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Semaglutide reduces hypothalamic glial cell damage in a streptozocin-induced model of Alzheimer's disease

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Abstract

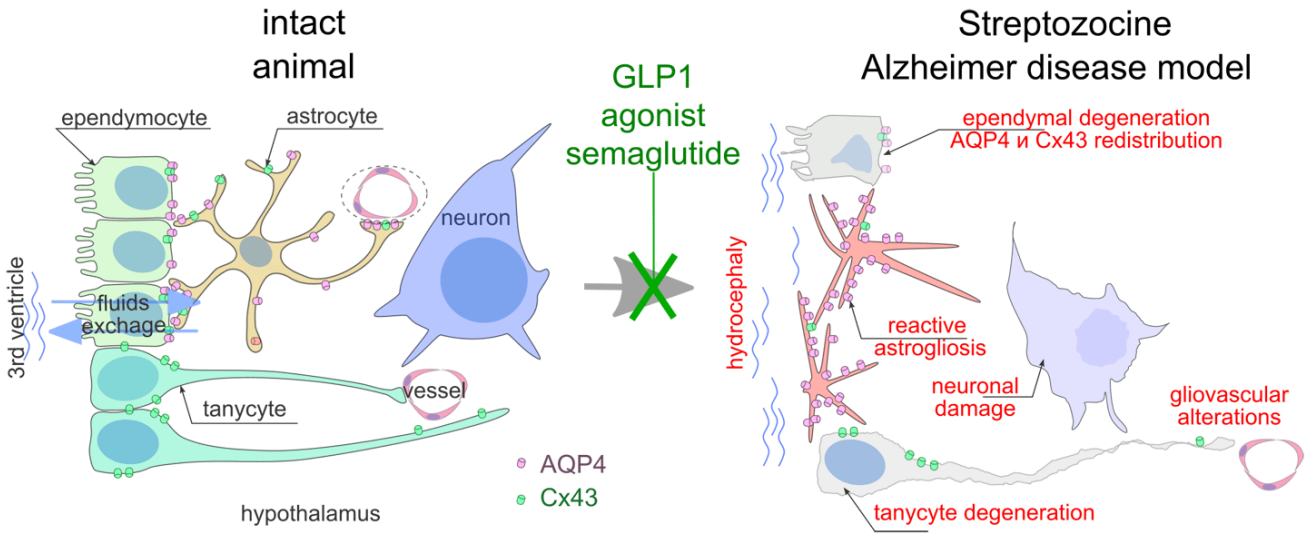
Introduction: Reactive changes in glial cells, as well as their dysfunction, particularly cerebrospinal fluid dynamics disturbances, are associated with multiple neurodegenerative diseases and Alzheimer's disease (AD). Intraventricular administration of streptozotocin (STZ) is considered a model of sporadic AD, though data on hypothalamic glial cell changes, ependymal glia, and tanycytes in this model remain limited. Of particular interest is the potential for glucagon-like peptide-1 (GLP-1) receptor agonists to address STZ-induced changes following intraventricular administration.

Material and Methods: Using immunomorphological methods, this study assessed changes in staining density and distribution of glial proteins (GFAP, aquaporine-4, connexin 43, vimentin) and neuronal alterations in hypothalamic structures following intraventricular STZ administration (3 mg/kg) and course treatment with intraperitoneal semaglutide (0.1 mg/kg, 16 injections).

Results: STZ caused neuronal damage in the ventromedial hypothalamic nucleus, disrupted the ependymal lining and tanycytes of the third ventricle, induced reactive astrogliosis, and altered the distribution of aquaporin-4 and connexin-43. Semaglutide administration reduced astroglial activation, normalized aquaporin and connexin distribution, decreased neuronal death, and suppressed caspase-3 activation in the ventromedial hypothalamic nucleus.

Conclusion: Intraventricular single-dose STZ administration causes long-term impairment of glial functions related to cerebrospinal fluid exchange. The course treatment GLP-1R agonist semaglutide (started 5 days after streptozocin administration, 16 injections every other day) demonstrated normalizing effects on both glial and neuronal parameters in the STZ-induced AD model.

Graphical Abstract



Keywords

astrocytes, ependymal cells, Alzheimer's disease, streptozotocin, semaglutide

Introduction

The combination of reactive and degenerative changes in astrocytes is characteristic of both AD and other neurodegenerative disorders, with some authors attributing a primary role to glial dysfunction in the pathogenesis of the disease. Both pro-inflammatory changes in astrocytes and their damage and degeneration play a crucial role in AD pathogenesis (Rodríguez-Giraldo et al. 2023), being associated with dysregulation of inflammatory response, antioxidant systems, metabolism of glutamate and other mediators, as well as neurovascular interactions leading to impaired transport of energy substrates. In the context of the hypothesis about local insulin resistance as a cause of AD (Yoon et al. 2023), it is significant that astrocytes participate in insulin transport into brain parenchyma. Joint modulation of brain glucose metabolism by insulin and insulin-like growth factor through their effects on astrocytes has been demonstrated (Fernandez et al. 2022). Proper functioning of interstitial fluid exchange is essential for the removal of pathological β-amyloid and tau protein forms, as well as for reducing excitotoxicity (Iliff et al. 2012, 2014; Silva et al. 2021). Impairments in this exchange, observed in astrocyte damage, are associated with multiple neurodegenerative diseases including AD.

The regulation of tissue homeostasis, nutrient exchange, and metabolite clearance in the brain is associated with the so-called “glymphatic system”, first postulated in 2012 by Jefferey Iliff and Maiken Nedergaard (Iliff et al. 2012). Research revealed that perivascular pathways and brain parenchyma astrocytes facilitate exchange between cerebrospinal and interstitial fluids while removing metabolic waste (Silva et al. 2021), alongside exchange occurring through ventricular surface pathways.

Astrocytes and ventricular lining cells – ependymocytes and tanycytes – serve as primary regulators of interstitial fluid composition and exchange. Key astrocyte-specific proteins maintaining water and ionic homeostasis include aquaporin-4 (AQP4) water channels, gap junction proteins (connexin-43, -30, -26) ensuring structural and metabolic syncytial integration, and inwardly rectifying potassium channels Kir4.1 (Zhou et al. 2024; Verkhratsky et al. 2023). Intracerebroventricular administration of streptozotocin (STZ) – a toxin inducing type 2 diabetes mellitus when administered systemically – leads to impaired insulin signaling pathways in the brain, severe neurodegenerative changes, and is considered a metabolic model of sporadic AD (Agrawal et al. 2011; Chen et al. 2013; Grieb 2016; Kamat et al. 2016; Voronkov et al. 2019).

Our previous studies demonstrated that intraventricular STZ administration causes damage to ependymocytes and tanycytes of the third cerebral ventricle, β-amyloid accumulation, and neuronal death in the hypothalamic arcuate nucleus, resulting in dysregulation of glucose metabolism and feeding behavior (Stavrovskaya et al. 2019; Voronkov et al. 2021). Tanycyte dysfunction has also been identified in genetic models of AD (APP/PS1) (Qi et al. 2025), consistent with hypotheses about the significance of these cell impairments in AD pathogenesis (Raikwar et al. 2019). However, the extent to which the STZ model reproduces glymphatic system impairments characteristic of AD remains to be elucidated.

Metabolic disorders in AD and their association with insulin resistance suggest the potential therapeutic application of insulinotropic antidiabetic drugs, such as glucagon-like peptide-1 (GLP-1) receptor agonists. It has been established that GLP-1 receptor agonists possess neuroprotective properties (Urkon et al. 2025) and can reduce glial activation, thereby mitigating neuroinflammation (Park et al. 2021). Regarding bioavailability and half-life, semaglutide stands out among other GLP-1 analogs, with ongoing phase III clinical trials in patients with early-onset AD (Cummings et al. 2025). However, the effects of semaglutide on components of the glymphatic system and hypothalamic nuclei under conditions modeling sporadic AD remain poorly understood, despite the hypothalamus being one of the regions particularly rich in GLP-1 receptors.

In light of the above, the study aimed to morphologically assess changes in the brain ventricular lining and astroglial cells in a streptozotocin-induced AD model, and evaluate the potential for their long-term management through course administration of the GLP-1 receptor agonist semaglutide.

Materials and Methods

Animal care

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. Animals were housed under standard vivarium conditions with free access to food and water under a 12-hour light/dark cycle.

Drugs

Semaglutide (PubChem CID 56843331) is an modified analog of human GLP-1. The modified long alkyl side chain induces interaction with plasma albumin resulting in extended half-life, make it resistant to degradation (Urkon et al. 2025).

Streptozocin (Streptozotocin, PubChem CID 29327) is a glucosamine nitrosourea chemical, an alkylating agent toxic to pancreatic beta-cells with system administration. Intracerebroventricular STZ animal models resembles sporadic AD by main pathomorphological and behavioral manifestations (Grieb, 2016).

Experimental groups

Animals were divided into the following experimental groups: 1) Controls (K, n=8) receiving intraventricular (i.c.v.) injections and intraperitonial (i.p.) administration of 0.9% NaCl isotonic solution; 2) Semaglutide administration group (Sm, n=8) receiving i.v. injections of 0.9% NaCl and i.p. administration of semaglutide; 3) Streptozotocin administration group (STZ, n=9) receiving i.v. injection of streptozotocin and i.p. administration of 0.9% NaCl; 4) Streptozotocin and semaglutide administration group (STZ+Sm, n=9) receiving i.v. injection of streptozotocin and i.p. administration of semaglutide.

Substance administration

Intracerebroventricular administration was performed stereotactically. Streptozocin (Abcam, UK) was dissolved in 0.9% NaCl at 3 mg/kg, and 5 µL of the solution was administered bilaterally into the lateral cerebral ventricles using a 26-gauge/51 mm needle microsyringe (Hamilton Bonaduz AG, Switzerland) mounted on a stereotactic manipulator (RWD, China) (coordinates: AP = -0.8; L = 1.5; V = 3.5). Control animals received 5 µL of 0.9% NaCl administered in the same manner. Anesthesia was induced with intramuscular Zoletil 100 (Valdepharm, France; solvent manufacturer, Delpharm Tours, France) at 30 mg/kg and Xylu (Interchemie Werken De Adelaar B.V., The Netherlands) at 3 mg/kg. Premedication consisted of subcutaneous atropine (Moscow Endocrine Plant, Russia) at 0.04 mg/kg administered 10–15 minutes before xylazine injection. Intraperitoneal administration of semaglutide (Semavik®;

Geropharm LLC, Russia) at 0.1 mg/kg was initiated 7 days after streptozocin administration and continued every other day for 5 weeks, with a total of 16 injections performed.

Immunomorphological study

Upon completion of the experiment, animals were decapitated using a guillotine. Brain samples were immersion-fixed for 24 hours in 4% formaldehyde solution in phosphate-buffered saline (PBS, pH=7.2), saturated with 30% sucrose solution, and frozen in O.C.T. matrix medium (Tissue Tek, USA) in a container with isopentane immersed in liquid nitrogen. Serial 10-µm thick sections were obtained using a Sakura Tissue Tek Cryo3 cryostat.

Target proteins (Table 1) were detected by immunofluorescence following a standard protocol. Heat-induced antigen retrieval was conducted in citrate buffer (0.01 M, pH=6.0) by heating sections in a steamer for 12 minutes (96–98°C). Washing was performed using phosphate-buffered saline (0.01 M, pH=7.2–7.4) containing Triton X-100 0.05%. Sections were incubated for 20 minutes in 1% bovine serum albumin solution, followed by 18–20 hour incubation with primary antibodies at room temperature in a humid chamber. For detection, goat anti-rabbit IgG conjugated with Alexa Fluor 488 (Abcam, ab150077; 1:350) and donkey anti-mouse IgG conjugated with Alexa Fluor 594 (Abcam, ab150112; 1:350) were used as secondary antibodies. Secondary antibodies were applied for 4 hours, after which sections were washed and placed in FluoroShield medium containing DAPI fluorochrome (4',6-diamidino-2-phenylindole) for nuclear staining.

Incubation without primary antibodies was performed for quality control of immunofluorescence staining (negative control). Rat intestinal sections were used for positive control of activated caspase-3 detection (apoptotic enterocytes served as control).

Table 1. Primary antibodies used in the study

Antigen	Abbreviation	Manufacturer, Catalog Number	Dilution
neuron nuclear protein	NeuN	Abcam (ab177487)	1 : 400
glial fibrillary acidic protein (astrocytes)	GFAP	Abcam (ab207165)	1 : 300
aquaporin-4, water channel protein (astroglia, ependymocytes)	AQP4	Sigma (HPA-014-784)	1 : 250
connexin-43, a gap junction protein (astroglia, endothelial cells)	Cx43	Abcam (ab11370)	1 : 400
vimentin (endothelial cells, astroglia, ependymocytes)	Vim	Abcam (ab92547)	1 : 450
activated caspase-3 (proteolytic fragment 17/19 kDa, Asp175)	Cas3	Cell Signaling (#9661)	1 : 350

Histological examinations and morphometry

Specimens were documented using a Nikon Eclipse Ni-u fluorescence microscope equipped with a DS-Qi1 camera and Nikon SMZ18 stereomicroscope. Morphometric analysis was performed using Nikon NIS Elements BR or ImageJ software. Serial sections of the median eminence of the hypothalamus were used for analysis (6–12 sections per staining method, spaced 150 µm apart). The area of the third ventricular lumen was assessed by outlining images from 5–6 consecutive sections at the median eminence level under low magnification for each animal. Immunofluorescence intensity for GFAP, AQP4, and Cx43 was quantified in manually selected regions of interest (ventromedial hypothalamic nucleus) using mean brightness values in 256 grayscale levels of 8-bit images. Cx43 distribution was analyzed using GLCM (gray level co-occurrence matrix) texture analysis in ImageJ. Assessment methods for histological images have been previously described (Voronkov et al. 2023; Dragić et al. 2019).

Neuronal density was assessed at 20x magnification by manual counting of NeuN-positive cells. The proportion of caspase-3-positive nuclei was calculated relative to total DAPI-stained nuclei in the field of view.

Statistical analysis

Statistical analysis was performed using Statistica and GraphPad Prism 8.0. Mean values per animal were calculated, between group comparisons made using the Kruskal-Wallis non-parametric test followed by Dunn's post hoc test. The changes were considered statistically significant at $p < 0.05$.

Results

Streptozotocin selectively damages the ependymal lining of the cerebral ventricles

Administration of streptozotocin (STZ) significantly disrupted the organization of the third ventricular wall and the ventricular system as a whole (Fig. 1). The choroid plexus of the third ventricle in STZ-treated animals showed reduced dimensions, with the most pronounced changes in the ependymal lining observed in hypothalamic structures, anterior horns of the lateral ventricles, and the hippocampal fimbria region (*fimbria hippocampi*). Degenerative changes were also detected in the subcommissural organ, median eminence of the hypothalamus, and tanycytes of the third ventricle.

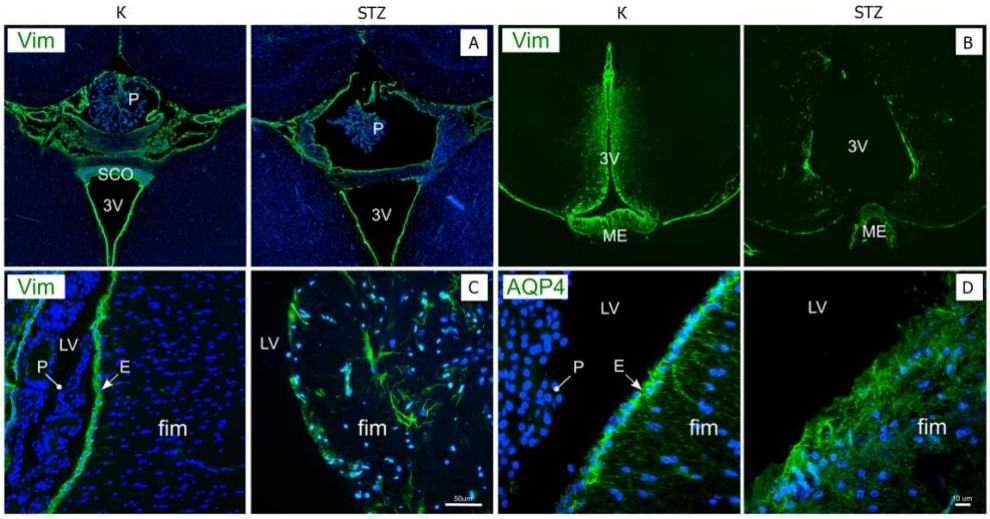


Figure 1. Alterations of the brain ventricles walls after i.c.v. streptozocin injection. ***Note:*** ("STZ"), in comparison with control animals ("K"). **A** – Dorsal part of the third ventricle (3V), reduction of the choroid plexus (P), degeneration of the subcommissural organ (SCO) after streptozocin injection; **B** – Ventral part of the third ventricle, increase in the lumen of the ventricle, degeneration of tanycytes and the median eminence (ME) of the hypothalamus; **C** – The lateral ventricle wall (LV) in the fimbria of the hippocampus (fim), degeneration of ependymocytes (E) and white matter; **D** – The lateral ventricle wall (LV) in the fimbria of the hippocampus, change in aquaporin-4 localization (AQP4);
A, B, C – detection of vimentin (Vim), D – detection of aquaporin-4 (AQP4).

Additionally, degeneration was identified in the white matter of the hippocampal fimbria adjacent to the lateral ventricle and in neurons of periventricular hypothalamic nuclei (arcuate and ventromedial) surrounding the third ventricle. In lesioned areas, the layer of Vim-positive ependymocytes became sparse or disappeared, with ectopic Vim-positive cells of altered morphology identified, likely reactive astrocytes mediating ventricular wall remodeling through replacement gliosis. Immunofluorescence staining revealed increased AQP4 expression in the ventricular wall, likely reflecting enhanced aquaporin-4 production in astrocytes replacing the ependymal lining.

Effect of semaglutide on STZ-induced astroglial changes in the hypothalamus

In control animals, the hypothalamic region most enriched with GFAP-positive astroglial processes was the marginal area of the third ventricular wall (Fig. 2). AQP4 and Cx43 showed relatively uniform distribution in the neuropil, with AQP4 additionally localized perivascularly, while Cx43 was detected in the ependymal layer of the third ventricle.
In STZ-treated animal groups, two distinct zones were identified based on glial protein staining intensity: 1) the immediate ventricular border area (area of replacement gliosis), and 2) the adjacent hypothalamic nuclei region with moderate changes, where measurements were performed.

The marginal area of the third ventricle in STZ-treated animals showed significant damage, with ventricular lining replaced by astrocytes (Fig. 2). The replacement gliosis area contained intensely stained bodies of reactive (scar-like) GFAP-positive astrocytes displaying polarized processes, intense staining, and disrupted distribution patterns of AQP4 and Cx43, which were detected in the soma and proximal processes. Overall, STZ administration induced reactive astrocytic changes accompanied by a significant increase in GFAP expression compared to controls (Fig. 3).

Away from the ventricular edge, in the area of moderate reactive glial changes within the ventromedial hypothalamic nucleus, a significant reduction in AQP4 and Cx43 immunostaining was observed (Figs 2, 3). Concurrently, the mean neuropil staining intensity for AQP4 and Cx43 markers in the ventromedial hypothalamic nucleus decreased, accompanied by their redistribution within astroglial processes. In STZ-treated groups, astrocytes with discernible process morphology were identified, associated with redistribution of AQP4 and Cx43 from distal to proximal segments of the processes. Both STZ-treated animal groups exhibited larger third ventricular dimensions compared to control groups; however, the STZ+Sm group showed significantly lower values than the STZ-only group.

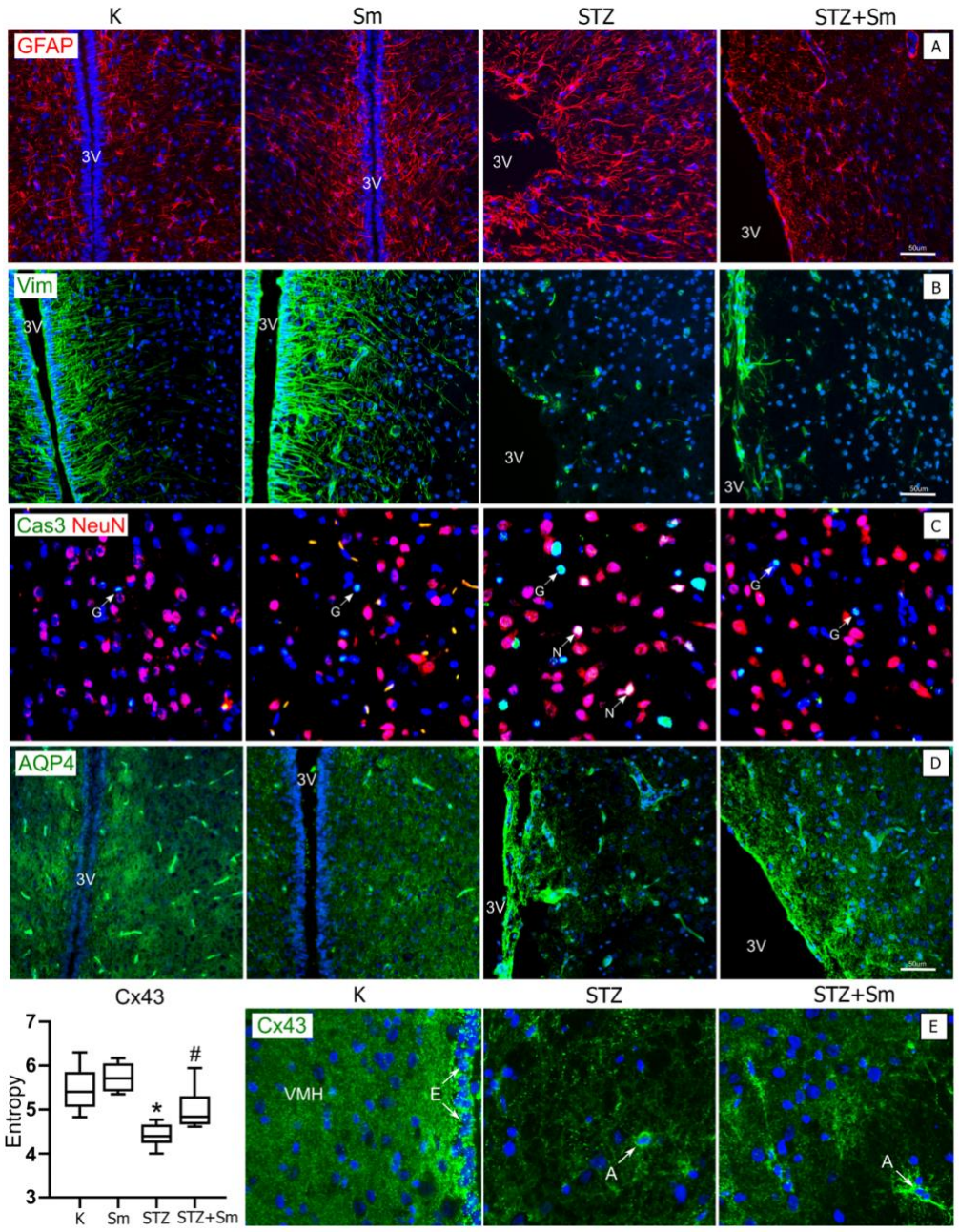


Figure 2. Alteration Pathomorphological changes after i.c.v. streptozocin ("STZ") and their attenuation in semaglutide treated group ("STZ+Sm"), compared to the control groups ("K", "Sm"). **Note: A** – Reactive changes of GFAP-positive astrogla in the "STZ" group and their reduction in the "STZ + Sm" group; **B** – Tanycytes degeneration of the third ventricle wall and reorganization of the ventricle wall in the "STZ + Sm" group; **C** – Increased intensity of immunofluorescent staining for caspase-3 (Cas3) in the ventromedial hypothalamic nucleus; **D** – Changes in the localization and intensity of aquaporin-4 (AQP4) staining, the formation of a shaft of AQP4 positive cells at the ventricular border and a decrease in AQP4 immunostaining in the ventromedial nucleus in the STZ group and normalization of AQP4 distribution in the STZ + Sm group; **E** – A decrease in the intensity of connexin-43 (Cx43) staining in the ventromedial nucleus of the hypothalamus in the "STZ" group and its redistribution in the bodies of reactive astrocytes ("A" with an arrow is an astrocyte), the graph shows the normalization of the distribution of the entropy index for staining on Cx43. * - $p < 0.05$ compared to the control group (K); # - $p<0.05$ compared to the group that received STZ.

Semaglutide administration did not significantly affect the area of replacement gliosis or the detection of studied glial proteins in the ventricular wall proper. In the STZ+Sm group, the ventricular edge was partially bordered by intact ependymocytes (not forming a dense layer) and vimentin-positive cells lacking the characteristic elongated basal processes of tanycytes, suggesting remodeling of the ventricular marginal layer by scar-forming, vimentine expressing astroglia or reactive ependymal changes (Fig. 2).

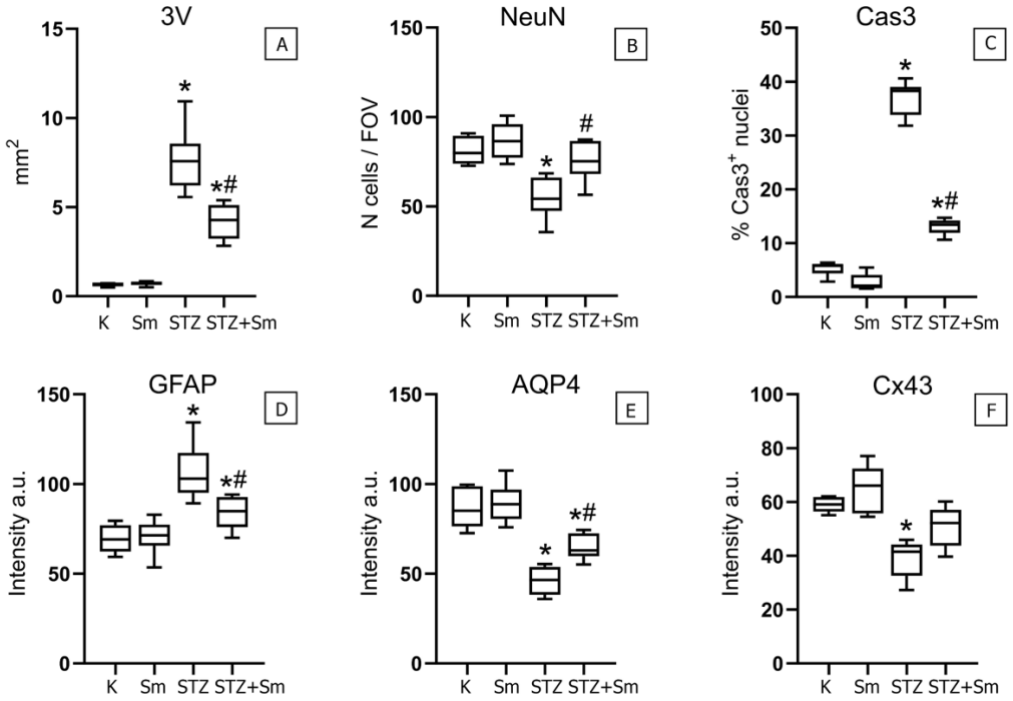


Figure 3. Ventromedial hypothalamus changes after i.c.v. streptozocin administration ("STZ") and their attenuation in semaglutide treated group ("STZ+Sm"). ***Note:*** A – Area of the third ventricle (3V) on the frontal brain sections; **B** – Density of NeuN-positive neurons (units / grain field) in the ventromedial hypothalamic nucleus; **C** – The proportion of nuclei positive for activated caspase-3 (Cas3) in the ventromedial hypothalamic nucleus; **D, E, F** – the intensity of immunofluorescent staining (brightness, units) for gliofibrillary protein GFAP (D), aquaporin-4 - AQP4 (E), connexin-43 – Cx43 (F) in the ventromedial hypothalamic nucleus. * – $p < 0.05$ compared to the control group (K); # - $p<0.05$ compared to the group that received STZ.

Away from the ventricular wall, the STZ + Sm group showed reduced astroglial reactivity and a significant decrease in GFAP staining intensity in the ventromedial hypothalamic nucleus, along with restoration of thin, homogeneous Cx43 and AQP4 staining in the neuropil. This was reflected by increased mean staining brightness in the STZ + Sm group compared to the STZ group. The image entropy parameter, inversely related to contrast and staining uniformity, significantly decreased for hypothalamic Cx43 in the STZ group due to observed staining clustering. The STZ + Sm group demonstrated a significant increase in entropy for Cx43 (Fig. 3) and a trend toward higher entropy for AQP4 (AQP4 entropy in the STZ group = 4.3 [3.9;4.6], in the STZ + Sm group = 4.8 [4.6;4.9], $p = 0.07$). Overall, changes in AQP4 and Cx43 were unidirectional across all groups.

Semaglutide reduces STZ-induced hypothalamic neuronal damage

Administration of semaglutide partially mitigated STZ-induced neuronal damage in the hypothalamus (Figs 2, 3). Neuron density in the hypothalamic ventromedial nucleus was significantly reduced in the STZ-treated group compared to controls, while the STZ + Sm group showed no difference from controls in neuronal count.

In the control group, Cas3+ neurons were sparse, with Cas3+ nuclei accounting for 5.9% of total nuclei in the field of view. Notably, increased activated caspase-3 levels are reported in literature not only during apoptosis, but also during glial cell activation (Aras et al. 2022).

STZ-treated animals exhibited intense Cas3 staining in both NeuN-positive neuronal nuclei and glial cell nuclei. The proportion of Cas3-positive cells significantly increased (to 39.5%) in the ventromedial nucleus of the STZ group compared to controls, suggesting activation of apoptotic cascades. Semaglutide treatment reduced the proportion of Cas3+ nuclei.

Discussion

Intraventricular administration of STZ caused significant damage to ventricular lining, circumventricular organs, and particularly tanycytes of the third ventricle, while inducing neuronal death in the ventromedial hypothalamic nucleus. Ventricular wall remodeling by scar-forming astrocytes and reactive glial changes were accompanied by disrupted Cx43 and AQP4 distribution patterns in the ventromedial hypothalamic nucleus. Other studies demonstrate that intraventricular streptozotocin administration reproduces many pathobiochemical and morphological features of AD. Morphological examinations in animals receiving intraventricular STZ injections reveal neurodegeneration, ventricular wall damage, white matter lesions, and β-amyloid deposition (Grieb 2016; Roy et al. 2022; Li et al. 2020). For instance, 4 weeks post-STZ intraventricular administration, we observed increased proinflammatory cytokines, astrocyte and microglial activation, β-amyloid accumulation, and tau protein hyperphosphorylation (Fan et al. 2022). Notably, damage to circumventricular organs (Zhang et al. 2024), including STZ-induced degeneration of the subcommissural organ demonstrated in our study, may affect neurogenesis, with such impairments being observed in other AD models following STZ administration (Masai et al. 2024).

Apparently, one of the important consequences of STZ administration is persistent disturbances in cerebrospinal fluid dynamics in the brain, as evidenced by ventricular enlargement in animals. In patients with AD at different stages of cognitive impairment, brain ventricular enlargement is accompanied by periventricular edema, accumulation of protein aggregates, and reactive gliosis of the ventricular ependymal layer (Liang et al. 2023; Zhang et al. 2023; Todd et al. 2018), which aligns with our findings.

The observed replacement of ependymal lining by astrocytes following STZ-induced damage is consistent with data obtained from hyh strain hydrocephalic mice (Roales-Buján et al. 2012). Notably, astrocytes demonstrate partial ability to restore the functional integrity of the ependymal barrier between cerebrospinal fluid and brain parenchyma.

The identified tanycyte damage may also contribute to Alzheimer's pathology, as previous studies have shown that impairment of their barrier functions disrupts central-peripheral metabolic control, causes glucose intolerance, induces insulin-resistant states, and leads to cognitive deficits (Raikwar et al. 2017; Duquenne et al. 2024). These findings should be considered when evaluating the hypothesis of AD pathogenesis as "type 3 diabetes".

As shown in our previous studies, early tanycyte damage represents a characteristic feature of the streptozotocin-induced AD model (Stavrovskaya et al. 2019; Voronkov et al. 2021). Recent studies have demonstrated degradation of tanycyte processes in AD patients and their involvement in the transport and utilization of pathological tau protein from cerebrospinal fluid to capillaries (Sauvé et al. 2022). According to the hypothesis proposed by Fabian-Fine et al. (2024), tanycytes form AQP4-associated channels that play a key role in the clearance of pathological proteins, including β-amyloid; moreover, the scientists suggests that β-amyloid normally functions to maintain the stability of these channels. Regarding the relationship between pathological tau protein and AQP4, although tau is primarily degraded intracellularly, it can also be released into the extracellular space. For instance, it has been demonstrated that *Aqp4* gene deletion causes tau accumulation following traumatic brain injury (Iliff et al. 2014). It remains unclear to what extent these pathological protein aggregates disrupt AQP4 localization (Zeppenfeld et al. 2017), versus how much inflammatory processes and astrocyte dysfunction contribute to impaired clearance and secondary accumulation of β-amyloid and tau in AD (Smith et al. 2019).

It is known that the expression and localization of AQP4 on astrocytic endfeet change during neuroinflammation in models of neurodegenerative diseases (Salman et al. 2022). Studies on human postmortem material have shown that AD and aging are associated with disrupted AQP4 localization, while preserved perivascular localization of the protein correlates with the absence of cognitive impairment in old age (Zeppenfeld et al. 2017; Valenza et al. 2020). Astroglial dystrophy, disruption of glial networks, and ionic homeostasis disturbances during aging lead to synaptic dysfunction (Popov et al. 2021), further highlighting astrocytes' critical role in age-associated diseases. Our findings of glial activation and ependymal lining impairment in cerebral ventricles under STZ exposure align with previously reported increases in GFAP and S100b glial markers in cerebrospinal fluid and blood in this model, indicating blood-brain barrier and blood-CSF barrier dysfunction (Biasibetti et al. 2017). A recent study demonstrated that intraventricular STZ administration increases AQP4 and Cx43 expression by Western blot analysis, accompanied by reduced hippocampal glucose uptake at 4 weeks post-injection (Gayger-Dias et al. 2024), reflecting early tissue barrier impairments. We hypothesize that the observed decrease in AQP4 expression is associated with the prolonged period following STZ administration, reflecting later stages of pathological changes and significant damage to interglial and

gliovascular contacts. Previous studies have demonstrated that the localization, expression, and functions of AQP4 and Cx43 are interdependent, and disruption of their normal distribution affects tissue edema development and increases BBB permeability (Cibelli et al. 2021), which supports our hypothesis.

In this study, semaglutide reduced reactive astrogliosis, alleviated hydrocephalus manifestations, and normalized the distribution and levels of AQP4 and Cx43. We propose this effect is linked to semaglutide which previously demonstrated anti-inflammatory properties. For instance, in a middle cerebral artery occlusion model, semaglutide induced astrocyte conversion from pro-inflammatory to anti-inflammatory phenotypes (Zhang et al. 2022). Another GLP-1 analog, exenatide-4, reduced microglial activation and astrogliosis in transgenic AD models (Park et al. 2021). The neuroprotective properties of GLP-1 receptor agonists, consistent with our findings, have been repeatedly documente – they restore neurovascular interactions and cerebral microcirculation in metabolic syndrome models (Estato et al. 2025), and normalize AQP4 distribution in reactive astrocytes in AD models (Sasaki et al. 2024). Studies in AD models have also demonstrated reduced amyloid aggregation in various brain regions (Teixeira et al. 2025) and vasoprotective effects (Kelly et al. 2015) under the influence of GLP-1 receptor agonists. Several studies have additionally shown that GLP-1 agonists reduce intracranial pressure and CSF secretion (Grech et al. 2024), likely by affecting the choroid plexus epithelium, which may serve as an additional neuroprotective factor in the STZ model combining neurodegeneration with CSF dynamics disturbances.

These findings align with the effects of semaglutide observed in the study, which, beyond reducing astroglial activation and normalizing AQP4 and Cx43 distribution, contributed to decreased caspase-3 activation and reduced neuronal damage in the ventromedial nucleus of the hypothalamus.

Conclusion

Intraventricular administration of streptozotocin (3 mg/kg, single bilateral injection) induces not only neuronal damage but also reactive astroglial changes, pronounced tanycyte degeneration, disruption of the ependymal lining in the third and lateral ventricles, astrocytic dysfunction, and altered distribution of aquaporin-4 and connexin-43 in hypothalamic structures. These findings highlight the importance of cerebrospinal fluid metabolism disturbances, interstitial fluid imbalance, and damage to CSF dynamics-associated cell populations in modeling AD-type pathology.

Administration of the GLP-1 receptor agonist semaglutide (0.1 mg/kg, started 5 days after streptozocin administration, 16 injections every other day) reduces streptozotocin-induced astrogliosis, normalizes aquaporin-4 and connexin-43 distribution patterns in hypothalamic structures, decreases neuronal loss, and inhibits caspase-3 activation in the ventromedial hypothalamic nucleus.

Additional Information

Conflict of interest

The authors declare the absence of a conflict of interests.

Funding

The study was supported by the grant from the Ministry of Higher Education and Science of the Russian Federation for conducting major scientific projects in priority areas of scientific and technological development (Project No. 075-15-2024-638).

Ethics statement

All animal procedures were performed in accordance with Recommendation No. 33 of the Council of the Eurasian Economic Commission dated November 14, 2023 On Guidelines for Handling Laboratory (Experimental) Animals in Preclinical (Non-Clinical) Studies, as well as The Rules for Handling Laboratory Rodents and Rabbits (State standard GOST 33216-2014).

The study protocol was approved by the Local Ethics Committee of the Federal State Budgetary Scientific Institution Research Center of Neurology and Neurosurgery (Approval No. 2-2/25 dated February 17, 2025).

Data availability

All of the data that support the findings of this study are available in the main text.

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