Semaglutide slows the progression of cognitive impairment and pathological changes in the hippocampus in a model of Alzheimer's disease

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Currently, glucagon-like peptide-1 receptor agonists (GLP-1RAs) are considered promising drugs for the treatment of Alzheimer's disease (AD) and other neurodegenerative diseases due to their complex mechanism of action, which includes (in addition to general somatic effects) an impact on neuroplasticity. This necessitates a detailed study of drugs in this group using appropriate informative experimental models.
Objective: *to characterise the effect of semaglutide, one of the main representatives of the GLP-1RAs class, on the development of neurodegenerative processes in the hippocampus and cognitive impairments in animals with a streptozocin (STZ) model of AD.*
Material and methods. *Streptozocin at a dose of 3 mg/kg was administered into the lateral ventricles of Wistar rats, and semaglutide at a dose of 0.1 mg/kg was administered intraperitoneally (every other day for 5 weeks). The behaviour of the animals was assessed in the 'Novel Object Recognition' and 'T-Maze' tests. Nine weeks after discontinuation of the drug, immunomorphological methods were used to determine the effect of semaglutide on neurodegenerative processes in the CA3 field of the hippocampus.*
Results. *Streptozocin caused impaired recognition of a new object and increased the latency period for entering the closed arm of the T-maze, as well as leading to tau protein accumulation and mitochondrial and synaptic abnormalities in the CA3 field of the hippocampus. Semaglutide significantly attenuated streptozocin-induced memory impairment and depression-like behaviour and improved morphological indicators of synaptic integrity (based on the detection of synaptophysin and PSD95 proteins) neuronal energy metabolism (as determined by the detection of glycolysis and oxidative phosphorylation enzymes), and reduced tau protein phosphorylation.*
Conclusion. *In a model of sporadic AD, semaglutide has been shown to attenuate cognitive impairment in laboratory animals and reduce the severity of morphological abnormalities in the CA3 region of the hippocampus, with the neuroprotective effect of the drug persisting after discontinuation of therapy.*

Keywords: *Alzheimer's disease; streptozocin model; semaglutide; hippocampus*
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Alzheimer's disease (AD) is the most common age-related neurodegenerative disease and the leading cause of dementia in modern society. The development of neurodegeneration in AD is mediated by a number of processes: accumulation of beta-amyloid in the brain parenchyma, formation of neurofibrillary tangles in dying neurons, and tau protein phosphorylation, which disrupt neuronal connectivity and synaptic transmission in the hippocampus, cerebral cortex, and other regions of the central nervous system [1]. Patients with AD also exhibit metabolic disturbances, including impaired carbohydrate metabolism and insulin resistance in peripheral tissues and in the brain, which may aggravate disease progression through effects on neuroinflammation, oxidative stress, and other mechanisms [2]. Current symptomatic therapy for AD does not affect disease progression or prognosis, and the first experience with anti-amyloid monoclonal antibodies has shown only a modest (about 30%) reduction in the rate of cognitive decline (CD) in early-stage AD [3,4]. Therefore, one of the key objectives remains the search for effective neuroprotective drugs capable of slowing or preventing the development of severe cognitive and behavioural impairments.

Given the partial overlap of molecular pathways involved in the pathogenesis of carbohydrate metabolism disorders and Alzheimer-type neurodegeneration, glucagon-like peptide-1 receptor agonists (GLP-1RAs), originally developed for the treatment of type 2 diabetes mellitus, may be promising for AD therapy [5]. Preclinical studies in various animal models have demonstrated that GLP-1RAs can reduce beta-amyloid accumulation in the brain and improve cognitive functions (CF) by restoring episodic and spatial memory [6–8]. In addition, GLP-1RAs can decrease the levels of mitochondrial reactive oxygen species in the hippocampus of AD model mice, thereby attenuating the toxic effects of beta-amyloid [6]. Semaglutide is one of the most promising agents in this class; it can cross the blood-brain barrier and modulate key mechanisms of local insulin resistance in different brain structures [9]. Compared with other agonists, semaglutide has a longer half-life (about 7 days) and a high affinity for serum albumin in plasma [10], which ensures sustained pharmacological activity. The drug is currently being evaluated in clinical trials in early-onset AD (i.e. in a form of the disease with a pronounced genetic component)

[11]. There is an obvious need for further semaglutide studies aimed at expanding the indications for its use, including in late-onset sporadic AD.

To assess the efficacy of new compounds with potential neuroprotective activity, a model of sporadic AD based on intracerebroventricular administration of the neurotoxin streptozocin is often used. This model adequately reproduces the key pathological features of the disease, including beta-amyloid accumulation, tau hyperphosphorylation, neuroinflammation, and oxidative stress [12].

The objective of the study was to investigate the effect of semaglutide on the development of neurodegenerative processes in the hippocampus and on cognitive impairment in animals in a model of sporadic AD.

Material and methods. The study was conducted on male Wistar rats (n=34) obtained from the breeding facility of the Federal State Budgetary Institution Scientific Center for Biomedical Technologies of the Federal Medical Biological Agency of Russia (Stolbovaya Branch), aged 3.5 months with body weights of 300–350 g at the start of the experiment. All experiments were carried out in compliance with relevant bioethical standards and the recommendations of the Board of the Eurasian Economic Commission on the use of laboratory animals, as well as the "Rules for working with laboratory rodents and rabbits" (GOST 33216–2014). The animals were housed under standard vivarium conditions with free access to food and water and a 12-h light/dark cycle.

Surgical procedures. Stereotaxic surgery was performed according to a protocol described in detail previously [13]. A solution of streptozotocin (Abcam, UK) in 0.9% NaCl at a dose of 3 mg/kg was administered bilaterally into the lateral ventricles of the brain [14]. Control animals received 0.9% NaCl in the same manner. For anaesthesia, Zoletil 100 (Valdepharm, France; solvent manufacturer – Delpharm Tours, France) was used at a dose of 30 mg/kg and Xyla (Interchemie Werken "De Adelaar" B.V., Netherlands) at 3 mg/kg intramuscularly; atropine (Moscow Endocrine Plant, Russia) at 0.04 mg/kg subcutaneously was used for premedication.

Drug administration. Intraperitoneal administration of 0.3 ml of Semavik® (containing 1.34 mg semaglutide; Geropharm LLC, Russia) at a dose of 0.1 mg/kg was initiated 7 days after streptozotocin injection and continued every other day for 5 weeks (16 injections in total).

The experimental animals were divided into four groups:

1) sham-operated rats with intraperitoneal saline administration ("NaCl", n=8);
2) sham-operated rats with intraperitoneal semaglutide administration ("NaCl+Sem", n=8);
3) rats receiving streptozotocin and intraperitoneal saline ("STZ", n=9);
4) rats receiving streptozotocin and intraperitoneal semaglutide ("STZ+Sem", n=9).

Behavioural testing. Behavioural testing was performed 3 months after intracerebroventricular STZ administration (15 weeks after the start of semaglutide treatment and 9 weeks after semaglutide discontinuation, respectively).

The apparatus for the Novel Object Recognition (NOR) test was a square arena (97–97 cm) with an illumination of 600 lx (Open Science, Russia). Testing was conducted over 2 days (sessions). On day 1 (training session), two identical objects were placed in the arena, and the time spent exploring each object was recorded; under normal conditions, both objects are novel and equivalent, so the exploration time should be similar. On day 2 (test session), one of the objects was replaced with a novel object differing in shape, and the time spent sniffing each object was recorded. The time spent exploring the novel object was taken as an indicator of preserved episodic hippocampus-dependent memory. The discrimination index was calculated as the ratio of the difference between the exploration time of the novel and familiar objects to the total exploration time for both objects. A positive discrimination index indicates a preference for the novel object and preserved memory, whereas a negative index reflects anxiety, sensory deficits, or neurological impairment [15].

Spatial memory was assessed using a T-maze (Open Science, Russia). The apparatus was elevated 70 cm above the floor and consisted of two closed arms with side and end walls 30 cm high and one open arm without walls; arm width was 14 cm, length – 50 cm, and the central platform at the intersection measured 14×14 cm. At the beginning of the trial, the rat was placed at the start of the open arm. The latency to enter a closed arm and the degree of "neuroticism" were assessed using a rating scale [16]. Testing was terminated when the animal entered a closed arm; the maximum test duration was 180 s. The test was performed over 2 days (sessions).

Immunomorphological study. The animals were decapitated, the brain was removed and fixed in 4% formalin solution. Series of frontal cryostat sections 10 μm thick were prepared, and immunofluorescence staining performed according to the antibody manufacturers' protocols. Appropriate secondary antibodies conjugated with Alexa Fluor 488 (Abcam, ab150077; 1:350) and Alexa Fluor 594 (Abcam, ab150112; 1:350) were used for detection. The sections were put into FluoroShield medium containing the nuclear counterstain DAPI (4',6-diamidino-2-phenylindole).

Morphometry. The tissue slides were examined with Nikon SMZ18 and Nikon Eclipse Ni_U fluorescence microscopes equipped with appropriate filter sets for the fluorochromes used and CCD cameras suitable for photometry. Image processing was performed using Nikon NIS-Elements BR software. Serial sections from the anterior third of the hippocampus were taken for analysis (6–12 sections per staining method, taken at 200-μm intervals). The immunofluorescent staining in CA3 pyramidal neurons was quantified as mean intensity (256 grayscale levels of 8-bit images). The areas of hippocampal regions were measured in the anterior third of the structure on slides stained for the neuronal marker NeuN, within manually outlined ROI's. Co-localisation of the synaptic proteins PSD95 and SYP was assessed in the CA3 field at the boundary with the stratum lucidum, as described previously [17,18].

Statistical analysis. Statistical analysis was performed using Statistica 12.0 and GraphPad Prism 8. To assess the significance of differences, factorial analysis of variance (ANOVA) with Fisher and Tukey post-hoc tests and the nonparametric Kruskal–Wallis test followed by Dunn's test were used. Normality of distribution was evaluated with the Shapiro–Wilk test, and differences were considered significant at $p<0.05$.

Results. Semaglutide exerted a beneficial effect on spatial memory and emotional state in the experimental rats. On day 1 of the NOR test, no significant differences in the exploration time of identical objects (cube) were observed between the groups (Fig. 1). On day 2, when a novel object was presented, the time spent exploring it was significantly higher in the control group

(p=0.0455) and in the semaglutide-treated groups ("NaCl+Sem": p=0.0293; "STZ+Sem": p=0.0411) compared with the familiar object, whereas in the "STZ" group the exploration time did not differ between the two objects (Fig. 1).

The discrimination index was greater than zero in the control and semaglutide-treated groups: 0.44±0.05 in "NaCl", 0.38±0.1 in "NaCl+Sem", and 0.39±0.1 in "STZ+Sem". In contrast, the index was negative in the "STZ" group (-0.012±0.14) and was significantly lower than in the "NaCl" (p=0.0285) and "STZ+Sem" (p=0.0151) groups.

In the T-maze test on day 1, the latency to enter the closed arm was significantly longer in the "STZ" group than in the "NaCl" (p=0.0244) and "STZ+Sem" (p=0.0098) groups (Fig. 2). On day 2, significant differences in latency were found between the "STZ" and "NaCl+Sem" groups (p=0.0039), as well as between "NaCl+Sem" and "NaCl" (p=0.0335); in "NaCl+Sem" rats, the latency differed significantly between days 1 and 2 (p=0.0175) (Fig. 2).

According to the neurotization scale, the total score was increased in the "STZ" group compared with "NaCl" (p=0.0496) and "NaCl+Sem" (p=0.0097), whereas semaglutide treatment reduced this score in the "STZ+Sem" group (p=0.0104) (Fig. 3).

Morphological findings were consistent with the behavioural data. Assessment of the granule cell layer area in the dentate gyrus (NeuN staining) (Fig. 4) showed a significant reduction in the group receiving STZ alone (by 46%, p<0.0001) and in the "STZ+Sem" group (by 28%, p=0.0036) compared with the only semaglutide-treated group, although the difference between "STZ" and "STZ+Sem" (172±26 vs 228±19 μm) was not statistically significant (p=0.1249). The area of the pyramidal layer in CA1–3 was also significantly reduced in STZ-treated animals: by 23% in the "STZ" group ("NaCl+Sem": 434±61 vs "STZ": 334±50; p=0.0014) and by 18% in the "STZ+Sem" group ("NaCl+Sem": 433±60.5 vs "STZ+Sem": 353.9±66.54; p=0.0155) compared with semaglutide alone.

STZ administration was associated with a marked increase in staining intensity for phosphorylated tau (p-tau-217) (p=0.0022), while semaglutide exerted a neuroprotective effect by preventing the accumulation of phosphorylated tau in "STZ+Sem" versus "STZ" (p<0.0001) (Fig. 4).

Hippocampal injury under STZ exposure was also supported by changes in mitochondrial and glycolytic markers in CA3 neurons (Fig. 3). In the "STZ" group, succinate dehydrogenase (SDH) immunofluorescence intensity was significantly decreased compared with controls (p=0.0009); although no significant differences were found between "STZ" and "STZ+Sem" (p=0.3132), the "STZ+Sem" group did not differ from the control group (p=0.3418), indicating a trend towards restoration of SDH content under semaglutide influence. Similarly, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) staining intensity in CA3 pyramidal neurons was significantly reduced after STZ (p=0.0008), and semaglutide increased this intensity, although the difference between "STZ" and "STZ+Sem" was not statistically significant (p=0.3294).

The deleterious effects of STZ on hippocampal neurons were also reflected in synaptic parameters (Fig. 4). In the *stratum lucidum* of CA3, co-localization of PSD95 and synaptophysin (SYP) was quantified using Manders' coefficient, which was significantly reduced in STZ-treated animals compared with controls (p=0.0056). Semaglutide prevented this decrease, and the "STZ" and "STZ+Sem" groups differed significantly (p=0.0446).

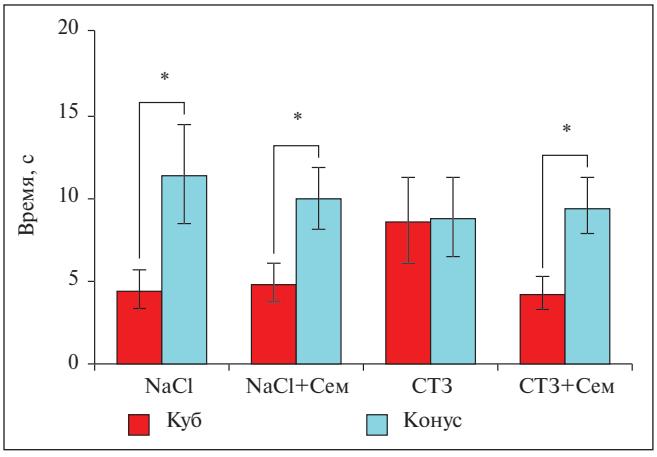

Fig. 1. *Time spent learning a new object in the NOR test. Data are presented as: mean ± standard error of the mean; * – differences are statistically significant when comparing the time spent learning familiar and new objects, p<0.05 (here and in Fig. 2, 3)*

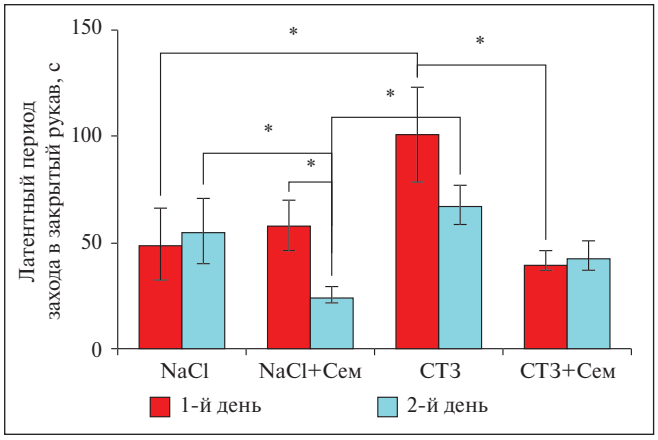

Fig. 2. *Latent period of entering the closed arm of the 'T-shaped maze'*

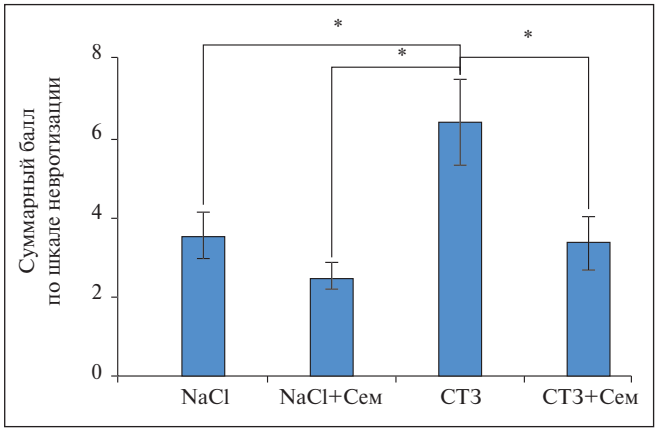

Fig. 3. *Assessment of the total score on the neuroticism scale in the 'T-maze' test*

Thus, the beneficial behavioural changes observed with semaglutide therapy-improved memory and reduced anxiety-like behaviour-were accompanied by decreased accumulation and phosphorylation of tau protein and restoration of synaptic organisation in the hippocampus. Recovery of synaptic plasticity likely contributed to improved cognitive functions such as learning and memory in the animals.

Discussion. The results of this study are consistent with published data showing that intracerebroventricular streptozotocin administration leads to pronounced cognitive impairment and behavioural changes comparable to those observed in sporadic AD [12,19].

In this work, an improvement in cognitive function was demonstrated for the first time in this STZ model in rats treated with semaglutide: these animals showed a greater ability to discriminate between familiar and novel objects in the NOR test than rats receiving toxin alone, indicating improved recognition, working memory, and emotional state. Similar findings have previously been reported for another GLP-1RA, liraglutide, in SAMP8 mice, where a trend towards improvement in the discrimination index suggested restoration of cognitive performance [20], and in APP/PS1 mice, where liraglutide treatment significantly increased interaction time with a novel object [21,22].

This study also, for the first time, demonstrated improved spatial memory and reduced anxiety-like behaviour under semaglutide treatment in the T-maze test. Other authors using the classical Morris water maze to assess spatial memory have likewise reported neuroprotective properties of GLP-1RAs, including liraglutide and exenatide, in 5xFAD and APP/PS1 transgenic models and in STZ-induced AD in rats, where these drugs enhanced learning of the platform location [6,21,23]. Moreover, mice treated with liraglutide adapted more rapidly to a new task than controls [21], which aligns with the present finding that semaglutide-treated animals more quickly located the closed arm of the T-maze on day 2 of testing.

The favourable cognitive changes observed in this work are consistent with the demonstrated ability of semaglutide to suppress neurodegenerative processes, including reducing the accumulation of phosphorylated tau, a classical AD marker. These data agree with reports of semaglutide effects in 3xTg-AD mice and with liraglutide administration in combined models of AD and type 2 diabetes [24,25]. In contrast, exenatide treatment in 3xTg-AD mice did not affect beta-amyloid aggregation or tau phosphorylation in CA1 neurons [26], which may reflect differences in pharmacokinetics between individual GLP-1RAs [10].

The present findings indicate that semaglutide can improve the function of the mitochondrial respiratory chain and glycolytic enzymes disrupted by STZ, complementing data on exenatide-mediated enhancement of mitochondrial and antioxidant function in 5xFAD mice [6]. In a genetic *PSEN-1*-associated AD model, exenatide increased glycolytic enzyme activity [24].

In AD, reduced levels of synaptic proteins (presynaptic synaptophysin, synapsin-1, and postsynaptic PSD-95) are detectable years before clinical symp-

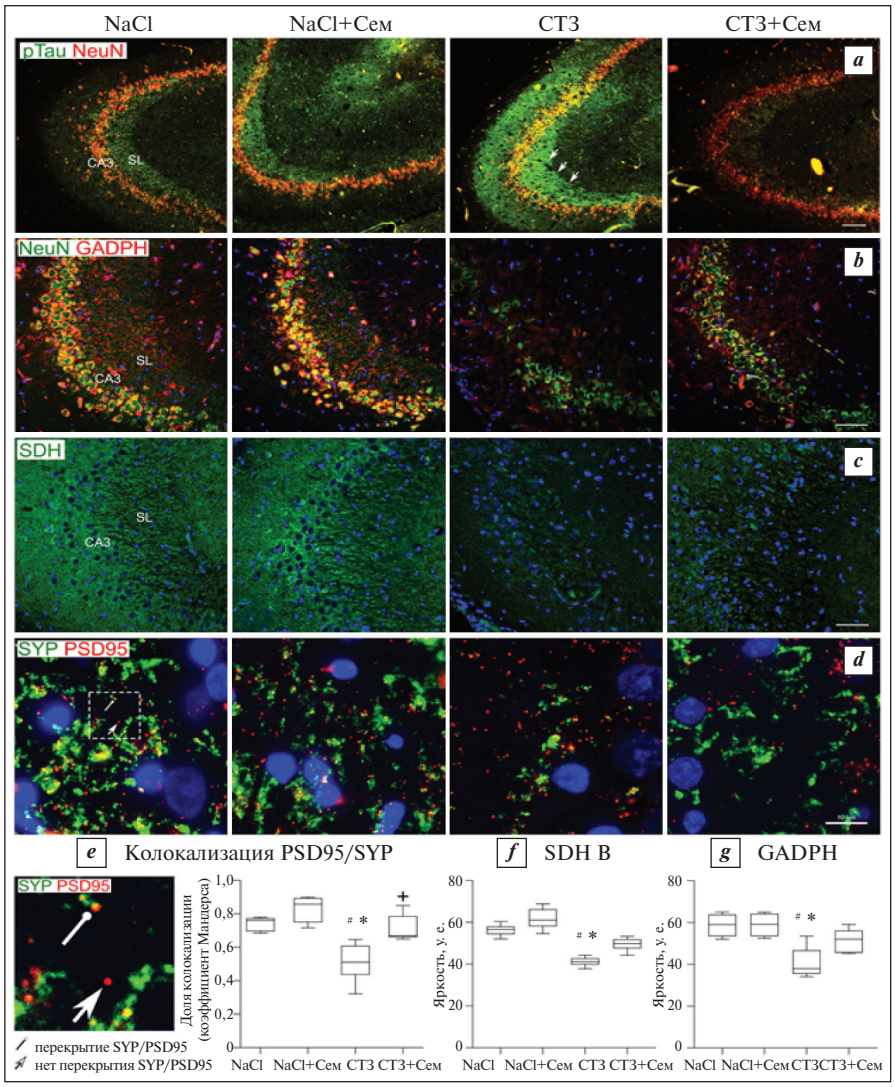

Fig. 4. *Morphological changes in the CA3 field of the hippocampus under the influence of streptozocin and their correction with semaglutide.*

*a – change in staining intensity for phosphorylated tau protein (green) and NeuN neuron marker protein (red); b – change in staining intensity for GADPH (red) and NeuN (green); c – change in staining intensity for SDH (green); d – detection of co-localisation of SYP (green) and the postsynaptic density protein PSD95 (red); e – Manders' coefficient of co-localisation (the inset shows areas without overlap of synaptic markers with an arrow, and areas with overlap with a dot pointer); f – assessment of the brightness of fluorescent immunostaining for SDH; g – assessment of the brightness of fluorescent immunostaining on GADPH. * – statistically significant differences between the '(STZ)' and 'NaCl' groups; # – statistically significant differences between the "(STZ)" and 'NaCl+Sem' groups at p<0.05*

toms appear [27], and the semaglutide-induced restoration of synaptic parameters in this study is consistent with previous findings for exenatide [6,21,22]. GLP-1RAs are known to activate the cAMP/PKA/CREB cascade, which is crucial for neuroplasticity, long-term memory formation, and neuronal survival, and they are also thought to influence neurogenesis [28,29]. In this context, the present data emphasise the importance of the intracerebroventricular STZ model as one that captures multiple aspects of AD pathogenesis and support consideration of semaglutide as a promising component of combination therapy for AD.

Conclusion. In the STZ-induced sporadic AD model, semaglutide exerted a complex beneficial effect on the structural and functional state of hippocampal neurons. The medication suppressed neurodegenerative processes, improved cognitive functions, and slowed the progression of pathology in model animals.

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Conflict of Interest Statement

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