

Original Article

## Role of rosiglitazone in experimental Wistar rats model of neurodegeneration: Effect of peroxisome proliferator-activated receptors- $\gamma$ as advanced glycation endproducts receptor of advanced glycation endproducts axis inhibitor

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### ABSTRACT

**Objectives:** The interaction between advanced glycation end products (AGEs) and their receptor of AGE (RAGE) contributes to various disorders, which impact neurological conditions and cognitive function. This work aims to explore the potential treatment using rosiglitazone to address these conditions.

**Materials and Methods:** The animal study was conducted on four different groups of male albino Wistar rats, each group containing six rats. Treatment of group 1 was saline (0.9%), group 2 was haloperidol (1 mg/kg/day) for 28-day intraperitoneal route, group 3 was haloperidol and rosiglitazone (10 mg/kg/day) for 28 days and group 4 was treated with the drug rosiglitazone (10 mg/kg/day) for 28 days. The test procedure was made so that the disease was induced using haloperidol, and treatment was done with the peroxisome proliferator-activated receptors- $\gamma$  (PPAR- $\gamma$ ) blocker rosiglitazone. This study utilised adult male Wistar rats to investigate the effects of rosiglitazone on haloperidol-induced neurodegeneration.

**Results:** The results from the behavioural parameters, antioxidant parameters and AGE-RAGE parameters indicate the action of rosiglitazone on the receptor of AGE and suppression of neurodegenerative disorder. Urine output and body weight improved in addition to rosiglitazone. Rosiglitazone improves the retention time (663.5 s) on the rotarod and the Morris water maze apparatus. The drug rosiglitazone acts on the reduction of free radicals, thus reducing the oxidant stress and also reducing diseased conditions. The level of interleukin-6, thrombosis necrosis factor- $\alpha$  and amyloid- $\beta$  protein was significantly reduced with the help of rosiglitazone.

**Conclusion:** The results conclude that the effect of PPAR- $\gamma$  blocker drugs can act by reducing the effect produced by the advanced glycation end product and blocking the receptor of the advanced glycation end product to cure neurological conditions.

**Keywords:** Advanced glycation end-product, Advanced glycation endproducts-Receptor of advanced glycation endproducts axis, Alzheimer's, Cognitive impairment, Neurodegeneration, Parkinson's

### INTRODUCTION

Longevity is the basic stipulation of every living organism. Hence, the food we take and the materials that are being categorised in the eatables need to be thoroughly under watch, as the

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eatables which are our daily routine intake can be dangerous and can also have the capability to produce reactions within the body and give rise to a hazardous end product as advanced glycation end product. It is not always possible for an ordinary person to keep track of their food intake, as the common man has no track of end products developed inside the body. In the race for survival of the fittest, humans require good health and the proper functioning of all bodily organs to ensure a long and joyful life. Considering neural health, the ministrations towards it becomes a foremost priority, and it is also because amyloid beta protein and tau protein, massed in neural cells, can produce neural damage. It is all a popular theory and a scientifically proven fact that the amyloid beta protein is the main culprit for all the ill health related to neurons and neural cells. It is also known that the amyloid beta proteins are generally formed by beta and gamma secretases, which is due to the oxidation process by the reactive oxygen species (ROS) or the free radicals present in our body.<sup>[1]</sup> The products that were earlier considered only as the blood sugar regulators (glycation) have an impact on the body and have these changes to produce neural changes. Hence, with these products showing rapid action, the possible treatment would be those drugs that can reduce the increased blood sugar content.

The advanced glycation end products (AGEs) were addressed for the first time by the scientist Louis Camille Maillard. He found a brown-coloured structure being produced in the reaction between carbohydrates and amino acids. The brown-coloured structure formed was the end product.<sup>[2]</sup> AGE molecules are formed from a reaction known as the Amadori rearrangement of the fructosamine structures, the product of chemical reactions of aldehyde and ketone with amino groups of the protein structures. These reactions are non-enzymatic and do not require any enzymatic catalyst.<sup>[3]</sup> Three stages of end products can be formed – the first and foremost is the reaction between the reducing sugar to produce a Schiff's base. The intermediate or mid-stage would be the generation of alpha-dicarbonyl or ox-aldehydes to produce the glyoxal, methylglyoxal and 3-deoxyglucosone.<sup>[4,5]</sup> It is firmer and has a stable Amadori structure. Later, rearrangements in the base can develop the most stable structures called advanced glycation end products. The researchers have also found the role of AGE in diseases such as Alzheimer's, Parkinson's and amyotrophic lateral sclerosis.<sup>[6,7]</sup> While animal studies and research have established a connection between AGEs and neurological conditions, the precise mechanism causing this effect is still unclear. This contributes to the further study of animal histopathology, which would lead to the structures which are additionally being developed. Synapse studies are also required by scientists to understand the effect of AGE in the synaptic gaps and other structures, such as microglia and astrocytes. In this study, some of the parameters are explained with the help of interleukin (IL)-6 and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), furnishing the inflammation structures.

On the other hand, in planning for the treatment of such conditions, we have an enzyme, sirtuin-1 (Sirt-1), which is an NAD-dependent deacetylase, which has a function in the ageing and antioxidant processes.<sup>[8,9]</sup> The antidiabetic drugs show action on various body organs where the AGE accumulation was the cause of disorders (such as cardiovascular diseases). Discussing the probable mechanism of action of these drugs in neural health, studies have proven their role in neuroprotection and healthy neural cell growth. It is because of its action in decreasing the oxidative stress within the neural cells and preventing neural damage and cell death. Sirt-1 activation and binding enhance the function of externally ingested antioxidants, thus reducing amyloid- $\beta$  (A $\beta$ ) accumulation, and suppress its production. This helps in the treatment of Alzheimer's disease (AD). In a study of the AD mouse model, Sirt-1 indicates the suppression in the production of A $\beta$  and  $\alpha$ -secretase. It is of interest as it can decrease the effects of AGE, as per the recent studies. This could be further tested in laboratories for an extensive study.<sup>[10,11]</sup>

The mechanism of Alzheimer's is still under investigation as many of the researchers and scientists have premises over it, but the conclusion is yet to be drawn. One of the mechanisms is AGE's involvement in AD.<sup>[12,13]</sup> The present animal study aims to show the correlation between them. We try to indicate the influence of AGEs on ROS. The development of AGEs promotes protease-resistant crosslinking that occurs between peptides and proteins. A $\beta$ , tau,  $\alpha$ -synuclein and prions are only a few of the proteins associated with neurodegenerative illnesses that are glycated, and the degree of glycation is connected to the patient's pathological condition.<sup>[14,15]</sup> The presence of AGE to such an extent is indicative of its role in neurodegenerative disorders. The activation of nuclear factor kappa (NF- $\kappa$ ) and the presence and accumulation show their involvement in the AGE action. The biochemical assays are indicative that the release of inflammatory mediator's cytokines, due to increased production of macrophage colony-stimulating factor in neuronal cells, has an impact on the extent of AD, and it is due to the activation of the receptor of AGE (RAGE).<sup>[16,17]</sup> The treatment procedure follows the blockage of peroxisome proliferator-activated receptors- $\gamma$  (PPAR- $\gamma$ ), which uses rosiglitazone in the present study. It reduces the burden produced by the A $\beta$  plaques, reduces the inflammation of the neuronal cells and reduces the conditions of neurodegeneration.<sup>[18,19]</sup> PPARs, especially PPAR- $\gamma$ , can influence the formation and accumulation of AGEs by regulating metabolic pathways. They help improve insulin sensitivity and glucose metabolism, thereby reducing the substrates available for glycation reactions. PPAR- $\gamma$  activation influences the metabolism of amyloid precursor protein, reducing the production of A $\beta$  peptides, which aggregate to form plaques in AD.

The impact of AGE-RAGE on neurodegeneration has been proven by various articles, and it explains the mechanism of neurodegeneration to be based on the high mobility group box-1, which is a s100 protein family member.<sup>[20]</sup> Proteins' gained structural strength can be altered by almost any kind of post-translational changes that should have at least two significant influences. First, these structural alterations destroy the active pocket of an enzyme, thereby making it less likely for a substrate to bind to its enzyme. Second, hydrophobic clusters within the protein core that are ordinarily hidden are exposed as a result of these changes. Such changes are therefore highly likely to increase the aggregation propensity of proteins, which also leads to the formation of deleterious oligomers. An open carbonyl group is produced at the reaction when the aforementioned carbonyl compounds, AGEs, react with Lys530. This results in oligomers that crosslink by reaction with the oligomer-forming lysines in other polypeptides. These changes ensure that the proteins involved with them have an untoward function.<sup>[21]</sup> All these mechanisms are still predictions as the complete clear explanation is unclear. This initiates research on missing links to connect all the possible reasons for neurodegeneration due to AGE-RAGE. In the present study, haloperidol was used as the neurodegeneration-inducing agent, and rosiglitazone was used as the drug to study the effects of PPAR- $\gamma$  inhibitors in neurodegeneration.

### Hypothesis

- AGE and RAGE have effects all over the biological system. Since 1992, a series of research has on role to find different systems affected by RAGE
- There are different levels of findings for the rage's mechanism towards cognitive impairment and neurodegeneration
- Its effect on ROS, microglial systems, and neural inflammation is no longer camouflaged
- Potential drugs acting on all these systems to protect neural hygiene have been researched till today
- Drugs studied under the class of PPAR- $\gamma$  with an improved action to decrease the effect of RAGE on different needs to be explored towards its function on neural hygiene
- PPAR- $\gamma$  has had a tremendous impact on various biological systems against the action of AGE and RAGE.

## MATERIALS AND METHODS

### Animals

To know the pharmacological expressions of rosiglitazone in the neural health function, 48 Wistar albino rats with a weight of approximately 200–250 g of either sex were obtained directly from the Indian Veterinary Research

Institute in Izzat Nagar, Bareilly. The choice of rats was made in this study as the rats are big and contain a comparatively bigger size of brain, and they show complex behaviours which help in the neurodegenerative study, as this opens the different behavioural parameters. Good health conditions were maintained by providing healthy supplements in a suitable environment. The rats were retained in the polypropylene cages with several rats in every cage, not exceeding the limit as mentioned in the Committee for Control and Supervision of Experiments on Animals guidelines. The effect of the temperature and other environmental behaviours on the health of the rats was neutralised by the maintenance of  $25 \pm 1^\circ\text{C}$  room temperature and 45–55% relative humidity.

### Induction of neurodegeneration and cognitive impairment disorders

The antipsychotic haloperidol is a potent drug. They have the potential to produce neurodegeneration and cognitive impairment, apart from their actual action of schizophrenia and reduction of biomass. This experiment was to estimate the potency of the rosiglitazone, which acts as a PPAR- $\gamma$  inhibitor and reduces the action of AGE.<sup>[21,22]</sup> The rats were given a dose of 1 mg/kg body weight for 10 days of haloperidol to produce neurodegeneration and were treated with rosiglitazone to observe the changes. The effect of the dose difference was also observed in the rats.<sup>[23,24]</sup>

### Experimental design

Forty-eight Wistar albino rats are used for this study. They were divided into equal groups, each group containing six rats. The study was arranged and regulated for 28 days.

- Group I: Normal control received 0.9% normal saline for 28 days
- Group II: Disease control haloperidol 1 mg/kg/day for 28-day intraperitoneal (IP) route.
- Group III: Drug control haloperidol 1 mg/kg and rosiglitazone 10 mg/kg/day continued for 28 days
- Group IV: *Per se*, rosiglitazone 10 mg/kg b.w/day continued for 28 days.

### Description of procedure to be used

The animals were subjected to both invasive and potentially stressful non-invasive procedures during the experiment. Invasive procedures included intraperitoneal injections and blood withdrawal under anesthesia. All procedures followed a predetermined schedule to minimize distress.<sup>[25]</sup>

### Detailed protocol

Haloperidol, an inducing agent, is used for neurodegeneration in rats at a dose of 1 mg/kg body weight. It was administered

through the IP route for 28 days. The dilutions were made such that the dose volume was given up to 1 mL.<sup>[26]</sup>

Rosiglitazone, a PPAR- $\gamma$  inhibitor and the treatment drug, is used for neurodegeneration in rats at a dose of 10 mg/kg body weight. It was administered through the IP route for 28 days. The dilutions were made such that the dose volume was given up to 1 mL.<sup>[27]</sup>

Final blood withdrawal for the investigation was collected by the cardiac puncture and retro-orbital plexus with the help of a capillary tube; the collection was made such that the volume of blood was up to 2 mL.<sup>[27]</sup>

### Physical parameter evaluation

The physical parameter evaluation is the characterisation of the rats based on their external appearance, such as body weight, locomotion of the rat and other external features. These external parameters were also a tool to identify, if desired, the extent of effect produced by the neurodegenerative and cognitive impairment drugs, so that the rats are not harmed and can be used for further studies. The estimated parameters were the rotarod activity, Morris's water maze and catalepsy activity.

### Body weight

The body weight of the rats was measured on the 1<sup>st</sup> day and the last day of the experiment. This was to identify the effect of the drug on rats before and after the administration of the drug. This external parameter also indicates any change in the body.<sup>[28]</sup>

### Water intake

In this parameter, the evaluation of the water intake and consumption was recorded. This recording was performed daily. The water consumption in the complete experimental study was also noted to find the amount of water intake by rats.<sup>[29]</sup>

### Food intake

The amount of food intake is an indicator of the illness. If the rat starts to decrease its diet intake after the administration of the extracts, it symbolises that the rat is ill, and the recording of the daily food intake before and after the injection of the extract is the correct way to determine if the rat is healthy after the dosage.<sup>[30]</sup>

### Behavioural parameters

#### Rotarod test

It is an indicator of memory loss and motor neuron loss, as the decrease in any of these functions also decreases

the rotarod activity. It is the test performed to identify the capability of a rat to stand on the given rod after complete training. The training period usually starts before any doses are given to the rats, but it is further continued with the dosing. The decrease in capability of the rat is being recorded, and this, when tested after treatment with rosiglitazone, results in the increased time on the rotarod. This indicates that the rat's neural and motor functions were regained after the subjection to rosiglitazone.<sup>[31]</sup>

#### Morris water maze test

It is also a test to identify neural cell damage or memory loss in the rats. This is a physical test evaluating the extent of damage probably caused by the haloperidol. The extent of the disease would make the rat consume more time for identification or regain the pattern of swimming. The diseased rats would take more time than the rats that are treated with rosiglitazone along with haloperidol, and the normal saline rats will be compared to the treatment control rats, and this will be compared to that of the *per se* group. The tests would further take the study to the histopathological studies to confirm the changes chemically, and also the biochemical tests to identify the changes, if any.<sup>[32]</sup>

#### Biochemical test

##### Blood sample collection

The blood samples of all the individual rats were collected. The blood collection was performed for the estimation of the number of changes observed in the rat after the dosing of the drug and the inducing agent. The blood was collected intravenously from the tail vein of the rat and the cardiac puncture.<sup>[33]</sup>

##### Preparation of tissue material

The preparation of the tissue material requires the animal's execution. The brain of the sacrificed animal was removed and cleaned with icy, chilled running water. Once the brain was cleaned, it was placed in the folds of clean paper to dry. Later, it was analysed for the analytical balance. The homogenate tissue was obtained using a homogeniser under the 0.05M buffer solution of phosphate at pH 7 and temperature maintained at 4°C. The homogenate was divided into parts, and some parts of it were used to test glutathione (GSH). The remaining content of the homogenate was subjected to separation by centrifugation at 10000–20000 rpm for 20 min. This process separated the cell fragments, the steady cells and the nucleus. Of the layers formed, the upper layer was separated for the estimation of superoxide dismutase (SOD), acetylcholinesterase and catalase (CAT) values.<sup>[34,35]</sup>

### Sodium oxide dismutase

It is an enzyme that is found in every living organism to reduce the oxidation parameters in that organism. The increase in the amount of SOD release indicates the increased rate of oxidation and vice versa. The conversion of free radicals into the oxygen molecule and hydrogen peroxide molecule would suppress the action of the free radicals and suppress oxidative stress.<sup>[36]</sup> Hence, in the diseased state, it is observed that the SOD action has increased and in the normal conditions, the values remain normal or less. The more the action of SOD indicates more oxidations being produced.

### GSH enzyme

Like that of SOD, GSH is also an enzyme that reduces the oxidation state of the rats after infection due to various sources. The increase in the GSH levels indicates increased oxidation, and hence, the diseased state and the decreased GSH levels indicate that the free radicals are very less or few present in the body.<sup>[37]</sup>

### CAT enzyme

It has a similar function to the above two enzymes. This enzyme helps in the conversion of hydrogen peroxide into water and oxygen molecules. The enzyme's higher production increased free radical species generation, and this is how the extent of oxidative stress can be studied.<sup>[38]</sup>

### AGE-RAGE parameter test

#### IL-6

The IL-6 is a parameter to understand the AGE role in neurodegeneration. The test was performed on the blood, which was first mixed with EDTA to remove any sort of coagulation in the blood; later, the blood was separated by the centrifugation technique. It was later tested with the anti-IL-6 kit; the spectra validation was at 246 nm.<sup>[39]</sup>

#### A $\beta$ protein

It was tested by the enzyme-linked immunosorbent assay (ELISA) technique, where the amount of  $\beta$ -amyloid was quantified after the tissue separation and centrifugation. The anti-amyloid peptides were used in the quantification test.<sup>[40]</sup>

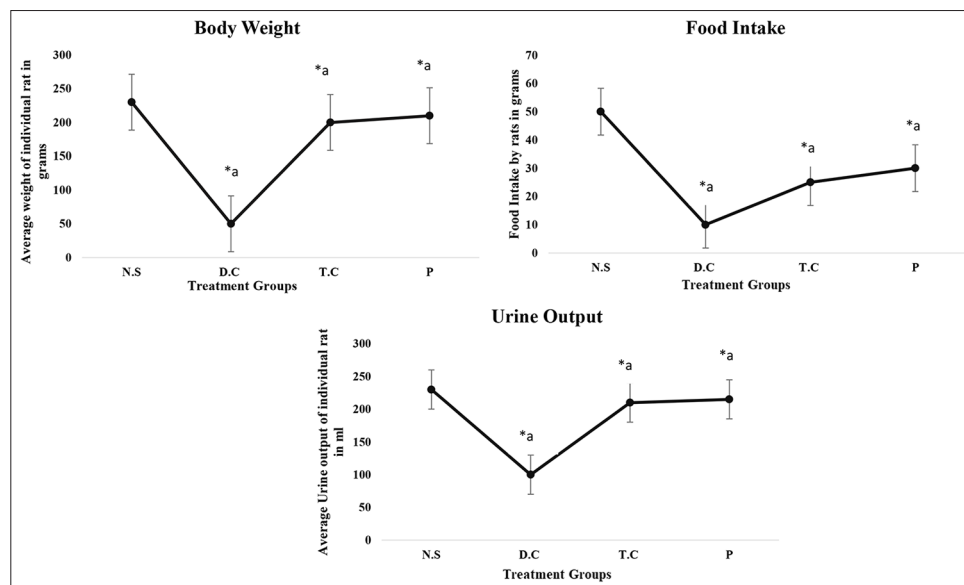
#### TNF- $\alpha$

It was tested by the ELISA technique, where the amount of TNF- $\alpha$  was quantified after the tissue separation and centrifugation. The anti-tumour necrosis peptides were used in the quantification test.<sup>[41]</sup>

## RESULTS

### Physical estimated parameters

The best way to identify a diseased condition is by estimating the body weight, food intake and urine output. In the



**Figure 1:** Physical estimated parameters, all values are expressed as mean  $\pm$  SD, when the number of rats used in each group ( $n = 6$ ). Data were subjected to one-way ANOVA followed by Dunnett's test when normal saline was compared to the haloperidol control group (disease control), haloperidol and rosiglitazone treated group (Test control) and per se were compared. \*a indicates  $P < 0.0001$  when compared to normal saline. NS: Normal saline, DC: Disease control, TC: Treatment control, P: per se. SD: Standard deviation.

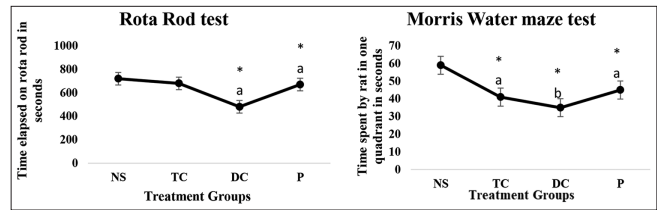
neurodegeneration induced by haloperidol, swallowing is difficult, and the induced animals reduce their food intake, which also reduces their weight of the patient. The urine output is also reduced as the induced animal faces difficulty in passing urine. These conditions were improved by the rosiglitazone. This can be better understood using the graphical representation of the amount of food intake, body weight of the rat and urine output [Figure 1].

### Behavioural parameters

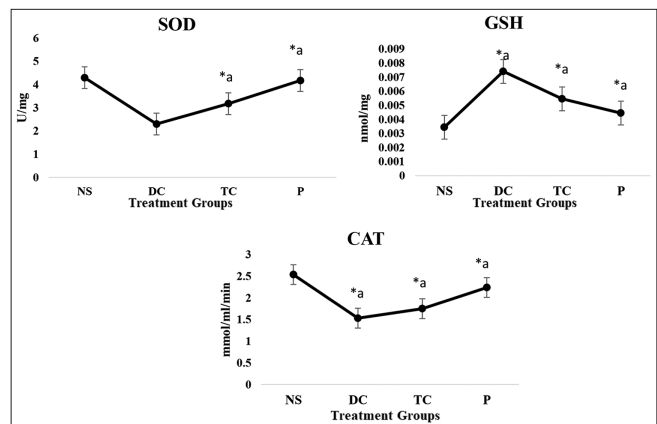
The externally observed characteristics of the rats after haloperidol treatment show an increase in weight, an increase in the movement of the rat within the cage and an increase in anxiety. These characteristics were indicative of the neural changes in the rats. The comparison study performed between the rosiglitazone-treated and haloperidol-treated rats shows the changes in the following pattern, and the trained rats did not retain on the rotarod for a longer duration of time. The rats were confused and showed additional time duration to find the retarding place or the marked place after subjection for training. It is one of the ways to identify externally, without the dissection of animals, the neural or mental condition of the rats. As the symptoms of neurodegeneration include the deterioration of neural and motor functions, the actions produced by the body of rats, such as the duration of time spent on the rot rod or the time taken by the animal to identify the marked location, can justify the need for further biochemical tests. The test shows the results as per the reviewed literature. In the rotarod test, the normal saline grouped rats could retain on the rod for 764.2 s, when the rats were injected with the haloperidol the time retained by the rats on the rod decreased to 562.3 s, when the rats were injected with the rosiglitazone and haloperidol the time was increased to the 663.5 s, this indicates that the rosiglitazone can improve the time retained. It is due to the increase in reduction in sugar-induced oxidative stress, which was increased due to the AGE action. The neural cell damage due to continuous oxidative stress, which is caused by the glucose and other sugar molecules in the body, can be suppressed by the action of rosiglitazone. It reduces the NF- $\kappa$ B and other inflammatory mediators to show beneficial effects in neurodegeneration. It is also indicative of the biochemical test results and the histopathological studies that are performed on the rats [Figure 2].

### The biochemical tests

It is theoretically being studied that oxidation and inflammation are the root causes of neurodegeneration. The study of the different oxidation parameters in the brain homogenate would provide the extent of the disorder. The values of SOD, GSH and CAT indicate that accordingly. The mean of SOD values for normal control was found to



**Figure 2:** Behavioral parameters, all values are expressed as mean  $\pm$  SD, when number of rats used in each group ( $n = 6$ ). Data were subjected to one-way ANOVA followed by Dennett's test when normal saline was compared to haloperidol control group (disease control), haloperidol and rosiglitazone treated group (Test control) and per se were compared. \*a indicates  $P < 0.0001$ , \*b indicates when compared to normal saline. NS: Normal saline, DC: Disease control, TC: Treatment control, P: *per se*. SD: Standard deviation.



**Figure 3:** The biochemical tests, all values are expressed as mean  $\pm$  SD, when the number of rats used in each group ( $n = 6$ ). Data were subjected to one-way ANOVA followed by Dunnett's test when normal saline was compared to the haloperidol control group (disease control), haloperidol and rosiglitazone treated group (Test control), and per se were compared. \*a indicates  $P < 0.0001$ , when compared to normal saline. NS: Normal saline, DC: Disease control, TC: Treatment control, P: *per se*. SD: Standard deviation, GSH: Glutathione, SOD: Superoxide dismutase, CAT: Catalase.

be 2.3 U/mg, 0.0036 nmol/mg and 2.54 mmol/mL, and the haloperidol increased the oxidation levels to 4.34 U/mg, 0.0074 nmol/mg and 1.54 mmol/mL, which was reduced to 3.24 U/mg, 0.0058 nmol/mg and 1.76 mmol/mL with rosiglitazone. In the rats, subjected to the rosiglitazone alone the SOD level was found to be 2.54 U/mg, 0.0048 nmol/mg and 2.20 mmol/mL. The increased levels of SOD, GSH and CAT indicate higher reactions with the oxidant molecules. The drug rosiglitazone acts on the reduction of the free radicals, thereby reducing the oxidant stress and reducing the diseased conditions [Figure 3].

### AGE-RAGE parameters

The AGE-RAGE parameters show the increased levels of values in diseased rats, indicating the presence of

neurodegeneration. The readings of IL-6, TNF- $\alpha$  and A $\beta$  protein are low, i.e. at the 3  $\mu\text{g/L}$  mL, 23  $\mu\text{g/L}$  mL and 0.7 ng/L. The values increased to 10  $\mu\text{g/L}$  mL, 70  $\mu\text{g/L}$  mL and 3.5 ng/L; these readings were reduced with the help of rosiglitazone [Figure 4].

### Histopathological studies

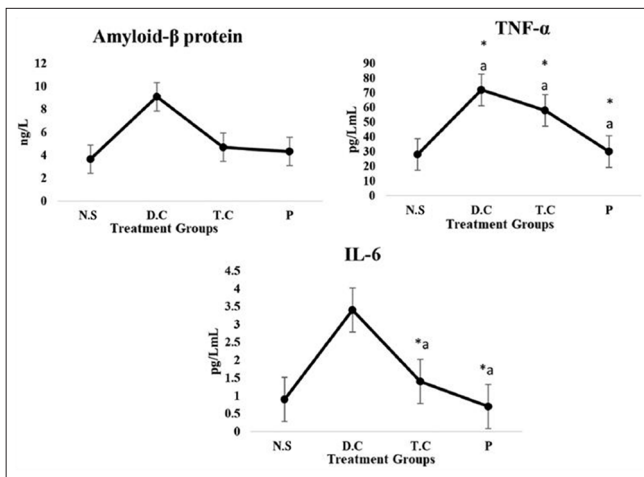
The cerebrum of the rats was examined under a microscope to study their neural cells, assess damage, and evaluate neurological conditions. This is also required to understand the extent of the treatment after the rosiglitazone ingestion. As it is the comparative parameter, the study also needs the comparison along with the normal saline and *per se* groups, which would indicate if any changes were to be nullified during the study. The histopathology of the brain tissue of the rats belonging to the normal control group revealed normal cerebral cortex cell bodies and glands. It is due to the group not being treated with any harmful substance. This indicates that no notable abnormalities, such as neuronal degeneration or gliosis (the accumulation of glial cells), were seen in the cerebral cortex tissue. The treatment group serves as a comparative group to assess the effects of rosiglitazone therapy and haloperidol-induced neurotoxicity. The cerebral cortex tissue in this group had significant gliosis, or an accumulation of glial cells, according to the results of the histological study. Significant neuronal deterioration was also noticed. These results suggest that haloperidol administration resulted in significant neuronal death and gliosis. Haloperidol

is thus a neurodegenerative agent which acts upon the neural cells and worsens the condition of the disease. The study of cerebral tissue of this group of rats (histopathological study) demonstrates significant gliosis (build-up of glial cells) in the cerebral cortex tissue. This is mild in the condition, as it is the haloperidol and rosiglitazone-treated group that shows significant neuronal deterioration. This shows that the gliosis and neuronal degeneration were reduced due to the rosiglitazone administered along with haloperidol. The cerebral cortex cell bodies in this group's brain tissue were normal according to the histological analysis. This shows that rosiglitazone injection alone did not result in any appreciable alterations in the cerebral cortex tissue, indicating that it did not result in gliosis or neuronal degeneration. The complete histopathological analysis shows that rosiglitazone is the drug of choice in neural deterioration. Rosiglitazone does not show any action on the neural damage and helps to reduce the damage which is produced by the haloperidol [Figure 5].

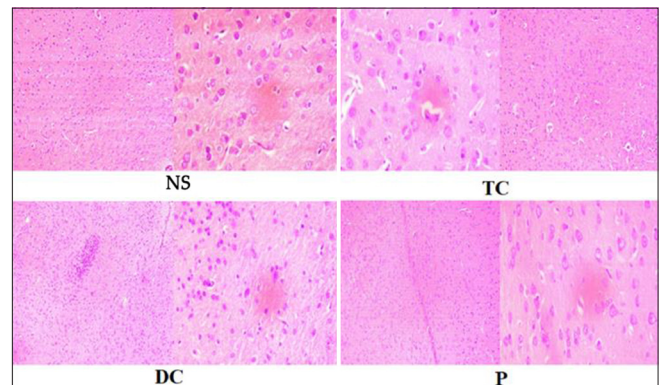
### DISCUSSION

The change in the body weight of the rat is an external parameter that can be a marker to indicate the required action of haloperidol as a prompt toward neurodegeneration.<sup>[42]</sup> The effect on dopamine 2 receptor, antagonist action by the haloperidol has a negative effect, which induces neurodegenerative disorder, and rosiglitazone was tested to treat this neurodegeneration.<sup>[43]</sup> The effect of rosiglitazone was found to be such that the parameters deciding the fate and extent of neurological disorder were reduced by the rosiglitazone treatment. It is known that the advanced glycation end product has a role in the prognosis of neurodegeneration.<sup>[44]</sup>

All these theoretical assessments are true if the biochemical and histopathological changes indicate the same. The test



**Figure 4:** AGE-RAGE parameter, all values are expressed as mean  $\pm$  SD, when the number of rats used in each group ( $n = 6$ ). Data were subjected to one-way ANOVA followed by Dunnett's test when normal saline was compared to haloperidol control group (disease control), haloperidol and rosiglitazone treated group (Test control) and *per se* were compared. \*a indicates  $P < 0.0001$  when compared to normal saline. NS: Normal saline, DC: Disease control, TC: Treatment control, P: *per se*, TNF: Tumour necrosis factor, IL: Interleukin. SD: Standard deviation.



**Figure 5:** Histopathology of rat cerebrum, images representing the microscopical characters of the rat's brain in the Transverse section (TS) and Virtual section (VS), where NS is normal saline, DC is disease control, TC is treatment control, and P is for *per se*. The tissue were analysed using haematoxylin & eosin stain, at 10 $\times$ .

starts with some external and behavioural parameters and leads to biochemical and histopathological studies. The behavioural test marked the memory loss and also the loss of ability to withstand the pressure induced by it. The normal control rats, which were able to withstand a higher degree of pressure or show resistance to a greater extent, were reduced in the diseased rats. The ability of rats was brought to near normal after treatment. Similar action was seen in the biochemical tests where the increased oxidation products such as CAT, SOD and GSH were reduced after treatment with rosiglitazone. Further investigation of the drug's action on AGE parameters has helped to understand its action on convalescents in this study. The parameters TNF- $\alpha$ , IL-6 and A $\beta$  protein accumulation, indicating the rise in the AGE, were reduced by the rosiglitazone. There are various models through which neurodegeneration has already been studied, and the impact of neurodegeneration through the AGE-RAGE axis and designing an animal model that includes a maximum number of parameters, including oxidation, was a priority of this study. The screening of brain histopathology was designed to understand the impact of cell damage caused by haloperidol and its treatment with rosiglitazone, which inhibits the glycation structures that are expressed with reduced gliosis structure and neural regeneration structures, indicating the impact of rosiglitazone in the treatment of neurodegenerative disorder. The action of the synaptic vesicles and other neural structures is for further studies and needs additional attention. This could further contribute to the changes that are to be considered to understand the impact of PPAR- $\gamma$  on AGE-RAGE. When compared to a similar study involving haloperidol-induced neurodegeneration, behavioural assessments, including tests such as the Morris water maze and open-field test, highlighted significant cognitive and motor deficits. Treatment with pioglitazone, another PPAR- $\gamma$  agonist, showed comparable improvements in cognitive and behavioural outcomes, suggesting a shared mechanism of action through PPAR- $\gamma$  modulation.<sup>[45]</sup> Similarly, with the antioxidant studies, comparable pre-clinical studies have shown that PPAR- $\gamma$  agonists, including rosiglitazone and pioglitazone, enhance antioxidative defences by upregulating the expression of antioxidant enzymes. For instance, studies in Parkinson's disease models also reported reduced oxidative markers after treatment with these drugs, suggesting a generalisable antioxidative mechanism across neurodegenerative conditions. Similar results were seen in the histopathological studies, and this shows that rosiglitazone can deliver the required action against neurodegeneration.<sup>[46]</sup> The study that has to be further taken up or still to be considered as a limitation is the investigation and comparison of other pathways acting as the neurodegenerative disorder treatment with that of the action pathway of rosiglitazone.

## CONCLUSION

These results suggest that the blockage of AGE has an effect on the neurodegeneration and the development of the rat model. It is indicative from the pathway discussed that the effect of PPAR- $\gamma$  blocker drugs can act by reducing the effect produced by the AGE and blocking the RAGE to cure neurological conditions. It was indicative from the results that the disease control has a higher amount of the antioxidant being produced which acts on the neurological cells as said earlier and the *per se* treated group which was subjected to the drug only showed values equivalent to that of the normal and the treated groups also show that the disease has been caused which is reduced by the drug and the conditions are improvised by the drug. The present study is everlasting since the AGE is associated with the diet and can have several other triggering centres as well, which is not easy to explore. Further study on the extent of impact needs to be considered.

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