanted into the CNS, NSPCs can positively influence the microenvironment and secrete neurotrophic factors (BDNF, NGF, VEGF, IGF-1, etc.), exerting paracrine and autocrine effects *in vivo* [19]. They also secrete exosomes containing various molecules

(miR-146a, proteins, lipids, microRNAs), which help reduce oxidative stress [19, 26]. The described mechanisms contribute to the survival of transplanted NSPCs and modulate their functional activity in the brain. NSPC migration to sites of neurodegeneration is driven by chemotactic signals secreted by resident CNS cells in the damaged area [8, 19, 26].

Notably, the PKH26 labeling has certain limitations, including non-specific staining of cellular debris and potential dye transfer [27]. However, in our previous research, we demonstrated survival and migration of both PKH26-labeled OECs [14] and OECs with expression of green fluorescent protein (GFP) [28] in CNS. Both approaches yielded comparable results in terms of transplanted cell survival, migration, and localization of transplanted cells in the brain and spinal cord at 4 weeks post-transplantation.

Conversely, certain studies have reported limited survival rates of transplanted NSPCs within the brain. For instance, in a mouse model of hypoxic-ischemic brain injury, up to 90% of transplanted NSPCs underwent caspase-3-dependent apoptosis [29]. However, even dying NSPCs were demonstrated to secrete factors that contribute to neuroprotective effects *in vivo*. Transplantation timing, cell dosage, and the presence of neuroinflammation at the injection site may influence the survival, integration, and microenvironmental effects of transplanted NSPCs [19]. Exogenous administration of neurotrophic factors in conjunction with transplantation of genetically modified cells may enhance cell survival and therapeutic efficacy in AD [30].

Conclusion

The present study demonstrates the survival of olfactory mucosa-derived neural stem/progenitor cells for up to 4 weeks, their directed migration to adjacent brain regions, and their differentiation into neuronal and glial lineages following transplantation into the hippocampus of rats with experimental Alzheimer's disease. These findings support the therapeutic potential of these cells in Alzheimer's disease. The observed differentiation of olfactory mucosa-derived neural stem/progenitor cells into neurons and glial cells after intracerebral transplantation may reflect their intrinsic neuroregenerative capacity in the context of Alzheimer's disease. An additional advantage of employing these cells is the feasibility of obtaining olfactory mucosa biopsies through minimally invasive procedures that do not impair olfactory function. Collectively, these results provide a rationale for further research of olfactory mucosa-derived neural stem/progenitor cells as a basis for personalized therapeutic strategies for Alzheimer's disease.

Author contributions

Conceived the study and designed the experiment – E.K. Karsuntseva, A.D. Voronova, O.V. Stepanova, V.P. Chekhonin.

Collected the data and performed the analysis – E.K. Karsuntseva, V.Yu. Pokidko, A.I. Mukhina, V.S. Shishkina, A.V. Chadin, G.A. Fursa, A.V. Fedorov.

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Написание текста – Е.К. Карсунцева, А.Д. Воронова.

Редактирование – О.В. Степанова, В.П. Чехонин.

Disclosure. The authors declare no conflict of interest.

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

Acknowledgment

The authors gratefully acknowledge Elena V. Voznyakovskaya, Head of the Experimental and Biological Clinic of the V.P. Serbsky National Medical Research Centre for Psychiatry and Narcology, for her assistance with postoperative animal care.

Благодарность

Выражаем признательность руководителю экспериментально-биологической клиники НМИЦ психиатрии и наркологии им. В.П. Сербского Е.В. Возняковской за помощь в послеоперационном уходе за животными.

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