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EFFECTIVENESS OF DIPEPTIDYL PEPTIDASE - 4 INHIBITORS IN STREPTOZOTOCIN INDUCED NEURODEGENERATIVE MICE

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Keywords:

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ABSTRACT: **Introduction:** Neurodegenerative diseases are incurable and debilitating condition that results in progressive degeneration and / or death of nerve cells. Anti-oxidants, Antihyper-glycemics and insulin sensitizing agents are reported for reducing cognitive dysfunction in diabetes. Decreasing GLP-1 degradation using Dipeptidyl Peptidase-4 (DPP-4) inhibitors has been shown to be effective for treating type-2 diabetes and neurodegeneration. **Objective:** In present study neuroprotective effect of sitagliptin and saxagliptin on streptozotocin induced neurodegenerative mice had been evaluated. **Materials and Methods:** Neurodegeneration was induced by single dose of Streptozotocin (120mg/kg I.P) and started drug treatment (Sitagliptin and Saxagliptin) after 28 days of Streptozotocin single dose treatment for next 21 days. Streptozotocin induced memory decline was confirmed by behavioural study and Inflexion Ratio – IR. **Results:** Memory decline was overturned by Saxagliptin (0.5 and 1mg/kg p.o) and Sitagliptin (10 and 20mg/kg p.o). In addition to above, Saxagliptin (1mg/kg p.o) and Sitagliptin (20mg/kg p.o) had reversed levels of dopamine, nor-adrenaline and serotonin in brain as compared to only Streptozotocin treated animals, suggesting neuroprotective activity of chosen two DPP-4 inhibitors (saxagliptin and sitagliptin). **Conclusion:** These results demonstrate that DPP-4 inhibitors drugs that are effective in treatment of type-2 diabetes have neuroprotective properties also. Further research is required to clarify the molecular mechanism involved in neuroprotection.

INTRODUCTION: Neurodegeneration is the umbrella term for the progressive loss of structure or function of neurons, including death of neurons. High glucose concentration, a major pathological characteristic of diabetes, may have toxic effects on neurons in the brain through defective insulin action, metabolic / mitochondrial dysfunction, oxidative stress, advanced glycation end products (AGEs) formation, increased aldose reductase activity, activated protein kinase C (PKC) and increased hexosamine pathway flux, which in turn leads to neuronal injury¹.

Since the beginning of the 20th century, evidence has suggested that hormones secreted by intestinal epithelial cells in response to food intake can affect whole body glucose utilization. In the 1930s, these hormones were named incretins - two main are glucose dependent insulin tropic peptide (GIP) and glucagon-like peptide-1 (GLP-1).

This research will focus primarily on GLP-1 due to its neuroprotective functions. GLP-1 receptors are GPCR widely expressed throughout the body, including the pancreas, intestines, heart, and lungs, as well as the central and peripheral nervous systems. Activation of GLP-1 receptors leads to facilitation of glucose utilization and antiapoptotic effects in various organs. GLP-1 is an endogenous 30-amino acid peptide hormone, released by intestinal L-cells in the ileum and colon after meals, which serves several significant physiological functions, including increasing beta

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cell sensitivity to glucose in pancreatic cells, decreasing glucagon secretion, inhibiting gastric secretion to delay absorption, and contributing to feelings of satiety. GLP-1 secretion is primarily stimulated by meal ingestion, as well as activation of intracellular signals such as protein kinase A (PKA), protein kinase C (PKC), calcium, and mitogen activated protein kinase (MAPK). Glucagon like peptide 1 (GLP-1) receptor analog or dipeptidyl peptidase-IV (DPP-IV) inhibitors have been classified as a novel treatment option for type 2 diabetes. Dipeptidylpeptidase - 4 (DPP-4) inhibitors inhibit the enzyme DPP - 4, a serine protease that degrades the incretin hormone, glucagon like peptide-1 (GLP-1), rapidly to its inactive form.

A number of clinical data suggested that the GLP - 1 pathway regulates blood glucose levels and has beneficial effects on beta cell proliferation and function, including insulin biosynthesis and secretion, in a glucose dependent manner¹. This study suggested a possible role for the GLP-1 pathway in the treatment of diverse neurodegenerative disorders. The efficacy of DPP-IV inhibitors is mainly mediated by GLP-1 stabilization, so the prevention of GLP-1 inactivation by DPP-IV inhibition results in the increase and prolongation of the endogenously released GLP-1. The purpose of the present study was to investigate any neuroprotective possibilities of the GLP-1 pathway by using a DPP-IV inhibitor in experimental model of diabetes independent of glucose levels²⁻⁷.

MATERIALS AND METHODS:

Animals: Wistar Albino mice weighing 20 - 40g were obtained from the central animal facility of Maliba Pharmacy College, Tarsadi, Gujarat, India. The animals were acclimatized to laboratory conditions ten days prior to the commencement of the experiment in order to adapt to the environmental conditions of light dark cycle (12:12 h), relative humidity (55 - 65%) and temperature (21 ± 10 °C). The animals were housed in polypropylene cages with sterilized paddy husk bedding. Food and water were available *ad libitum* throughout the experimental period. All the experiments were carried out with prior approval of the institutional animal ethics committee (Protocol number - MPC/IAEC/03/2014).

Experimental Procedure:

Induction of Neurodegeneration: Thirty animals were randomly selected. Blood glucose level, behavioural memory test, locomotion and catalepsy test were performed then injected streptozotocin (STZ) dissolved in citrate buffer (pH - 4.5) at a single dose of 120mg/kg i.p. After STZ administration blood Glucose level was measured at every weekend and animals had blood glucose level > 200mg/dl and significant behavioural memory loss were divided into five groups each having six animals (**Fig. 1**) (**Table 1**)^{1,5,6}.

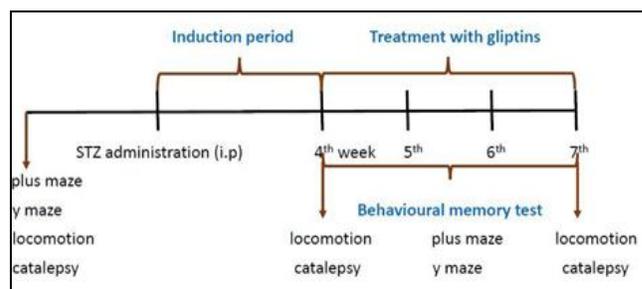


FIG. 1: SCHEME OF EXPERIMENTAL PROCEDURE

TABLE 1: GROUP DISTRIBUTION OF MICE

Groups	Treatments
Group-1	STZ (120mg/kg. single dose, i.p.)
Group-2	STZ + Sitagliptin (10mg/kg/day, p.o.)
Group-3	STZ + Sitagliptin (20mg/kg/day, p.o.)
Group-4	STZ + Saxagliptin (0.5mg/kg/day, p.o.)
Group-5	STZ + Saxagliptin (1mg/kg/day, p.o.)

Behavioural Tests:

Elevated Plus Maze Test: Using elevated plus maze [height 25cm, two open arms (16 × 5cm) and two enclosed arms (16 × 5 × 12cm)] the transfer latency for memory was calculated. Transfer latency (TL) of first day reflected learning behavior of animals whereas of second day reflected retention of information or memory. Mice were placed individually at end of an open arm facing away from central platform and the time took to move from the end of open arm to either of closed arm (Transfer latency, TL) was recorded. If the animal did not enter into one of the enclosed arms within 90 sec, it was gently pushed into one of the two enclosed arms and the TL was assigned as 90 sec.

The mice was allowed to explore the maze for another 10 sec and then returned to its home cage. Retention of this learned - task was examined 24 h after the first day trial.

Transfer latency after 24 h was expressed as "Inflexion Ratio, IR" using the formula described by Jaiswal and Bhattacharya (1992)⁸: $IR = (L_1 - L_0) / L_0$. Where L_0 is the transfer latency after 24 h and L_1 is the initial transfer latency in seconds. This test was performed before STZ administration, after STZ administration and after every 7 days of treatment started^{9,10}.

Y - Maze Test: Spontaneous alternation was assessed using a Y- maze composed of three equally spaced arms (120°, 30cm long and 15cm high). The floor of each arm is made of Perspex and is 5cm wide. Each mouse was placed in one of the arm compartments and was allowed to move freely until its tail completely enters another arm. The sequence of arm entries is manually recorded, the arms being labelled A, B, or C. An alternation is defined as entry into all three arms consecutively, for instance if the animal makes the following arm entries; ACB, CA, B, C, A, CAB, C, A, in this example, the animal made 13 arm entries, 8 of which are correct alternations. The number of maximum spontaneous alternations is then the total number of arms entered minus two, and the percentage alternation is calculated as $\{(actual\ alternations / maximum\ alternations) \times 100\}$. For each animal the Y-maze testing was carried out for 5 minutes. The apparatus was cleaned with 5% alcohol and allowed to dry between sessions. This test was performed before STZ administration, after STZ administration and after every 7 days of treatment started^{11,12}.

Locomotion Test: Each animal was placed individually in actophotometer and the basal activity score of the animals was noted which displayed on screen. This test was performed before STZ administration, after STZ administration (28th day) and after treatment of drugs. Percentage decrease in activity = $\{(1 - W_a / W_b) \times 100\}$, where W_a and W_b are average activity scores of treatment group and control group, respectively^{13,14}.

Catalepsy Test: Catalepsy, defined as a reduced ability to initiate movement and a failure to achieve correct posture, was measured by the bar test. Mice were positioned so that their hindquarters were on the bench and their forelimbs rested on a 1cm diameter horizontal bar that was 4cm above the

bench. Mice were judged to be cataleptic if they maintained this position for 30 s or more¹⁵.

Bio Chemical Study:

Estimation of Various Brain Neurotransmitters Level:

Extraction: The brain tissue (1.55mg) was homogenized in 0.1 ml HCl - butanol (0.85ml 37% HCl in 1 liter n-butanol for spectroscopy) for 1 min in a glass homogenizer made from a small centrifuge tube (vol. 1.5ml). The total volume was considered to give 0.105ml, taking account of the tissue volume (1mg = 0.001ml). The sample was then centrifuged for 10 min at 2000g. An aliquot of the supernatant phase (0.08ml) was removed and added to an Eppendorf reagent tube (vol. 1.5ml) containing 0.2ml heptane (for spectroscopy) and 0.025ml HCl 0.1 M. After 10 min of vigorous shaking, the tube was centrifuged under the same conditions as above in order to separate the two phases, and the overlaying organic phase was discarded. The aqueous phase (0.02ml) was then taken either for 5-HT or NA and DA assay. All steps were carried out at 0 °C¹⁶.

Serotonin Assay: For 5-HT determination, the o-phthalaldehyde method was employed. From the OPT reagent (20mg % in conc. HCl) 0.025ml were added to 0.02ml of the HCl extract. The fluorophore was developed by heating to 100 °C for 10 min. After the samples reached equilibrium with the ambient temperature, excitation / emission spectra or intensity readings at 360 - 470 nm were taken in the micro cuvette described above¹⁶.

Nor-adrenaline (Na) and Dopamine (Da) Assay:

The assay represents a miniaturization of the trihydroxyindole method. To 0.02ml of the HCl phase, 0.305ml 0.4 M HCl and 0.01ml EDTA / sodium acetate buffer (pH 6.9) were added, followed by 0.01ml iodine solution (0.1 M in ethanol) for oxidation. The reaction was stopped after 2 min by addition of 0.01ml Na₂SO₃ in 5 M NaOH (0.5g Na₂SO₃ in 2ml H₂O + 18ml 5 M NaOH). Acetic acid (0.01ml, 10 M) was added 15 min later. The solution was then heated to 100 °C for 6 min. When the sample again reached room temperature, excitation and emission spectra were read in the micro cuvette as with 5-HT; in some cases, the readings were limited to the excitation /

emission maxima (395 - 485nm for NA, 330 - 375nm for DA) ¹⁶.

Standards, Blanks and Recovery: Tissue blanks for the catecholamine assay were prepared by adding the reagents of the oxidation step in reversed order (Na₂SO₃ before I₂). For serotonin tissue blank, 0.025 conc. HCl without OPT was added. Internal reagent standards were obtained by adding 10ng 5-HT or 10ng NA and 20ng DA in 0.005ml bi-distilled water to 0.1ml HCl - butanol, which was then carried through the entire extraction procedure. For the internal reagent blank 0.005ml water was added to 0.1ml HCl - butanol. Spectral studies were also performed on standards containing all three amines in twice the volume mentioned above. No cross interference was noted. Corrected recoveries ranged from 60 to 70 per cent for all three amines ¹⁶.

Statistical Analysis: The data is represented as mean \pm SEM. Behavioural parameters were analysed by Repeated measure ANOVA followed by Bonferroni test. Biochemical parameters were analysed using one-way ANOVA followed by Bonferroni tests. Values are said to be significant when $p < 0.05$.

RESULTS:

Behavioural Test:

Effect of Sitagliptin and Saxagliptin on Inflexion Ratio on Elevated Plus Maze: Marked decrease is seen in inflexion ratio after 28 days of STZ ($p < 0.001$) administration.

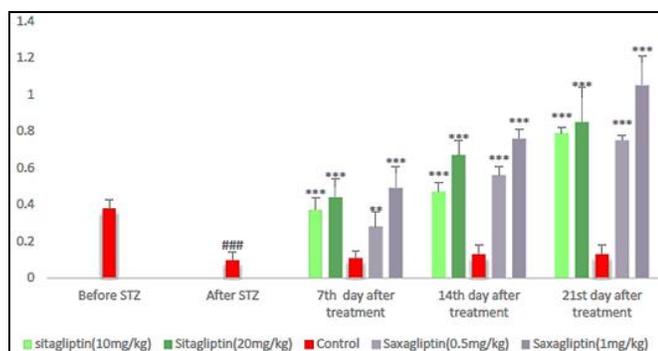


FIG. 2: EFFECT OF SAXAGLIPTIN AND SITAGLIPTIN ON INFLEXION RATIO OF DIABETIC NEURODEGENERATIVE MICE. Values are expressed as Mean \pm SEM (n = 30 for before and after STZ and n = 6 for after treatment). ### $p < 0.001$ vs Before STZ, *** $p < 0.001$ vs STZ control, ** $p < 0.01$ vs STZ control, Repeated measure ANOVA followed by Bonferroni post hoc test.

Sitagliptin (10 and 20mg/kg) and saxagliptin (0.5 and 1mg/kg) both significantly increase the

inflexion ratio at both dose level on 7th, 14th and 21st day post treatment as STZ treated mice. There was no significant difference between sitagliptin and saxagliptin treated group (Fig. 2).

Effect of Sitagliptin and Saxagliptin on Alteration Percentage on Y Maze: As shown in Fig. 3 there was significant decrease in alteration percentage on 7th, 14th and 21st day post treatment as compare to STZ treated mice. It also describe that there was no significant difference in two doses of sitagliptin and saxagliptin and also no significant difference between saxagliptin and sitagliptin.

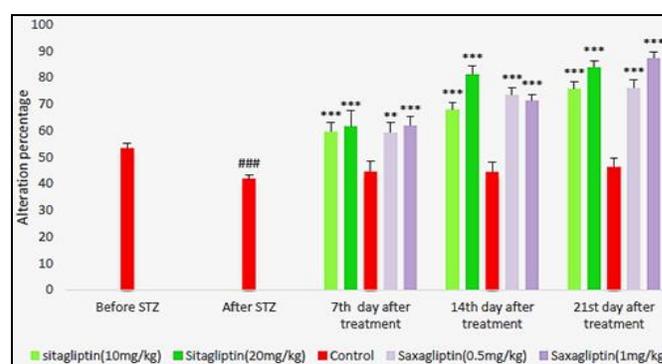


FIG. 3: EFFECT OF SITAGLIPTIN AND SAXAGLIPTIN ON ALTERATION PERCENTAGE OF DIABETIC NEURODEGENERATIVE MICE. Values are expressed as Mean \pm SEM (n = 30 for before and after STZ and n = 6 for after treatment). ### $p < 0.001$ vs Before STZ *** $p < 0.001$ vs STZ control, ** $p < 0.01$ vs STZ control, Repeated measure ANOVA followed by Bonferroni post hoc test.

Effect of Sitagliptin and Saxagliptin on Catalepsy Test: As shown in Fig. 4 there was increase the time of mice using at least one front paw on bar but it was not significant. After treatment of sitagliptin and saxagliptin the time spend on bar using at least one front paw was decreased but not significantly decreased.

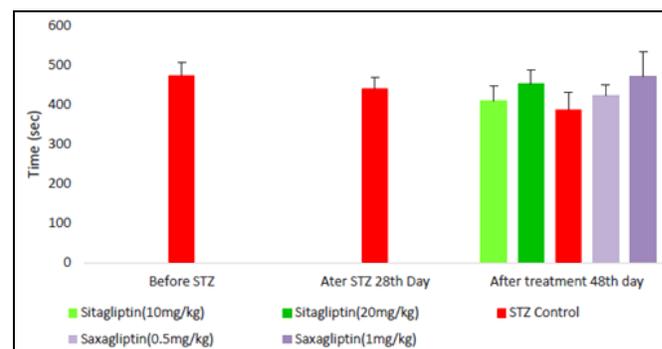


FIG. 4: EFFECT OF SITAGLIPTIN AND SAXAGLIPTIN ON CATALEPSY OF DIABETIC NEURO-DEGENERATIVE MICE. Values are expressed as Mean \pm SEM (n = 30 for before and after STZ and n=6 for after treatment). Repeated measure ANOVA followed by Bonferroni post hoc test.

Effect of Sitagliptin and Saxagliptin on Locomotion Activity: There was no significant change in locomotion activity of mice after STZ treatment and also no significant change in locomotion activity after sitagliptin and saxagliptin treatment (Fig. 5).

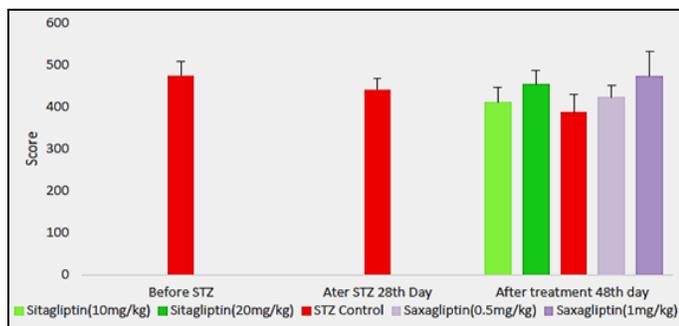


FIG. 5: EFFECT OF SITAGLIPTIN AND SAXAGLIPTIN ON LOCOMOTION ACTIVITY OF DIABETIC NEURODEGENERATIVE MICE. Values are expressed as Mean ± SEM (n = 30 for before and after STZ and n = 6 for after treatment). Repeated measure ANOVA followed by Bonferroni post hoc test

Biochemical Parameters:

Blood Glucose Level: Blood glucose level was measured using glucocareultima instrument, and data are shown in figure. Levels of blood glucose level were significantly decreased after the saxagliptin and sitagliptin treatment followed by STZ treatment. There was no significant difference between sitagliptin and saxagliptin treated mice (Fig. 6).

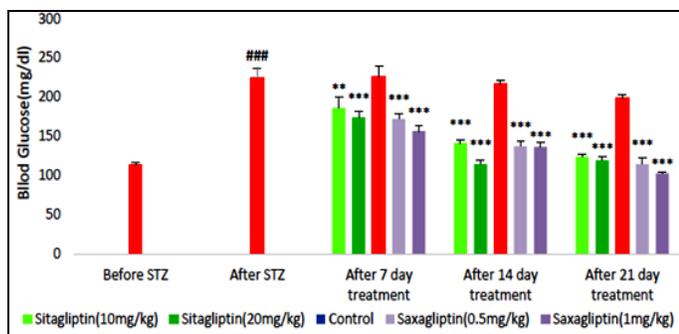


FIG. 6: EFFECT OF SITAGLIPTIN AND SAXAGLIPTIN ON BLOOD GLUCOSE LEVEL (mg/dl) OF DIABETIC NEURODEGENERATIVE MICE. Values are expressed as Mean ± SEM (n = 30 for before and after STZ and n = 6 for after treatment). ###p < 0.001 vs Before STZ, ***p < 0.001 vs STZ control, **p < 0.01 vs STZ control, Repeated measure ANOVA followed by Bonferroni post hoc test.

Brain Neurotransmitters Level: As shown in Fig. 7, 8 and 9, the level of serotonin, dopamine and nor adrenaline was decreased in the STZ control mice than normal mice but it was not significant. In high dose group of sitagliptin (p < 0.01) and saxagliptin (p < 0.01) treated mice there was significant increase the serotonin, nor adrenalin and dopamine

level as compare to STZ control group. There was no significant difference between saxagliptin and sitagliptin treated mice.

Other Parameters:

Effect of Saxagliptin and Sitagliptin on Body Weight of Mice: Normal control animals were found to be stable in their body weight but diabetic mice showed significant reduction in body weight during 28 days. STZ mediated body weight reduction was significantly reversed by saxagliptin (p < 0.05) and sitagliptin (p < 0.05) as compared to STZ control (Fig. 10 and 11).

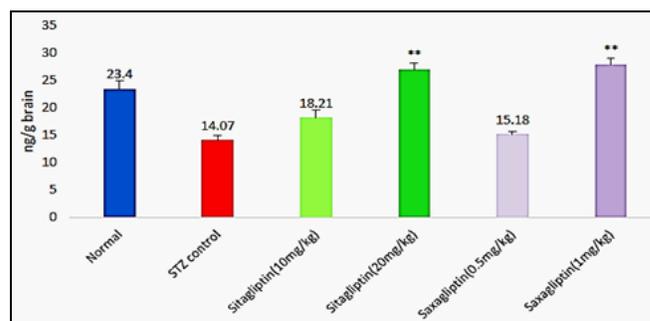


FIG. 7: EFFECT OF SITAGLIPTIN AND SAXAGLIPTIN ON BRAIN SEROTONIN LEVEL OF DIABETIC NEURODEGENERATIVE MICE. Values are expressed as Mean ± SEM (n = 6). ###p < 0.01 vs normal control, **p < 0.01 vs STZ control. One way ANOVA followed by Tukey's test.

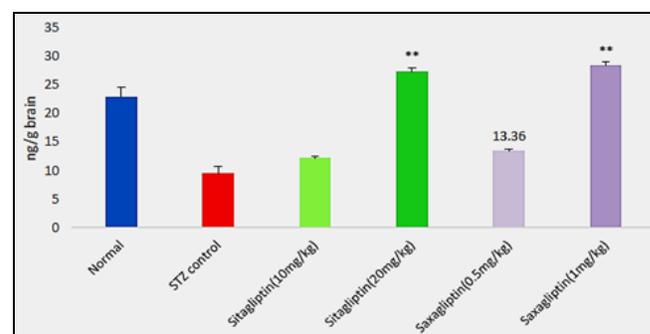


FIG. 8: EFFECT OF SITAGLIPTIN AND SAXAGLIPTIN ON NORADRENALIN LEVEL OF DIABETIC NEURODEGENERATIVE MICE. Values are expressed as Mean ± SEM (n = 6). ###p < 0.01 vs normal control, **p < 0.01 vs STZ control. One way ANOVA followed by Tukey's test.

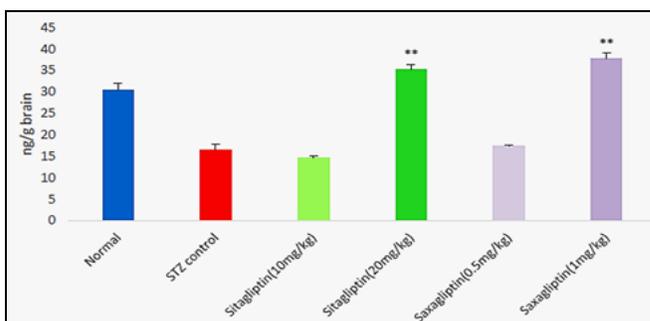


FIG. 9: EFFECT OF SITAGLIPTIN AND SAXAGLIPTIN ON BRAIN DOPAMINE LEVEL OF DIABETIC NEURODEGENERATIVE MICE. Values are expressed as Mean ± SEM (n = 6). ###p < 0.01 vs normal control, **p < 0.01 vs STZ control. One way ANOVA followed by Tukey's test.

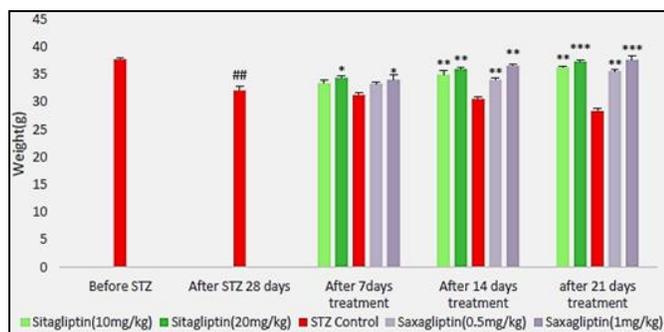


FIG. 10: EFFECT OF SITAGLIPTIN AND SAXAGLIPTIN ON BODY WEIGHT OF DIABETIC NEURODEGENERATIVE MICE. Values are expressed as Mean \pm SEM (n = 30 for before and after STZ and n = 6 for after treatment). ## p < 0.01 vs Before STZ, **p < 0.01 vs STZ control, * p < 0.05 vs STZ control. Repeated measure ANOVA followed by Bonferroni post hoc test.

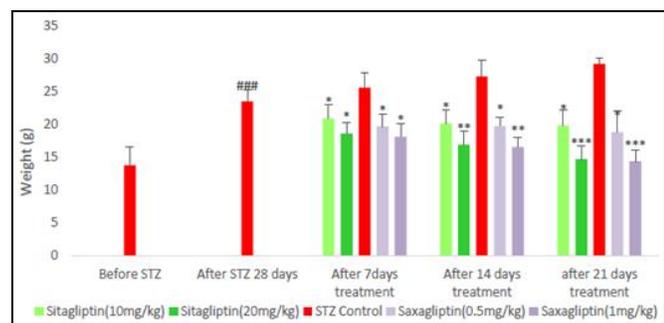


FIG. 11: EFFECT OF SITAGLIPTIN AND SAXAGLIPTIN ON FOOD INTAKE (g/DAY) OF NEURO-DEGENERATIVE MICE. Values are expressed as Mean \pm SEM (n = 30 for before and after STZ and n = 6 for after treatment). ## p < 0.01 vs Before STZ, *** p < 0.001 vs STZ control, ** p < 0.01 vs STZ control, * p < 0.05 vs STZ control. Repeated measure ANOVA followed by Bonferroni post hoc test

DISCUSSION: High glucose concentration, a major pathological characteristic of diabetes, may have toxic effects on neurons in the brain through defective insulin action, metabolic / mitochondrial dysfunction, oxidative stress, advanced glycation end products (AGEs) formation, increased aldose reductase activity, activated protein kinase C (PKC) and increased hexosamine pathway flux, which in turn leads to neuronal injury². Neurodegenerative disease are incurable and debilitating condition that results in progressive degeneration and / or death of nerve cells, which leads to loss in memory or problem with movement (ataxia). Further, literature suggested that GLP-1, an endogenous peptide, not only regulates blood glucose level but also has antiapoptotic and neurotrophic effect on neuronal cells¹. In present study we had evaluated the neuroprotective effect of sitagliptin and saxagliptin on STZ induce neurodegenerative mice. Literature mentions that the high single dose of STZ in mice produce

diabetes by damage the pancreatic cells, further long term high blood glucose level damage the brain neuron and produce cognitive dysfunctions, which is due to damage of hippocampus⁵.

In present study elevated plus maze (EPM) was employed to evaluate short term and long term memory function. An increase in inflexion ratio in EPM demonstrated improvement of memory following administration of STZ, memory deterioration was observed in control group of animal which was reverted by administration sitagliptin and saxagliptin both dose level for 21 days. Further, Y - maze test was done for assessment of learning and memory an increase correct choice and decrease in error in Y - maze demonstrates intact learning and memory function.

Results showed memory decline overturned by treatment with saxagliptin (0.5 and 1mg/kg, p.o) and sitagliptin (10 and 20mg/kg, p.o.). In addition, saxagliptin (1mg/kg, p.o) and sitagliptin (20mg/kg, p.o.) had reversed the level of dopamine, nor-adrenaline and serotonin in whole brain in comparison with STZ - treated animals, suggesting neuroprotective activity of DPP-4 inhibitors (Saxagliptin and Sitagliptin). STZ leads to degeneration of neurons in hippocampus region, while ataxia and motor coordination is control by cerebellum. With this fact, present study also shows that STZ was unable to induced ataxia and locomotor activity change. In addition, treatment with saxagliptin and sitagliptin also showed no effect in haloperidol induced catalepsy and locomotor activity in comparison to normal and control group. Our findings also constant with previous study by Kosaraju *et al.*,⁵

The present approach of DPP-4 inhibitors using sitagliptin and saxagliptin promise to be neuroprotective in neurodegeneration induced by STZ and further studies will investigate the exact mechanism behind DPP-4 inhibitor for neuroprotection.

CONCLUSION: This research concludes that DPP-IV inhibitors (Saxagliptin and Sitagliptin) show neuroprotective effect in addition to anti diabetic effect by complete reversal of defects induced by Streptozotocin. For molecular mechanism further study is required.

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CONFLICT OF INTEREST: The authors have no conflict of interests to declare regarding the publication of this paper.

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