







# Psychopharmacological and Neuroregeneration Effects of the NF- $\kappa$ B Inhibitor JSH-23 in Modeling Alzheimer's Disease

Gleb Nikolaevich Zyuz'kov <sup>1,\*</sup> , Larisa Arkad'evna Miroshnichenko <sup>1</sup> ,  
Tatyana Yur'evna Polykova <sup>1</sup> , Elena Vladislavovna Simanina <sup>1</sup> ,  
Alexander Vasil'evich Chayikovskiy <sup>1</sup> , Polina Olegovna Zyuz'kova <sup>1</sup> 

<sup>1</sup> Laboratory of Pathological Physiology and Experimental Therapy, Goldberg Research Institute of Pharmacology and Regenerative Medicine, Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk, Russia, 3 Lenin Prospect, Tomsk, 634028, Russia; [nii@pharmso.ru](mailto:nii@pharmso.ru);

\* Correspondence: [zgn@pharmso.ru](mailto:zgn@pharmso.ru) (G.N.Z.);

Scopus Author ID 6508338421

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**Abstract:** All currently existing pharmacotherapy strategies for Alzheimer's disease (AD) are low effective. In this regard, it is relevant to develop novel concepts for correcting disorders that arise in this senile dementia. In recent years, data have been obtained on these prospects within the paradigm of targeting individual intracellular signaling pathways in regenerative-competent cells. This work aimed to study the possibility of correcting the dysfunction of progenitor cells of nervous tissue and the cognitive profile of C57BL/6 mice using the NF- $\kappa$ B inhibitor JSH-23 in the conditions of AD modeling with long-term administration of scopolamine hydrobromide (SH). We have shown that the development of persistent disturbances in exploratory behavior and mnemonic function of the central nervous system accompanies a 4-week administration of SH to mice. The corrective effect of the NF- $\kappa$ B inhibitor was revealed in relation to these cognitive disorders characteristic of AD. At the same time, an increase in the content of neural stem cells and committed neuronal precursors was found in the subventricular zone of the hemisphere against the background of an increase in their proliferative activity. The results indicate the high prospects of creating fundamentally novel approaches to AD treatment using NF- $\kappa$ B blockers.

**Keywords:** Alzheimer's disease; NF- $\kappa$ B inhibitors; neural stem cells; committed neuronal precursors; intracellular signal transduction.

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## 1. Introduction

Alzheimer's disease (AD) is the most common severe neurodegenerative disease characterized by steadily progressive cognitive impairment accompanied by loss of behavioral and social skills [1,2]. All currently existing pharmacotherapy strategies for AD are low effective [3,4]. In this regard, it is relevant to develop novel concepts for correcting disorders in this senile dementia. Moreover, they should be based on the effect of fundamentally new targets [5].

There is still no detailed understanding of the pathogenesis of AD. However, some aspects of pathogenesis are quite well-studied. For example, it is known that the loss of neuroplasticity in AD is caused by impaired neurogenesis due to the dysfunction of the brain's

regeneration-competent cells (RCCs) under conditions of constantly increasing neuronal death [6,7]. At the same time, in recent years, unique data have been obtained on the formation of a qualitatively new pattern of intracellular signaling in the progenitors of nervous tissue in AD [4,5,7-9]. This is most accurately demonstrated in neural stem cells (NSCs) and committed precursors of neurons (NCPs) in the subventricular zone (SVZ) of the cerebral hemispheres. Moreover, a relationship between the occurrence of these features of signal transduction in progenitor cells and the desynchronization of their activity, one of the main reasons for ineffective neurogenesis in AD, has been revealed [10-13].

This was the basis for developing a new paradigm for stimulating neurogenesis in AD [5], which consists of selective targeting intracellular signaling molecules in regenerative-competent brain cells. Individual links of intracellular cascades have been identified as the most promising targets for implementing this strategy [4,11].

Under conditions of modeling  $\beta$ -amyloid-induced neurodegeneration ( $\beta$ AIN), the triggering participation of NF- $\kappa$ B-dependent intracellular pathways in the uncoupling of proliferation and differentiation of NSCs was revealed [4, 9]. In addition, in vitro experiments have shown the ability of NF- $\kappa$ B inhibitors to synchronize the activity of NSCs and NPCs when modeling AD neurodegeneration [7]. The corrective effect of NF- $\kappa$ B blockers on the neurotrophic function of certain types of neuroglial cells [14], the intensity of neuroinflammation [15], and other factors involved in the pathogenesis of AD is also known [3,16,17].

It is known that anticholinergic disorders play an important role in the development of AD [18,19]. At the same time, the model of scopolamine amnesia, caused by a single administration of an appropriate anticholinergic drug, is a screening model for assessing the antiamnestic properties of pharmacological substances [20,21]. However, it has a number of disadvantages, associated primarily with the high rate of recovery of modeled anticholinergic disorders, which is especially unacceptable when studying the potential prolonged effects of pharmacological substances in AD.

However, it has a number of disadvantages, which are especially important when studying the potential prolonged effects of pharmacological substances in AD, associated primarily with the high rate of recovery of modeled anticholinergic disorders.

This work aimed to study the possibility of correcting the dysfunction of nervous tissue progenitors and the cognitive profile of experimental animals using the NF- $\kappa$ B inhibitor JSH-23 in AD modeling conditions with long-term scopolamine hydrobromide (SH) administration.

## **2. Materials and Methods**

### *2.1. Chemicals.*

Scopolamine hydrobromide (SH) (Sigma-Aldrich, USA); NF- $\kappa$ B inhibitor JSH-23 (J4455, Sigma-Aldrich, USA); MACS Neuro Medium (MiltenyiBiotec B.V. & Co. KG, Germany); anti-PSA-NCAM MicroBeads (MiltenyiBiotec B.V. & Co. KG, Germany); hydroxycarbamide hydurea (Calbiochem, USA); dimethyl sulfoxide (DMSO) (Calbiochem, USA); Cell Culture Plate (96 wells) (Corning, USA).

### *2.2. Animals and experimental design.*

The experiments were carried out in compliance with the rules for the humane treatment of animals (European Convention for the Protection of Vertebrate Animals Used for <https://nanobioletters.com/>

Experimental or Other Scientific Purposes, EU Directive 2010/63/EU). Approval from the institute's local ethics committee (protocol IACUC-2022-04/17). The studies used 72 C57BL/6 mice aged 2-2.5 months.

To simulate Alzheimer's disease, mice were intraperitoneally injected with SH daily for 28 days at a dose of 5 mg/kg [20, 21]. The NF- $\kappa$ B inhibitor JSH-23 began to be administered 3 days after the last administration of SH to mice: subcutaneously once a day for 5 days at a dose of 1 mg/kg. The day of initiation of NF- $\kappa$ B inhibitor administration is considered day "0" in the future when describing the study design. Control mice received the corresponding solvents in similar modes and equivalent volumes (0.2 ml): distilled water (intraperitoneally for 28 days) and 0.2% DMSO (subcutaneous within 5 days).

Psychopharmacological effects (cognitive profile) were assessed using functional (behavioral) methods (n=15 each in the control and experimental groups). On the 1<sup>st</sup>, 7<sup>th</sup>, 14<sup>th</sup>, and 21<sup>st</sup> days, the registration of exploratory behavior in the "open field" was carried out (separately during the first and two subsequent minutes). On the 7<sup>th</sup>, 14<sup>th</sup>, and 21<sup>st</sup> days, the integrity of the conditioned reflex of passive avoidance (CPAR), developed on the 3<sup>rd</sup> day [7,8].

On the 3<sup>rd</sup>, 7<sup>th</sup>, and 14<sup>th</sup> days after the start of JSH-23 administration, the content of NSCs and NCPs in the subventricular zone of the cerebral hemispheres (SVZ) of experimental animals (n=42 each in the control and experimental groups), as well as their proliferative activity and the intensity of specialization processes were determined (differentiation/maturation) [4,22].

### 2.3. Cognitive profile.

#### 2.3.1. Exploratory behavior testing.

In the "open field" test [7,8], the exploratory behavior of mice was studied. The "open field" installation (40x40x20 cm) was made of white plexiglas. The "open field" floor was divided into 16 identical squares with a circular hole (3 cm). The installation was illuminated by an LED lamp (7 W). The behavior (total, horizontal, and vertical locomotor activity, hole-board exploration, self-grooming, and defecation) of the mice was recorded for 3 min. In this case, the studied parameters were assessed separately in the first and 2-3 minutes.

#### 2.3.2. Conditional reflex activity testing

To assess changes in the mnemonic function of the brain, we used the CPAR test [7,8]. We studied the reproduction of the acquired skill of passive avoidance by animals of pain from electric current (0.45 mA) when entering the dark compartment of the installation for the CPAR test. The test is based on assessing the suppression of the unconditioned reflex in rodents by choosing a dark compartment of the chamber in which, during the development of CPAR, they received electrical pain. Therefore, when checking the integrity of the conditioned reflex, they had to be in the light compartment of the chamber, which was "uncomfortable" for rodents. The reflex was considered developed if, during testing, the animal did not move into the dark compartment of the installation for 3 minutes. The latent time of the reflex (based on the time before the animal entered the dark compartment) and the period the animals spent in the dark compartment were also determined.

2.4. Cell culture assays.

The content of NSCs and NPCs in the cellular material from the SVZ was determined by the clonogenic activity of cultures of unfractionated and CD56+ cells. CD56+ cells were isolated by positive immunomagnetic sorting for PSA-NCAM (MInMACS Cell Separator (MilteNY Biotec, Germany)) [4,22]. The isolated cells were cultured in MACS Neuro Medium (105/ml) in a CO2 incubator under standard conditions for 5 days. The number of progenitors was determined by the number of colony-forming units in the culture of the corresponding cells (CFU, neurospheres of more than 100 cells).

In addition, the content of mitotically active NSCs and NPCs was assessed. In particular, the number of CFU located in the S-phase of the cell cycle was determined (using a blocker of cell mitosis in this phase of the cell cycle - hydroxycarbamide hydrorea (1 μM)).

Also, based on the ratio of the number of cluster-forming units (CFU, small neurospheres (30-80 cells)) to CFU, the index of progenitor specialization (the intensity of their differentiation and maturation) was determined.

2.5. Statistical analysis.

The results were processed using a one-way analysis of variance (using Dunnett, Wilcoxon, and Mann-Whitney tests). The analysis package STATISTICA 12.0 was used. The results in the tables are indicated in the form of arithmetic means and standard error of the mean (M±SEM); in the figures - arithmetic mean, differences were considered statistically significant at p < 0.05 [23].

3. Results and Discussion

3.1. Cognitive and behavioral disorders.

The long-term administration of SH led to pronounced disturbances in the psychoneurological status of experimental animals. There was a significant increase in the number of horizontal movements of mice in the “open field” during almost all periods of the study. Moreover, these changes were recorded both in the first minute (on days 1, 7, 14) and in 2-3 minutes (on days 7, 14) of observation. At the same time, on the 14<sup>th</sup> and 21<sup>st</sup> days, the number of recorded vertical stands of the animals decreased. Thus, there was an “impoverishment” of their locomotor activity, which was additionally evidenced by an increase in the coefficient of movement asymmetry during all experiment periods (Table 1).

**Table 1.** Locomotor activity in the “open field” of intact mice of the C57BL/6 line (1); mice with cholinolytic disorders of the CNS (2), and mice with the administration of an NF-κB inhibitor to mice with cholinolytic disorders (3), arb. units (M±SEM).

Groups	Horizontal activity	Vertical activity	Hole-board exploration	Self-grooming	Defecation	Total activity	Asymmetry coefficient
Day 1							
Frist period (minute 1)							
1	23.58 ± 1.43	2.58 ± 0.47	13.75 ± 1.18	0.08 ± 0.08	0.75 ± 0.33	40.75 ± 2.07	0.58 ± 0.02
2	32.18 ± 2.01*	2.45 ± 0.64	14.09 ± 1.73	0.09 ± 0.09	0.00 ± 0.00	48.82 ± 2.02*	0.66 ± 0.01*
3	24.92 ± 1.75#	4.50 ± 1.00	19.33 ± 2.72	0.17 ± 0.11	0.00 ± 0.00	48.92 ± 3.01	0.52 ± 0.03#
Second period (minutes 2-3)							
1	26.67 ± 2.70	4.25 ± 1.02	26.17 ± 2.72	0.42 ± 0.19	1.25 ± 0.37	58.75 ± 3.97	0.45 ± 0.02
2	37.36 ± 3.32*	3.09 ± 0.59	27.09 ± 3.35	0.64 ± 0.18	0.45 ± 0.28	68.64 ± 4.50	0.54 ± 0.03*
3	38.92 ± 5.56	7.00 ± 1.29#	33.75 ± 2.66*#	0.33 ± 0.19	0.25 ± 0.13*	80.25 ± 7.22	0.42 ± 0.03#
Day 7							
Frist period (minute 1)							

Groups	Horizontal activity	Vertical activity	Hole-board exploration	Self-grooming	Defecation	Total activity	Asymmetry coefficient
1	18.33 ± 1.96	2.08 ± 0.83	9.58 ± 1.88	0.08 ± 0.08	0.00 ± 0.00	30.08 ± 3.93	0.64 ± 0.03
2	26.36 ± 2.86*	1.55 ± 0.64	7.91 ± 1.49	0.18 ± 0.12	0.55 ± 0.28	36.55 ± 4.25	0.73 ± 0.03*
3	21.08 ± 2.12	0.83 ± 0.30	12.08 ± 1.95	0.08 ± 0.08	0.00 ± 0.00	34.08 ± 3.63	0.63 ± 0.02#
Second period (minutes 2-3)							
1	28.17 ± 3.59	4.33 ± 1.32	14.67 ± 3.52	0.83 ± 0.17	0.67 ± 0.19	48.67 ± 6.76	0.60 ± 0.03
2	35.18 ± 5.98	4.36 ± 1.45	11.55 ± 2.62	1.00 ± 0.23	0.73 ± 0.24	52.82 ± 9.53	0.70 ± 0.02*
3	24.00 ± 3.50	3.00 ± 1.07	17.83 ± 3.65	1.08 ± 0.15	0.50 ± 0.15	46.42 ± 7.27	0.50 ± 0.04#
Day 14							
Frist period (minute 1)							
1	22.83 ± 2.01	1.67 ± 0.38	10.67 ± 1.45	0.17 ± 0.11	0.00 ± 0.00	35.33 ± 2.70	0.65 ± 0.02
2	32.00 ± 2.20*	1.36 ± 0.45	11.36 ± 1.79	0.18 ± 0.12	0.18 ± 0.12	45.09 ± 3.08*	0.72 ± 0.02*
3	27.67 ± 1.21#	1.42 ± 0.42	15.25 ± 1.07*#	0.00 ± 0.00	0.00 ± 0.00	44.33 ± 4.72	0.63 ± 0.02#
Second period (minutes 2-3)							
1	31.33 ± 1.99	4.42 ± 0.71	19.62 ± 2.66	0.50 ± 0.23	0.50 ± 0.15	53.67 ± 4.43	0.60 ± 0.03
2	38.73 ± 2.22*	2.64 ± 0.49*	16.45 ± 2.59	1.18 ± 0.26	0.73 ± 0.19	59.73 ± 4.30	0.66 ± 0.02
3	30.42 ± 2.69#	4.58 ± 1.04#	20.00 ± 3.14	0.00 ± 0.00	0.58 ± 0.23	55.58 ± 6.72	0.56 ± 0.02#
Day 21							
Frist period (minute 1)							
1	13.00 ± 2.00	2.67 ± 0.58	2.75 ± 0.64	0.33 ± 0.19	0.25 ± 0.13	19.00 ± 2.71	0.63 ± 0.06
2	9.60 ± 1.50	0.30 ± 0.21*	1.40 ± 0.60	0.00 ± 0.00	0.10 ± 0.10	11.40 ± 1.88*	0.82 ± 0.04*
3	10.00 ± 1.00	1.30 ± 0.42	1.50 ± 0.48	0.00 ± 0.00	0.30 ± 0.15	11.10 ± 1.69*	0.63 ± 0.06#
Second period (minutes 2-3)							
1	9.17 ± 2.24	3.08 ± 0.96	2.50 ± 0.83	1.83 ± 0.55	0.58 ± 0.26	17.17 ± 3.61	0.46 ± 0.08
2	12.50 ± 0.58	3.00 ± 1.02	1.20 ± 0.53	0.60 ± 0.27	0.50 ± 0.17	16.80 ± 1.78	0.73 ± 0.05*
3	8.30 ± 1.36#	1.90 ± 0.48	1.90 ± 0.50	1.00 ± 0.37	0.80 ± 0.20	13.90 ± 3.02	0.52 ± 0.06#

*p* < 0.05 in comparison with \* intact mice; # mice with anticholinergic disorders.

In addition, after a four-week administration of an anticholinergic agent, there was a natural [19-21] drop in the level of reproduction of CPAR on days 7, 14, and 21 (reaching 21.4% of the level of the same indicator in intact mice on day 21). At the same time, on the 7<sup>th</sup> day, there was also a statistically significant decrease in the latent time of the reflex (up to 59.1% of the intact control) (Table 2).

The results obtained indicated high anxiety in animals in conditions of modeling cholinolytic disorders of the central nervous system (CNS) (this was indicated by changes in motor activity indicators in the first minute of observation in the “open field” [7,14,22], and significant cognitive impairment (what was indicated by the parameters of orienting-exploratory behavior in 2-3 minutes of observation and disorders of mnestic abilities (CPAR)) [7,8]. Thus, the long-term administration of an anticholinergic drug was accompanied by the formation of pronounced long-lasting disturbances in psychoneurological status, probably associated with “persistent” changes in the biochemical continuum in the nervous tissue, characteristic, among other things, of AD [8,24,25].

**Table 2.** CPAR parameters of the intact mice C57BL/6 (1); mice with cholinolytic disorders of the CNS (2), and mice with the administration of an NF-κB inhibitor to mice with cholinolytic disorders (3), (M±SEM).

Day	Groups	Latent time of the reflex, sec	Time spent in the dark compartment, sec	Percentage of animals with reflex,%
7	1	157.83 ± 11.59	7.25 ± 4.73	0.75 ± 0.13
	2	93.27 ± 21.13*	24.36 ± 9.17	0.36 ± 0.15*
	3	161.73 ± 12.26#	7.45 ± 5.12	0.82 ± 0.12#
14	1	91.42 ± 22.64	49.83 ± 16.00	0.42 ± 0.15
	2	66.73 ± 18.17	51.64 ± 9.98	0.09 ± 0.09*
	3	119.17 ± 16.46	18.25 ± 6.11#	0.42 ± 0.15#
21	1	95.17 ± 30.75	48.42 ± 22.57	0.42 ± 0.15
	2	70.73 ± 24.58	41.82 ± 14.21	0.09 ± 0.09*
	3	108.83 ± 22.95	28.00 ± 12.51	0.33 ± 0.14

*p* < 0.05 in comparison with \* intact mice; # mice with anticholinergic disorders.

### 3.2. Effects of the NF- $\kappa$ B inhibitor on cognitive and behavioral disorders.

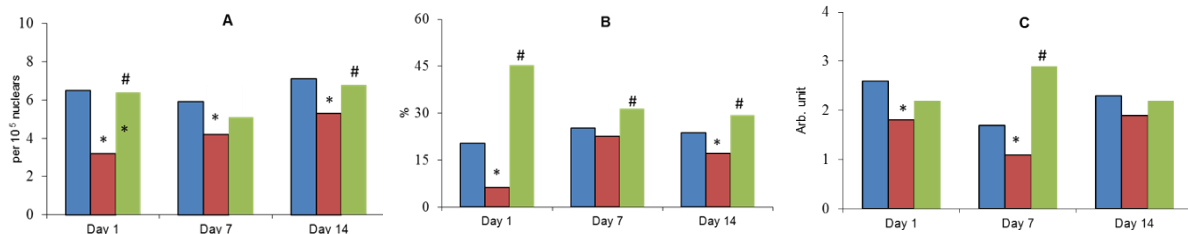
The introduction of the NF- $\kappa$ B inhibitor after long-term use of SH significantly corrected disturbances in the explorative behavior of animals in the “open field” (Table 1). There was a normalization of the horizontal activity of mice and the coefficient of asymmetry of movements during all periods of the experiment. Moreover, in the first observation period (1 min), statistically significant differences in these parameters relative to the control were recorded already on the 1st day after the start of administration of the Nuclear factor- $\kappa$ B blocker. This circumstance was a reflection of a decrease in excitability (anxiety level) of animals associated with the known anti-inflammatory effects of NF- $\kappa$ B inhibitors [7,8] and, as a consequence - a rapid decrease in the intensity of neuroinflammation (developing with long-term administration of a cholinolytic agent [26]). At the same time, a significant decrease in the number of horizontal movements in the second period (2-3 minutes) of observation was noted starting from the 14th day.

These changes in exploratory behavior (a pronounced delayed effect reflecting the correction of cognitive functions [22]) suggest the likely participation of the “deep reserve” cellular renewal system (associated with resident progenitor cells of the nervous tissue [6,10]) in the implementation of the identified therapeutic action of the NF- $\kappa$ B inhibitor.

Moreover, the effect of NF- $\kappa$ B inactivation, specifically on the cognitive ability of experimental animals, was confirmed by the leveling of the development of amnesia in them after long-term administration of the anticholinergic drug. The level of reproduction of CPAR in the experimental group was comparable to that in intact mice (Table 2).

### 3.3. Effect of the NF- $\kappa$ B inhibitor on progenitor functioning.

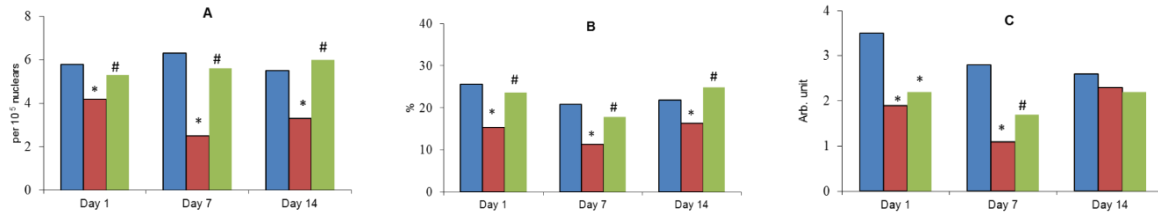
The study of the state of pools of multipotent (NSCs) and committed progenitors (NCPs) in the SVZ under conditions of AD modeling revealed interesting phenomena. It was found that long-term administration of an anticholinergic drug was accompanied by a decrease in the content of both types of progenitors in the nervous tissue (Figures 1A; 2A) against the background of a decrease in their mitotic activity (Figures 1B; 2B) and the intensity of specialization (Figures 1B; 2B). These changes are quite consistent with the literature on the participation of muscarinic (mAChR) and nicotinic (nAChR) acetylcholine receptors expressed on neural progenitor cells in the regulation of the processes of their proliferation and differentiation [27,28].



**Figure 1.** (A) NSC amount; (B) NSC proliferative activity; (C) NSC differentiation index. In intact C57BL/6 mice (blue bars); mice with cholinolytic disorders of the CNS (red bars), and mice with the administration of an NF- $\kappa$ B inhibitor to mice with cholinolytic disorders (green bars); \*- differences at  $p < 0.05$ .

The study of the NF- $\kappa$ B inhibitor effect on the functioning of progenitors under conditions of modeling cholinolytic disorders of the CNS revealed that it has significant neuroregenerative potential. Blockade of signal transduction through NF- $\kappa$ B led to a significant increase in the number (Figures 1A; 2A), including actively proliferating (Figures 1B; 2B)

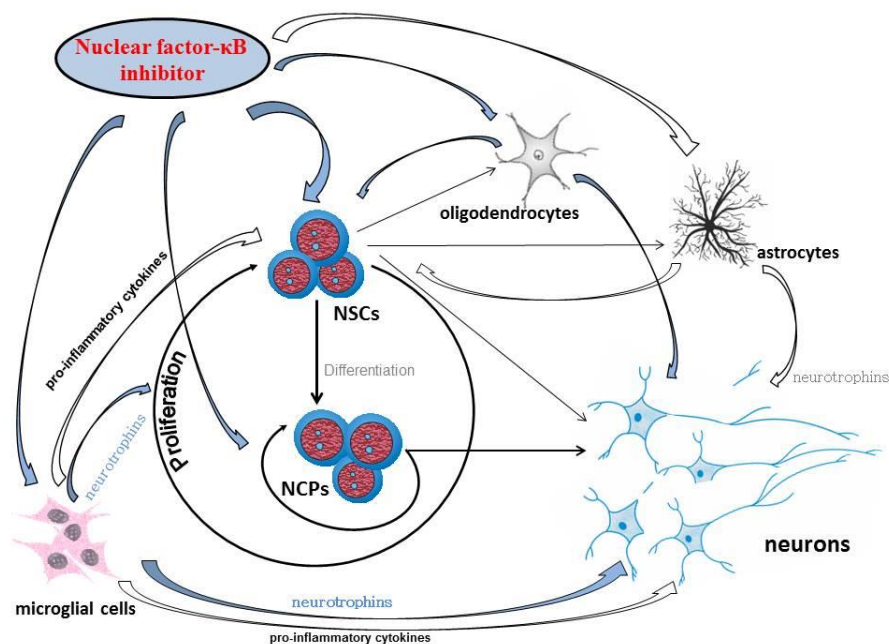
NSCs (3 and 14 days) and NCPs (3, 7, 14 days) in the SVZ. In addition, inactivation of the nuclear transcription factor in both cases (NSCs and NCPs) stimulated the progenitor specialization. However, the severity of intensification of NSC differentiation under the influence of the NF- $\kappa$ B inhibitor was significantly higher than that of NSCs (Figures 1C; 2C). Moreover, on the 7<sup>th</sup> day after the start of the administration of the anticholinergic agent, the NSC specialization index was significantly higher than even the same indicator in the intact control.



**Figure 2.** (A) NCP amount; (B) NCP proliferative activity; (C) NCP differentiation index. In intact C57BL/6 mice (blue bars); mice with cholinolytic disorders of the CNS (red bars), and mice with the administration of an NF- $\kappa$ B inhibitor to mice with cholinolytic disorders (green bars); \*- differences at  $p < 0.05$ .

In general, for the first time, in the AD model caused by long-term administration of an SH, results were obtained that confirm the data on the pronounced therapeutic activity of NF- $\kappa$ B inhibitors in experiments on other models of this disease [4,7,9]. The significant correction of psycho-emotional (decrease in the level of anxiety) and cognitive disorders (explorative behavior and mnemonic functions of the CNS) was revealed in experimental animals with pharmacologically induced cholinergic deficiency in the nervous tissue [20,25].

At the same time, as in aged C57BL/6 mice (characterized by a high endogenous level of amyloid formation in the nervous tissue from 8-10 months of life [7]) in the process of realizing the effects of the Nuclear factor- $\kappa$ B blocker, obviously, the mechanisms of regeneration of the “deep reserve” are involved - progenitor cells of the SVZ [6,9,10]. It was found that inactivation of NF- $\kappa$ B is accompanied by restoration (suppressed under conditions of depletion of the cholinergic system) of pro-regenerative functions (proliferation and specialization) of both multipotent NSCs and NCPs.



**Figure 3.** Effect of the NF- $\kappa$ B inhibitor on RCCs in AD modeling. Thick lines and wide blue arrows – stimulation; thin lines and wide white arrows – inhibition.

Stimulation of the realization of the growth potential of progenitors was carried out both through the formation directly in them of a new pattern of intracellular signaling (under the influence of the direct action of a pharmacological agent) [4,5] and through enhancing the production of neurotrophins (including growth factors), primarily by oligodendrocytes [7,9,29]. In addition, when assessing the feasibility of further development of treatments for Alzheimer's disease based on NF- $\kappa$ B inhibitors, one should take into account data on their known pronounced anti-inflammatory properties [30, 31] and corrective effects on reactive astrogliosis in AD [32,33] (Figure 3).

#### 4. Conclusions

The results promise to create fundamentally novel approaches (within the paradigm of targeted regulation of intracellular signal transduction [5]) to treat Alzheimer's disease using NF- $\kappa$ B blockers. The therapeutic effect will be associated with the stimulation of neuroregeneration due to the coordinated activation of different compartments of RRCs of nervous tissue and with neuroprotection through several mechanisms.

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#### Conflicts of Interest

The authors declare no conflict of interest.

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