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Effect of Rosiglitazone in the Management of Cognitive Impairment by Exploring Its Role on Advanced Glycation End Products and Their Receptors

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KEYWORDS
AGE-RAGE axis, Neurodegeneration, Cognitive impairment, Parkinson, Alzheimer, Advanced glycation end-product.

ABSTRACT:

Introduction

The impact of Advance Glycation Endproduct and Receptor for Advanced Glycation Endproduct is evident on various system such as vascular system and the neurological impact of it, in the recent researches it is being found that not only the molecular changes but the daily impact on Advanced Glycation Endproduct also produces neurodegeneration and cognitive impairment. We here understand the impact of Rosiglitazone being one of Peroxisome proliferator-activated receptors-γ as the saviour and also admire the action produced by it.

Methods

This animal study was conducted on the 4 different group of rats which consists of six rats in a group. The rats were induced to cognitive impairment disorder using Cisplatin, the rats were treated with the help of rosiglitazone. All the assessment was finally conducted by different parameters.

Result

The animal study for the impact of Advanced Glycation Endproducts impact on the cognitive impairment disorder and its treatment using Rosiglitazone was a successful done and changes which Cisplatin induced in a rat was nullified or reduced with the Rosiglitazone, the study was made on different parameter. The result show that the values of parameters were brought to normal with the rosiglitazone.

Conclusion

The results conclude with the positive effect of the rosiglitazone and this was evident by all the tests performed on the rats.

1. Introduction

Cognitive impairment is loss of ability to think, learn, remember, judgement and decisions. The pathological symbols indicating the decline in cognitive ability is decrease in the neurons in the substantia nigra, which impacts on the various other visual ability of a person. Scientists have already worked upon number of elusive evidences explaining the causes, but some additional receptors showing action advice additional researches, which led to the Advanced glycation end product and its receptor. It has role in number of mechanisms including the oxidative stress, neuronal inflammation, accumulation of NF-κ and other such protein structures [1].

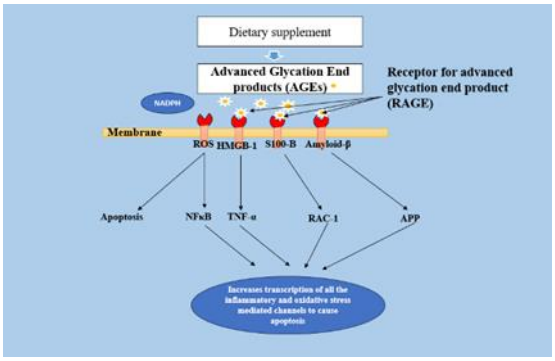

Fig: 1 Chart explaining the causes of cognitive impairment due to the AGEs.

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Reaction of proteins or fats with that of the glucose has the capability to form different accumulative structures and aggregated proteins. As some of the research's hint, is responsible for the motor dysfunction [2]. The mechanisms of AGEs formation and its accumulation explaining the Parkinson and other neurodegenerative diseases orginates from AGEs binding its Receptors (RAGE). This initiates a series of pathological and physiological reactions. This includes the production of amyloid plaques and neurofibril tangles. It further impacts at the loss of the synapses and further causing neuronal cell death. Which has the contribution in the progression of the cognitive impairment and decline in the patient's functional abilities [3].

Seeing the big picture: potential mechanism of cognitive impairment due to Receptor of Advanced Glycation Endproduct

Elevated levels of AGEs in the body, has a role to play in the formation of Reactive oxygen species and nitrogen species. These fugitive agents play roles in various different extent and level of neurological disorders [4]. AGEs from blood stream and the macrophage, bind the site of RAGE, this increases the oxidative stress and leads to mitochondrial accumulation of calcium, this leads to a cell death. It can also impact on the mitochondrial dysfunction which is also a reason for the neuron cell death, this is an important factor which plays a role in the pathogenesis of neurological disorders [5]. This being the general mechanism of AGEs impact on the cognitive impairment and neurological disorders. The molecular level of changes can better explain the extent and various mechanisms through which these neurological disorders are formed [6].

There are number of mechanisms which are described for the cause of cognitive impairment, which includes, inflammation, oxidative stress, plaque formation, impaired Blood Brain Barrier and vascular damage. These mechanisms involve some of molecular structures such as TNF-α, Amyloid-β protein, ROS, Tau protein and α-syn. All these structures are being activated by AGEs and RAGE [7].

The AGE-RAGE interaction causes the production of ROS to happen more often and this process results in the oxidative damage to the cells of the neurons. Extended exposure to ROS forces the neurons, which are generally at a higher risk of oxidative stress due to their high oxygen consumption and low levels of antioxidant defense, to undergo apoptosis [8].

Besides that, AGEs are deposited in the cerebrovascular system, where they meet the RAGE and take off the integrity of the blood-brain barrier's integrity (BBB). This grief gives a assisting hand to the transportation of peripheral inflammatory chemicals and cells into the brain, giving rise to local inflammation and neuronal damage [9].

The AGE-RAGE interaction creates an inflammatory environment that triggers the expression of beta-site APP cleaving enzyme 1 (BACE1) and amyloid precursor protein (APP), both of which are necessary for the synthesis of beta-amyloid (Aβ) peptides. Amyloid plaques, which are characteristic of Alzheimer's disease (AD), are formed as a result of aggregated Aβ peptides that are closely associated with synaptic dysfunction and neurological death [10].

RAGE-stimulated inflammation pathways also cause a tau protein to become hyperphosphorylated, leading to the growth of neurofibrillary tangles, which represent another symptom of AD. These tangles kill cells and also disturb ordinary brain functioning [11].

Taking an example of Alzheimer's disease (AD) which is a common dementia mostly among elderly patients, although aging is the single most prominent risk factor for AD, recent insights gained from the field of genetic technology indicate that inflammation-related lipids and cytokines, along with their signaling in the CNS myeloid cells called microglia, play a major contributory role to the illness. Particularly, human GWAS has a very strong connectivity to vital lipid and cholesterol molecules, e.g., Triggering Receptor Expressed on Myeloid Cells 2 (TREM2), ABCA7, Apolipoprotein E variant 4 (APOE4), etc., which are involved in AD susceptibility alongside inflammatory pathways such as complement and chemokines. The glycated molecules such as AGE also impact on the changes which are further responsible for the AD [12].

PPAR-γ agonist diminishes the activity of AGE

When we have a look at the treatment targeting AGE, PPAR-γ drugs have shown an impact in the cardio vascular diseases caused based on the increased

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production of AGE. Serious ailments involving cardiovascular diseases and autoimmune disorders explaining the root cause involvement of AGE and RAGE, have shown response to the PPAR-γ agonists, or drugs acting on this mechanism. PPARγ's influence on the uptake of fatty acids, the sensitivity to insulin, together with the stability of glucose levels within circulation is beyond doubt, but its role in the damage that AGE does to chondrocytes is still not clear [13]. According to an ever-increasing number of studies, there is diminished PPARγ expression on amyloid-β expression and reduces inflammation. One specific drug class called PPARγ agonists, which includes rosiglitazone can slow down the progression of cognitive impairment in mice and rats. This is further studied in the present animal study [14].

2. Materials and Methods

Animals

To understand the impact of Rosiglitazone on Cognitive impairment disorder, the rat blood and brain were tested biochemically and histopathological. For this test to be performed in an unbiased and statistically understandable manner, the rats were divided into 4 groups, and each group consisted of 6 rats. It was made sure that the rats were in the range of 200–250-gram weight and were jumbled with male and female rats. The health conditions of the Rats were maintained with the natural supplements, they were dwelled in polypropylene cages. The external factors such as temperature and humidity were maintained as per the CPCSEA guidelines.

Experimental design

Twenty-four wistar albino rats are used for this study. They were divided into equal groups each group contains 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 Cisplatin 1mg/kg/day for 28 days intraperitoneal (i.p.) route

Group III: Drug control Cisplatin 1mg/kg/BW/week and Rosiglitazone 2 mg/kg/p.o/day continued for 28 days.

Group IV: *Perse* Rosiglitazone 2 *mg*/kg/p.o b.w/day continued for 28 days.

Cisplatin

The 2 mg/kg/ip/week body weight dose of Cisplatin required for inducing cognitive impairment in rats. It was procured from a medical store and the manufacturer was Biochem Pharmaceutical Industries with the trade name or brand name as Cisplat, the dose was induced such that the rats received the doses at regular intervals. Once the rats indicated the cognitive impairment behavior, the rats were treated with the Rosiglitazone to find the extent of treatment.

Rosiglitazone

It was the drug of choice which was brought from Sigma Aldrich company, the dose required for the treatment of cognitive impairment was found to be 2 mg/kg/per oral body weight of the rat. This PPAR-γ agonist drug was given to treatment control rats after the disease was produced in the rats by cisplatin. The drug was given to identify the extent of the disease induced and this could only be found when the rats have disease with in them. It was also given to the *perse* group to identify and neglect the additional role of rosiglitazone in the complete study i.e., if the rat had any changes which is specific to the disease could be easily monitored.

Physical Parameters evaluation

Here after the disease and treatment induction into the patient rats, they are compared for a different physical tests and parameters. The physical evaluation reveals the internal condition of rats. The changes which can be external assessed are weight of the animal, activity of the animal, and other externally observable changes such as food intake and urine output. These are just indicators of disease condition. The symptoms might persist due to various reasons and this requires the additional test to prove that the external changes were indicating the same as assessed. There are some tests which can be used on

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the rats when it is the test of cognitive impairment and neurodegeneration. It is only possible after the training and it includes Rota Rod test, Morris Water Maze, Catalepsy test.

Body weight

The body weight of the rats was measured on regular interval during the course of experiment. This was to identify weight gain or weight loss of rats on drug administration. This external parameter also indicates the primary changes in the body [15].

Water Intake

Water intake is also a parameter which indicates the disease condition of rats. The water intake can be high or low depending upon the extent of disease, daily observation of the amount of water intake can give the extent of diseased or treated condition of then rats. This was possible when the water was given to rats on a metered bottle, where the quantity of water is represented on the water bottles externally [16].

Food Intake

The amount food of intake is the indicator of the illness. If the rat starts to decrease the diet intake, after the administration of the extracts it symbolizes 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 find out if the rat is healthy after the dosage [17].

Behavioural Parameters

Rota rod test

It is the indicator of the memory loss and the mortar neuron loss as the decrease in any of these functions also decreases the rota rod activity. It is the test which performed to identify the capability of rat to stand on the given rod after the complete training. The training period is usually started before any doses is 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 the rosiglitazone the results with the increased time on the rota rod. This indicates that the rats neural and motor functions were regained after the subjection of rosiglitazone [18].

Morris water maze test

It is also a test to identify the neural cell damage or memory loss of 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 in the pattern of the swim. The diseased rats would take more time than the rats which are treated with rosiglitazone along with the haloperidol, the normal saline rats will be compared to the treatment control rats and this will be compared to that of the *perse* 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 [19].

Tail flick test

In order to do a tail-flick test, one holds the beast and pulls its tail out on level ground. A specific heat stimulus is applied to the animal's tail usually from underneath, and a timer is set for how long it takes for the animal to react by flicking its tail away. In the tail-withdrawal test, animals are made to lie still with only their backside submerged in hot water (46-52°C). This experiment measures the time between putting the animal into water until when it deliberately takes its out. In both cases, this behaviour follows a spinal reflex that researchers understand well enough but which is under control of higher brain areas. In terms of the stimulated surface areas and the kinetics of heat transfer into the tail, both experiments very much differ.

Biochemical test

Blood sample collection

The primary test for assessment of diseased condition of rats was by the blood test. For the blood test, samples were collected from all 24 rats. The blood test was also made to identify the changes in rodents after ingestion of drug dose. There are 3 procedures for collection of blood and all three procedures were involved in the present study.

1. Intravenous: This was through the tail of rodents.
2. Retroorbital: This was through the corners of the eye without impacting the cornea and retina.
3. Punctured heart: This is only possible after the death of rats. [20]

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Preparation of tissue material

Once the complete study of behavioural and external parameters was done and completed, the animals were executed to understand the internal changes. The brain was obtained from the rats after sacrifice and skull was opened with the help of forceps in Petri dish. Once the brain was carefully withdrawn from the skull, it was cleaned with extremely chilled running water. This was done to remove all the blood and skull crushed pieces or external dirt which are attached to the brain during the process of removal. The brain was dried, and preserved such that there is no role of external factor which can alter the test or hinder in the test. Now brain was subjected to homogenisation in high-speed homogeniser, using 0.05M phosphate buffer maintained at pH 7. The temperature of the complete system was maintained at 4°C. The homogenate was divided into 2 parts. A part of it was taken for GSH test. The remaining amount of homogenate was subjected to centrifugation for separation. The speed of centrifuge was maintained at 10000-20000 rpm for 20 minutes. The resultant obtained show different layers which consists of cell fragments, steady cell and nucleus. The top most layer of the centrifugation was used for the estimation of superoxide dismutase (SOD) and other antioxidant and AGE-RAGE parameters [21, 22].

Sodium oxide dismutase (SOD)

It is an enzyme which is found in every living organism to reduce the oxidation parameters in that particular organism. The increase in the amount of SOD release indicates the increase 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 would supress the oxidative stress [23]. So, in the diseased state it is observed that the SOD action has increased and in the normal conditions the values remain the normal or less. The more the action of SOD indicates more oxidation being produced.

Glutathione enzyme (GSH)

Similar to that of SOD GSH is also an enzyme which reduces the oxidation state of the rats after infection due to various different sources. The increase in the GSH levels indicate 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 [24].

Catalase enzyme (CAT)

It is having the similar function as the above two enzymes. This enzyme helps in the conversion of hydrogen peroxide into water and oxygen molecule. The enzyme higher production increased free radical species generation and this is how the extent of oxidative stress can be studied [25].

Thiobarbituric acid reactive substances (TBARS)

Up until the advent of recent findings, most individuals thought that the thiobarbituric acid (TBA) test predominantly determined malondialdehyde (MDA). However, this is no longer the case since TBA is now known to interact with other types of molecules resulting in its alternate name: TBARS (thiobarbituric acid reactive substances). These substances include MDA, 2-alkenals, 2, 4-alkadienals and 2-thiobarbituric acid among others which yield a red color material whose wavelength measures 532 nm [26].

AGE-RAGE parameters test

IL-6

The IL-6 is a parameter to understand the AGE role in the neurodegeneration. The test was performed on the blood which was first mixed with the 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 antiIL-6 kit; the spectra validation was at 246 nm [27].

Amyloid-β protein

It was tested by ELISA technique where the amount of β-amyloid was quantified after the tissue separation and centrifugation. The anti-amyloid peptides were used in the quantification test [28].

TNF-α

It was tested by ELISA technique where the amount of TNF-α was quantified after the tissue separation and centrifugation. The anti-tumour necrosis peptides were used in the quantification test.

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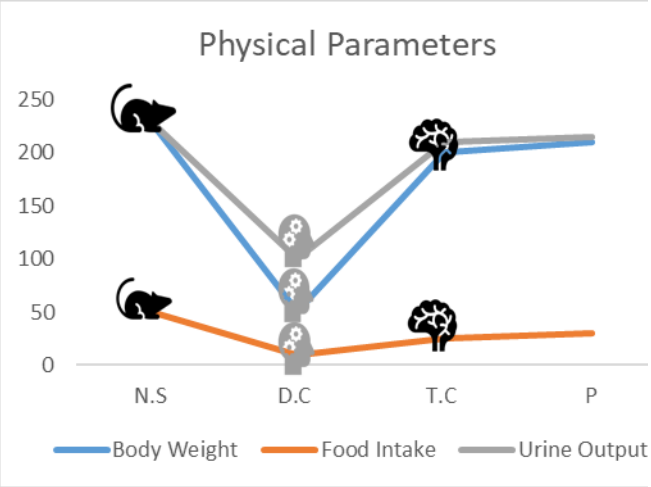
3. Results

In this study, the impact of AGE on cognitive impairment and its treatment methodology had been under experiment. The impact of AGE is on RAGE where the receptor has the further changes which makes the changes in the molecular levels, leading to cognitive impairment. In the present animal study initially, physical tests were used to understand the cognitive behavior which was compared to normal rats. The tests were further carried out on the molecular levels.

Physical Estimated parameters

The physical evaluation primarily indicates and starts with the change in weight or body weight, these changes are not particular but are the signs of cognitive impairment. It is because cognitive impairment impacts on the food and water intake reduction. It also impacts on the urine output as it reduces the urine output.



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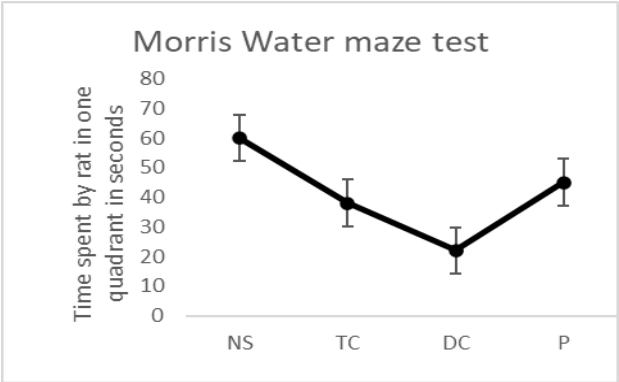
Here in the chart above it is observed that the N.S rats which are not exposed to any drug, show the values around 250 gram of food intake and urine output of around 250 ml where when exposed to cisplatin the D.C rats the amount of food intake capability and the urine output was reduced. After the ingestion of rosiglitazone, the capability of the food intake and urine output was regained similar to that of the N.S and the values were found to be above 200 grams for food intake and the Urine output was around 225 ml. The same behaviour with the food intake character of the rats can be seen.

Behavioral Parameters

The behavioural parameters are the depiction of symptoms which are common for all the cognitive impairment behaviour. Once the cognition is affected, the body decreases the activity of locomotion and understanding. This decreases the functioning of the body and hence decreases the movement of the limbs and also makes it difficult for the animal to understand the reaction which has to be shown. The animal is under the state of confusion and also has lost the ability to withhold the strength which it previously did in the normal condition.

The number of tests performed to understand the behaviour here are Morris water maze test, Rota rod test, Tail Flick test and assessment of thermal hyperalgesia.

In the Morris water maze and rota rod test the cognition impact was observed in the rats, it is when the retention time is affected on rota rod and the recognition time is affected in Morri's water maze. When we look at the normal saline data of both Morris water maze test and Rota rod test it shows that the recognition and swimming time for the rats was high and the rat was able to swim for a longer duration of time as its cognition was not affected and it could also retain the consistency holding the rota rod which was reduced as the Cisplatin was ingested in the rats and it regained back its time when the doses of rosiglitazone was given to it.



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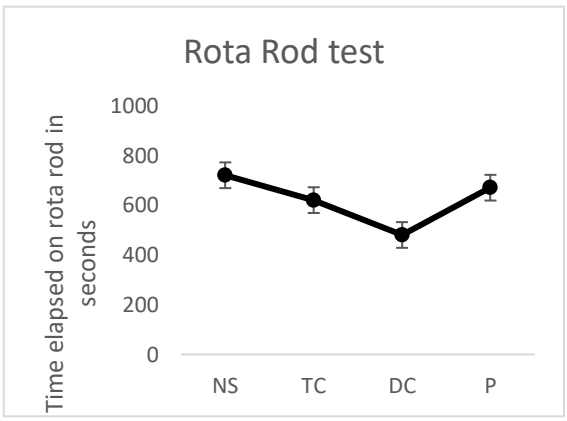
The readings for the Morris water maze normal saline rats were around 60 seconds which was reduced to 15 seconds when the rats were ingested with the cisplatin in disease control rats and it regained its strength on rosiglitazone ingestion and it was restored to around 40 seconds. The same was observed in the rota rod test and the readings of the normal saline rats was found to be 700 seconds which reduced to 500 seconds in the disease control rats and the restoration was seen in the rats categorised under treatment control the readings was found to be 600 seconds. The *perse* did not show much different results from the normal saline group as the cognitive impairment was not seen in the rats which were only treated with the rosiglitazone drug.



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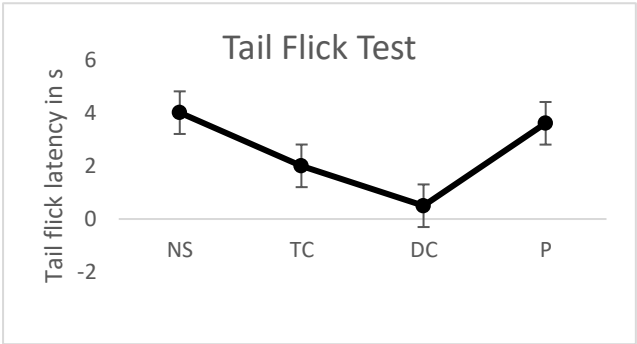
As discussed in the Morris water maze and Rota rod test similar results were seen in the tail flick test. The tail flick on the external stimuli did show changes in the normal saline as well as all the other group of the rats as the sensitivity was increased in the cognitive impairment induced rats i.e., the rats which were given Cisplatin the rats did not stop its tail flick and increased the tail flick movement. The tail flick movement on the external stimuli took 4 seconds in the rats which were just treated with normal saline and daily usual food and water intake. These tail flick movements were increased or the time of tail flick movement was reduced to 2 seconds when it was treated with rosiglitazone and disease control rats due to tremors or sensitivity increased the tail flick movements which is also due to the molecules and the rat is in the state of anxiety due to the release of chemicals within the brain of rats when the animals were given Cisplatin to induce Cognitive impairment. The value found was around a second.



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The biochemical tests

As it is theoretically being studied that the oxidation and inflammation are the root causes for the cognitive impairment. The study of the different oxidation parameters in the brain homogenate would provide the extent of the disorder. The values of SOD, GSH, CAT and TBARS indicate that accordingly. The mean of SOD values for normal control was found to be 2.3 U/mg, 0.0036 nmol/mg, 2.54 mmol/ml and 65.033 µmol/l, the cisplatin increased the oxidation levels 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, 1.76 mmol/ml and 85.83 µmol/l 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, 2.20mmol/ml and 78.33 µmol/l.

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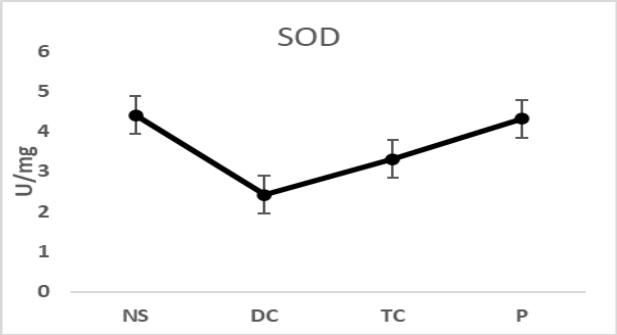
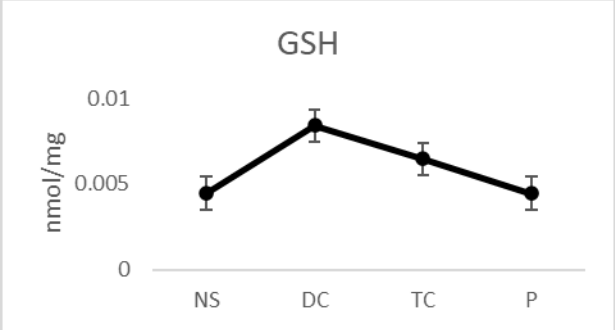
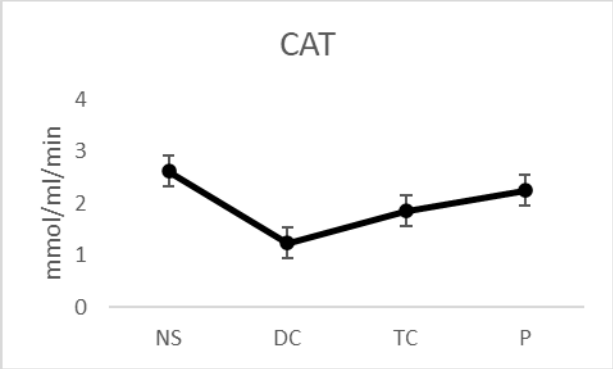
The increased levels of SOD, GSH, CAT and TBARS indicate higher reactions with the oxidant molecules. The drug rosiglitazone acts on reduction of the free radicals and thereby reducing the oxidant stress and also reducing the diseased conditions.







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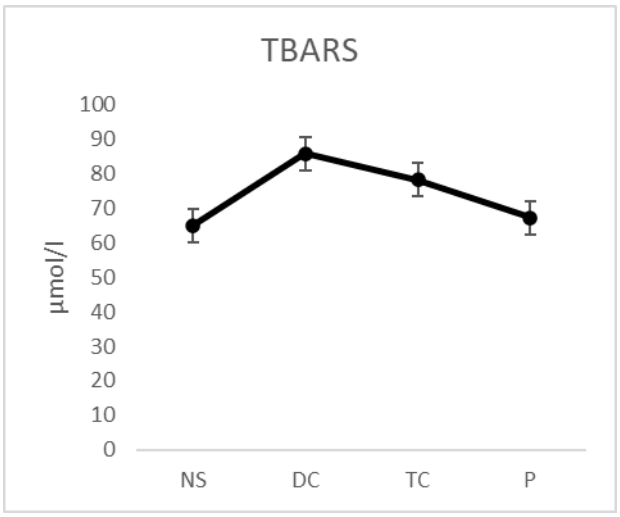
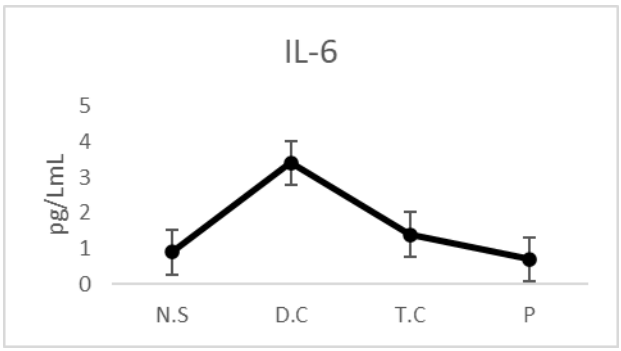
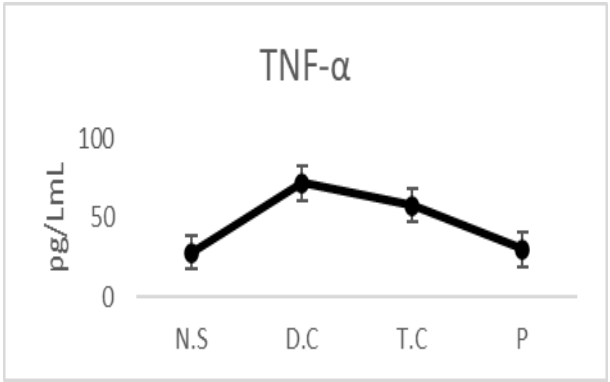
AGE-RAGE Parameters

The Age-Rage parameters show the increased levels of values in diseased rats indicating the presence of cognitive impairment. The readings of IL-6, TNF-α, Amyloid-β protein and GFAP are low i.e., at the 3 ρg/Lml, 23 ρg/Lml, 0.7 ng/L and 0.06 µg/L. The values increased to 10 ρg/Lml,70 ρg/Lml, 3.5 ng/L and 0.255 µg/L, these readings were reduced with the help of Rosiglitazone.







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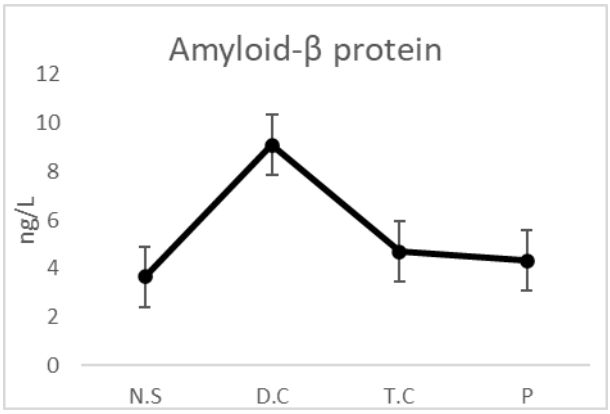

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4. Discussion

As discussed in the introduction the AGE has different mechanisms through which the cognitive impairment can be caused in any animal or human being. The most common of which is the ROS generation which further kills the cell which impacts on the cognition. This increase in ROS can only be estimated with the help of bloods and serum of the affected animal, the changes in the readings also indicate that the quantity of species such as SOD, CAT and GSH along with TBARS were increased in the blood of animal. In the present study the activity of rats was lost along with increase in the values of ROS. The AGE indicators also had a drastic change compared to normal which indicate that the Cisplatin had triggered AGE and was able to produce cognitive impairment. The amyloid-β protein and the IL-6 increment also indicate the cognitive impairment. It was also observed that the rosiglitazone was able to improve the conditions of the affected rats. This was because of the PPAR-γ impact, the drug Rosiglitazone was able to reduce all the elevated values. The ROS values were normalised by rosiglitazone and also the readings of AGE parameters were reduced.

5. Histopathological studies

Studying the cerebrum using microscope to study the neural cells of the rats to identify the damages and the neural conditions of the rats. 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 *perse* groups which would indicate if there are any changes which are 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 being not 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 in order to assess the effects of rosiglitazone therapy and cisplatin-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. Cisplatin thus is a cognitive impairment causing agent which acts upon the neural cells and increases the condition of disease. The study of cerebral tissue of this group of rats (histopathological study), demonstrates significant gliosis (buildup of glial cells) in the cerebral cortex tissue. This is mild in the condition as it is the haloperidol and rosiglitazone treated group, they show significant neuronal deterioration. This shows that the gliosis and neuronal degeneration was 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 also helps to reduce the damage which is produced by the cisplatin.

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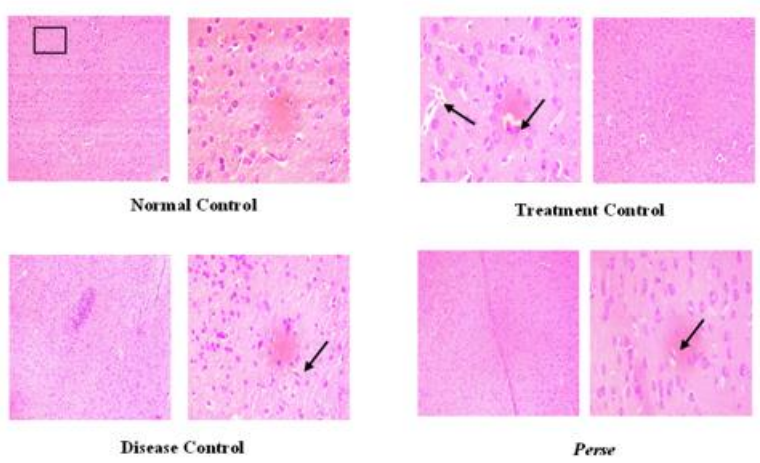

Fig 2: Histopathology of rat cerebrum

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Author contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Conflict of interest

The authors declare to have no conflict of interest.

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