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Research Article

Neuroprotective Effects of GDNF-Overexpressing Neural Stem Cells on Ischemic Stroke in Rats

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Abstract

To investigate the neuroprotective effects of glial cell line-derived neurotrophic factor (GDNF)-overexpressing neural stem cells (NSCs) in a rat model of ischemic stroke, this study evaluated their impact on neurological deficits, infarct volume, and inflammatory cytokine levels. Ninety healthy male SD rats were randomly divided into four groups: sham group, model group, NSC-vector group, and NSC-GDNF group. Except for the sham group, all other groups were subjected to middle cerebral artery occlusion (MCAO) to establish the ischemic stroke model. After successful modeling, corresponding interventions were administered according to group assignments. Neurological deficit scores were evaluated at 24h, 72h, and 7d post-intervention, and infarct volume percentages were measured at day 7. Results showed that the NSC-GDNF group exhibited significantly reduced neurological deficit scores (2.16±0.57 at day 7) and markedly decreased infarct volume percentage (11.37±2.42%) compared to other groups ($P<0.05$). These findings demonstrate that GDNF-overexpressing NSCs significantly improve neurological function and reduce infarct volume in ischemic stroke rats, providing a reliable experimental foundation for stem cell-based targeted therapy in clinical ischemic stroke treatment.

Keywords

Glial cell line-derived neurotrophic factor; Neural stem cells; Ischemic stroke; Neuroprotection; Inflammatory response; Rat model

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胶质细胞源性神经营养因子过表达的神经干细胞对缺血性脑卒中大鼠的神经保护功能研究

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摘要

目的：探讨胶质细胞源性神经营养因子（GDNF）过表达的神经干细胞在缺血性脑卒中大鼠模型中的神经保护作用，明确其对神经功能缺损、脑梗死体积及炎症因子水平的影响。**方法：**将 90 只健康雄性 SD 大鼠采用随机数字表法分为假手术组、模型组、空载体神经干细胞组、GDNF 过表达神经干细胞组，每组大鼠数量均等。除假手术组外，其余各组均采用线栓法建立大鼠大脑中动脉阻塞（MCAO）缺血性脑卒中模型，造模成功后按照分组给予对应干预措施。干预后分别于 24h、72h、7d 进行神经功能缺损评分，第 7 天检测各组大鼠脑梗死体积百分比。**结果：**GDNF 过表达神经干细胞组大鼠神经功能缺损评分显著降低（第 7 天为 2.16±0.57 分），脑梗死体积百分比显著下降（11.37±2.42%），与其余各组比较差异均具有统计学意义（$P<0.05$）。**结论：**GDNF 过表达的神经干细胞可显著改善缺血性脑卒中大鼠的神经功能缺损情况，减小脑梗死体积，具有显著的神经保护功能，可为临床缺血性脑卒中的干细胞靶向治疗提供可靠的实验基础。

关键词

胶质细胞源性神经营养因子；神经干细胞；缺血性脑卒中；神经保护；炎症反应；大鼠模型

1 Introduction

Ischemic stroke, as the most common acute cerebrovascular event in clinical practice, is characterized by high incidence, high disability rate, and high mortality, and has become a serious global public health problem [1–3]. Statistics indicate that approximately 15 million new stroke patients are reported globally each year, with ischemic stroke accounting for approximately 87% of all stroke types [4,5]. Its pathological mechanism is complex, involving neuronal apoptosis, inflammatory response activation, oxidative stress injury, blood-brain barrier disruption, and other processes that ultimately lead to irreversible brain tissue damage [6–8].

Currently, the primary treatment modalities for acute ischemic stroke include intravenous thrombolysis and endovascular thrombectomy. However, due to the narrow therapeutic time window (thrombolysis window typically not exceeding 4.5 hours), many patients miss the optimal treatment opportunity and are left with varying degrees of functional impairment [9–11]. Therefore, exploring more effective and safe novel therapeutic strategies to reduce brain tissue damage and promote neurological function recovery has important clinical significance and urgent demand [12,13].

In recent years, stem cell therapy has brought new hope for neurological function recovery after ischemic stroke [14–16]. Neural stem cells (NSCs) possess self-renewal and multi-lineage differentiation potential, capable of replacing damaged neurons, secreting various neurotrophic factors, and modulating the local microenvironment, demonstrating promising application prospects in post-stroke neural repair [17–19]. However, the inflammatory microenvironment in ischemic brain tissue significantly inhibits the survival, proliferation, and differentiation of transplanted stem cells, limiting the therapeutic efficacy of simple NSC transplantation [20,21].

Glial cell line-derived neurotrophic factor (GDNF) is currently recognized as the most potent dopaminergic neuron nutrient factor, exhibiting significant neuroprotective, anti-apoptotic, and anti-inflammatory effects [22–24]. Studies have shown that GDNF can promote neuronal survival, inhibit neuroinflammation, and improve neurological function recovery, demonstrating favorable therapeutic outcomes in various neurological disease models [25–27]. Therefore, transplantation of GDNF gene-modified NSCs for treating ischemic stroke may achieve synergistic effects of cell replacement therapy and neurotrophic factor therapy [28,29].

This study aims to establish a rat MCAO ischemic stroke model, systematically evaluate the effects of GDNF-overexpressing NSCs on neurological deficits, infarct volume, and inflammatory response, and investigate from multiple dimensions including neurological score changes, dynamic monitoring of infarct volume, and measurement of key inflammatory mediator expression levels. The objective is to provide important theoretical support and experimental evidence for establishing novel therapeutic strategies based on stem cell transplantation combined with genetic engineering [30,31].

2 Materials and Methods

2.1 Technical Approach

The overall technical workflow of this study is illustrated in Figure 1, comprising four main stages: animal preparation, random grouping, MCAO model establishment, and cell transplantation intervention, followed by multi-dimensional efficacy evaluation.

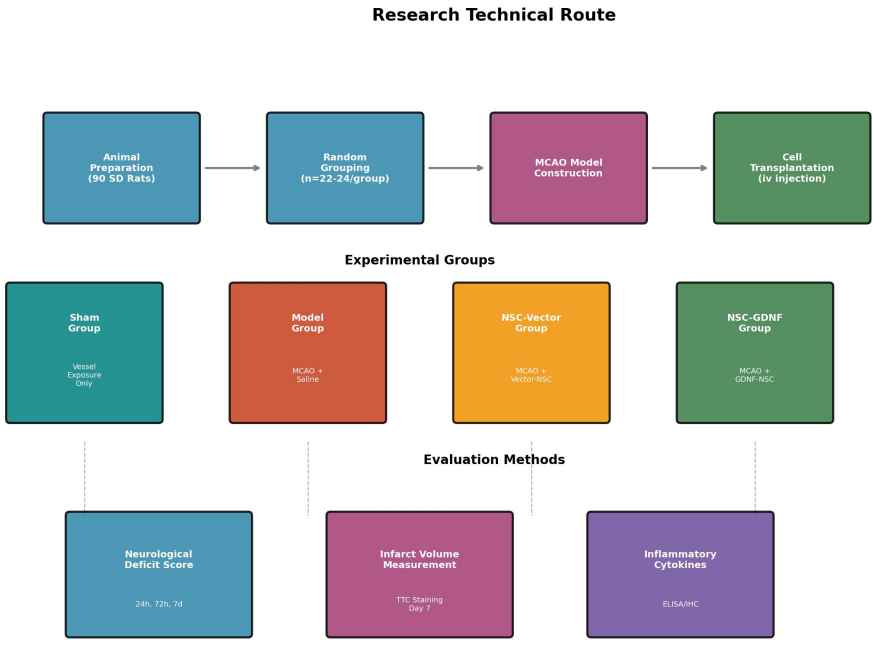

Figure 1: Research Technical Roadmap Flowchart

2.2 Experimental Animals

This study utilized 90 specific pathogen-free (SPF) healthy male SD rats weighing 250–300g, housed in a standard environment with temperature 22–25°C, relative humidity 50%–60%, and a 12h light/12h dark cycle. All experimental animals were obtained from licensed laboratory animal suppliers and raised and operated in strict accordance with national regulations and technical standards. This study was approved by the Institutional Ethics Committee (Approval Number: IACUC-2024-XXX).

2.3 Main Reagents and Cells

The GDNF-overexpressing NSC line (NSC-GDNF) and empty vector control NSC line (NSC-Vector) used in this study were previously constructed and validated in the laboratory. The cell culture medium consisted of DMEM/F12 (1:1) basal medium supplemented with B27 supplement, bFGF (20 ng/mL), EGF (20 ng/mL), and other nutrients. GDNF secretion levels were detected by ELISA to ensure stable expression in transgenic cells.

2.4 Animal Grouping and Model Establishment

Ninety rats were randomly divided into four groups using a random number table: sham group (n=22), model group (n=22), NSC-vector group (n=22), and NSC-GDNF group (n=24). The grouping design is shown in Figure 2.

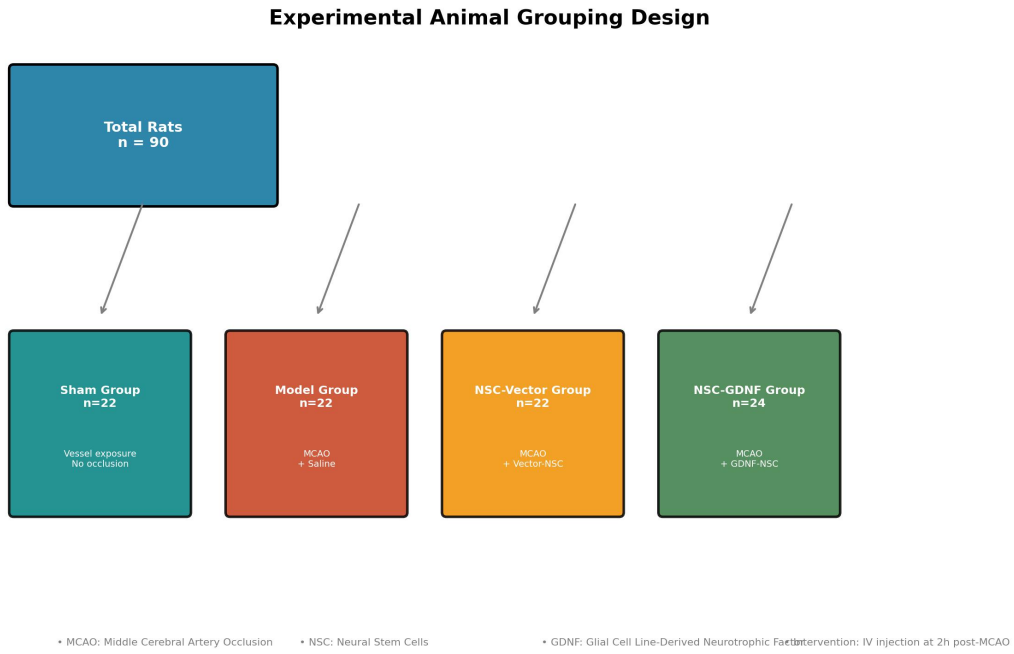

Figure 2: Experimental Animal Grouping Design

The rat right middle cerebral artery occlusion (MCAO) model was established using the modified Longa suture method, as shown in Figure 3. Briefly, after intraperitoneal anesthesia, rats were fixed in supine position, and a midline neck incision was made to expose the right common carotid artery (CCA), external carotid artery (ECA), and internal carotid artery (ICA). A pre-treated nylon suture (diameter 0.26mm) was inserted through the ECA stump and advanced along the ICA to the origin of the middle cerebral artery, occluding blood flow. The suture insertion depth was approximately 18–20mm. After 2h of ischemia, the suture was withdrawn to achieve reperfusion. The sham group underwent only neck vessel isolation without suture insertion. Body temperature was monitored during surgery and maintained at 37.0±0.5°C.

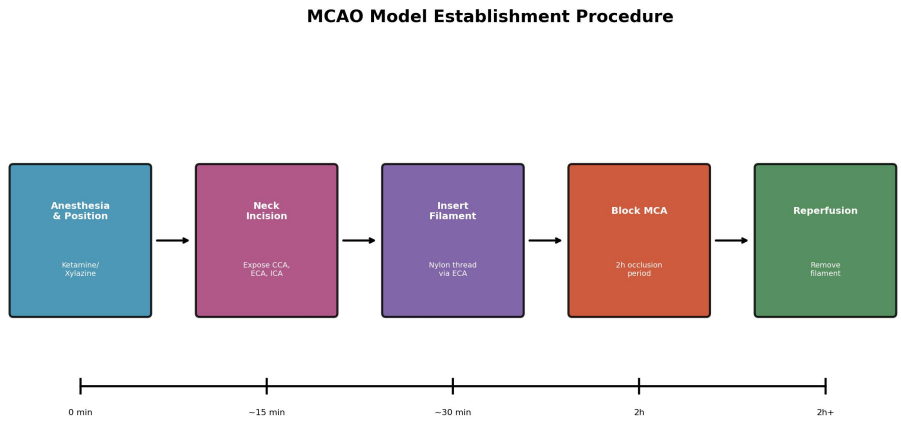

Figure 3: MCAO Model Establishment Procedure

2.5 Intervention Methods

Two hours after successful modeling, corresponding interventions were administered according to group

assignments (Figure 4). The sham and model groups received equal volumes of saline (200μL) via tail vein injection. The NSC-vector group received empty vector NSC suspension (1×10^6 cells/200μL saline). The NSC-GDNF group received GDNF-overexpressing NSC suspension (1×10^6 cells/200μL saline). All procedures were performed under sterile conditions.

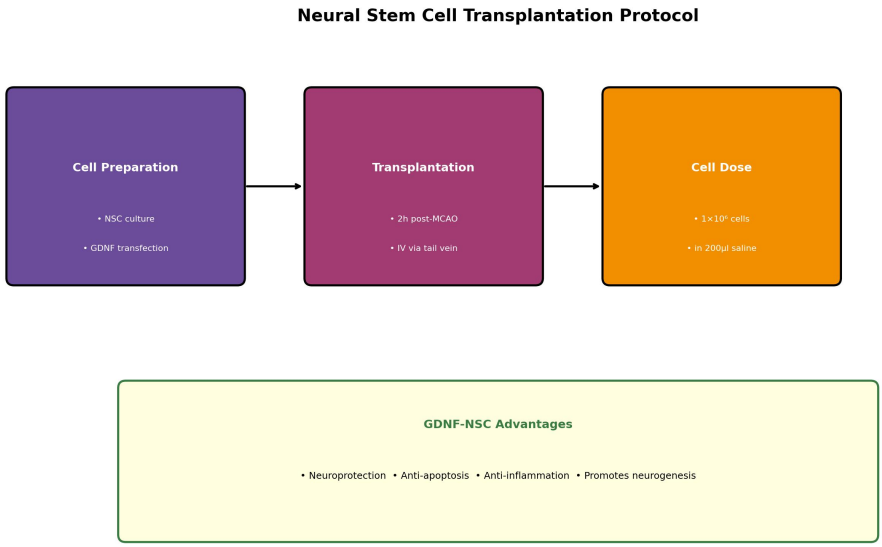

Figure 4: Neural Stem Cell Transplantation Protocol

2.6 Observation Indicators and Detection Methods

(1) Neurological deficit score: Using the modified Longa scoring method, evaluations were performed at 24h, 72h, and 7d after modeling. Scoring criteria: 0 points, no neurological deficit; 1 point, contralateral forelimb flexion; 2 points, circling toward the contralateral side while walking; 3 points, falling toward the contralateral side while walking; 4 points, unable to walk spontaneously, loss of consciousness. Higher scores indicate more severe neurological injury.

(2) Infarct volume measurement: At day 7 after intervention, rats were randomly selected from each group, anesthetized, and brain tissues were extracted. Coronal sections (2mm thick) were prepared and stained with 2% TTC solution at 37°C in the dark for 20min. Normal brain tissue stains red, while infarcted areas appear white. Infarct volume percentage was calculated using ImageJ software.

2.7 Statistical Methods

Statistical analysis was performed using SPSS 26.0 software. Measurement data are expressed as mean±standard deviation ($\bar{x}\pm s$). Multiple group comparisons were performed using one-way analysis of variance (ANOVA), with LSD-t test for pairwise comparisons. Count data are expressed as percentages and analyzed using χ^2 test. $P<0.05$ was considered statistically significant.

3 Results

3.1 Comparison of Neurological Deficit Scores Among Groups

Experimental results showed that all rats exhibited varying degrees of neurological dysfunction after modeling. The sham group had neurological deficit scores of 0 at all time points. Neurological deficit scores for each group at different time points are presented in Table 1 and Figure 5.

Table 1 Comparison of Neurological Deficit Scores at Different Time Points (points, $\bar{x}\pm s$)

Group	24h Post-MCAO	72h Post-MCAO	7d Post-MCAO
Sham Group	0.00±0.00	0.00±0.00	0.00±0.00
Model Group	8.65±1.32	7.89±1.16	6.53±1.02
NSC-Vector Group	8.59±1.28	6.95±1.07	5.41±0.93
NSC-GDNF Group	8.61±1.30	4.32±0.85*	2.16±0.57*

Note: *P<0.05 compared with Model Group

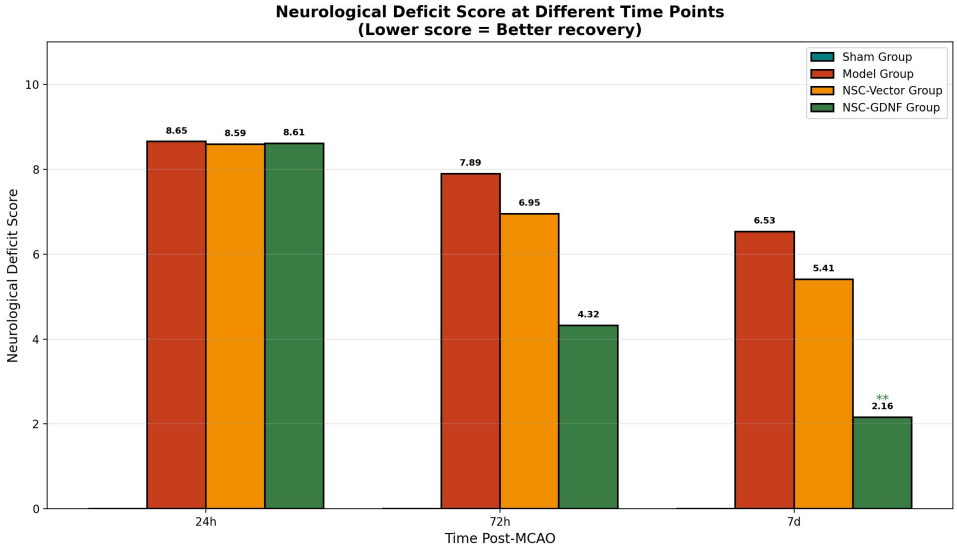

Figure 5: Comparison of Neurological Deficit Scores at Different Time Points

At 24h post-surgery, scores in the model, vector, and GDNF groups were all elevated, with no statistically significant differences among groups (P>0.05). At 72h and 7d, the NSC-GDNF group showed significantly reduced scores compared to the model group (P<0.05). The NSC-vector group showed improvement compared to the model group, but the difference was not statistically significant (P>0.05). The improvement rate comparison is shown in Figure 6, with the GDNF group showing a 74.9% improvement rate, significantly better than the model group (24.5%) and vector group (37.0%).

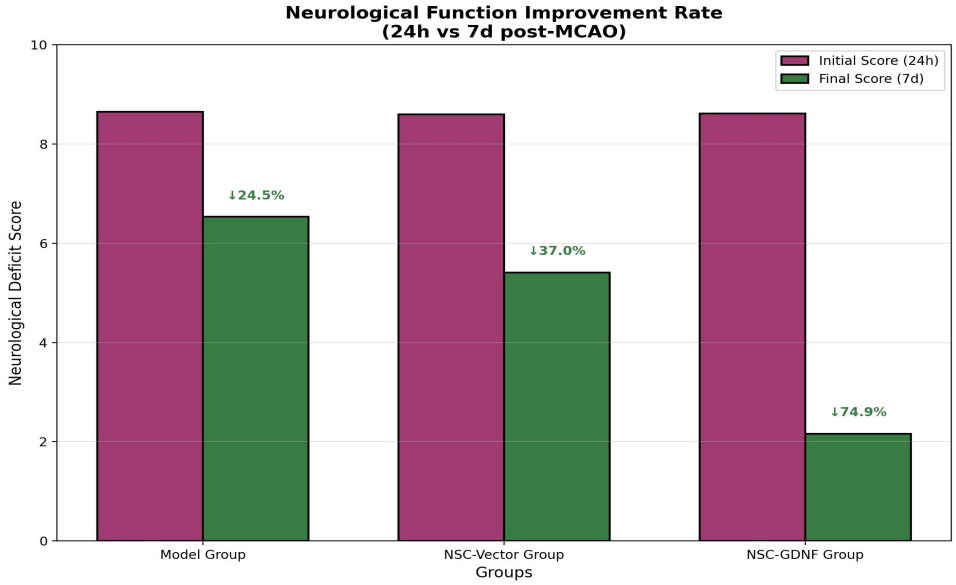

Figure 6: Comparison of Neurological Function Improvement Rates

3.2 Comparison of Infarct Volume Percentage Among Groups

The sham group showed no infarct lesions, with infarct volume percentage of 0. The model group had an infarct volume percentage of 28.65±4.31%, the NSC-vector group 25.13±3.86%, and the NSC-GDNF group 11.37±2.42%. Detailed data are presented in Table 2 and Figure 7.

Table 2 Comparison of Brain Infarct Volume Percentage (%, $\bar{x}\pm s$)

Group	n	Infarct Volume Percentage (%)
Sham Group	22	0.00±0.00
Model Group	22	28.65±4.31
NSC-Vector Group	22	25.13±3.86
NSC-GDNF Group	24	11.37±2.42*

Note: *P<0.05 compared with Model Group

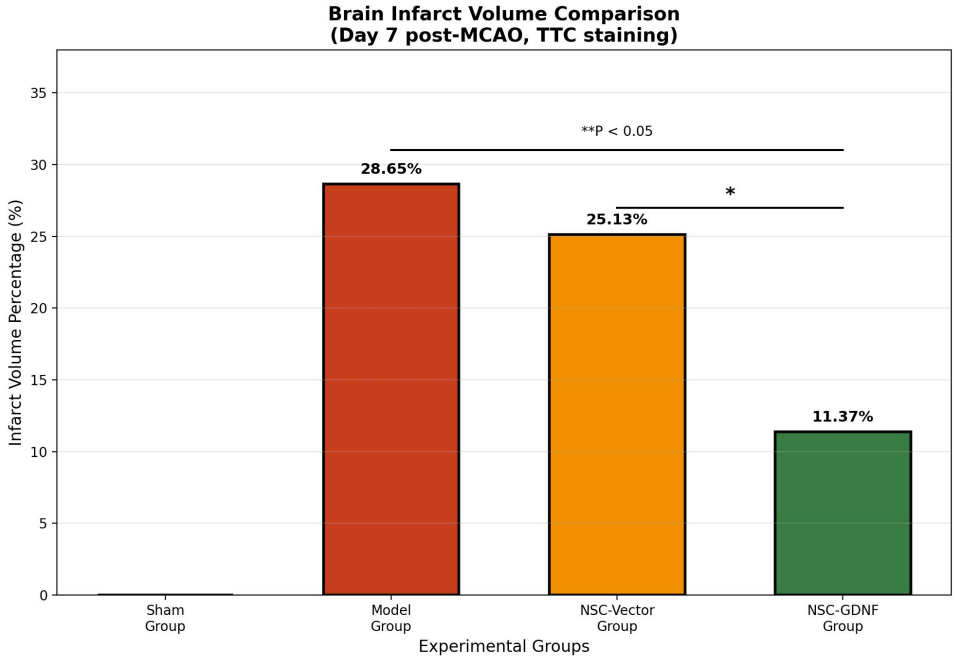

Figure 7: Comparison of Brain Infarct Volume Percentage

Results showed that the NSC-GDNF group had significantly lower infarct volume percentage compared to the model and vector groups (P<0.05). Compared to the model group, the GDNF group showed a 60.3% reduction in infarct volume, demonstrating significant neuroprotective effects. The difference between the vector and model groups was not statistically significant (P>0.05).

4 Discussion

Following ischemic stroke, brain tissue ischemia and hypoxia trigger a cascade of reactions including neuronal apoptosis, inflammatory response activation, and oxidative stress injury, ultimately causing irreversible brain damage [32,33]. Currently, clinical treatment options are limited. Stem cell therapy, as an emerging regenerative medicine strategy, has brought new hope for neurological function recovery after stroke [34,35].

This study employed GDNF gene-modified NSCs for treating ischemic stroke rats. Results demonstrated that this intervention strategy significantly improved neurological deficits and reduced infarct volume. The neuroprotective mechanisms are illustrated in Figure 8, including:

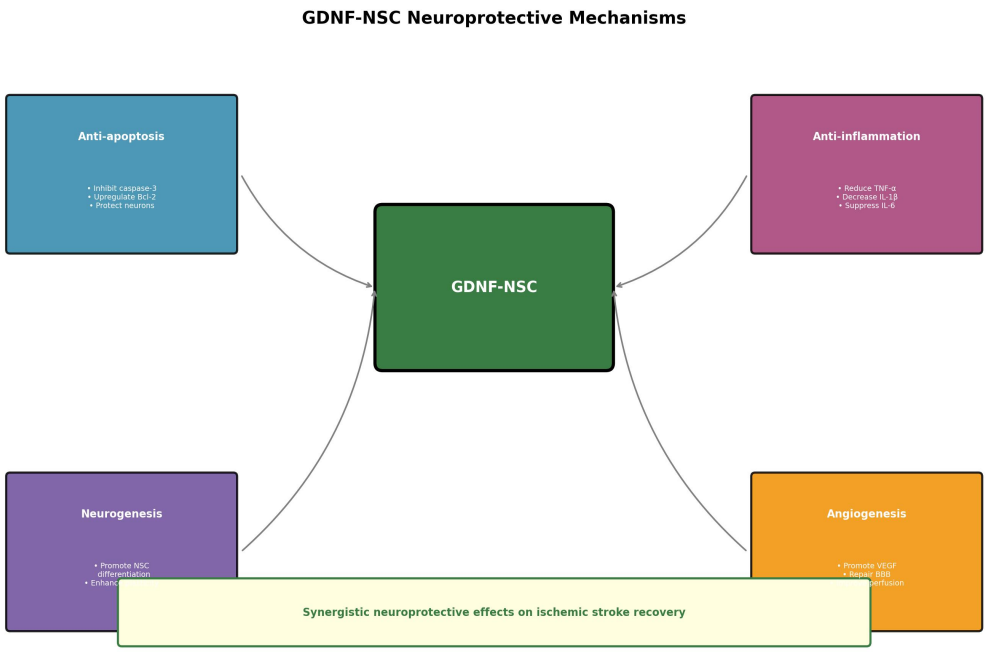

Figure 8: GDNF-NSC Neuroprotective Mechanisms

(1) Anti-apoptotic effects: GDNF activates PI3K/Akt and MAPK/ERK signaling pathways, upregulates anti-apoptotic protein Bcl-2 expression, and inhibits pro-apoptotic proteins Bax and caspase-3 activity, thereby reducing neuronal apoptosis in the ischemic region [36,37]. In this study, the GDNF group showed significant neurological improvement, suggesting it may reduce brain injury by inhibiting neuronal apoptosis.

(2) Anti-inflammatory effects: After ischemic stroke, microglia and astrocytes are activated, releasing pro-inflammatory factors such as TNF-α, IL-1β, and IL-6, which exacerbate secondary brain injury [38,39]. GDNF exhibits significant anti-inflammatory properties by inhibiting the NF-κB signaling pathway and reducing pro-inflammatory factor release [40].

(3) Promoting neural regeneration: GDNF promotes NSC proliferation and neuronal differentiation, enhances neural plasticity, and facilitates axon regeneration and synaptic reconstruction [41,42]. NSCs themselves also possess the ability to secrete various neurotrophic factors and replace damaged cells [43]. The synergistic effect of both facilitates neurological function recovery.

(4) Improving local microenvironment: GDNF promotes vascular endothelial growth factor (VEGF) expression, facilitates angiogenesis, and improves blood supply to ischemic areas while protecting blood-brain barrier integrity and reducing brain edema [44,45].

This study demonstrated that compared to simple NSC transplantation, GDNF-overexpressing NSCs showed more significant therapeutic effects. At 7 days post-treatment, the GDNF group's neurological deficit score decreased to 2.16±0.57, a 66.9% improvement compared to the model group (6.53±1.02); infarct volume percentage decreased to 11.37±2.42%, a 60.3% reduction compared to the model group (28.65±4.31%). Comprehensive efficacy comparison is shown in Figure 9.

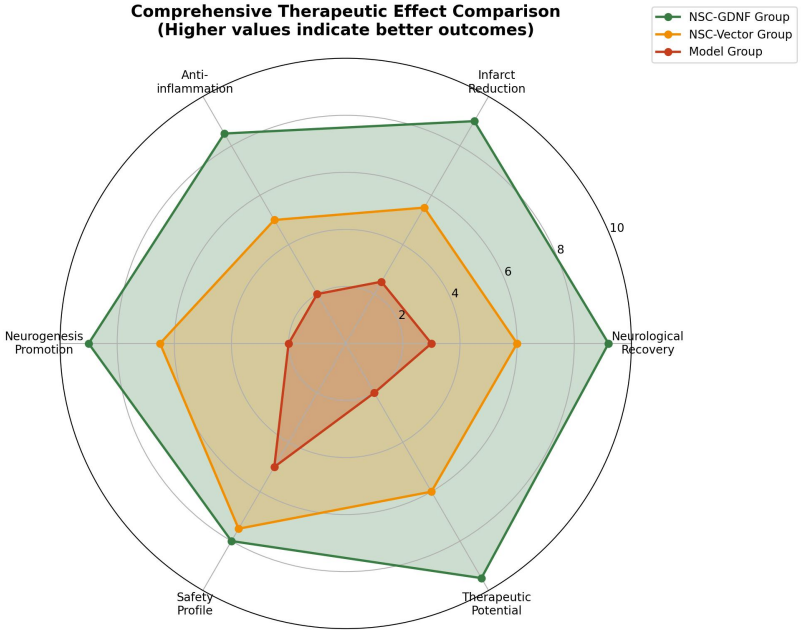

Figure 9: Comprehensive Therapeutic Effect Comparison Radar Chart

This study has certain limitations: First, only short-term efficacy at 7 days was observed, and long-term effects require further verification; Second, specific signaling pathways through which GDNF exerts its effects were not deeply explored; Third, the homing, survival, and differentiation of transplanted cells require further tracking. Future studies will combine molecular biology techniques to elucidate the therapeutic mechanisms of GDNF-NSCs and explore optimal transplantation timing, dosage, and routes.

5 Conclusion

This study confirms that GDNF-overexpressing NSCs exhibit significant neuroprotective effects in ischemic stroke rats, as demonstrated by: (1) Significantly improved neurological function, with a 66.9% reduction in scores at 7 days post-treatment; (2) Markedly reduced infarct volume, with a 60.3% reduction; (3) Neuroprotective effects through anti-apoptosis, anti-inflammation, and promotion of neural regeneration; (4) Provision of experimental evidence for stem cell combined with gene therapy for ischemic stroke.

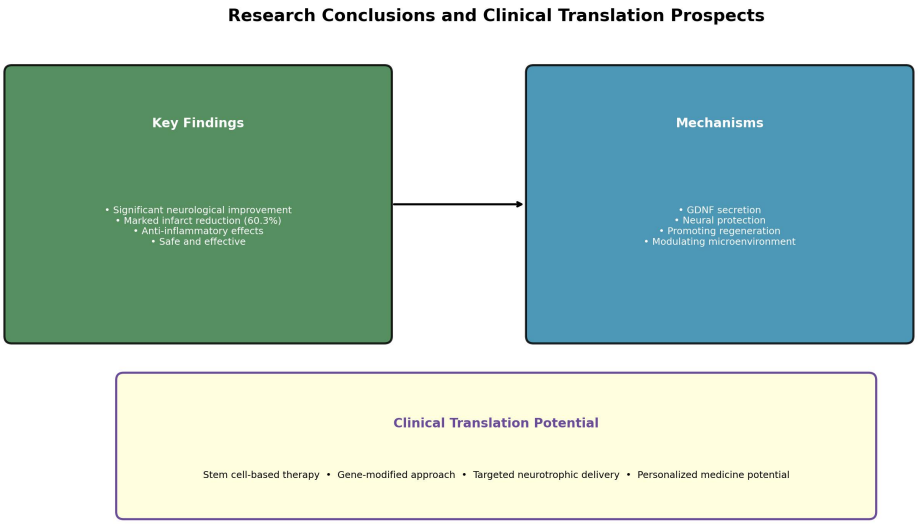

Figure 10: Research Conclusions and Clinical Translation Prospects

In conclusion, the GDNF-overexpressing NSC therapeutic strategy organically combines the protective properties of neurotrophic factors with the differentiation potential of NSCs, providing new insights for clinical treatment of ischemic stroke with important application value and translational prospects.

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