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Ras Homolog Family Member A Regulates Interleukin-6 Expression in Streptozotocin-Pretreated Mice with Relevance to Alzheimer's Disease-Related Inflammation

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Abstract

Background and objective: Alzheimer's disease (AD) is a slowly worsening brain disorder linked to ongoing inflammation, with interleukin-6 (IL-6) playing a significant role in its progression. Ras Homolog Family Member A (RhoA) regulates inflammatory signaling and may influence IL-6 expression in AD. This research aimed to investigate the impact of RhoA inhibition on IL-6 expression and neuropathology in a streptozotocin (STZ)-induced AD mouse model.

Methods: A total of 15 male Swiss albino mice, aged 8–9 weeks and weighing 25–30 g, were randomly assigned into three groups (n = 5 per group): Control (control), STZ-pretreated (diabetes-associated cognitive impairment like Alzheimer's diseasemodel), and Y-27632+STZ (RhoA inhibitor-treated). The treatment group received 5 mg/kg Y-27632 before STZ administration. ELISA measured IL-6, amyloid beta 42 (Aβ42), and tau levels in brain and serum. Histopathological analysis assessed neuroinflammation and neuronal damage.

Results: STZ significantly increased Aβ42, tau, and IL-6 levels ($P < 0.05$). Y-27632 treatment reduced these markers, indicating neuroprotection. Histological analysis revealed severe neuroinflammation and neuronal damage in the STZ group, while Y-27632 reduced inflammatory cell infiltration and brain injury scores ($P < 0.05$).

Conclusion: RhoA inhibition attenuates IL-6-mediated neuroinflammation, decreases tau and amyloid plaque pathology, and mitigates neurodegeneration in AD. Targeting RhoA may offer a promising therapeutic approach for AD management.

Keywords: Alzheimer's disease, RhoA, IL-6, Amyloid beta 42, Tau protein, Streptozotocin.

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Introduction

Alzheimer's disease (AD) is a progressive degenerative brain condition that slowly impairmemory, behavior, and thinking, eventually leading to dementia. It is the major cause of dementia among elderly and is linked to brain inflammation, problems with energy production in cells, damage caused by harmful free radicals, and damage to the blood-brain barrier (BBB) (1). Pathological hallmarks include amyloid-β accumulation, tau hyperphosphorylation, reduced acetylcholine levels, and impaired cerebral blood flow (2). AD is categorized into Initial-onset, which develops before age 65 and is less common, making up about 5-10% of cases, and delayed-onset, which occurs at 65 or older (3). Inherited traits like genetic mutations in PSEN1, APP, PSEN2, and the Apolipoprotein E epsilon 4 allele (APOE ε4) allele increase risk, while environmental influences like chronic stress and vascular health also contribute (4). The activation of glial cells and the secretion of inflammatory signaling molecules such as IL-1β, IL-6, and TNF-α are the primary mechanisms by which neuroinflammation is initiated in the progression of Alzheimer's disease (5). The breakdown of the BBB further exacerbates neuroinflammation by allowing toxic substances into the brain (6). Microglia, the brain's immune cells, respond to amyloid-β and tau aggregates, perpetuating inflammation and neuronal damage. Mechanisms such as necroptosis and apoptosis exacerbate neuronal degeneration and cognitive deterioration (7, 8). Interleukin-6 (IL-6) is a multifunctional signaling molecule that plays a role in immune responses and inflammation. Increased IL-6 concentrations in AD are associated with increased neuroinflammation, neuronal death, and BBB permeability (9, 10). IL-6 signaling, particularly via the STAT3 pathway, contributes to the neurodegenerative process and may affect the cyclic GMP-AMP synthase–stimulator of interferon genes pathway (cGAS-STING), a critical innate immune signaling mechanism that detects cytosolic DNA and triggers an antiviral and inflammatory response, thereby exacerbating AD pathology (11).

Inhibition of IL-6 has shown potential in reducing amyloid plaque accumulation and improving cognitive function in AD models (12). RhoA is a type of small GTP-binding protein regulating cellular processes like growth, migration, and survival. It serves a pivotal function in cytoskeletal dynamics and neuronal integrity (13). RhoA activation in microglia contributes to synaptic loss and beta-amyloid plaque formation in Alzheimer’s disease through the Src signaling pathway, which consists of non-receptor tyrosine kinases. This pathway regulates immune and structural responses in cells, and when over activated in the brain, it promotes inflammation and amyloid buildup,

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worsening disease progression (14). Additionally, RhoA regulates IL-6 synthesis through the triggering of transcription factors such as NF-Kb (15). Inhibition of RhoA/ROCK signaling significantly reduces IL-6 levels, suggesting a therapeutic target for controlling chronic neuroinflammation in AD (16). Targeting this pathway could mitigate microglial dysregulation and reduce inflammation-driven neurodegeneration (17). This research investigates the impacts of RhoA inhibition on IL-6 expression and neuropathology in a streptozotocin (STZ)-induced diabetes-associated cognitive impairment like Alzheimer's disease model.

Materials and methods

Study Design

In this study, the 15 male Swiss albino mice, were divided to three groups using the simple random sample technique with a sample size of five. The first group functioned as the negative group of controls, while the second group served as the positive group of controls (STZ). The third group served as treatment group (Y-27632 +STZ). The research was performed in the animal facility of Hawler Medical University. Data were collected from 3 December 2024 to 31 December 2024.

Animals

In this study we have used Swiss albino male mice with weights ranging from 25 to 30 grams. The mice were aged 8 to 9 weeks. College of Pharmacy, Hawler Medical University, Iraq complies with ethical guidelines for animal care and regulation and has received clearance from the regional animal experimentation ethical committee. The inclusion criteria were limited to male mice weighing 25–30 g; female mice and mice weighing more than 30 g were excluded. The animals were housed in a sterile environment under controlled conditions with a 12-hour light/dark cycle, maintained at a temperature of 24°C and a relative humidity of 55% ± 5%. Food and water were provided twice a day. Pure drinking water was supplied ad libitum via a designated nipple. Prior to the start of the trials, all subjects experienced a 7-day acclimatization phase to adapt to the experimental circumstances. Animals were categorized into three groups: the control group (receiving only saline injections), the vehicle group (receiving streptozotocin injections), and the treatment group (pretreated with Y-27632 followed by streptozotocin, Y-27632+STZ). Each group consisted of five mice, housed in cages with no more than five individuals per group, with environmental enrichment provided.

Materials

Streptozotocin (STZ; sourced from Sigma-Aldrich, Merck KGaA, Darmstadt, Germany), is the agent utilized to produce diabetes mellitus (18). A citrate

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buffer is utilized for the manufacture of Streptozotocin, the pH of the mixture was changed to 4.5 by adding hydrochloric acid (HCl) to the solvent after dissolving 0.84 grams of citric acid and 6.07 grams of sodium citrate in 200 ml of distilled water. Y-27632, also known as (R)-(+)-trans-4-(1-aminoethyl)-N-(4-pyridyl) cyclohexanecarboxamide dihydrochloride, Solarbio Science & Technology Co., Ltd. China. A GlucoNavii blood glucose meter was used for the purpose of monitoring the blood glucose levels.

Animal Experiments

At the start of the experiment, three groups of mice sham (control), streptozotocin (STZ), and Y-27632 + STZ treatment were subjected to a fasting period of approximately 6–9 hours, during which they had unlimited access to water. Prior to the administration of injections, fasting blood glucose levels and body weights were recorded for each mouse. For the preparation of STZ, 11.25 mg of it was measured into a glass tube covered with aluminum foil and placed in a container filled with ice. Citrate buffer (pH 4.5) was then added to the glass tube to dissolve the STZ.

In the control group, mice received an intraperitoneal injection of citrate buffer (pH 4.5)[19] In the STZ group, a single dose of STZ was administered at 45 mg/kg body weight to induce diabetes mellitus in the experimental animals (20). In the treatment group, 5 mg/kg of RhoA inhibitor (Y-27632), was injected intraperitoneally. This dose was chosen based on previous research (21, 22). After a 30-minute interval, the (Y-27632 + STZ) group received an injection of STZ. Following STZ administration, the animals exhibited signs of hypoglycemia. To alleviate this condition, a 5% (w/v) glucose solution was provided to the animals for one day.

Following the STZ injection, the mice's fasting blood sugar levels were assessed from the vein in the tail within one week to verify the induction of diabetes. More than 70% of the mice had blood glucose concentration more than 200 mg/dL (11.1 mmol/L). These results demonstrated that the STZ and Y-27632+ STZ groups were at the early stages of diabetes. In diabetic mice, fasting blood glucose levels was defined as exceeding 11.1 mmol/L (23).

After 21 days (24), all mice were anesthetized intraperitoneally with 25 mg/kg of xylazine and 75 mg/kg of ketamine (20). Blood was obtained from the vena cava;serum was separated by centrifuging the samples at 2000–3000 rpm for 20 minutes, and stored it in Eppendorf tubes at -20°C for subsequent ELISA testing. The brains of the mice were divided into two sections: one was immobilized in a 10% formalin solution for histopathological examination, and the other was placed in an Eppendorf tube, mixed with a few

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drops of phosphate buffer (pH 7.4), and homogenized with an Intelligent Ultrasonic Processor. After centrifuging the homogenate to remove the supernatant, we moved it to an Eppendorf tube and preserved it at -20°C for further ELISA analysis.

Biochemical Determination

Blood sugar levels of all experimental animals were monitored prior to the initiation of the procedure. Fasting blood sugar was routinely assessed until the onset of diabetes was evident. Mice were classified as diabetic if fasting blood sugar levels reached or exceeded 11.11 mmol/L. The concentrations of glucose were determined using a GlucoNavii blood glucose meter, and blood samples (0.5–1 µL) were taken from the tail capillaries.

ELISA

Tau and Aβ42 levels were measured in brain tissue, while IL-6 levels were assessed in brain tissue and serum across all groups of animals. For the tests, the Mouse Interleukin-6 (IL-6) ELISA Kit (Cat. No. SL0326Mo), the Mouse Tau Proteins (TAU) ELISA Kit (Cat. No. SL0868Mo), and the Mouse Amyloid Beta Peptide 1-42 (Aβ1-42) ELISA Kit (Cat. No. SL0040Mo) were used. All kits were obtained from SunLong Biotech Co., Ltd. (Hangzhou, China). Absorbance was measured at 450 nm in accordance with the manufacturer's guidelines. IL-6 levels were reported in ng/L, while Tau and Aβ42 levels were expressed in pg/mL.

Histology

The brain was preserved overnight in a 10% formaldehyde solution prior to dehydration and embedding in paraffin. To stain micrometer-sized fragments, hematoxylin and eosin were employed. A revised assessment method was employed to objectively assess brain damage using a blinded study design (25). Consisting of a mixture of inflammatory cells, edema, scattered pyknosis (degeneration), myeloid gliosis, necrosis (irreversible damage), and vascular congestion. The aforementioned criteria were evaluated and classified as mild, moderate, and severe, (0) normal histology; (1) mild involvement (<25%); (2) moderate involvement (25–50%); and (3) severe involvement (>50% of the affected tissues). The mean value was determined by analyzing five randomly selected regions of each tissue sample. The histopathology score was calculated by adding up all six criteria. This part was performed in the histology lab of the Par Hospital.

Statistical Analysis

The findings are presented as mean values with standard error of the mean (SEM). Nonparametric tests (Mann-Whitney) were implemented to evaluate the data. The entire number of mice in each group is denoted by "n".

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A P-value of less than 0.05 was used to be regarded as statistically significant. SPSS (IBM Corp., Armonk, N.Y., USA) (version 26) software was employed to conduct all analyses.

Ethical approval

Ethical approval was obtained from the College of Health Sciences / Hawler Medical University. Ethical number: Sc.E.C.11B1

RESULTS

Brain Amyloid Levels

Brain amyloid levels were assessed in the Control, STZ, and Y-27632 -treated groups. The results indicate a substantial increase in amyloid accumulation following STZ administration, while RHO treatment reduced amyloid levels, Control 65.1 ± 20.3, STZ 134.1 ± 84.2, and Y-27632 58.2 ± 18.9. The STZ group exhibited a significant increase in brain amyloid deposition, while Y-27632 treatment mitigated this effect, suggesting a neuroprotective role “Figure 1”

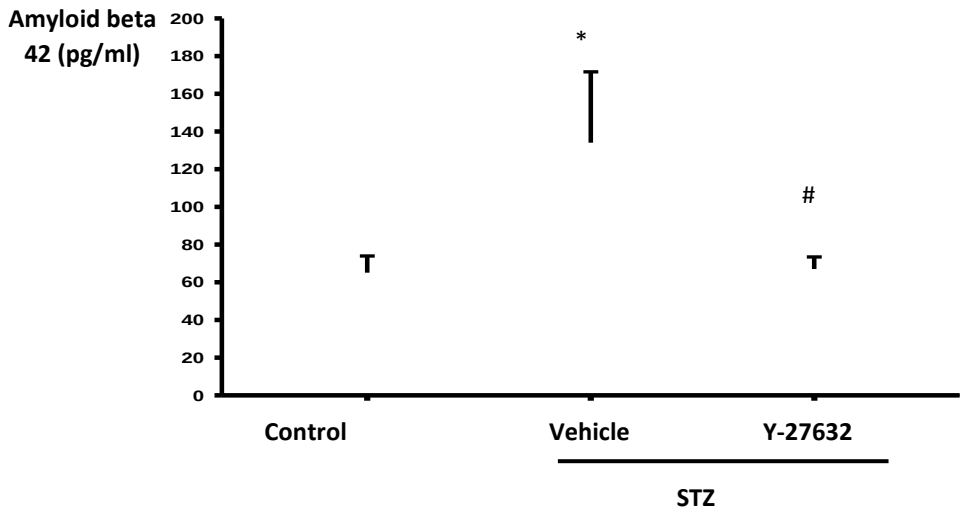

Figure 1. ELISA was utilized to measure the concentrations of Amyloid Beta 42 (Aβ42) in the brains of mice suffering from diabetes-associated cognitive impairment like Alzheimer’s disease. The data are presented as mean ± SEM (Control: n = 5, Vehicle: n = 5, Y-27632: n = 5). The vehicle-treated group exhibited a substantial elevation in Aβ42 levels relative to the control group (*P = 0.032 vs. control). #: Indicate significant vehicle versus Y-27632 #P = 0.016

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Brain Tau Levels

Tau protein levels were significantly higher in STZ-treated animals compared to control. However, Y-27632 administration reduced tau levels in some instances. The mean values were, control 305.9 ± 33.7, STZ 565.9 ± 251.4, and Y-27632 347.0 ± 26.8. The STZ group showed a notable increase in tau protein aggregation, a hallmark of neurodegeneration. Y-27632 treatment resulted in a decrease, though not to control levels, indicating partial mitigation “Figure 2”

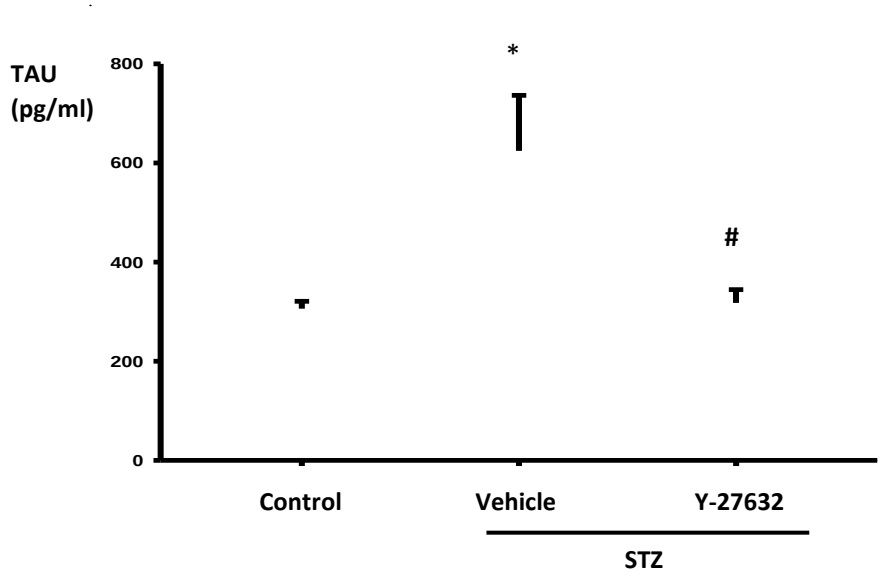

Figure 2. ELISA was employed to measure the concentrations of Microtubule-Associated Protein TAU f in the brains of mice suffering from diabetes-associated cognitive impairment like Alzheimer's disease. The results are presented as mean± SEM (control: n = 5, vehicle: n = 5, Y-27632: n = 5). The vehicle-treated group exhibited a substantial elevation in TAU levels compared to the control group (*P = 0.008 vs. control), while the Y-27632-treated group showed a significant reduction relative to the vehicle group (#P = 0.016 vs. vehicle)

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Brain IL-6 Levels

IL-6, a key inflammatory cytokine, was markedly elevated in the STZ group. The mean levels were: Control 67.8 ±10.1, STZ 158.1 ± 26.7, and Y-27632 67.8 ± 22.3. STZ therapy produced an effective inflammatory response, as indicated by elevated Levels of IL-6, although Y-27632 administration reduced IL-6 expression, suggesting an anti-inflammatory effect "Figure 3".

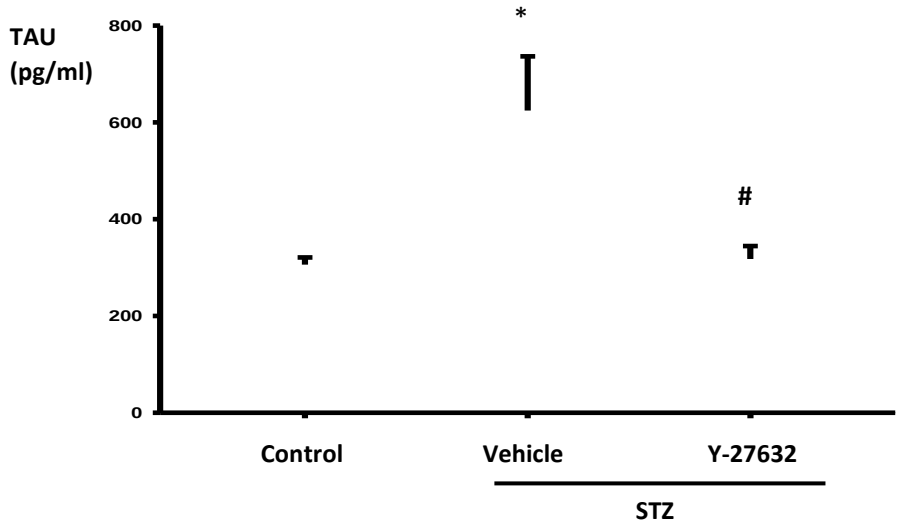

Figure 3. ELISA was performed to quantify interleukin-6 (IL-6) levels in the brains of mice suffering from Alzheimer's disease. Data are expressed as mean ± SEM (control: n = 5; vehicle: n = 5; Y-27632 + STZ: n = 5). IL-6 concentrations were markedly elevated in the vehicle-treated group Compared to the control and Y-27632 + STZ groups (P = 0.029) versus control). *Indicates significant

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Serum IL-6 Levels

Serum IL-6 levels were also evaluated to assess systemic inflammation. The values were: Control 59.0 ± 2.3, STZ 83.1 ± 25.4, and Y-27632 53.0 ± 5.1. The STZ group showed elevated IL-6 levels in the serum, indicating systemic inflammation. Y-27632 treatment successfully restored IL-6 levels close to Control values “Figure 4”.

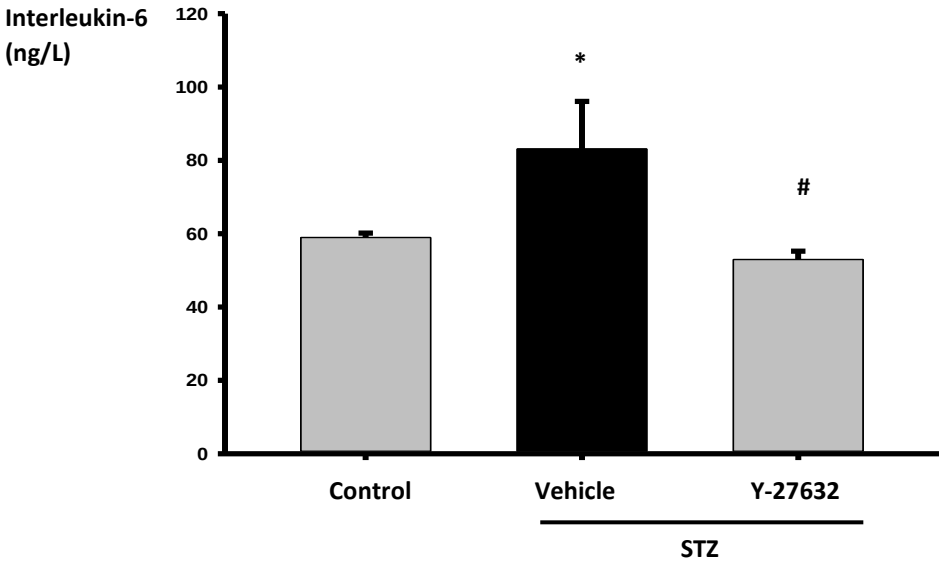

Figure 4. ELISA was conducted to measure interleukin-6 (IL-6) concentrations in the blood of mice suffering from diabetes-associated cognitive impairment like Alzheimer's disease. Data are presented as mean ± SEM (control: n = 5, vehicle: n = 5, Y-27632: n = 5). There was significant change in IL-6 levels, as the difference was observed between the vehicle-treated and control groups (P = 0.05)

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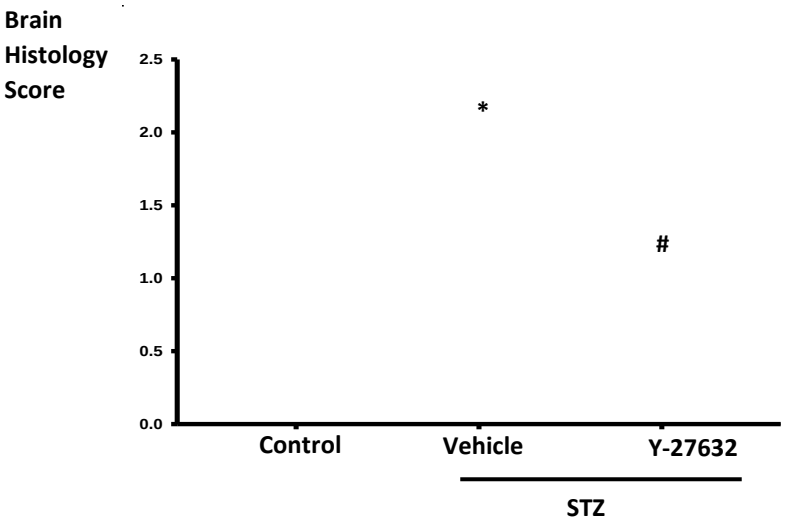
Histological Alterations in the Brain of the Alzheimer's Disease Mouse Model

Histological analysis of Alzheimer's disease-induced mouse brains revealed significant neurodegenerative and inflammatory changes. This included infiltration of inflammatory cells (lymphocytes, microglia, and neutrophils), edema indicating blood-brain barrier disruption, and scattered pyknosis as a sign of neuronal apoptosis. Myeloid gliosis, necrosis, and vascular congestion were also observed, reflecting immune activation, tissue damage, and impaired cerebral circulation. The induction of diabetes-associated cognitive impairment like ADvia streptozotocin (STZ) injection resulted in a moderate degree of brain injury (25–50%), with a significantly higher histological injury score in the AD group (2.00 ± 0.00) compared to the control group (0.00 ± 0.00), the difference was significant (P = 0.008). However, administration of Y-27632, effectively mitigated histological damage, reducing the histological score to 1.00 ± 0.00, (P = 0.008) "Figure 5". These results suggest that Y-27632 protects neurons by easing the damage caused by STZ and lowering the changes that come with Alzheimer's disease.

(A)



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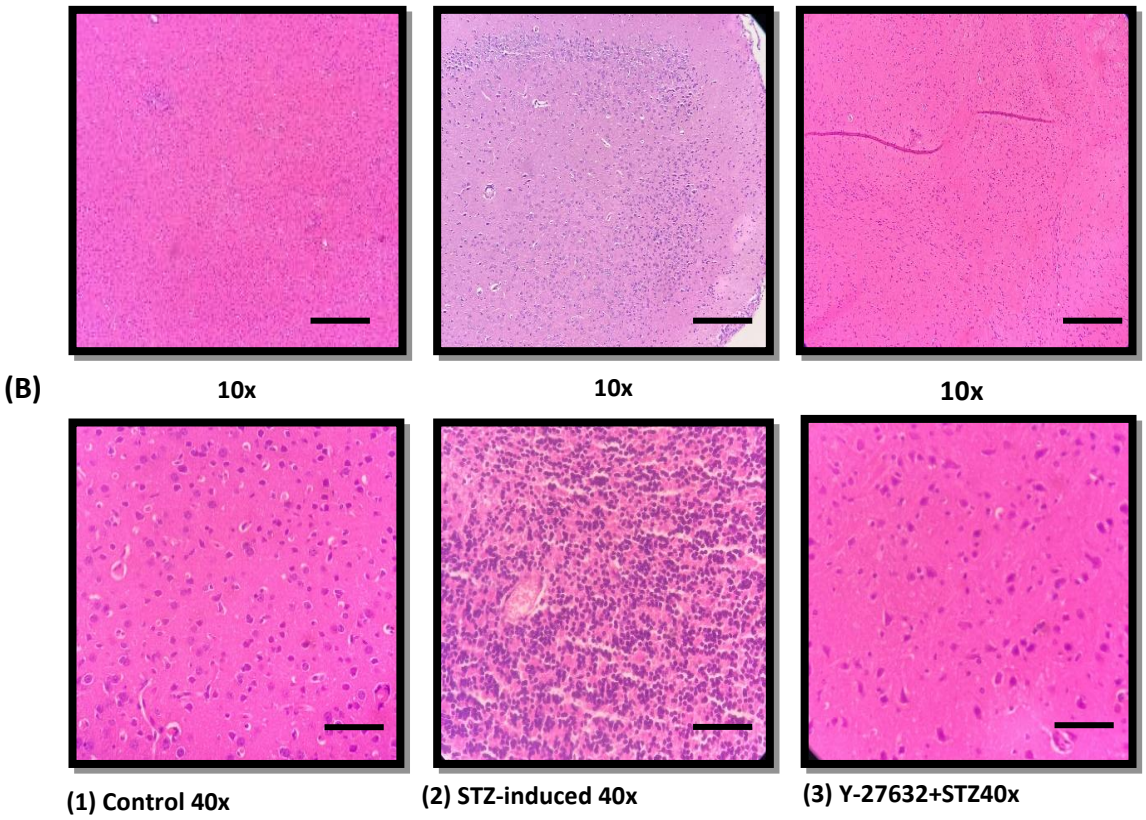

Figure 5. In Alzheimer's disease, RhoA affects neuronal degeneration. (A) are brain histology scores. (B) Representative hematoxylin and eosin (H&E)-stained coronal brain sections from each experimental group (Control, STZ and Y-27632+STZ) are shown at 10× and 40× magnifications. Scale bar = 50 µm. Prior to streptozotocin-induced diabetes mellitus induction, mice were given either STZ (vehicle) or a RhoA inhibitor (Y-27632), Negative controls were performed using control animals. *P = 0.008 when compared to Control; #P = 0.008 when compared to Y-27632 + STZ. The data are shown as mean ± SEM, and the sample size is 5

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Discussion

This study provides evidence that RhoA inhibition via Y-27632 mitigates neuroinflammation in a streptozotocin (STZ)-induced diabetes-associated cognitive impairment like Alzheimer's disease (AD) by reducing IL-6 expression and neurodegenerative markers such as amyloid beta 42 (Aβ42) and tau protein. Neuroinflammation is a key contributor to AD pathology, primarily driven by pro-inflammatory cytokines, including IL-6, which exacerbates neuronal damage and promotes disease progression (9, 10).

Our findings support previous research indicating that RhoA is essential for inflammatory pathways, such as IL-6 regulation through NF-κB activation (15). A related study using the same streptozotocin-induced mouse model found that inhibition of Rac1, another Rho-family GTPase, similarly reduced TNF-α-mediated neuroinflammation, tau, and amyloid beta 42 pathology, supporting a broader role for Rho-family GTPases in AD-related neuroinflammation (27). A substantial elevation in IL-6 concentrations was observed in both the brain and serum, indicating systemic and neuroinflammation (Figures 3 and 4). These findings align with studies demonstrating that STZ administration triggers glial activation and cytokine release, contributing to neurodegeneration (23).

However, Y-27632 administration effectively reduced IL-6 expression, suggesting that RhoA inhibition modulates inflammatory responses, potentially through disruption of NF-κB and STAT3 signaling pathways (11). Furthermore, amyloid and tau pathologies, hallmarks of AD, were markedly increased in STZ-treated mice, confirming the neurotoxic impacts of STZ-induced insulin resistance and oxidative stress (12).

Notably, Y-27632 treatment led to a reduction in Aβ42 and tau levels, reinforcing the hypothesis that RhoA inhibition exerts neuroprotective effects by reducing amyloid plaque formation and tau hyperphosphorylation (Figures 2 and 3). This is consistent with studies highlighting the role of RhoA in cytoskeletal destabilization and synaptic loss (13, 26). Histopathological analysis revealed severe neuronal damage, vascular congestion, and inflammatory cell infiltration in the STZ group, which were significantly alleviated with RhoA inhibition (Figure 5).

These results align with previous reports demonstrating that RhoA/ROCK inhibitors reduce neuroinflammation and improve neuronal survival in neurodegenerative models 16,17. Given that RhoA is involved in microglial activation, our findings suggest that targeting this pathway may attenuate neuroinflammation and associated neuronal loss in AD (7, 8).

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Despite the promising results, this study has certain limitations. Age and gender were not analyzed separately, although both are known to influence the progression of Alzheimer's disease and associated inflammatory responses. Females may exhibit greater susceptibility to amyloid and tau pathology, while aging is associated with elevated baseline inflammation, potentially affecting disease severity and treatment outcomes. Future research should incorporate both sexes and a range of age groups to better evaluate the impact of RhoA inhibition. Additionally, the long-term effects and underlying molecular mechanisms warrant further investigation.

Conclusion

This study emphasizes the importance of inhibiting RhoA as a therapeutic approach for AD. By reducing IL-6 expression, amyloid burden, and tau pathology, Y-27632 exhibits neuroprotective effects that warrant further investigation. Future studies should evaluate cognitive outcomes and assess the therapeutic efficacy of RhoA inhibitors in human AD models.

Competing interest

The authors declare that they have no competing interests.

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