NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

RESEARCH ARTICLE

Arch Neuropsychiatry 2023;60:68–72
https://doi.org/10.29399/npa.28112

The Effect of Lidocaine on the Experimental Model of Streptozotocin-Induced Alzheimer's Disease

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ABSTRACT

Introduction: Alzheimer's disease (AD) is a neurodegenerative disease caused by the accumulation of amyloid plaques in the cerebral cortex and hippocampus. In this study, the effects of local anesthetic lidocaine on neurodegeneration markers and memory were investigated for the first time in streptozotocin-induced rat AD model.

Methods: Streptozotocin (STZ) was administered intracerebroventricularly (ICV) into Wistar rats to develop AD model. For lidocaine group (n=14), lidocaine (5 mg/kg) was administered intraperitoneally (IP) in addition to STZ injection. Control group animals (n=9) were treated with saline for 21 days. Morris Water Maze (MWM) test was performed to evaluate memory after the injections were completed. Also, the serum levels of TAR DNA-binding protein-43 (TDP-43), amyloid precursor protein (APP), β-secretase 1, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), response element binding protein (CREB), c-FOS were measured using ELISA test and compared between groups.

Results: Lidocaine group animals showed lower escape latency and time in quadrant scores in MWM inferring better memory performance. Furthermore, lidocaine administration caused a significant decline in TDP-43 levels. However, the expression of APP and β-secretase were significantly higher in AD and lidocaine groups compared to control group. Moreover, lidocaine group markedly had higher serum NGF, BDNF, CREB, and c-FOS levels compared to those in the AD group.

Conclusion: In addition to neuroprotective effects in STZ-induced AD model, Lidocaine also appears to improve memory. This effect might be associated with increased levels of several growth factors and associated intracellular molecules. The therapeutic role of lidocaine in the pathophysiology of AD should be studied in the future.

Keywords: Alzheimer's disease, animal model, lidocaine, local anesthetic, memory, neuroprotection

Cite this article as: Tamam Y, Yokuş B, Tamam C, Yüceer H, Karahan S, Em B, et al. The Effect of Lidocaine on the Experimental Model of Streptozotocin-Induced Alzheimer's Disease. Arch Neuropsychiatry 2023;60:68–72.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease that develops as a result of accumulation of amyloid plaques in the cerebral cortex and hippocampus. It is characterized by glial cell activation-mediated neuroinflammation, oxidative damage and cholinergic neuron loss (1). Decreased cholinergic activity is manifested by loss of sensation, movement, learning, and memory (2).

Amyloid precursor protein (APP) is a transmembrane protein found in the brains of healthy individuals as well as in people with AD. Amyloid precursor protein forms neurotoxic β-amyloid-protein (Aβ). This plays a key role in the pathophysiology of AD (3). It is argued that if the accumulated Aβ is the cause of the pathological changes in the brain in AD. Other views suggest that clinical manifestations of the disease are correlated with tau deposition, and amyloid deposition which is an epiphenomenon (4).

While there is no definitive treatment for AD, the drugs used provide results only in terms of symptomatic treatment. On the other hand, drugs are insufficient to improve the pathophysiology of the disease. Therefore, experimental AD models are created and new treatment options, effective on the prevention, onset and prognosis of the disease are emphasized (1,2).

Highlights

- **Lidocaine has been shown to improve memory and have a neuroprotective effect.**
- **This neuroprotective effect may be related to neuronal survival mechanisms.**
- **The level of many growth factors increases with lidocaine treatment.**
- **Lidocaine administration does not appear to reverse amyloid pathology.**

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Received: 25.01.2022, **Accepted:** 10.03.2022, **Available Online Date:** 18.02.2023

Streptozotocin (STZ), a glucosamine-nitrosurea compound used in experimental models of AD, is primarily an antineoplastic drug. Streptozotocin causes alkylation of DNA after entry into pancreatic β-cells. The agent is also used to induce experimental diabetes by reducing NAD+ and cellular ATP after alkylation. Intracerebroventricular administration of STZ in experimental animals has also been shown to disrupt brain glucose and energy metabolism, as in sporadic AD, and may lead to loss of cognitive functions such as memory and learning by damaging cholinergic transmission (5,6).

Lidocaine is a sodium channel blocker and it is used as an anti-arrhythmic and local anesthetic. In recent years, there are studies showing the neuroprotective effects of lidocaine (7–10). The effect of lidocaine on the nervous system occurs indirectly by reducing repetitive presynaptic stimulation, decreasing sympathetic activation, and decreasing the activity of nerves in the wide dynamic range stimulated by the sympathetic nervous system (11).

In this pilot study, the neuroprotective effects of lidocaine in STZ-induced AD rat model were questioned for the first time in the literature. To this end, the memory performance of the AD animals with or without lidocaine treatment was evaluated and compared with control group. Also, the serum levels of neurodegeneration markers such as TAR DNA-binding protein 43 (TDP-43), APP, β-secretase 1, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), cyclic AMP response element binding protein (CREB), and c-FOS were determined for both AD, lidocaine, and control groups.

METHODS

This study has been conducted at Dicle University Health Sciences Research and Application Center. Ethical approval for the study was obtained from the Dicle University Animal Experiments Local Ethics Committee (DÜHADEK: 2018-16) and the research continued based on the standards set out in the Helsinki Declaration.

Animals

Total of 30 male Wistar albino rats with an average weight of 250–300 grams were used. Experimental animals were obtained from Dicle University Health Sciences Research and Application Center (DÜSAM). The subjects were housed at room temperature (22±2°C) with free access to water and food in a room that was cycled for 12 hours dark and 12 hours light.

Before starting the applications, the weights of all rats were determined. The groups were divided into 3 groups as AD (n=7), lidocaine (n=14), and control (n=9). The body weight averages for each group were closest to each other. According to the experimental protocol, daily injections were administered at the same time each day. Thus, the injection stress that the animals exposed to was balanced and the experimental protocol was standardized for all groups.

Stereotaxic Surgery and ICV Injection of STZ

Rats were anesthetized intraperitoneally with 100 mg/kg ketamine (Richter Pharma AG, Australia), 8 mg/kg xylazine (Bayer, USA). After making sure that the animals were under anesthesia and their scalps with spontaneous movements were lost, they were shaved and made ready for the operation.

The stereotaxic coordinates of the lateral ventricle were determined through the Paxinos & Watson rat brain atlas (12). The lateral ventricular entry point was determined by going 0.8 mm posterior from the bregma, 1.4 mm lateral from the sagittal suture, and 4.8 mm vertically from the skull bone.

In order to create an AD rat model, the animals were fixed on the stereotaxic device (KOPF Apparatus, USA) by their ears and mouth so that the surface of the head was exactly parallel to the ground. The skull skin was cut with a scalpel to reach the bone structure, and the bone surface was cleaned to allow a clear view of the bregma. Starting from the bregma, which was accepted as the reference point, the part of the bone to be drilled was determined according to the previously determined coordinates and drilled with a micromotor drill without damaging the dura. Bilateral STZ (3 mg/kg) and artificial cerebrospinal fluid (CSF) (for control group) were applied from the punctured points with a Hamilton (5uL) injector. The injection was repeated 48 hours later (13). After the surgical procedure, recovery of the animals was observed for 14 days.

Lidocaine and Saline Treatments

Alongside the first ICV application to the animals in the control group, IP saline application was also performed for 21 days. The animals in the AD group were administered IP saline for 21 days along with the first ICV STZ application. The animals in the lidocaine group were administered IP lidocaine (5 mg/kg) for 7 days, together with the first ICV STZ application. The drugs were injected by dissolving in 1 ml of 0.9% saline, while the control group was only administered 1 ml of 0.9% saline solution. Fourteen days after the injections were completed, behavioral measurements were performed.

Morris Water Maze Test

Morris Water Maze Test (MWM) tank was used to test the animals' spatial learning and memory (14). Morris Water Maze is 40 cm high, 120 cm diameter, made of stainless steel, black and large circular pool. The temperature of the water was automatically maintained at 25±1°C. A 10 cm long square platform was placed 1 cm below the water levels. The water in the pool was opaque with a non-toxic black paint (Mixol concentrated colorant-black) to hide the platform. The data were obtained with the help of a camera connected to the video surveillance system fixed above the center of the pool, which is hypothetically divided into four sections as north, south, east and west.

Prior to the MWM test, rats in all groups were challenged to swim exercises for 3 consecutive days without a platform to acclimate to the environment. No visible markings were used at this stage. Morris Water Maze testing was started 14 days after administration/surgical procedures and was repeated four times a day for four days. Each rat was floated for 90 seconds to find the platform. During this time, rats that found the platform were allowed to stay on the platform for 20 seconds. Rats that could not find the platform within 90 seconds were retrieved and left on the platform and kept on it for 20 seconds. The time to reach the platform was analyzed by recording the time as percentage of time to find the platform with the video recording system (15).

On the 5th day, the platform in the MWM was removed and the rats were forced to swim for 5 min. In the acquisition trials, the time spent by the rats in the quarter region (target quadrant) with the platform was recorded and examined as percentage time after the platform was removed.

Obtaining Biological Materials

After the behavioral tests were completed, intracardiac blood was obtained from rats under ether anesthesia. Whole blood samples were centrifuged, and the sera were separated. The sera were kept in suitable conditions for further processing.

ELISA Studies

In line with the manufacturer's recommendations serum TDP-43, APP, β-secretase 1, NGF, BDNF, CREB, c-FOS levels were determined using

Table 1. Mean values (mean ± SD) of the time it took for animals to find the platform in the Morris water maze acquisition trials

Groups	Day 1 (s)	Day 2 (s)	Day 3 (s)	Day 4 (s)
Control	71.110±5.607	52.012±4.843	44.497±3.918	34.684±1.252
AD	72.057±3.198	66.717±2.912[a]	63.071±2.537[b]	57.85±1.538[b]
Lidocaine	72.995±2.935	59.572±3.634	49.425±2.536[c]	38.574±2.222[d]

[a]p<0.05 Compared with the control group.
[b]p<0.001 Compared with the control group.
[c]p<0.05 compared with Alzheimer's group.
[d]p<0.001 compared with Alzheimer's group.
One-way analysis of variance (ANOVA) was used in the calculations.
Post-hoc Tukey was used for multiple comparisons of the groups.

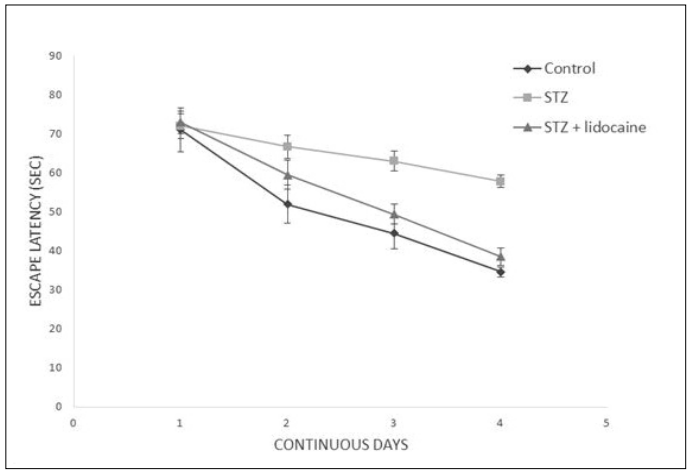

Figure 1. Plot (mean ± SD) of escape latency for animals to find the platform in the Morris water maze acquisition trials (a p<0.05 Compared with the control group. b p<0.001 Compared with the control group. c p<0.05 compared with Alzheimer's group.d p<0.001 compared with Alzheimer's group. One-way analysis of variance (ANOVA) was used in the calculations. Post-hoc Tukey was used for multiple comparisons of the groups).

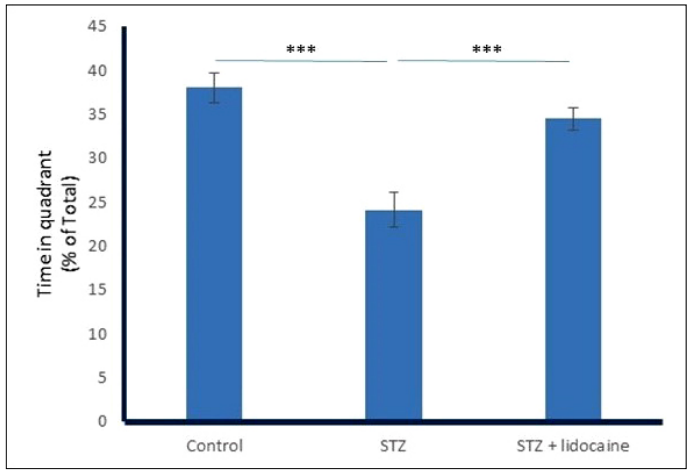

Figure 2. Plot of mean values (mean ± SD) of time spent in target quadrant during probe trial (a p<0.001 Compared with the control group. b p<0.001 compared with Alzheimer's group. One-way analysis of variance (ANOVA) was used in the calculations. Post-hoc Tukey was used for multiple comparisons of the groups).

commercial enzyme-linked immunosorbent assay (ELISA) kit (Sunred Biological Technology, Shanghai, China). Plates were read at 450 nm and results were expressed in pg/mL and ng/mL.

Statistics

SPSS 16.0 program was used for statistical evaluation. Through the analysis of variance (ANOVA) test it was determined if the difference between the means of the groups were significant. Post-hoc Tukey was used for multiple comparisons between the groups. The degree of significance of the test parameters was accepted as p<0.05 and the confidence interval as 95%.

RESULTS

Behavioral Assessments

During the study, the animals were weighed every two days while their body weights were examined both during the recovery period (14 days) and behavioral tests after surgery. No significant difference was observed between the groups in terms of the subjects' body weights (data not shown).

Table 2. Mean values (mean ± SD) of time spent in the target quadrant during the probe trial

Groups	Probe
Control	38.072±1.703
AD	24.134±1.956[a]
Lidocaine	34.525±1.280[b]

[a]p<0.001 Compared with the control group.
[b]p<0.001 compared with Alzheimer's group.
One-way analysis of variance (ANOVA) was used in the calculations.
Post-hoc Tukey was used for multiple comparisons of the groups.

The MWM test, which was carried out to examine the effects of lidocaine on spatial memory in animals in the STZ-induced experimental AD model, was analyzed by comparing the escape latency in all groups with the control group. There was no significant difference between the groups in terms of the time the animals found the platform on the first day during the acquisition trials. In acquisition trials performed 15 days after STZ injection, animals in the AD group showed a longer escape latency to find the hidden platform compared to the control group (p<0.001, Table 1, Figure 1). Animals administered lidocaine were found to exhibit a statistically shorter escape latency to find the hidden platform compared to animals in the AD group (p<0.001, Table 1, Figure 1).

In probe trials, a statistically significant decrease was observed in the AD group compared to the control group in terms of time spent in the target quadrant (p<0.001, Table 2, Figure 2). This decrease in the AD group was reversed with lidocaine administration and the time spent in the target quadrant increased statistically significantly compared to the AD group. (p<0.001, Table 2, Figure 2)

Biochemical Findings

The serum levels of the TDP-43, APP, β-secretase 1, NGF, BDNF, CREB, c-FOS were measured by ELISA to determine the neuroprotective effects of lidocaine (Figure 3). The levels of TPD-43 were significantly reduced with lidocaine treatment compared to AD group with only STZ injection (p=0.024). On the other hand, APP levels were significantly different between control and lidocaine groups (p=0.024). Similarly, β-secretase

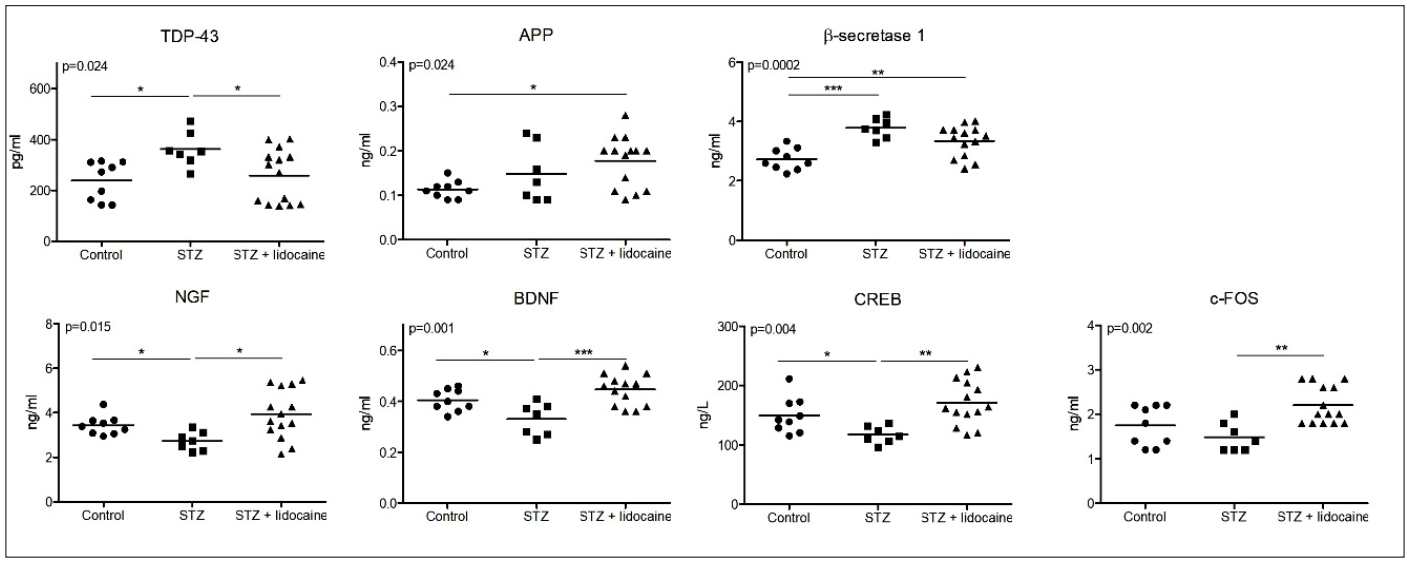

Figure 3. Serum levels of markers used to determine the neuroprotective effects of lidocaine (The p-values obtained by ANOVA are indicated at the top left of the panels. *p<0.05; **p<0.01; ***p<0.001).

1 levels were significantly increased in both AD and lidocaine groups compared to control group animals (p=0.0002). However, in the lidocaine group, the levels of NGF (p=0.015) and BDNF (p=0.001) as well as CREB (p=0.004) and c-FOS (p=0.002) were similar to those in the control group which confirms the neuroprotective impact of lidocaine treatment.

DISCUSSION

The present study preliminarily explored the neuroprotective effect of lidocaine in the experimental model of STZ-induced AD for the first time in the literature. Memory performance in MWM was found to be increased with lidocaine administration in rats with AD. Nonetheless, lidocaine does not seem to exert this neuroprotective effect by reversing amyloid pathology. Normally, APP and β-secretase levels are high in AD. When APP is cleaved by β-secretase, toxic Aβ is formed, which is the major component of senile plaques (3). However, the levels of APP and β-secretase 1 indicating amyloid pathology were increased in our experimental model. In one study, the elevated levels of cortical β-APP expression with lidocaine treatment due to the lowered cholinergic neurotransmission was mentioned (16). Another study reported that lidocaine did not alter the expression of β-amyloid peptide, phospho-tau, and total tau in the cerebral cortex while ameliorating memory performance (10). Apparently, lidocaine seems to exert its neuroprotective effect by different mechanisms rather than affecting amyloid pathology.

Another intriguing data was the reduced expression of TDP-43 in lidocaine administered AD group. TAR DNA-binding protein-43 is a neurodegeneration marker gaining importance recently in AD pathophysiology. Hyperphosphorylated and ubiquitinated TDP-43 protein inclusions is known to be prominent in limbic region of AD patients (17). Contrary to above findings, TDP-43 related neurodegeneration was inhibited in our STZ-induced AD model. Rojas et al. also identified that motor neuron degeneration triggered by TDP-43 is rescued with Na channel blocker mexiletine (lidocaine analog) treatment in amyotrophic lateral sclerosis (ALS) (18). Hence, it is possible that lidocaine prohibits the activation of intracellular stress mediated pathway and affects Na channel activity in the current AD model.

In general, lidocaine plays a protective and conceivably anti-inflammatory role in various diseases including hypoxia, ischemia, postoperative cognitive dysfunction, and neuroendocrine diseases such as diabetes (7–9,19). On the other hand, the possibility of neurotoxicity induced by lidocaine was also remarked in several conditions. A number of researchers have reported that treatment with growth factors like NGF and BDNF attenuates the consequences of lidocaine-induced neurotoxicity (20–22). However, in our study, NGF, BDNF and intracellular molecules associated with them such as CREB, c-FOS were found to create a protective impact against neuronal degeneration when lidocaine was administered. In case of AD, NGF deprivation and related decrease in cholinergic transmission is known (23). Also, c-FOS, which regulates NGF action, was increased in lidocaine treated group. Moreover, the transcription of c-FOS and BDNF is controlled by CREB, and CREB levels are lowered in AD patients (24). Brain-derived neurotrophic factor is another growth factor that ensures neuronal survival. Lower levels of BDNF were also reported in AD cases (25). Overall, all of these growth factor related factors were elevated after lidocaine administration. Little is known about how lidocaine may regulate the expression of all of these factors. Lidocaine may have divergent effects on mitochondrial functions, neuronal apoptosis, and inflammatory mechanisms (7). Furthermore, growth factors have a regulatory role in microglial homeostatic activities (26). Besides, inhibition of reactive microglia mediators may result in decreased severity of AD (27). Additionally, the administration type of lidocaine may also be significant. Especially, local and acute lidocaine administration was proposed to produce neurotoxicity by blocking neural transmission (28). Along with our findings, the neuroprotective effect of lidocaine, when administered chronically, is thought to be predominant by means of increasing the expression of growth factors.

Overall, this preliminary study outlines a critical role for lidocaine as a potential neuroprotective agent for AD treatment. The neuroprotective effect of lidocaine on STZ-induced AD rat model was found to be associated more with the neuronal growth and survival markers rather than reversing the amyloid pathology. Further imaging and pathology studies as well as measuring memory with different tests will better elucidate the underlying neuronal and inflammatory mechanisms prompted by lidocaine administration in the future.

Ethics Committee Approval: Dicle University Animal Experiments Local Ethics Committee (DÜHADEK: 2018-16) has given ethical approval for the study and the research continued based on the standards set out in the Helsinki Declaration.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- YT, BY, CT, ŞBT; Design- YT, BT, CT, SK, BE; Supervision- YT, BY, CT, SK, BE, ŞBT, SK; Resource- YT, BY, CT, SK, ŞBT; Materials- BY, SK, BE; Data Collection and/or Processing- YT, BY, CT, HY, SK, ET; Analysis and/or Interpretation- YT, HY, ET; Literature Search- YT, BY, CT, ŞBT, BE, ET, HY; Writing- HY, ET, YT; Critical Reviews- YT, BY, CT, HY, SK, BE, ŞBT, ET.

Conflict of Interest: The authors declared that there is no conflict of interest.

Financial Disclosure: This study has been financially supported by Dicle University Scientific Research Projects Unit with the project number DUBAP-TIP.21.015.

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