NEURODEGENERATIVE CHANGES INDUCED BY INJECTION OF β-AMYLOID PEPTIDE FRAGMENT (25-35) IN HIPPOCAMPUS ARE ASSOCIATED WITH NGF-SIGNALLING ACTIVATION

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β-amyloid peptide (Aβ) is an important component of the neurodegeneration mechanism in Alzheimer's disease. This work investigates the effect of intrahippocampal injection of Aβ(25–35) fragment on nerve growth factor (NGF) signalling. Aggregated Aβ(25–35) was injected into rat dorsal hippocampus. Rats in the control group received injections of the peptide with an inverted amino acid sequence and a solvent. It was shown that Aβ(25–35) induces neuron death in rat hippocampus. Neurodegeneration was accompanied by a statistically significant increase ($p < 0.05$) in p75NTR neurotrophin receptor expression in all animals who had received exogenous peptides, and by an increased level of NGF in the hippocampus of those rats who had been injected with Aβ(25–35). The study results demonstrate that changes in the hippocampus induced by Aβ(25–35) are accompanied by increased NGF signalling, which, to some extent, supports the current clinical data obtained from patients with Alzheimer's. The changes mentioned above are compensatory. However, both damage reparation and further degenerative processes can be the ultimate outcome.

Keywords: β-amyloid peptide, hippocampus, nerve growth factor, p75NTR receptor, neurodegeneration, Alzheimer's disease

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НЕЙРОДЕГЕНЕРАТИВНЫЕ ИЗМЕНЕНИЯ, ВЫЗВАННЫЕ ВВЕДЕНИЕМ ФРАГМЕНТА (25–35) β-АМИЛОИДНОГО ПЕПТИДА В ГИППОКАМП, СВЯЗАНЫ С АКТИВАЦИЕЙ NGF-СИГНАЛИНГА

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В механизме нейродегенерации при болезни Альцгеймера важную роль играет β-амилоидный пептид (Aβ). В работе исследовали влияние интрагиппокампальной инъекции фрагмента Aβ(25–35) на систему сигналинга фактора роста нервов (NGF). Крысам вводили агрегированный Aβ(25–35) в область дорзального гиппокампа. Контрольной группе проводили инъекции пептида с обратной аминокислотной последовательностью и растворителя. Показано, что Aβ(25–35) вызывал гибель нейронов в гиппокампе крыс. Нейродегенеративные процессы сопровождались достоверным ($p < 0,05$) увеличением экспрессии рецептора нейротрофинов p75NTR у всех животных, получавших экзогенные пептиды, и повышением уровня NGF в гиппокампе только тех крыс, которым делали инъекцию Aβ(25–35). Результаты исследования демонстрируют, что вызванные Aβ(25–35) изменения в гиппокампе сопровождаются усилением NGF-сигналинга. Данное усиление в определенной степени подтверждает имеющиеся данные клинических наблюдений у пациентов с болезнью Альцгеймера. Указанные изменения носят компенсаторный характер, однако конечным результатом может быть как репарация повреждения, так и дальнейшее усиление дегенеративного процесса.

Ключевые слова: β-амилоидный пептид, гиппокамп, фактор роста нервов, рецептор p75NTR, нейродегенерация, болезнь Альцгеймера

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One of the key components of Alzheimer's disease pathogenesis is a β-amyloid peptide (Aβ). It consists of 40 to 42 amino acids and is an intramembrane fragment of a large transmembrane protein precursor. Aβ is a product of its precursor proteolytic processing in the amyloidogenic pathway. Though the ultimate role of Aβ is still unclear, its accumulation in patient's brain in the form of soluble aggregates and insoluble deposits is the most important marker of Alzheimer's disease. Because Aβ exhibits toxicity to neurons, intracerebral injections of this peptide in animals can help to model some aspects of a complicated pattern of Alzheimer's disease. Toxicity is characteristic of both a full-length Aβ peptide and some of its shortened fragments,

in particular Aβ(25–35) undecapeptide that is often seen as a functional domain of Aβ and is responsible for its aggregating properties [1, 2].

Aβ(25–35) neurotoxicity following its injection into the hippocampus was demonstrated by D. R. Rush et al [3]. Aβ(25–35) injection induced the adjacent tissue loss and neuronal degeneration [3]. However, other authors [4] found no neurotoxic effect of Aβ(25–35) following its administration into the ventral pallidum and substantia innominata . They observed the formation of cavities containing protein aggregates that were positively stained with congo red. Aggregated Aβ(25–35) caused more conspicuous damage of the CA1 pyramidal layer in the hippocampus compared to the peptide synthesized from the same amino acids in the reversed sequence, Aβ(35–25) [5–8]. Degenerating neurons were also detected in the temporal cortex following the Aβ(25–35) injection into the nucleus basalis magnocellularis of rats [9]. It is important to note that undecapeptide injection into some brain structures can induce transsynaptic cytoskeletal damage and astroglial activation that are observed in the actual injection area and also spread to more distant brain areas. Such changes were detected in the hippocampus following the Aβ(25–35) injection into the amygdala [10]. Our previous work showed that Aβ(25–35) also induced the activation of astrocytes and microglia in the hippocampus after being injected into this structure [8].

Neuroglial activation in the lesion is a controversial phenomenon. On the one hand, being the actual components of neuroinflammation, activated astrocytes and microgliocytes contribute to the degeneration. When triggered, the mechanisms of neuroinflammation can lead to the dysfunction and death of neurons, which exacerbates further inflammation. Thus, the vicious circle is established in which neuroinflammation causes neurodegeneration [11]. On the other hand, glial activation is a distinct compensatory tissue response, with microglia actively phagocyting a pathogen that caused tissue damage, e.g., injected Aβ or amyloid plaque components, and astrocytes contributing to a better supply of neurons with substances necessary for their repair, such as neutrophins.

One of the most important neutrophins of the mammalian brain is a nerve growth factor (NGF). NGF is the main neutrophin that ensures support and functioning of cholinergic neurons in the brain of adult mammals [12, 13]. It is synthesized and released into the extracellular medium by hippocampal and neocortical cells, targets for cholinergic neurons of basal nuclei. In turn, cholinergic neurons in the brain of young, adult and senescing animals express a high affinity NGF receptor (TrkA) and a low affinity NGF receptor (p75NTR) [14], which demonstrates the dependence of the metabolism of those cells on the levels of neutrophins in both the developing and the mature brain. A signal cascade triggered by NGF becomes particularly important in Alzheimer's development. On early stages of the disease (mild cognitive decline) NGF levels are reduced [15], while later stages (severe dementia) are associated with their increase [15, 16]. Considering a specific role of Aβ at different stages of the disease, it is likely to be involved in NGF metabolism regulation in Alzheimer's.

The aim of this work was to study the changes in NGF signaling system in the hippocampus of rats following the administration of aggregated Aβ(25–35).

METHODS

Experiments on animals were conducted in compliance with the Directive of the European Parliament and of European Council, dated September 22, 2010, and the Order № 267 of the Ministry of Healthcare of the Russian Federation, dated June 19, 2003, on the protection of animals used for scientific experiments. The protocol of the experiment was approved by the Ethics Committee of the Institute of Higher Nervous Activity and Neurophysiology, RAS.

The study was carried out in male Wistar rats from Stolbovaya breeding nursery of the Medical Center for Biomedical Technologies, FMBA (Moscow oblast, Russia), with weights ranging from 290 to 350 g. The rats were kept in plastic cells in fives under vivarium housing conditions with 12h artificial lighting (8:00 — 20:00) and free access to water and food.

The rats were anaesthetized by an intraperitoneal injection of chloral hydrate (350 mg/kg). Aqueous solutions of Aβ(25–35), a control peptide synthesized from the same amino acids in the reversed sequence Aβ(35–25), and a vehicle (sterile water) were administered bilaterally in the hippocampus at AP –3.8 mm; L ± 2.0 mm; DV +3.8 mm from bregma using Model 900 stereotaxic instrument (David Kopf Instruments, USA) [17]. The rats were injected with 3 nmol aggregated Aβ(25–35) or Aβ(35–25) (Bachem, Switzerland) in a total volume of 2 μL (1.5 nmol/μL), the control group received the equal volume of sterile water. Injections were performed at a rate of 1 μL/min. The needle was left in the injection site for 5 minutes for proper substance distribution and for preventing its leakage. Peptide aggregation was performed as described in [18].

7 days after the surgery the rats were decapitated, their brains removed and washed in ice-cold 0.9 % NaCl solution; hippocampus and cerebral cortex were isolated on ice. Those brain structures were frozen and stored at –85 °C for analysis. To measure the NGF level, the tissue was homogenized at the ratio of 1:10 (mass/volume) in a buffer consisting of 100 mM Tris-HCL (pH 7.0), 2 % bovine serum albumin, 1 M NaCl, 4 mM Na2EDTA, 2 % Triton X-100, 0.1 % NaN3 and protease inhibitors, namely, 157 μg/mL benzamidine, 0.1 μg/mL pepstatin A and 17 μg/mL PMSF.

The total amount of NGF was measured using ChemiKine Nerve Growth Factor Sandwich ELISA Kit, a reagents kit for the enzyme-linked immunosorbent assay (Merck Millipore, USA), according to the manufacturer's guide. Measurements were performed using Wallac VICTOR 1420 multitasking reader (PerkinElmer, Finland). Protein concentration in the tissue was measured using Coomassie Brilliant Blue G-250 dye. The NGF content was presented in pg/mg protein.

For the histological and enzyme immunoassay, the rats were re-anaesthetized with chloral hydrate (450 mg/kg). Then the brains were fixed by intracardiac perfusion of 4 % paraformaldehyde solution in 0.1 M phosphate buffer (pH 7.4) and stored in the same fixative for 24 hours. 50 μm thick frontal sections were prepared using VT1200 S vibrating microtome (Leica Biosystems, Germany) and stored at –20 °C in a cryoprotectant. The sections were Nissl-stained with cresyl violet (Merck, Germany). The expression of p75NTR receptor was evaluated on free-floating sections by immunohystological assay using polyclonal rabbit antibodies (Sigma-Aldrich, USA) and diluted 1:100. Antibody binding was detected using goat-anti-rabbit IgG conjugated with biotin (Sigma-Aldrich, USA) diluted 1: 800, and VECTASTAIN Elite ABC Kit (Vector Laboratories, USA), an avidin-biotin complex with horseradish peroxidase. Diaminobenzidine (SIGMA Fast kit; Sigma-Aldrich, USA) was used as a chromogen.

A quantitative evaluation of damage degree was performed using the images of Nissl-stained sections taken with Camedia C-4000 (Olympus, Japan). The length of lesions in the dentate gyrus and CA1 hippocampal field was measured using Image-J

(NIH, USA) software. Based on the length and thickness of the sections, the total CA1 damaged area was measured as described in our earlier work [19]. Evaluation of p75NTR expression was based on the total area exhibiting positive staining in three sections with the most severe hippocampal damage located 500 μm from each other. To estimate the level of expression in an individual animal, the results were averaged and presented in pixels (pxl).

Reagents by Sigma-Aldrich (USA) were used in the study if not specified otherwise

Data were presented as a group arithmetic mean (M) and a standard error mean (SEM). The impact of peptides on the lesion size was evaluated by Kruskal–Wallis test. Differences between the groups were calculated using Mann - Whitney test.

RESULTS

The study of structural changes was carried out in animals (n = 5) that received 3 nmol aggregated Aβ(25–35) injection in the dorsal hippocampus of the left hemisphere 7 days after the peptide had been administered. 3 nmol Aβ(35–25) were injected in the dorsal hippocampus of the right hemisphere of the same animals. To assess the effect of the vehicle, the controls (n = 5) were injected with the equal volume of sterile water in the hippocampus of the left hemisphere and sterile 0.9% NaCl solution into the hippocampus of the right hemisphere. The majority of neurons in the assayed brain sections of the controls had normal morphology. Chromatophilic neurons in neocortex and primary olfactory cortex were rarely observed. Injections of isotonic solution did not induce a considerable damage in rat hippocampus. Small lesions associated with the needle penetration were found in the vicinity of the injection site after the vehicle had been introduced to the CA1 hippocampal field. Single chromatophilic cells were found in the CA3 field. At the same time, distinct structural changes of dentate gyrus (DG) were observed. In the first place, those changes were reflected in the considerable cell death of the DG upper blade. It should be mentioned that lesions were most conspicuous in the injection area and decreased in size further from the injection site. On the whole, these data correlate with the results of our previous works [8, 20].

Intrahippocampial administration of non-toxic Aβ(35–25) resulted in the conspicuous cavitation in the studied brain area. Along with it, a substantial damage of the DG upper and sometimes lower blades was observed. The degree of CA1 hippocampal field damage was comparable to the one in the brains of the controls who had received sterile water. In contrast to Aβ(35–25), administration of toxic aggregated peptide Aβ(25–35) induced a more statistically significant ($p < 0.05$) damage in the CA1 field (Fig. 1). Variance analysis showed the dependence of the CA1 field lesion size on Aβ(25–35) activity [$H(2.15) = 8.9$; $p < 0.02$]. The CA1 field lesion size was significantly ($p < 0.05$) bigger compared to the hippocampus of the control rats that had been injected with water and to the hemisphere where a non-toxic peptide had been injected. No correlation was observed between the DG lesion size and the peptide administration [$H(2.15) = 4.0$; $p = 0.1$] (Fig. 2). Thus, a higher sensitivity of CA1 neurons to a toxic effect of Aβ(25–35) was shown compared to DG neurons.

The development of neurodegenerative processes induced by Aβ(25–35) administration in the hippocampus is accompanied by significant changes in the system of neurotrophin supply. Thus, in the hippocampus of rats a statistically significant ($p < 0.05$) change in the expression of p75NTR receptor was observed. A statistically significant expansion of the area stained with specific antibodies to p75NTR protein was observed after both Aβ(35–25) and toxic Aβ(25–35) injections (Fig. 3). No specific effect of Aβ(25–35) on this value was detected. Peptide injections in the hippocampus resulted in the increased levels of NGF in this brain region (Fig. 4). At the same time, the injection of toxic Aβ(25–35) produced a more prominent effect on NGF levels compared to Aβ(35–25).

DISCUSSION

This work has demonstrated that Aβ(25–35) injection in the hippocampus leads to neurodegeneration that is most conspicuously expressed in the pyramidal layer of CA1 field cells. Cell damage and death were localized mainly in the injection area; the lesion size in the pyramidal layer was significantly bigger in the rats that had received the injection of Aβ(25–35), in contrast to the injections of the control peptide with a reversed amino acid sequence or the vehicle (sterile water). We should note that DG damage was observed in the hippocampus of animals in all groups except for those that had been injected with sterile isotonic NaCl solution. The damage of this structure is likely to have been caused by the syringe point being at the edge of the dentate gyrus lateral blade in accordance with the stereotaxic atlas coordinates, and granule cells were subjected to osmotic shock.

Neurodegenerative processes were accompanied by the increased p75NTR neurotrophin receptor expression that was observed in the hippocampus of the rats that had been administered to both Aβ(25–35) and Aβ(35–25). The functions of this receptor in the brain are diverse [21]. It can contribute to the survival of damaged neurons by enhancing the effective functioning of Trk receptors; it can also induce apoptosis of

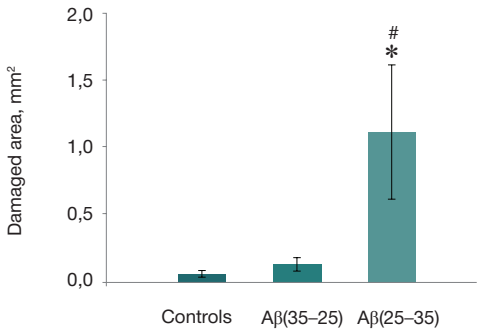

Fig. 1. Effect of amyloid peptide injection on the lesion size in CA1 hippocampal field of rats. * — $p < 0.05$ compared to the controls (vehicle injection), # — $p < 0.05$ compared to the group injected with Aβ(35–25); Mann–Whitney test

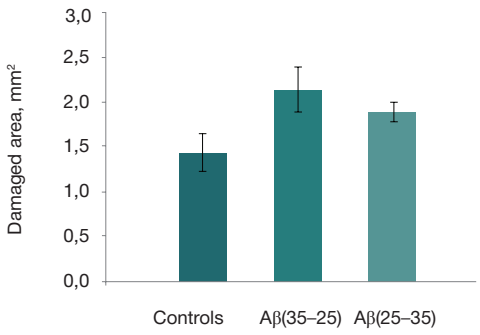

Fig. 2. Effect of amyloid peptide injection on the lesion size in dentate gyrus of rats

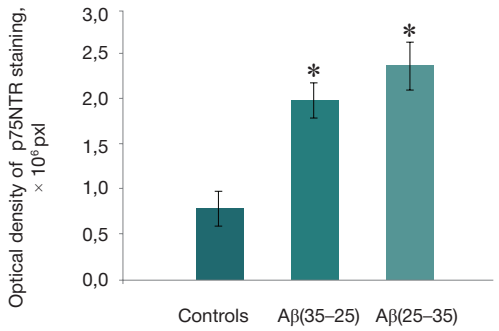

Fig. 3. Effect of amyloid peptide injection on p75NTR receptor expression in the hippocampus of rats

∗ — p <0.05 compared to the controls (vehicle injection); Mann–Whitney test.

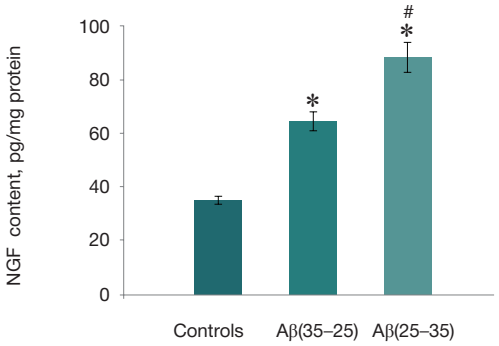

Fig. 4. Effect of amyloid peptide injection on the amount of NGF in the hippocampus of rats

∗ — p <0.05 compared to the controls (vehicle injection),
— p <0.05 compared to the group injected with Aβ(35–25); Mann–Whitney test.

damaged cells to reduce the inflammatory response, maintain the microenvironment for regeneration purposes, and control neuroinflammation. It is known that the expression of this receptor increases considerably in the hippocampus of patients with Alzheimer's, where Aβ can interact with p75NTR, contributing to cell death [22]. It was shown that in SH-SY5Y neuroblastoma cell culture Aβ(25–35) can bind to this receptor just as the full length peptide Aβ(1–42) [23]. At the same time, a peptide with a reversed amino acid sequence Aβ(42–1) did not display such properties. It should be noted that the mechanisms that help Aβ trigger the expression of p75NTR have not been fully understood. Moreover, it is a common belief that in the hippocampus p75NTR is expressed only on the afferent endings of basal nuclei cholinergic neurons [22].

Some authors indicate that p75NTR can be present in the membranes of subgranular zone neuroblasts [24] and in the dendritic spines and afferent terminals of CA1 pyramidal cells [25]. Besides, hippocampal astrocytes can actively express p75NTR, for example, in response to NMDA-receptor antagonists [26]. Microglial cells also express this receptor [27]. Administration of exogenous peptides into the hippocampus of rats similar to the one described in this work led to the significant activation of astrocytes and microglia [8, 19]. No significant difference in p75NTR levels can be explained by the increased expression of astrocytes and microglial cells in response to Aβ(25–35) and Aβ(35–25) injections.

After Aβ(25–35) injections the accumulation of NGF in the hippocampus was more conspicuous than after the injection of a peptide with a reversed amino acid sequence. Alzheimers's pathogenesis is associated with the fluctuations in NGF synthesis. Later disease stages, at which patients are diagnosed with dementia and neurodegeneration, are characterized by the increased NGF levels in brain structures [15, 16]. In contrast to earlier ontogenesis stages, the accumulation of NGF in the brain in pathology can be a controversial phenomenon. On the one hand, NGF is the main neurotrophin that ensures the survival of cholinergic neurons of basal nuclei due to the interaction of its mature form with TrkA and p75NTR receptors [28]. On the other hand, the binding of NGF pro-form to p75NTR receptor can trigger neuronal death [29]. The enzyme immunoassay used in this work for assessing the levels of NGF in tissue did not allow us to separately estimate the levels of NGF pro-form and mature form. Considering the works of other researchers, we can hypothesize that after interaction with Aβ(25–35), NGF pro-form will be a prevailing NGF molecule in the hippocampus [30]. Thus, it is possible that more intense interaction of NGF pro-form with a large number of p75NTR receptors will contribute to further neuronal death in the hippocampus and the lesion expansion.

CONCLUSIONS

The data obtained in this study show that aggregated Aβ(25–35) administration into the hippocampus of rats leads to neuronal degeneration in the CA1 field accompanied by the increased levels of NGF. The expression of p75NTR receptor increases in all animals that received Aβ(25–35) or Aβ(35–25) exogenous peptides. We hypothesize that Aβ(25–35) induces NGF signaling activation that contributes to the lesion expansion in the pyramidal cell layer of the hippocampus. Further research is necessary to clarify the molecular mechanisms of the developing neurodegeneration.

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