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EVALUATING NEUROPROTECTIVE EFFECTS OF ASCORBIC ACID AGAINST 3-NITROPROPIONIC ACID INDUCED HUNTINGTON'S DISEASE IN RATS: POSSIBLE INVOLVEMENT OF GABAA RECEPTORS

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ABSTRACT

Huntington's disease (HD) is a genetic, progressive and fatal neurodegenerative disorder characterized by the gradual development of involuntary muscle movements and associated with severe degeneration of basal ganglia neurons (Paulsen et al., 2008; Raymond et al., 2011). An expanded unstable CAG trinucleotide repeat within the coding region of the HD gene has been identified as the genetic mutation responsible for the disease (HD Collaborative Research Group, 1993). The progression of disease is generally late-onset and characterized by psychiatric, cognitive and motor disturbances (Shannon, 2011) due to progressive neurodegeneration in the cerebral cortex, hippocampus, striatum and basal ganglia (Bates, 2004; Hart et al., 2013). In some cases, involuntary movements may be prominent even in the early stages. As documented, first signs of HD are behavioral disturbances and learning difficulties (Paulsen & Canybeare, 2005; Stout et al., 2012).

KEYWORDS: *Disease, Generally Late-Onset,Characterized By Psychiatric Cognitive*

INTRODUCTION

Huntingtin is proteolysed by caspase-1 and caspase-3 (Goldberg *et al.,* 1997; Wellington *et al.,* 2000). In HD models and in presymptomatic and early symptomatic stages of HD patients caspase-1 and caspase-3 gene expression is transcriptionally up-regulated (Chen *et al.,* 2000). This leads to an increase of caspase-mediated cleavage of huntingtin and increases the generation of N-terminal huntingtin fragments that are prone to form toxic aggregates in neurons (Hackam *et al.,* 1998; Wellington *et al.,* 2000), while depleting wild type huntingtin (Kiechle *et al.,* 2002). It appears that some features of HD result from the depletion of huntingtin protein function, whereas the consequent N-terminal toxic fragments themselves may exert toxic effects on the cell by transcriptional disruption of other genes (Nucifora *et al.,* 2001; Hickey *et al.,* 2003; Landles *et al.,* 2004).

HD symptoms and signs begin insidiously and onset usually occurs during the fourth or fifth decade of life with a mean survival of 15 to 20 years after disease onset (Vonsattel *et al.,* 2004). However, the age of disease onset can vary from childhood until old age and can be correlated with the length of the polyglutamine repeat in the huntingtin gene (Raymond *et al.,* 2011). In patients with juvenile-onset HD, with disease onset before the age of 20 years, the signs and symptoms are somewhat different; they include bradykinesia, rigidity and dystonia while chorea can be completely absent. Involuntary movements can take the form of tremor or myoclonus and affected children often develop epileptic seizures (Rubinsztein, 2002; Vonsattel *et al.,* 2004). As to epidemiology, the incidence and prevalence of HD varies between ethnic

groups. The disorder is more common among European populations with a prevalence of almost 1 in 10,000, in comparison with Japanese and African populations, where the prevalence may be less than 1 in 1,000,000 (Vonsattel *et al.*, 1998; Vonsattel *et al*., 2004).

3-Nitropropionic acid (3-NP) is a natural environmental toxin obtained from various plants and fungi which can induce HD (Coles *et al.*, 1979; Kumar and Kumar, 2008). 3-NP is a non-competitive inhibitor of mitochondrial succinate dehydrogenases (SDH) in the brain (Gould *et al.*, 1985; Alexi *et al.*, 1998; Brouillet *et al*., 1998), an enzyme located in the mitochondrial inner membrane and causes rapid suppression of energy metabolism in the brain (Beal, 1994; Guyot *et al*., 1997). This phenomenon results in the release of excitotoxic neuromediators induces a reduction in the ATP production and gives rise to free radicals (Tabrizi *et al.*, 2000; Perez-Severino *et al.*, 2002). Both, nitric oxide and reactive oxygen species produced by3-NPdisturbs glutathione redox cycle (Beal, 1998; Tunez *et al.*, 2004) and causes oxidative stress.It has also been reported that 3-NP administration results in striatal lesions similar to that of HD brains (Brouillet *et al*., 1999).

Vitamin C (Ascorbic acid) is the most important vitamin in fruits and vegetables, and has been regarded as the most potent natural antioxidant (Vissers *et al.*, 2011). Although, most of the higher animals can synthesize vitamin C in their liver or kidneys, but in humans, the terminal enzyme in its synthetic pathway is absent and thus, vitamin C has become an essential dietary component for human survival (Vissers *et al.*, 2011). Ascorbic acid is a versatile water soluble radical scavenger widely distributed in aerobic organisms that play a central role in the protection of cellular components against oxidative damage by free radicals and oxidants that are involved in the development and exacerbation of a multitude of chronic diseases (Ozkanlar & Akcay, 2012; Myung *et al.*, 2013).Studies have reported that Ascorbic acid being an endogenous redox agent is highly concentrated in the various regions of the CNS and is found to be accumulated in high concentration in neurons and glial cell (Harrison *et al*., 2009).Ascorbic acid serves as a neuromodulator in normal brainfunctioning and as a neuroprotective agent in various conditions of oxidative stress (Grunewald, 1993). Previous studies have indicated that ascorbic acid is cardio-protective, hepatoprotective, anticonvulsant as well as reno-protective in nature (Korkmaz *et al.*, 2009).

γ-aminobutyric acid (GABA) has been found to play an important role in the basal ganglia function (Graybiel *et al.*,1990). The GABA system is the major inhibitory system in the rat brain (Wallace *et al.*, 2007). The evidences suggest that GABA may play a supplementary role in brain diseases by modulating dopamine and serotonin. A GABAergic deficit is particularly apparent in insomnia, anxiety disorders, epilepsy, and schizophrenia (Wallace *et al*., 2001; Scheffer *et al*., 2003). The caudate nucleus and putamen of the brain have high levels of GABA (Graybiel *et al.*,1983).

The substantianigra (SN) is a major division of the basal ganglia, a group of subcortical nuclei involved in a variety of functions including movement, memory and cognition (Celada *et al*., 1999). Most of the effects of GABA in the SN are mediated through postsynaptic GABA-A receptors, which cause an increase in chloride conductance that underlies fast inhibitory postsynaptic potentials (Pirker *et al.*, 2000; Schwarzer *et al.*, 2001). Dysfunctions of GABAergic transmission in the SN have been implicated in a variety of diseases and their models. Excitotoxic lesions of the striatum leads to a loss of striatonigral GABAergic neurons and to changes in striatal targets that are similar to the changes that occur in Huntington's disease and, as such, have been used as models of this disease (Glass *et al.*, 2000). Furthermore, functional changes have been reported in nigral GABA-A receptors in an in vitro expression system following excitotoxic

lesions of the striatum in the rat (Sanna *et al.,* 1998). Inappropriate disinhibition of basal ganglia targets have been proposed to underlie the abnormal involuntary movements associated with Huntington's disease (Albin *et al.,* 1989; DeLong, 1990).

Bicuculline acts as a competitive antagonist at GABAA receptors (Andrews and Johnston, 1979). This evidence is supported by functional studies. Single channel studies have shown that bicuculline reduces GABA activated conductance by reducing both channel opening times and opening frequency (Macdonald *et al.,* 1989). In this study, bicuculline is employed as an antagonist to confirm the involvement of GABA receptor.

There has been a lot of research at various levels involving GABA-A receptors in HD. But, direct involvement of Ascorbic acid in HD and its action through GABA-A receptor has not been studied. So, present study is designed to investigate the activation of GABA-A receptor as a potential molecular mechanism in Ascorbic acid-mediated protection against 3-NP induced HD.

MATERIALS AND METHODS

Experimental Animals

Male wistar rats (procured from National Institute of Pharmaceutical Education and Research, Mohali) maintained in the central animal house of the facility of Chandigarh College of Pharmacy, Landran, Mohali, Punjab and weighing between 200 and 250g of were used. The animals were kept under standard conditions of light and dark cycle with food and water ad libitum in plastic cages with husk bedding. All the experiments were carried out between 09:00 and 15:00 hr in semi- sound proof laboratory conditions. The protocol was approved by the Institutional Animal Ethics Committee vide no (1201/a/08/CPCSEA) and carried out in accordance with the Indian National Academy Guidelines for the use and care of animals. Adequate measures were taken to minimize the pain and discomfort to the animals. The care of the animals was carried out as per the guidelines of the Committee for the Purpose of Control and Supervision of Experimental Animals (CPCSEA), Ministry of Environment and Forests, Government of India.

Drugs and Chemicals

All chemicals and biochemical reagents of analytical grade and highest purity were used. The following agents were used in the present study: 3-Nitropropionic acid (Sigma-Aldrich Corporation, India) was diluted with saline (adjusted pH 7.4 with NaOH) and administered intraperitoneally *(i.p*), Ascorbic Acid (LobaChemiePvt.LTD.), Bicuculline (Cayman chemicals company) was used as an antagonist of GABA receptors and Mifepristone (1mg/kg, *i.p)* was used as progesterone antagonist. DMSO and Olive Oil was used to Bicuculline and Mifepristone.

Animal Model for Huntington's Disease

3-nitropropionic acid (10mg/kg) was administered intraperitoneally (i.p) once daily for a period of 14 days to induce the symptoms of HD (Kumar & Kumar, 2009). 3-NP injection was freshly prepared in normal saline (0.5 ml of normal saline per 100gm of animal weight) before administration. Only rats with positive behavioral effects were included in the study. All animals were trained for 4 days before administration. All the behavioral parameters were observed before drug administration and 24 hrs after first dose and 24 hrs after the last dose, that on the 15^{th} day after the start of 3-NP treatment.

Measurement of Body Weight

Body weight was noted in the first and last days of the experiment. Percentage change in body weight was calculated in comparison with an initial body weight on the first day of experimentation.

BEHAVIOURAL ASSESSMENTS

- **Elevated Plus Maze Paradigm**

Elevated plus maze is used to test learning and memory (Kumar *et al.,* 2010). The elevated plus maze consisted of two opposite open arms crossed with two closed arms of the same dimensions. The arms are connected to a central square. Acquisition of memory was assessed on the day 1st before initiating 3-NP treatment in the control group. Rats were placed individually at one end of an open arm facing away from the central square. The time taken by the animal to move from the open arm into the closed arm is recorded as the initial transfer latency. The animals were allowed to explore the maze for 30sec after recording the initial latency and then returned to its home cage. If the animal did not enter an enclosed arm within 90sec, it was gently pushed into the enclosed arm and the transfer latency is assigned as 90sec. Retention of memory was assessed by similarly placing a rat on an open arm and noting the retention latency 24 hr (day 2) and 4 days (day 5) after the initial transfer latency (ITL). These times were referred to as the first retention transfer latency and second retention transfer latency, respectively (Kulkarni *et al.,* 1993).

- **Morris Water Maze (Spatial Navigation Task)**

The acquisition and retention of the spatial task were examined using the Morris water maze. Animals were trained to swim to a platform in a circular pool located in a test room. The pool was filled with water (24+ 2c) to a depth of 40 cm. A movable circular platform, 9 cm in diameter and mounted on a column was placed in the pool 1 cm above the water level (visible platform) for the maze acquisition test. Another movable platform, 9 cm in diameter and mounted on a column, was placed in the pool 1 cm below the water level (hidden platform) for the maze retention test.

Maze Acquisition Test (Training)

Animals received a training session consisting of 4 trails in day for four days before 3-NP administration. In all 4 days, the starting positions were different. The latency to find the escape platform was recorded up to a maximum of 2 min. The visible platform was fixed in the centre of one of the 4 quadrants and remained there throughout the experiment. The time taken by a rat to reach the platform on the fourth day was recorded as the initial acquisition latency.

Maze Retention Test (Testing For Retention of the Learned Task)

Following 24 h (day 5) and 14 days (day 15) after the initial acquisition latency (IAL), rats were randomly released at any edges facing the wall of the pool and tested for the retention of the response. The time taken to reach the hidden platform on days 5 and 15 following initiation of 3-NP treatment was recorded and termed as the first retention latency and second retention latency, respectively (Frautschy *et al.,* 2001).

- **Assessment of Gross Loco motor Activity by Using Act photometer**

The locomotor activity was monitored using Actophotometer on 1st, 5th, 15th, day of 3-NP administered and Ascorbic Acid treated groups (Kumar *et al.,* 2010). The horizontal motor activity was detected by two perpendicular arrays

of 15 infrared beams located 2.5 cm above the floor of the testing area. Each interruption of a beam on the x or y-axis generated an electric impulse, which was presented on a digital counter. Similarly, the vertical motor activity was recorded using the additional row of infrared sensors located 12 cm above the floor. Each animal was observed over a period of 5 min and values expressed as counts per 5 min. The apparatus was placed in a darkened, light and sound attenuated and ventilated testing room (Reddy *et al.*, 1998)

- **Assessment of Grip Strength Activity by Using Rotarod**

All animals were evaluated for motor ability and balance by using the rotarod on 1st, 5th, and 15th day of treatment (Kumar *et al.*, 2010). The rats were given a prior training session before initialization of any therapy to acclimate them to Rotarod apparatus. Rats were placed on the rotating rod with a diameter of 7 cm (speed 25 rpm). The length of time in the rod was taken as the measure of competency. The cutoff time as 180 sec and each rat performed three separate trials. The average result was recorded (Kulkarni, 1999).

- **Assessment of the Biochemical Parameters**

Biochemical tests were carried out after the last behavioural test.

- **Tissue Preparation**

Animals were sacrificed by decapitation and the brains were removed and rinsed with ice-cold isotonic saline. Brain tissue samples were then homogenized (10 times (w/v) with ice –cold 0.1M phosphate buffer (ph 7.4). the homogenate was centrifuged at 10,000xg for 15 min and aliquots of supernatant were separated and used for biochemical experiments.

- **Thiobarbituric Acid Reactive Substances (TBARS)**

The quantitative measurement of thiobarbituric acid reactive substances (TBARS), an index of lipid peroxidation in renal tissue was performed according to method of Nichans and Samuelson, (1968). In this method, malondialdehyde and other TBARS was measured by their reactivity with thiobarbituric acid in an acidic condition to generate pink colouredchromophore which will be measured spectrophotometrically at 535 nm. To 1.0 mL of tissue homogenate, 2 mL of trichloroacetic acid-thiobarbituric acid-hydrochloric acid (TCA-TBA-HCl) reagent will be added and mixed thoroughly. The mixture will be kept in a boiling water bath for 15 min. After cooling the tubes will be centrifuged at 10000 g for 10 min. The colour developed in the supernatant will be measured at 535 nm against blank reagent. A series of standard solutions of tetra methoxy propane in the concentration of 1 to 10 nM will be treated in the similar manner. Values will be expressed as nano moles per mg of protein.

PREPARATION OF REAGENTS

Preparation of 0.37% Thiobarbituric acid (TBA) Solution

0.37g of thiobarbituric acid was dissolved in 100ml distilled water.

Preparation of 15% Trichloroacetic acid (TCA) Solution

15 ml of TCA was dissolved in 100ml distilled water.

Preparation of 0.25N of Hydrochloric acid (HCL) Solution

2.23 ml of HCL was taken in measuring cylinder and volume was made upto 1000 ml with distilled water.

Preparation of 1nM 1,1,3,3-Tetraethoxy Propane

0.82 ml of standard 1,1,3,3-tetraethoxy propane was diluted to 5 ml with diluted water to make 1M solution. 1ml of this solution was further diluted to 10 ml with distilled water and this diluted process was further repeated for eight times to get 1nM 1,1,3,3-Tetraethoxy propane

Reduced Glutathione (GSH) Level

The whole brain level was estimated by method of Beutler et al, (1963). The supernatant of tissue homogenate were mixed withtrichloroacetic acid (10%w/v) in 1:1 ratio. The tubes were centrifuged at 1000g for 10 min at 4 . The supernatant obtained (0.5 ml) was mixed with 2 ml of 0.3 M disodium hydrogen phosphate. Then 0.25 ml of 0.001 M freshly prepared DTNB dissolved in 1% w/v sodium citrate was added and absorbance would be noted spectrophotometrically at 412 nm. Different concentrations of reduced glutathione (GSH) standard were processed similarly to prepare a standard curve (10-100 µm). Results were expressed as micromoles of reduced glutathione per mg of protein.

PREPARATION OF REAGENTS

Preparation of 5, 5'-Dithiobis 2-Nitrobenzoic Acid (DTNB) Solution

7.92 mg of DTNB was dissolve in 20 ml of 1% of sodium citrate.

Preparation of 1% of Sodium Citratesoultion

1g of sodium citrate was dissolve in 100 ml of water.

Preparation of 0.3 M Disodium Hydrogen Phosphate (8.4pH)

4.26 g of anhydrous disodium hydrogen phosphate was dissolve in 100 ml distilled water.

Preparation of 10% Trichloroacetic Acid Solution

10 g trichloroacetic acid was dissolved in 100 ml distilled water.

Preparation of 100 µM reduced glutathione

6.14 mg of reduced glutathione was dissolved in 200 ml distilled water

Estimation of Total Protein Content

Brain total protein was estimated by the method of Lowry *et al*. (1951) with slight modifications using bovine serum albumin (BSA) as a standard. 0.15 ml of supernatant tissue homogenate was diluted to 1 ml with distilled water and 5 ml of Lowry reagent was added. The contents were mixed thoroughly and the mixture was kept for 15 min at room temperature (37°C). Then, 0.5 ml 0f 1:1 v/v diluted Folin-Ciocalteu's reagent was added. The content was then be vortexed vigorously and incubated at room temperature (37°C) for 30 min. The protein content was determined spectrophotometrically at 750 nm against suitably prepared blank and a standard curve using 0.2-2.4 mg/ml of BSA was

plotted. The amount of total protein was expressed in mg/ml. The absorbance from a standard curve generated using 1,1,3,3 tetra-methoxy propane as standard (range = 1nmol -10 nmol) wasextrapolated. The values was expressed as nmol per gm tissue.

PREPARATION OF REAGENTS

Preparation of Lowry Reagent:

Lowry reagent was prepared by mixing 1%w/v of copper sulphate, 2% w/v sodium potassium tartrate, 2% w/v of sodium carbonate in 0.1 M sodium hydroxide in a ratio of 1:1:98.

Preparation of 1%w/v of Copper Sulphate Solution

1g cupric sulphate was dissolved in 100ml distilled water.

Preparation of 2%w/v Sodium Potassium Tartrate Solution

2g of sodium potassium tartrate was dissolved in 100ml distilled water.

Preparation of 2% w/v of Sodium Carbonate Solution (Na2 Co3)

2g sodium carbonate was dissolved in 100ml distilled water.

Preparation of 0.1 M Sodium Hydroxide Solution

4g of NaOH was dissolved in 1000 ml distilled water.

Preparation of 2.4 mg/ml Bovine Serum Albumin (BSA) Solution

24 mg of BSA was dissolved in 10 ml distilled water.

Preparation of Folin-Ciocalteu'sphenol Reagent Solution

Folin-ciocalteu's phenol reagent was prepared by diluting the equal volume of folin-ciocalteu's phenol reagent with distilled water in the ratio of 1:1.

Estimation of Brain Nitrite / Nitrate Concentration Level

The accumulation of nitrite in the supernatant was measured as an indicator of the production of nitric oxide determined by the method of Green *et al.(* 1982) using a colorimetric assay with the Gries reagent (0.1% N-(1-napthyl) ethylenediaminedihydrochloride, 1% sulphanilamide and mixture was incubated for 10 min at room temperature in the dark, and the absorbance was measured at 540 nm using a (UV-1800 spectrophotometer, shimadzu). The standard curve of sodium nitrite (5 to 50µM) was plotted to calculate concentration of brain nitrite.

Prepartion of Reagents

Griess reagent was prepared by dissolving 1:1 solution of 1.0% of sulphanilamide in 5 M HCL solution and 0.1% N-napthyl-ethylene-diamine in water.

Prepartion of 1.0% Sulphanilamide Solution

1g of sulphanilamide was dissolved in 5 M HCL and volume was made upto 100 ml.

Prepartion of 0.1 N- Nathy Lethylenediamine Solution

100 mg N- nathylethylenediamine was dissolved in 100 ml of distilled water.

Prepartion of 5M HCL Solution

44.65 ml of concentration HCL was in 100 ml of distilled water.

Estimation of Brain Acetyl Cholinesterase (AChE) Activity

The cholinergic neuron marker acetyl-cholinesterase, will be estimated in whole brain according to the method of Ellman *et al.* (1961) with slight modifications (Koladiya *et al*., 2009). It is measured on the basis of the formation of yellow color due to the reaction of thiocholine with dithiobisnitrobenzoate. The rate of formation of thiocholine from acetylthiocholine iodide in the presence of brain cholinesterase was measured using a spectrophotometer. 0.5 ml of supernatant of the brain homogenate was pipette out into a 25 ml volumetric flask and diluted with freshly prepared DTNB solution (10 mg DTNB in 100 ml of Sorenson phosphate buffer, pH 8.0). From volumetric flask, two 4 ml portions will be pipette out into two test tubes. Into one of the test tubes, two drops of eserine solution to be added. Then 1 ml of substrate solution (75 mg acetylcholine iodide per 50 ml of distilled water) will be pipette out into both of the test tubes. The test tube containing eserine was taken as blank and the change in absorbance per minute of the test sample was read using a spectrophotometer at 412 nm (Abhinav *et al*., 2010; Kumar *et al*., 2009).AChE activity was calculated using the following formula:

$$R=\frac{\delta O.D.*volumeofassay}{E*mgofprotein}$$

Where;

R = rate of enzyme activity in ‘n’ mole of acetylcholine iodide hydrolyzed/min/mg protein,

δ O.D. = change in absorbance/min,

E = Extinction coefficient (13600/M/cm)

PREPARATION OF REAGENTS

Preparation of 5,5’-Dithiobis (2-nitrobenzoic acid) DTNB

10 mg of DTNB was dissolved in 100 ml of Sorensen phosphate buffer

Preparation of Sorensen Phosphate Buffer (PH 7.4)

Sorensen phosphate buffer was freshly prepared by mixing 47.35 ml of 0.2 M dibasic sodium phosphate and 2.65 ml of 0.2 M monobasic sodium phosphate.

Preparation of 0.2 M Dibasic Sodium Phosphate Solution

0.2 M dibasic sodium phosphate was prepared by dissolving 35.6 g of dibasic sodium phosphate in distilled water and volume was made upto 1 litre with distilled water.

Preparation of 0.2 M Monobasic Sodium Phosphate Solution

0.2 M monobasic sodium phosphate was prepared by dissolving 27.6 g of monobasic sodium phosphate in

distilled water and volume was made upto 1 litre with distilled water.

Preparation of Acetylthiocholine Iodide Solution

75 mg of acetylthiocholine iodide was dissolved in 50 ml of distilled water.

Myeloperoxidase Activity

The myeloperoxidase (MPO) activity which is measured as an index of neutrophil accumulation which can be measured by using method of Krawisz *et al*., (1984). In the pellet obtained after tissue homogenization 10 mL of ice-cold potassium phosphate buffer (pH 6.0) containing 0.5% hexadecyltrimethyl ammonium bromide (HETAB) and 10 mM ethylene diamine tetra acetic acid (EDTA) will be added and subjected to one cycle of freezing and thawing and then sonication for has been taken for 15 s. The contents will be centrifuged at 15,000 g for 20 minutes. 0.1 mL of supernatant obtained after centrifugation and mixed with 2.9 mL of phosphate buffer containing 0.16 mg/mL of o-dianisidine hydrochloride and 0.0005% hydrogen peroxide (H_2O_2). The change in absorbance was measured byusing spectrophotometer at 460 nm. The MPO activity is expressed as unit per gram of tissue weight where 1 unit is the quantity of enzyme able to convert 1 µM of $H_2O_2$to water in 1 minute at room temperature. The calculation of MPO activity will be done using formula:

MPO activity (U/g) = X / Weight of the tissue

Where X = 10 x change in absorbance per minute/volume of supernatant taken in mL

Histological Evaluation

Haematoxylin and eosin staining of brain tissue will be done for histological parameters. The brain tissues will be preserved in 10% formalin and dehydrated in graded concentrations ofethanol, immersed in xylene and then embedded in paraffin. The sections of 4 µm thickness will be cut and placed on slide using commercial Baker's mounting fluid. Paraffin wax will be removed by warming the slide gently, until the wax melts and then will be washed with xylene. This was followed by washings with absolute alcohol and water to hydrate the sections and stained with haematoxylin and eosin described by Clayden (1971). The hydrated sections were stained with haematoxylin for 15 min. The stained sections will be washed with water and they will be treated with 1% acid alcohol mixture for 20s. The acid alcohol mixture washed off with water and sections will be counterstained with 1% aqueous solution of eosin for 2 minutes. After washing with water to remove excess of eosin, the sections was dehydrated using absolute alcohol and then mounted using Canada balsam as mounting agent. The slides were observed for gross histopathological changes and neutrophil accumulation.

Treatment Schedule

All animals were acclimatized for atleast 2 hrs before testing unless otherwise specified in all the experiments. Animals were divided in seven groups and each group consisted of six animals as approved by IAEC for the post emptive paradigms. To evaluate the effect of Ascorbic Acid (100, 200 mg/kg, *i.p*) treatment was initiated on the 1st day and continued till 14th day and 3-nitropropionic acid was also administered along with Ascorbic Acid.

EXPERIMENTAL PROTOCOL

Group I (Control, n= 6)

Rats were administered with normal saline (10 mg/kg/day, i.p) 30 min before the acquisition trails conducted from day 1 to day 4 and 30 min before retrieval trail conducted on day 5 using Morris water maze (MWM) test.

Group II (DMSO Conrol, n= 6)

Rats were administered with DMSO (1mg/kg/day, i.p) daily for 14 days followed by exposure to MWM test.

Group III (Olive Oil Control, n=6)

Rats were administered with Olive Oil (1mg/kg/day, i.p) daily for 14 days followed by exposure to MWM test.

Group IV (3- NP Control, n= 6)

The rats were administered with 3- Nitro-proponic acid (3- NP) dose (10 mg/kg/day, i.p, 0.9 % w/v, i.p) for 14 days followed by the exposure to the MWM test.

Group V (Ascorbic Acid per se, n= 6)

Rats were administered with ascorbic acid (200 mg/kg/day, i.p), 30 mins before acquisition trails from day 1 to day 4

Group VI (3-NP + Ascorbic acid (LD), n=6)

Ascorbic acid (100 mg/kg/day, i.p) was administered to rats 30 mins before 3-NP (10 mg/kg/day, i.p) administration.

Group VII (3- NP + Ascorbic acid (HD), n=6)

Ascorbic acid (200 mg/kg/day, i.p) was administered to rats 30 mins before 3- NP (10 mg/kg/day, i.p) administration.

Group VIII (Bicuculline + Ascorbic acid (HD) + 3NP, n=6)

Bicuculline (10 mg/kg/day,i.p) was administered to rats 30 mins before Ascorbic acid. Ascorbic acid (200 mg/kg/day,i.p) was administered 30 mins before 3-NP.

Group IX (Mifepristone + Ascorbic acid (HD) + 3-NP. N=6)

Mifepristone (1mg/kg/day, *i.p*) was administered to rats 30 mins before Ascorbic acid. Ascorbic acid (200mg/kg/day, *i.p*) was administered 30 mins before 3-NP (10mg/kg/day, *i.p*).

RESULTS

Effect of Ascorbic Acid on Body Weight of Animals

There was no change in the initial and final body weight of control animals. However, 3-NP treatment caused a significant decrease in body weight on day 15th as compared to control group. Ascorbic Acid *per se* (200 mg/kg, *i.p*) and vehicle treatment had no effect on body weight, however pre-treatment with Ascorbic Acid (100 mg/kg and 200 mg/kg, *i.p*) on 3-NP treated rats significantly and dose dependently prevented the decrease in the body weight (Table 1). Moreover

treatment with Bicuculline (1 mg/kg, *i.p*) and Mifepristone (1mg/kg/day, *i.p)* significantly abolished the effects of Ascorbic acid.

Effect of Ascorbic Acid on Memory and Learning using Morris Water Maze

All the animals showed an initial increase in escape latency, which declined with continued training during the acquisition of a spatial navigation task. The mean retention latencies to escape onto the hidden platform did not alter in control rats on all days throughout the experiment. However, the mean retention latencies in the 3-NP (10 mg/kg, i.p) treated rats were increased significantly ($p<0.05$) after initial training in the water maze on days $5^{th}$and 15^{th} of 3-NP as compared to control group. The time spent in the target quadrant (TSTQ) was also decreased in the 3-NP treated rats as compared to control group. Ascorbic acid (200 mg/kg i.p.) *per se*and vehicle treatment had no effect on memory and learning when compared with control group. Moreover, treatment with bicuculline (1 mg/kg, *i.p*) abolished and Mifepristone (1mg/kg/day, *i.p)* the ascorbic acid mediated reduction in retention latencies (Figure 1).

Effect of Ascorbic Acid on Elevated Plus Maze Activity

In this study, the mean initial transfer latencies (ITL) on day 1 before 3-NP treatment for each rat was relatively stable and showed no significant variation. All the rats entered the closed arm within 96 sec. The vehicle and control treated rats entered the closed arm quickly, and the mean retention transfer latencies (1^{st} RTL and 2^{nd} RTL) to enter the closed arm on days 5 and 15 were shorter as compared to the ITL on day 1 of each group. In contrast, the 3-NP (10 mg/kg, i.p) treated rats performed poorly throughout the experiment and an increase in the mean retention transfer latencies on day 5 and 15 was noted as compared to the pre-training latency on day 1, demonstrating 3-NP induced cognitive dysfunction. Ascorbic Acid administration (100 mg/kg and 200 mg/kg, *i.p*) to 3-NP (10 mg/kg, i.p) treated rats significantly decreased the mean retention latencies on day 5 and day 15 indicating an improvement in memory impairement induced by 3-NP.However, ascorbic acid (200 mg/kg i.p.) *per se* treatment had no effect on memory when compared with control group. Moreover, treatment with bicuculline (1 mg/kg, *i.p*) and Mifepristone (1mg/kg/day, *i.p)* abolished the effect of ascorbic acid (Figure 2).

Effect of Ascorbic Acid on Grip Strength Using Rotarod Activity

3-NP (10 mg/kg, i.p) treatment impaired grip strength as assessed by rotarod test on 5^{th} day and 15^{th} day. Pre-treatment with ascorbic acid (100 mg/kg and 200 mg/kg, *i.p*) significantly ($P<0.05$) attenuated the 3-NP induced decrease in grip strength in a dose dependent manner on day 5 and 15. However, ascorbic acid *per se* (200 mg/kg, *i.p*) and vehicle treatment had no effect on grip strength activity when compared with control group. Moreover, treatment with Bicuculline (1 mg/kg, *i.p*) and Mifepristone (1mg/kg/day, *i.p)* significantly abolished the Ascorbic acid mediated increase in grip strength (figure 3).

Effects of Ascorbic Acid on Gross Locomotor Activity Using Actophotometer

3-NP administration caused significant decrease in the locomotor activity on day 5 and day 15 as compared to control group. Pre-treatment with ascorbic acid (100 mg/kg and 200 mg/kg, *i.p*) significantly ($P<0.05$) attenuated the 3-NP (10 mg/kg, i.p) induced decrease in motor activity in a dose dependent manner on day 5 and day 15 and there was no change in the locomotor activity of vehicle treated rats as compared to control group. However, ascorbic acid *per se* (200 mg/kg, *i.p.*) and vehicle treatment had no effect on gross behavioral activity when compared with control group. Moreover,

treatment with bicuculline (1 mg/kg, *i.p*) and Mifepristone (1mg/kg/day, *i.p)* significantly abolished the ascorbic acid mediated increase in motor activity (figure 4).

Effects of Ascorbic Acid on Brain Reduced Glutathione Levels

GSH levels in 3-NP (10 mg/kg, i.p) administered rats have shown significant (P<0.05) decrease as compared with control group whereas, there was no effect of ascorbic acid (200 mg/kg, *i.p*) *per se* and vehicle treatment on brain GSH levels. Pre-treatment with ascorbic acid (100 mg/kg and 200 mg/kg, *i.p*) significantly (P<0.05) attenuated 3-NP induced decrease in GSH levels. Moreover, treatment with bicuculline (1 mg/kg, *i.p*) and Mifepristone (1mg/kg/day, *i.p)* abolished the ascorbic acid mediated increase in brain GSH levels (Figure 5).

Effect of Ascorbic Acid on Brain Lipid Peroxidation Level

Systemic administration of 3-NP (10 mg/kg, i.p) caused a marked increase in lipid peroxidation in addition to a decline in antioxidant defense, as indicated by a significant (P<0.05) rise in brain MDA levels as compared to the control rats. Further, there were no alterations in the brain MDA level due to ascorbic acid (200 mg/kg, *i.p*) *per se* and vehicle treatment as compared to control group. Pretreatment with ascorbic acid (100 mg/kg and 200 mg/kg, *i.p*) significantly (P<0.05) prevented the increase in MDA levels, with marked effect observed at the highest dose when compared to the 3-NP treated group. Moreover, treatment with bicuculline (1 mg/kg, *i.p*) and Mifepristone (1mg/kg/day, *i.p)* abolished the protective effects of ascorbic acid (Figure 6).

Effect of Ascorbic Acid on Brain Nitrite Levels in 3-Nitropropionic Acid Treated Rats

In present study, there was no significant effect of ascorbic acid *per se* (200 mg/kg, *i.p*) and vehicle treatment on brain nitrite levels as compared to control rats. Systemic 3-NP (10 mg/kg, i.p) administration caused a significant (P<0.05) increase in brain nitrite levels, which was significantly (P<0.05) prevented by pretreatment with ascorbic acid (100 mg/kg and 200 mg/kg, *i.p*) in a dose dependent manner. Moreover, treatment with bicuculline (1mg/kg, *i.p*) and Mifepristone (1mg/kg/day, *i.p)* abolished the ascorbic acid mediated reduction in brain nitrite levels (Figure 7).

Effect of Ascorbic Acid on Acetylcholinesterase Levels

3-NP (10 mg/kg, *i.p*) administration caused significant (P<0.05) increase in acetylcholinesterase enzyme levels of test animals when compared to control group. Ascorbic acid treatment significantly (P<0.05) attenuated acetylcholinesterase enzyme activity as compared to 3-NP treated rats. Moreover, there was no significant effect of ascorbic acid (200mg/kg, *i.p*) *per se* and vehicle treatment on brain acetylcholinesterase levels as compared to control group. Furthermore, treatment with bicuculline (1mg/kg, *i.p*) and Mifepristone (1mg/kg/day, *i.p)* abolished the ascorbic acid mediated reduction in acetylcholinestrase enzyme levels (Figure 8).

Effect of Ascorbic Acid on Brain Myeloperoxidase (MPO) Activity

Systemic administration of 3-NP (10 mg/kg, i.p) caused a marked increase in MPO activity as compared to the control group. Further, there were no alterations in the brain MPO activity due to ascorbic acid (200 mg/kg, *i.p*) *per se* and vehicle treatment as compared to control rats. Ascorbic acid (100 mg/kg and 200mg/kg, *i.p*) administration for 14 days, however, significantly (P<0.05) prevented the increase in MPO activity, with marked effect observed at the highest dose when compared to 3-NP treated group. Moreover, treatment with bicuculline (1 mg/kg, *i.p*) and Mifepristone (1mg/kg/day,

i.p) abolished the ascorbic acid mediated reduction in brain MPO activity (Figure 9).

Table 1: **Effects of Various Interventions on Body Weight of Animals**

Group. No	Treatment	Initial Body weight(g)	Final Body weight(g)
1	Control	222.5±6.5	219±7.4
2	DMSO	220.6±9.2	218.3±8.3
3	Olive Oil	220.4±7.6	219.5±4.6
4	3-NP	221.6±8.8[a]	208.0±8.4
5	Ascorbic acid	220.0±10.4	218.3±6.5
6	LD + 3-NP	220.6±9.7[b]	213.6±7.3
7	HD + 3-NP	220.0±7.7[b]	217.3±7.6
8	Bicuc + Ascorbic acid(HD) + 3-NP	221.6±8.5[c]	210.3±6.0
9	Mife + Ascorbic acid (HD) + 3-NP	220.5±8.6[c]	218.5±6.7

Values are the Mean ± S.E.M

a= p<0.05 as compared to the normal control

b= p< 0.05 as compared to the 3-NP injected group

c= p< 0.05 as compared to HD+ 3-NP group.

D=p<0.05 as compared to Bicuc+ Ascorbic acid (HD) +3-NP

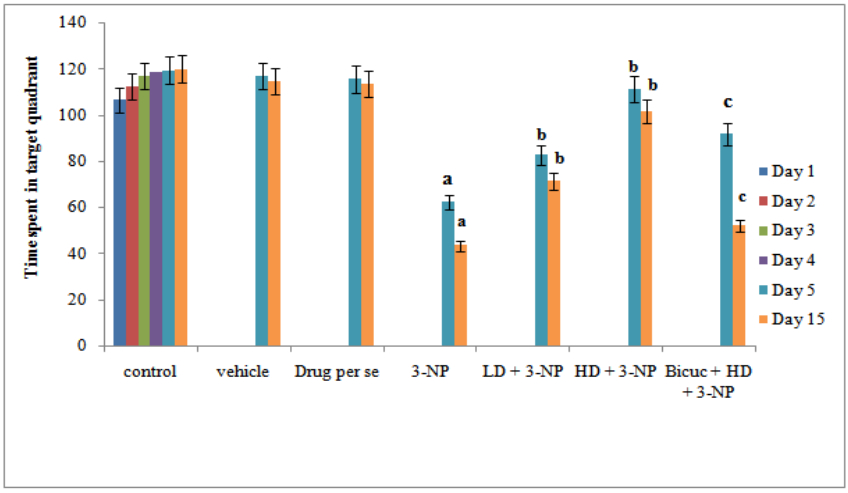

Figure 1: Effects of Ascorbic Acid on Memory and Learning Using Morris Water Maze (MWM) Test

Values are the mean ± SEM.

a= p<0.05 as compared to the normal control

b= p< 0.05 as compared to the 3-NP injected group

c= p< 0.05 as compared to HD+ 3-NP group.

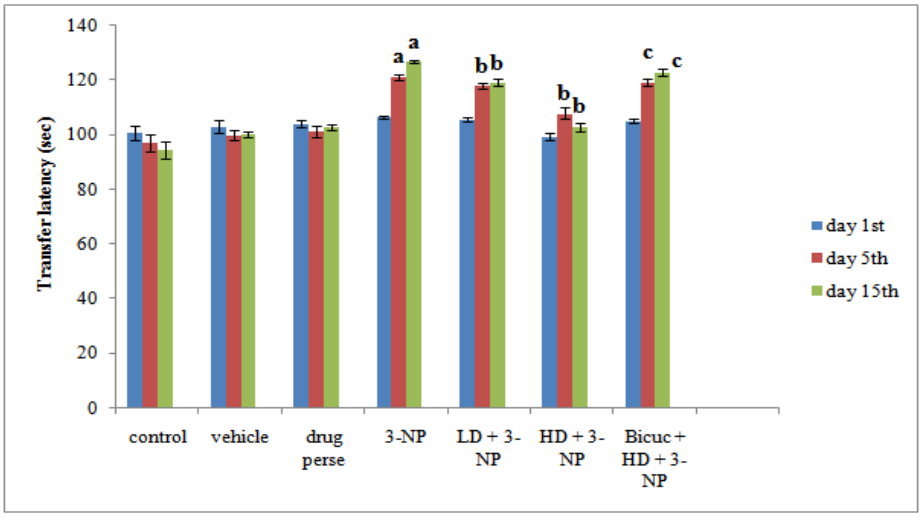

Figure 2: Effects of Ascorbic Acid on Memory Performance in Elevated plus Maze Test

Values are the mean ± SEM

a= p<0.05 as compared to the normal control

b= p< as compared to the 3NP injected group

c= p< 0.05 as compared to HD+ 3-NP group.

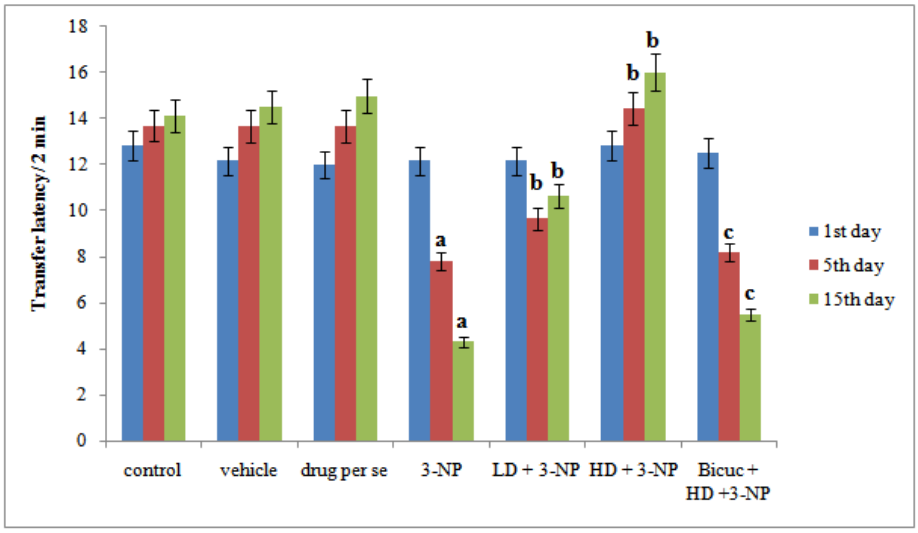

Figure 3: Effects of Ascorbic Acid on Grip Strength Using Rota Rod Test

Values are the mean ± SEM

a= p< 0.05 as compared to the normal control

b= p< 0.05 as compared to the 3-NP injected group

c= p< 0.05 as compared to HD+ 3-NP group.

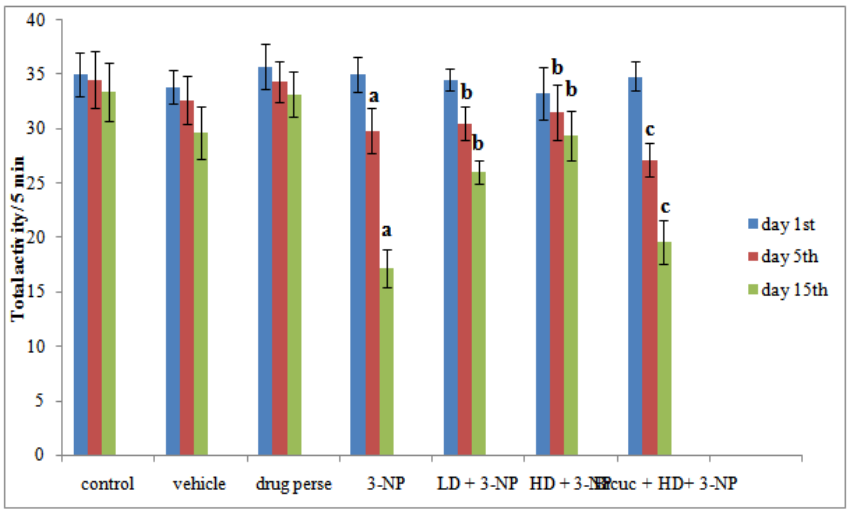

Figure 4: Effects of Ascorbic Acid on Locomotor Activity Using Actophotometer

Values are the mean ± SEM.

a= p<0.05 as compared to the normal control

b= p< 0.05 as compared to the 3-NP injected group

c= p< 0.05 as compared to HD+ 3-NP group.

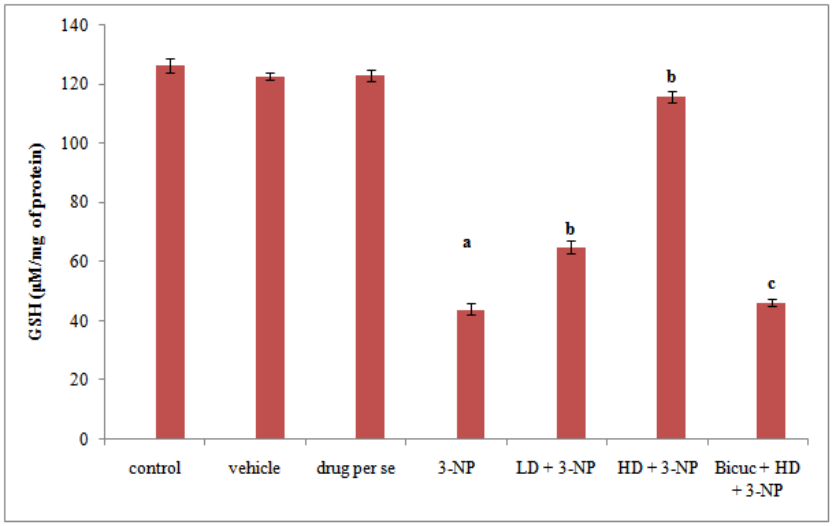

Figure 5: Effects of Ascorbic Acid on Reduced Glutathione Levels

Values are the mean ± SEM

a= p< 0.05 as compared to the normal control

b= p< 0.05 as compared to 3-NP injected group

c= p< 0.05 as compared to HD+ 3-NP group.

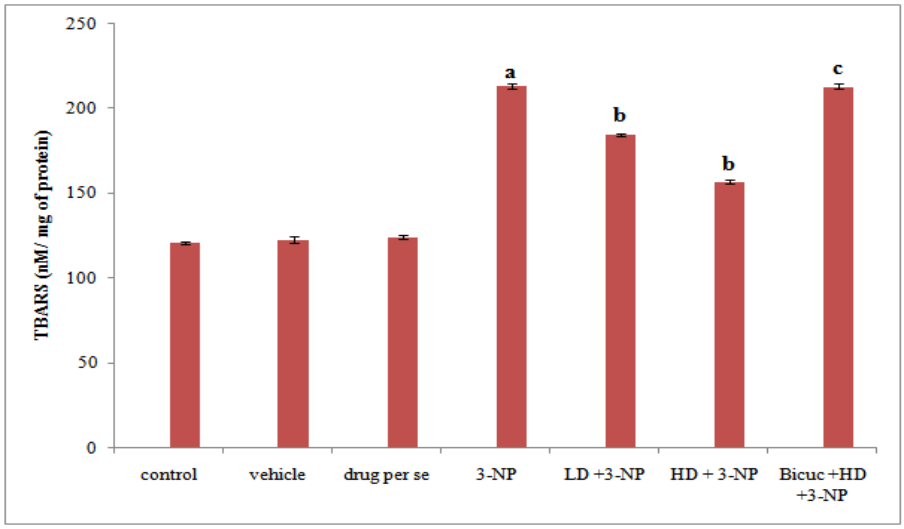

Figure 6: Effects of Ascorbic Acid on Lipid Peroxidation

Values are the mean ± SEM

a= p< 0.05 as compared to the normal control

b= p< 0.05 as compared to 3-NP injected group

c= p< 0.05 as compared to HD+ 3-NP group.

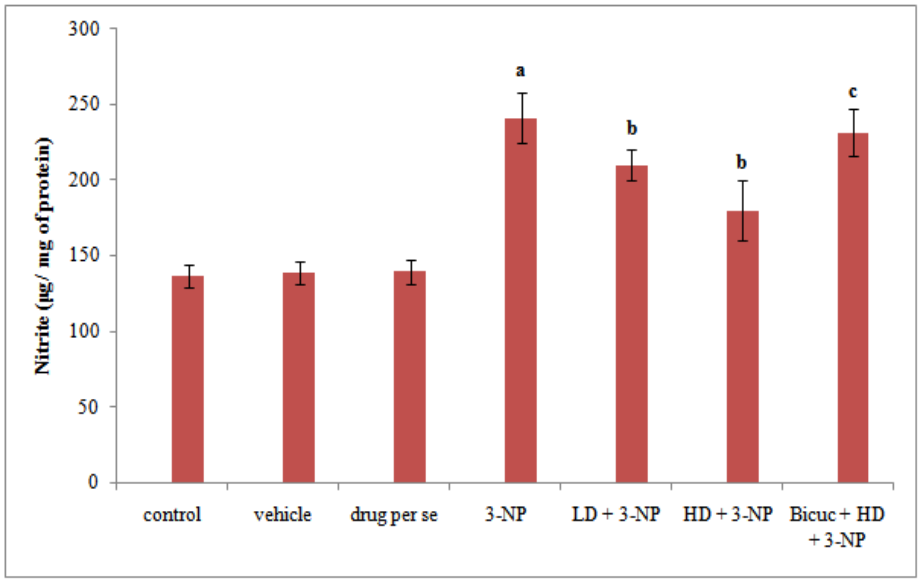

Figure 7: Effects of Ascorbic Acid on Brain Nitrite/ Nitrate Levels

Values are the mean ± SEM

a= p< 0.05 as compared to the normal control

b= p< 0.05 as compared to 3-NP injected group

c= p< 0.05 as compared to HD+ 3-NP group.

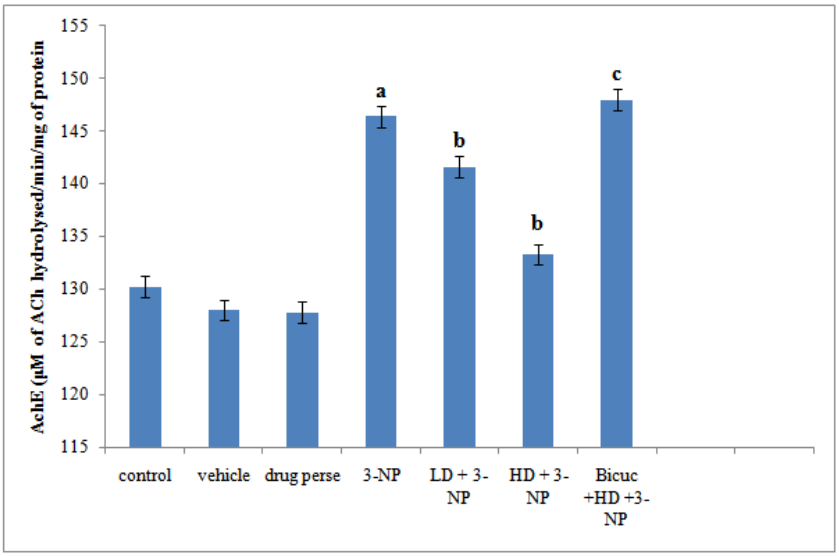

Figure 8: Effects of Ascorbic Acid on Brain Acetylcholinesterase (AchE) Activity

Values are the mean ± SEM

a= p< 0.05 as compared to the normal control

b= p< 0.05 as compared to 3-NP injected group

c= p< 0.05 as compared to HD+ 3-NP group.

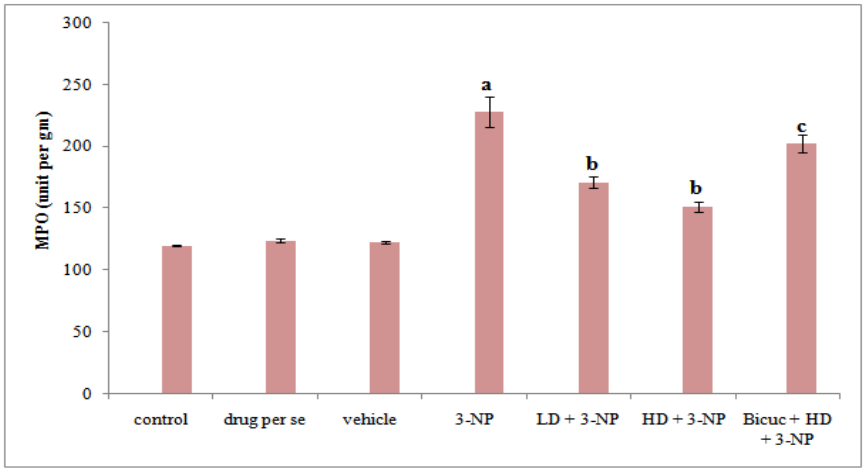

Figure 9: Effects of Ascorbic Acid on Myeloperoxidase (MPO) Activity

Values are the mean ± SEM

a= p< 0.05 as compared to the normal control

b= p<0.05 as compared to 3-NP injected group

c= p< 0.05 as compared to HD+ 3-NP group

CONCLUSIONS

The present study was designed to evaluate the neuroprotective effects of Ascorbic Acid against 3-NP induced Huntington's disease in rats and possible involvement of $GABA_A$ receptors.

On the basis of results obtained in the present study, the following salient findings are summarized:

- Control group animals had shown a good performance on MWM test and EMP test as reflected by normal memory and learning. In addition, they have shown normal motor activity in rota rod test and in actophotometer.
- Administration of ascorbic acid (200 mg/kg, *i.p.*) *per se* had no effect on acquisition, memory, motor activity and various biochemical parameters as compared to control group animals.
- Systemic administration of 3-NP (10 mg/kg, *i.p.* for 14 days) produced symptoms similar to Huntington's disease in rats such as declined motor function, poor retention of memory, exaggerated oxidative stress (↓GSH, ↑MDA & ↑iNOS), ↑AChE levels and ↑MPO activity along with neuro-degeneration.
- Pre-treatment with Ascorbic Acid (100 mg/kg and 200 mg/kg, *i.p.*) once daily for a period of 14 days attenuated 3-NP induced motor and cognitive impairment together with improvement in biochemical parameters (↑GSH, ↓ MDA, ↓ AChE, ↓ MPO& ↓ iNOS) in a dose dependent manner in rats.
- Pre-treatment with Bicuculline (1 mg/g, *i.p.*) once daily for a period of 14 days abolished the neuroprotective effects of ascorbic acid on 3-NP treated rats. In addition, histopathological changes in present study have further justified the approach.

In conclusion, the results of the present study demonstrate that ascorbic acid has shown neuroprotective effects against 3-NP induced behavioral and biochemical alterations similar to Huntington's disease in rats and the said role of ascorbic acid involves the activation of GABA-A receptors.

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