Annexure – IX

UNIVERSITY GRANTS COMMISSION
BAHADUR SHAH ZAFAR MARG
NEW DELHI – 110 002

PROFORMA FOR SUBMISSION OF INFORMATION AT THE TIME OF SENDING THE FINAL REPORT OF THE WORK DONE ON THE PROJECT

1. Title of the Project: "Evaluation of Molecular Marker(s) and Therapy by Multi-targeted Drugs for Parkinson's Diseases in Paraquat-induced mice model."
2. NAME AND ADDRESS OF THE PRINCIPAL INVESTIGATOR: Nilkanta Chakrabarti, Department of Physiology, University of Calcutta
3. NAME AND ADDRESS OF THE INSTITUTION: Department of Physiology, University Colleges of Science and Technology, 92, A.P.C. Road, Kolkata-700 009
4. UGC APPROVAL LETTER NO. AND DATE: F. No. – 43-563/2014(SR) Dated- 17 Nov 2015
5. DATE OF IMPLEMENTATION: 07.01.2016 (Approved by Hon'ble VC, University of Calcutta)
6. TENURE OF THE PROJECT: 3 Years
7. TOTAL GRANT ALLOCATED: Rs. 10,11,465/- (vide final audit report)
8. TOTAL GRANT RECEIVED: Rs. 9,26,148/- (vide final audit report)
9. FINAL EXPENDITURE: Rs. 8,46,298/- (vide final audit report)
10. TITLE OF THE PROJECT: "Evaluation of Molecular Marker(s) and Therapy by Multi-targeted Drugs for Parkinson's Diseases in Paraquat-induced mice model."
11. OBJECTIVES OF THE PROJECT: Attached in Detailed Progress Report
12. WHETHER OBJECTIVES WERE ACHIEVED: Attached in Detailed Progress Report
    (GIVE DETAILS)
13. ACHIEVEMENTS FROM THE PROJECT: Attached in Detailed Progress Report
14. SUMMARY OF THE FINDINGS: Attached in Detailed Progress Report
    (IN 500 WORDS)
15. CONTRIBUTION TO THE SOCIETY: Attached in Detailed Progress Report
    (GIVE DETAILS)
16. WHETHER ANY PH.D. ENROLLED/PRODUCED OUT OF THE PROJECT: No
17. NO. OF PUBLICATIONS OUT OF THE PROJECT: Peer Reviewed Journal – Nil
    Abstract in Conference (International held in India) - 04

(PLEASE ATTACH) – attached

28/11/2019

डा: अमित पाल / Dr. Amit Pal
(वैज्ञानिक - एफ / Scientist F)
राष्ट्रीय कॉलरा और आंत्र रोग संस्थान
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(PRINCIPAL INVESTIGATOR)

(REGISTRAR/PRINCIPAL)

(Seal)
REGISTRAR
UNIVERSITY OF CALCUTTA

(CO-INVESTIGATOR)
Arindam Bhattacharyya
Professor
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Annexure – XI

Final Report Assessment / Evaluation Certificate
(Two Members Expert Committee Not Belonging to the Institute of Principal Investigator)
(to be submitted with the final report)

It is certified that the final report of Major Research Project (F.43-563/2014 (SR), dt. 17.11.2015) entitled **"Evaluation of Molecular Marker(s) and Therapy by Multi-targeted Drugs for Parkinson's Diseases in Paraquat-induced mice model"** by Dr./**Prof. Nilkanta Chakrabarti (PI), Department of Physiology, University of Calcutta** and **Prof. Arindam Bhattacharyay (Co-PI), Department of Zoology, University of Calcutta** has been assessed by the committee consisting the following members for final submission of the report to the UGC, New Delhi under the scheme of Major Research Project.

Comments/Suggestions of the Expert Committee:-

The report of the research project have been presented successfully.
The findings of the research project fulfil greater part of the objectives of the research project. The part of the results have been presented and published as abstract format in International Conference held in India.
The findings of the research project have greater values in clinical aspects and thus have social impacts.

It is certified that the UGC-Major research project has been completed successfully.

Name & Signatures of Experts with Date:-

	Name of Expert Date	University/College name	Signature with
1.	Atanu Biswas (MD, DM)	Bangur Institute of Neurosciences (BIN) IPGME&R,SSKM Hospital, Govt. of WB, Kolkata	DR. ATANU BISWAS, MD, DM Professor Department of Neurology Bangur Institute of Neurosciences Kolkata - 700025
2.	Amit Pal (M.Sc., Ph.D.)	National Institute of Cholera& Enteric Disease (NICED) Beliaghata, Kolkata	डा: अमित पाल / Dr. Amit Pal (वैज्ञानिक - एफ / Scientist F) राष्ट्रीय कॉलरा और आंत्र रोग संस्थान National Institute of Cholera & Enteric Diseases पी-३३, सी. आई. टी रोड, स्कीम-१०एम, बेलियाघाटा P-33, CIT Road, Scheme-XM, Beliaghata कोलकाता-७०००१० / Kolkata-700010

It is certified that the final report has been uploaded on UGC-MRP portal on .....

It is also certified that final report, Executive summary of the report, Research documents, monograph academic papers provided under Major Research Project have been posted on the website of the University/College.

(Registrar/Principal)

Seal REGISTRAR
UNIVERSITY OF CALCUTTA

UGC-Major Research Project

Final Report

File No. : 43-563/2014(SR) date- 17/11/2015
Code: MRP-MAJOR-ZOOL-2013-16383 (GENERAL)

DETAILED PROGRESS REPORT OF RESEARCH WORK
(01/07/2015 - 30/06/2017)

Principal Investigator: Nilkanta Chakrabarti
Professor, Department of Physiology
University of Calcutta
Co-Principal Investigator: Arindam Bhattacharyya
Professor, Department of Zoology
University of Calcutta
Department and University/College where work has progressed:
Department of Physiology, University of Calcutta, 92 A.P.C. Road, Kolkata – 700 009

Final report as per proforma

10. Title Of the Project:

Evaluation of Molecular Marker(s) and Therapy by Multi-targeted Drugs for Parkinson's Disease in Paraquat-induced mice model

11. Objective of the Project

The present research proposal is a mechanistic approach against neurodegenerative disease to develop a diagnostic view and a better treatment strategy targeted to the cause of disease rather the symptoms of the diseases. The results of the present project appear to unveil the cellular and molecular mechanism of PD and its progression with suitable diagnosis and therapeutic process. The objectives of the present studies are,

(1) **Finding the status of dopaminergic neurons (DAT), neuroinflammation (TSPO) and anti-inflammatory neuroprotective target (α7nAChR) in different brain regions in PQ-induced PD model of mice**: Substantia nigra pars compacta (SNpc) is the target site of dopaminergic neurodegeneration in animal models of PD. We have considered the hippocampus and cerebral cortex as additional brain areas of interest for finding cellular and molecular mediators of cognitive impairment in PD that may appear at early stage prior to the onset of primary motor symptoms.

(2) **Development of Multi-targeted therapeutic approaches to prevent Neuro-inflammation in this animal model** : The status of DAT, TSPO and α7 nAChR had been proposed to follow with and without supplementation of pharmacological drugs including potential anti-inflammatory neuroprotective compounds (α7 nAChR agonist, NSAID) and antioxidant agent (tocopherol) separately and in combinations.

12. Whether the objectives were achieved

The findings of the research project have fulfilled the greater part of the objectives of the research project.

Achievement of Objective-1: Three brain regions like substantia nigra (positive site for Parkinson model), cerebral cortex and cerebellum (two brain regions associated with learning/memory cognitive functions), had been used for experimentations. PQ induced alterations of **cognitive function** of mice had been evaluated by assessment of **behavioural studies.** PQ caused **oxidative stress** and that had been evaluated by measuring ROS levels in different areas of brain. However, the dopaminergic status and inflammatory aspects are yet to perform. As the **alternative of** the finding of status of **α7nAChR** (Acetylcholine receptor), **acetylcholinesterase activity** (that limits cholinergic neurotransmitter function) of brain regions had been measured to evaluate cholinergic status in brain regions.

Achievement of Objective-2: The supplementation of **antioxidant agent (tocopherol)** had been executed and results had been evaluated on behavioural status, ROS levels and AChE activities.

13. Achievement from the project

Methodology applied

Animal Handling and Maintenance

Young male *Swiss Albino* mice (2-3months of age) were maintained on a regular 12:12-hr light-dark cycle at constant room temperature (22±2°C) and humidity with continuous access to food and water *ad libitum*. The experimental protocols were pre-approved by the Institutional Animal Ethics Committee (IAEC), Department of Physiology, University of Calcutta.

Treatment protocol was followed by our previous reports [1]. The treatment of PQ and vehicle (saline) were followed twice a week for consecutive 4 weeks. Thereafter, α-tocopherol and its

vehicle (edible oil) were treated for consecutive 5 days after the last dose of PQ treatment. All treatments were done intraperitonealy. Therefore, four groups of animals were used in the present study i.e. control (0.9%NaCl followed by edible oil) (n=8), control + α-tocopherol treated (20mg/kg body weight) (n=8), PQ treated (sub-lethal dose with 10 mg/kg body weight) (n=8), and PQ + α-tocopherol treated group (n=8).

BIOCHEMICAL ANALYSIS

Tissue processing

Tissues were homogenized (10%w/v) in ice cold phosphate buffer saline (P^H7.4) followed by isolation of mitochondrial and post-mitochondrial fractions by differential centrifugation method [1].

Spectrophotometric assay

Protein estimation

Tissue protein had been estimated by Bradford protein assay method [2].

Determination of Catalase activity

Catalase was measured using standard method with some modifications [1, 3]. Catalase enzyme was allowed to split H_2O_2 for particular time period. The remaining H_2O_2 was determined by measuring chromic acetate spectrophotometrically at 570nm. Enzyme activity was expressed as changes in μmol of H_2O_2/min/mg protein.

Determination of Superoxide dismutase (SOD) activity

SOD was measured using the standard protocol with some modifications [1, 3]. In presence of SOD enzyme, the rate of haematoxylin auto-oxidation (λmax 560nm) is inhibited and the percentage of inhibition was linearly proportional to the amount of SOD present. Enzyme activity was expressed as Unit of enzyme activity/mg of tissue protein.

Determination of reduced glutathione (GSH) level

The GSH was assayed by following the method of with some modifications [3, 4]. The GSH reacted with DTNB and formed a yellow coloured complex which was monitored at 412nm in spectrophotometer.

Determination of acetylcholinesterase (AChE) activity

The AChE Activity was assayed by Ellman's method [5] with some modifications. Thiocholine (the hydrolysis product by AChE) on reaction with DTNB produces yellow coloured complex 5-thio-2-nitobenzoate that has maximum absorption at 412nm.

Spectrofluorometric assay

Detection of ROS in post-mitochondrial fraction

The post-mitochondrial ROS was determined by spectrofluorometric analysis using DCFDA dye (Ex495nm/Em525nm) [3].

Fluorescence-activated cell sorting (FACS) analysis

Measurement of Reactive oxygen species (ROS) in mitochondrial fraction

The mitochondrial ROS was determined by flowcytometer (FACS) using DCF-DA dye. DCFDA was oxidized by ROS to form DCF which can be detected by FACS (Ex495nm/Em525nm) analyzer [6].

Behavioural studies of mice

The behavioral study had been executed as per standard protocol of our previous publication [7]. Open Filed Test (OFT) in circular big arena was done for the assessment of locomotor activities. Elevated Plus Maze (EPM) test was conducted to assess anxiety like behavior and Novel Object Recognition (NOR) test was done to assess short term memory performances.

(B) STATISTICAL ANALYSIS

The values of all parameters were presented as mean ± SEM. Level of significance had been established using the two-way analysis of variance (ANOVA) followed by post-hoc (Tukey-HSD) analysis.

Results

PQ induced changes in ROS level

PQ-treatment increased activities of anti-oxidative enzymes (namely SOD and Catalase) and decreased GSH levels in cerebral cortex and substantia nigra of young adult male mice (Fig. 1A, 1B, 1C). PQ increased the ROS levels in post-mitochondrial fraction of cerebral cortex and

substantia nigra (Fig. 1D, 2C, 2D). On the other hand, PQ increased mitochondrial ROS level in substantia nigra, whereas mitochondrial ROS level remained unaltered in cerebral cortex during PQ-treatment (Fig. 2A, 2D). PQ-treatment increased activities of SOD and Catalase but GSH level remained unaltered in hippocampus of young adult male mice (Fig. 1A, 1B). PQ increased mitochondrial ROS level in hippocampus, however, post-mitochondrial ROS level decreased in hippocampus during PQ-treatment (Fig. 1D). α-tocopherol, an antioxidant, supplementation ameliorated the effect of PQ-toxicity in all these parameters of cerebral cortex, hippocampus and substantia nigra in young adult male mice (Fig. 1, 2).

PQ induced changes in AChE activity

PQ treatment increased AChE activity in cerebral cortex and substantia nigra of young adult male mice whereas decreased the enzyme activity significantly in hippocampus. α-tocopherol, an antioxidant, supplementation ameliorated the AChE activities in three brain regions of interest.

PQ induced changes in Behavioural status

PQ treatment significantly decreased locomotor activities as evident by lowering the average speed of young adult male mice in OFT. PQ treatment significantly decreased the total time spent in open arm of EPM by the animals which implies that PQ-treatment caused anxiety like behavior in animals. In NOR test for short term memory, PQ treated young adult male mice showed significantly lower levels of discrimination indices which indicate that PQ treatment decreased the memory (short term) performances of animals. α-tocopherol supplementation ameliorated the behavioral status in young adult male mice.

Discussion

PQ-induced parkinsonism caused oxidative stress differentially in three regions of brain of mice namely, substantia nigra, cerebral cortex and hippocampus. In substantia nigra (positive brain region for Parkinsonism), PQ induced oxidative stress in mitochondrial as well as post-mitochondrial fractions of tissues. Whereas, PQ-induced oxidative stress in mitochondrial fraction and post-mitochondrial fraction varied in other regions namely, cerebral cortex and hippocampus (regions related to cognition). It is reported that, PQ increases the ROS level and altered antioxidant enzymes activity including SOD, catalase, and glutathione peroxidase in substantia nigra, frontal cortex and hippocampus of young males and, α-tocopherol supplementation ameliorates the effects of PQ in the same model [8, 9].

Alpha 7-nicotinic acetylcholine receptors (α7-nAChR) are expressed in neurons as well as in microglia. In microglia, the ACh binding with α7nAChR activates cholinergic anti-inflammatory pathway [10]. In neurons, the activation of α7-nAChR promotes Ca^{2+} influx and trigger Ca^{2+}-dependent cellular processes including synaptic plasticity, neurotransmitter release, cell migration, and survival [11]. AChE activity regulates the availability of α7nAChR agonist i.e. ACh. Apoptosis is the major cause of dopaminergic neuronal loss in Parkinson's disease [12]. AChE expression is increased during apoptosis indicating that AChE has a potential role in neuronal cell death [13]. In our study, PQ treatment caused increase in AChE activities in cerebral cortex and substantia nigra indicating major dopaminergic and cholinergic neuronal loss via apoptosis in these areas. On the other hand AChE activity decreased in hippocampus. ACh signaling in hippocampus is associated with behaviors related to anxiety and depression [14]. In the present study, the PQ induced decrease in AChE activity and increase in ROS in hippocampus might be associated with development of anxiety and depression like behaviors in mice. The loss of structural and functional plasticity [15] and the increase in activity of AChE [16] in motor cortex are reported to associate with the movement impairment. The PQ induced impairment of motor activities might be associated with several factors including the increment of AChE activity in cerebral cortex in the present study. Both increase [17] and decrease [18] in AChE activities in hippocampus are reported to concern with memory impairment. In the present study, PQ induced inhibition of AChE activity in hippocampus might be associated with failure of short-term memory performances.

14. Summary of the findings

Therefore, the present study reports the novel results that PQ-induced parkinsonism is associated with differential pattern of molecular changes in three regions of brain which might cause alterations of behavioural activities including locomotor activities, anxiety-like behaviour and memory performances. The antioxidant, α-tocopherol supplementation ameliorated all changes.

15. Contribution to the society

Such novel findings of our present study may be helpful to find the possible way of strategy to select drug supplementation at clinical level to ameliorate the parkinsonism in human subjects.

17. Number of publications out of the project

Abstract publication and presentation research findings in conferences

1. S. Datta, D. Samanta, N Chakrabarti*, **Paraquat treatment causes Oxidative Stress in Skeletal Muscle and Decline Muscle Strength in Adult Mice**, In: 15th Annual meeting of Society of Free Radical Research (SFRR-India 2017), BARC, Mumbai, INDIA, January 9-12, 2017. (Poster presentation).
2. S. Datta, D. Samanta, N Chakrabarti*, **Paraquat induced Parkinsonism alters brain regional levels of Neurotransmitters differentially and changes Behavioral patterns in young male mice**, In: Neurodegenerative Disorders: Current and Future Perspective, The Oberoi Grand, Kolkata, India, February 10-12, 2017. (Oral presentation).
3. A. Choudhary, S. Datta, D. Samanta, T. Bhatta, N. Chakrabarti*, **Paraquat induced inhibition of ACHE activities in brain and skeletal muscle causes impairment of locomotor activities in young adult mice,** In: XXXVI Annual Meeting of Indian Academy of Neurosciences, Banaras Hindu University, Varanasi, India , October 29 - 31, 2018. (Poster presentation).
4. T R. Bhatta, S. Datta, D. Samanta, A. Choudhary, N. Chakrabarti*, **Rise in anxiety and deterioration of memory performance in mice after Paraquat treatment,** In: XXXVI Annual Meeting of Indian Academy of Neurosciences, Banaras Hindu University, Varanasi, India , October 29 - 31, 2018. (Poster presentation).

Figures and Legends

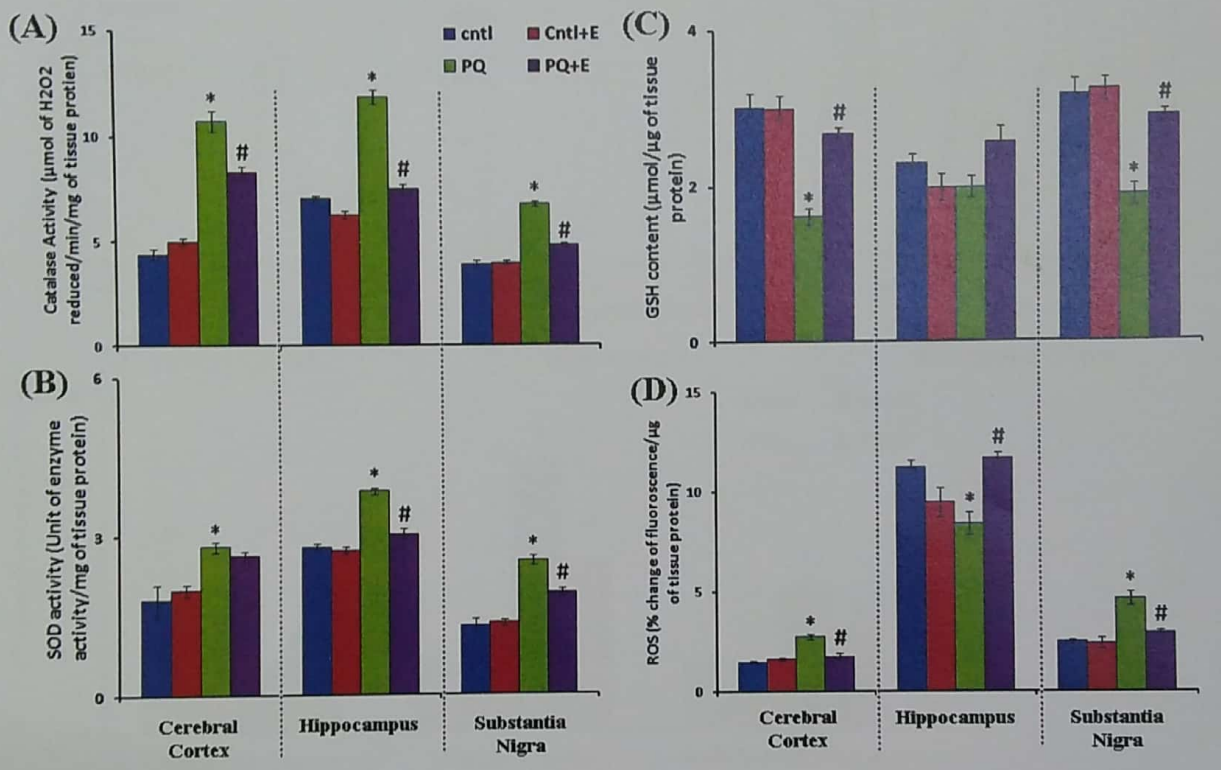

Fig: 1 Changes in the pattern of oxidative stress related molecules and enzymes activities of post-mitochondrial fractions isolated from different brain regions of young male mice during PQ treatment and α-tocopherol supplementation study. The figure represents (a) catalase activity, (b) SOD activity, (c) GSH content, (d) Post-mitochondrial ROS level. The values are represented as mean±SEM. The parametric values are analyzed by two-way ANOVA followed by post-hoc (TukeyHSD) analysis with significance level at $p<0.05$. Cntl, Cntl+E, PQ and PQ+E stand for control, control+α-tocopherol supplementation, PQ-treated, PQ-treated+α-tocopherol supplementation mice respectively. Asterisks (*) indicate significant difference in PQ treatment group compared to control group. Hash-tag (#) sign represents ameliorative effect of α-tocopherol supplementation compared to PQ-treatment group.

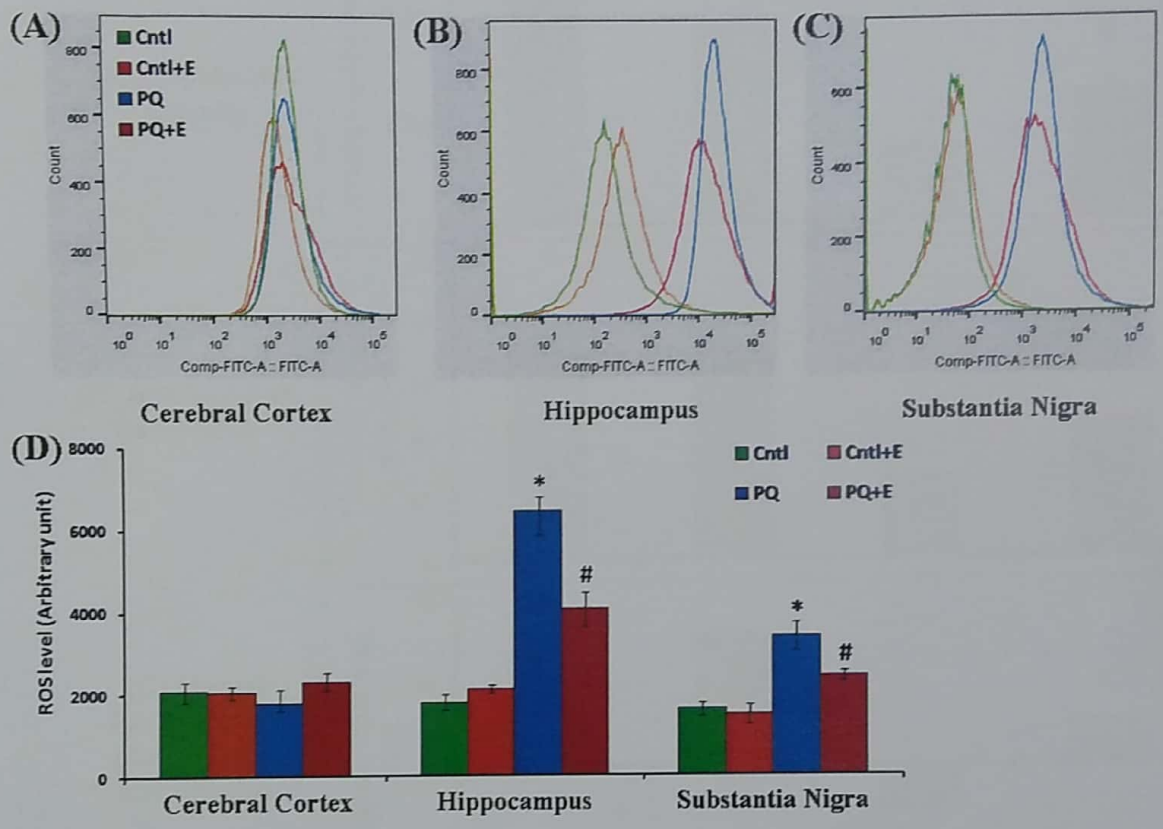

Fig 2: Changes in the pattern of mitochondrial ROS level isolated from different brain regions of young male mice during PQ treatment and α-tocopherol supplementation study. The figure represents (a) Histogram of cerebral cortex, (b) Histogram of hippocampus, (c) Histogram of substantianigra, (d) mitochondrial ROS level. The values are represented as mean±SEM. The parametric values are analyzed by two-way ANOVA followed by post-hoc (TukeyHSD) analysis with significance level at $p<0.05$. Cntl, Cntl+E, PQ and PQ+E stand for control, control+α-tocopherol supplementation, PQ-treated, PQ-treated+α-tocopherol supplementation mice respectively. Asterisks (*) indicate significant difference in PQ treatment group compared to control group. Hash-tag (#) sign represents ameliorative effect of α-tocopherol supplementation compared to PQ-treatment group.

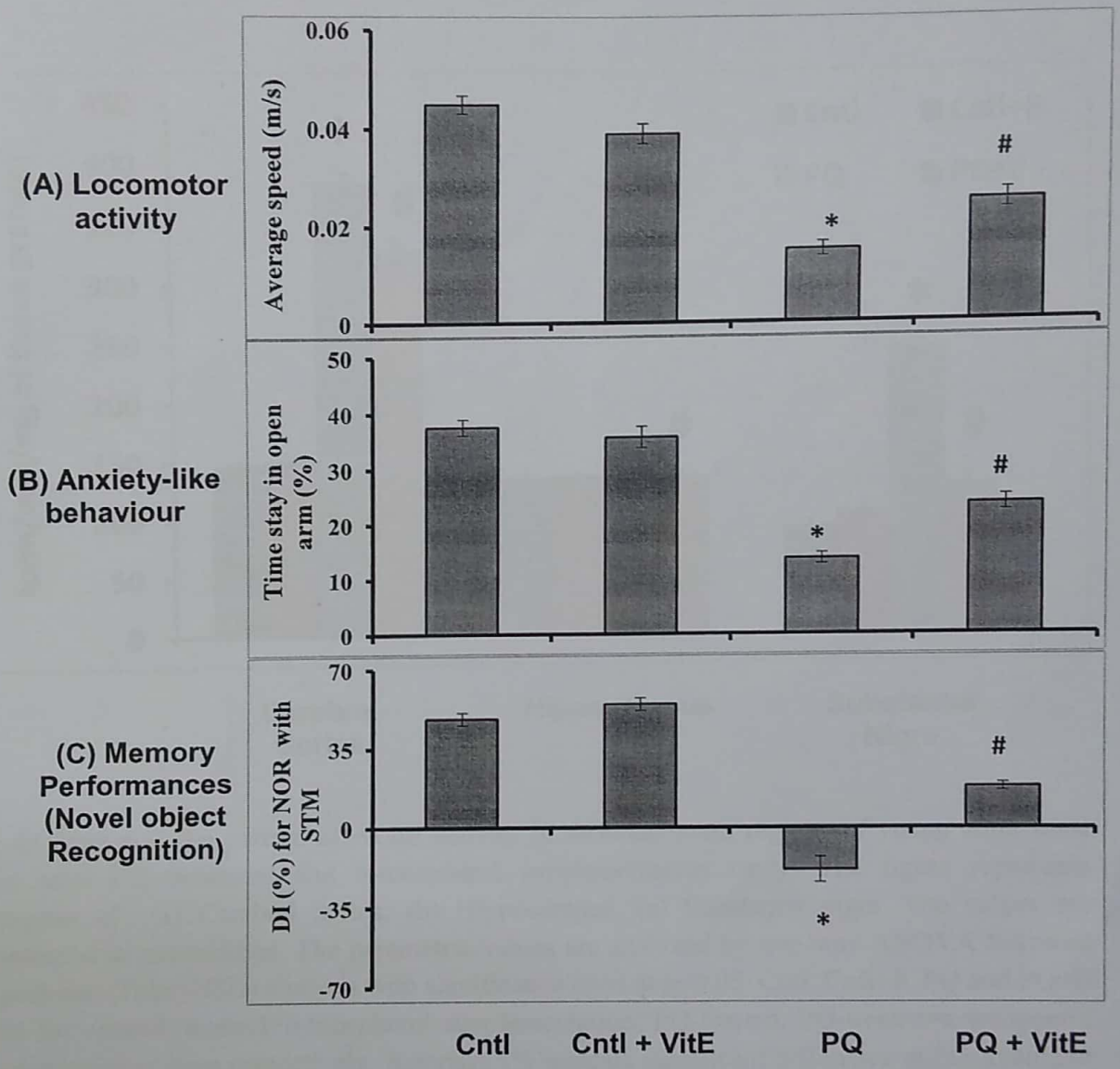

Fig 3: Effect of paraquat (PQ) on behavior of young adult male mice. (A) Open field activity which correspond to the average speed (m/s) (B) Anxiety like behavior represented by percentage of time stay in open arm and (C) Novel Object Recognition Memory by quantitative measurement of discrimination index (DI).The values are represented as mean±SEM. The parametric values are analyzed by two-way ANOVA followed by post-hoc (TukeyHSD) analysis with significance level at $p<0.05$. Cntl, Cntl+E, PQ and PQ+E stand for control, control+α-tocopherol supplementation, PQ-treated, PQ-treated+α-tocopherol supplementation micerespectively. Asterisks (*) indicate significant difference in PQ treatment group compared to control group. Hash-tag (#) sign represents ameliorative effect of α-tocopherol supplementation compared to PQ-treatment group.

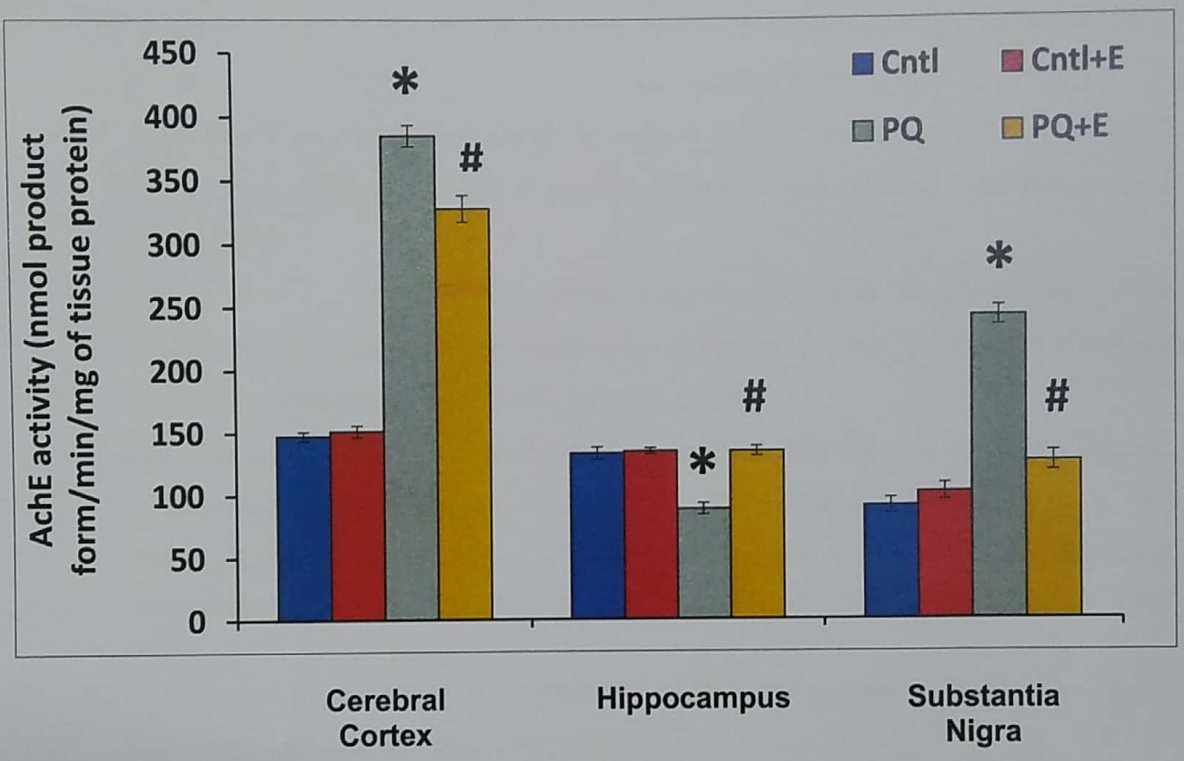

Fig 4: Changes in the pattern of AChE activity in different brain regions of young adult male mice after PQ treatment and α-tocopherol supplementation study. The figure represents histogram of (a) Cerebral cortex, (b) Hippocampus, (c) Substantia nigra. The values are represented as mean±SEM. The parametric values are analyzed by two-way ANOVA followed by post-hoc (TukeyHSD) analysis with significance level at $p<0.05$. Cntl, Cntl+E, PQ and PQ+E stand for control, control+α-tocopherol supplementation, PQ-treated, PQ-treated+α-tocopherol supplementation mice respectively. Asterisks (*) indicate significant difference in PQ treatment group compared to control group. Hash-tag (#) sign represents ameliorative effect of α-tocopherol supplementation compared to PQ-treatment group.

References

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16. Guo L, Xiong H, Kim JI, Wu YW, Lalchandani RR, Cui Y, Shu Y, Xu T, Ding JB. Dynamic rewiring of neural circuits in the motor cortex in mouse models of Parkinson's disease. Nature neuroscience. 2015 Sep;18(9):1299.
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18. Sudha S, Lakshmana MK, Pradhan N. Changes in learning and memory, acetylcholinesterase activity and monoamines in brain after chronic carbamazepine administration in rats. Epilepsia. 1995 Apr;36(4):416-22.

Nilkanta Chakrabarti 28/05/2019

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28/5/19

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Signature of Co-PI

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