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Original Article

Investigating cerebellar oxidative stress, inflammation and apoptosis following sub-acute MPTP administration in Balb/c mice

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ABSTRACT

Background and aim: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administered mice is a known model of Parkinson's disease (PD) which is characterized by neurodegeneration primarily in the substantia nigra; however, increasing evidence highlights the role of the cerebellum in both motor and non-motor symptoms. This study investigates the effects of sub-acute MPTP administration on oxidative stress, inflammation, and apoptosis in the cerebellum of adult male Balb/c mice.

Methods: Twenty adult male Balb/c mice, weighing 20-30 g, were acclimatized for 14 days and assigned to control (n=10, PBS) and MPTP groups (n=10, 20 mg/kg body weight of MPTP, intraperitoneally administered daily for five consecutive days). Behavioral assessments were performed using an open field test on day seven, focusing on cerebellar-related behaviors. Following this, histological, immunohistochemical, and biochemical analyses were conducted to evaluate markers of oxidative stress (nuclear factor erythroid 2-related factor 2 along with glutathione peroxidase), inflammation (tumor necrosis factor-alpha as well as nuclear factor kappa B), and apoptosis (B-cell lymphoma 2).

Results: MPTP administration significantly reduced nuclear factor erythroid 2-related factor 2 along with glutathione peroxidase while increasing tumor necrosis factor-alpha as well as nuclear factor kappa B in the cerebellum, coinciding with enhanced apoptosis as indicated by a lower B-cell lymphoma 2 level. Behavioral results revealed significant reductions in the grooming frequency of MPTP-treated mice compared to controls.

Conclusion: The findings indicate that MPTP induces oxidative stress, inflammation, and apoptosis in the cerebellum of adult male Balb/c mice, it might be worthwhile to observe the cerebellar changes in the diagnosis and management of PD.

Keywords:
Proinflammatory markers; Balb/c mice; MPTP; Cerebellum; Parkinson's disease

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INTRODUCTION

Parkinson's disease (PD) is one of the most prevalent neurodegenerative diseases(Prajjwal *et al.,* 2023). It is a continuous neurodegenerative disorder that majorly affects the substantial nigra of the midbrain. It causes symptoms like rigidity, bradykinesia, tremors, abnormal Gait *e.t.c.* (Aarsland *et al.,* 2021). Despite extensive research, the mechanisms underlying the neuropathology of PD are still largely unknown. However, it is believed that multiple genetic and environmental influence is a crucial factor that play critical roles in the development of the disease (Prajjwal *et al.,* 2023). The majority of the research on PD is performed on the substantia nigra, whereas the cerebellum has received little to no attention. However, increasing anatomical, pathophysiological and clinical evidence suggests cerebellar involvement in the clinical symptoms of PD; this may explain why Parkinsonian resting tremor is corrected by either the stimulation or lesioning of the thalamic ventral intermediate nucleus receiving cerebellar efferent(Wu and Hallett 2013) . Positron emission tomography (PET) studies found a correlation between PD akinesia and elevated levels of regional cerebral blood flow in the cerebellum, (Wu and Hallett 2013) as well as cerebellar involvement in nonmotor symptoms of PD via cerebello-thalamo-striatal-cortical loops(Riou *et al.,* 2021). Additionally, subthalamic nucleus stimulation improves motor signs and reduces cerebellum and pedunculopontine nuclei regional cerebral blood flow (Payoux *et al.,* 2004; Karimi *et al.,* 2008).

The cerebellum and basal ganglia are key subcortical structures that play significant roles in various aspects of motor, cognitive, and emotional behavior(Yoshida *et al.,* 2022). These

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structures establish complex multi-synaptic pathways with the cerebral cortex (Bostan and Strick 2018). The cerebellum, in particular, is recognized for its impact on both motor and cognitive functions through the cerebello-thalamo-cortical circuit (Rudolph *et al.,* 2023). Research has indicated that pathological alterations in the cerebellum can occur due to dopaminergic degeneration, as seen in patients with Parkinson's disease and corresponding animal studies(Kawabata *et al.,* 2020). However, the spread of the neurologic insult to other brain regions besides the nigrostriatal axis is still not thoroughly characterized. Therefore, understanding the broader damage, as well as the effects of therapeutic strategies in other areas, is essential to fully characterizing the pathogenic mechanisms involved in PD.

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) as a structural analogue of meperidine was an unintended product during 1-methyl-4-phenyl-4-propionoxypiperidine synthesis (Mat Taib and Mustapha 2020 Dec 14). It causes marked dopamine depletion in the striatum as well as the destruction of nigrostriatal dopaminergic neurons in human, primate and rodent brains. Induction of Parkinsonism by MPTP in rodents has generated a wealth of neurochemical, pharmacological and anatomical findings. Rats are generally resistant to MPTP neurotoxicity, but mice, are susceptible (Meredith and Rademacher 2011). However, most of the studies conducted on rodents involved SNpc and the striatum. Hence, In the present study, we investigated the impact of sub-acute MPTP administration on the cerebellum of adult male Balb/c mice.

MATERIALS AND METHODS

Animal handling and administration

Twenty adult male Balb/c mice were used for this study, weighing 20-30g. They were purchased from Tosab laboratory Ogbomosho, Oyo State, Nigeria and were housed at the animal house in the Central Research Lab, University of Ilorin. They were provided with feed and water *ad libitum*; they were acclimatized for 14 days prior to the start of the experiment. Animal handling was in line with guidelines recommended by the Animals Ethics Committee of the University of Ilorin (UERC/ASN/2021/2136).

The mice used for this study were divided into two groups of 10 mice each. The control animals were given 0.2mls of phosphate-buffered saline (PBS) daily for five consecutive days, while the MPTP group received 20mg/kg body weight of MPTP daily for five consecutive days (Yang *et al.,* 1998). Both administrations were done intraperitoneally.

Behavioural studies

On day 7 of the experiment, which corresponds to 2 days after the last MPTP administration, the mice were subjected to an open field test to evaluate behaviors linked to cerebellar function. Mice were placed in a standardized, well-lit box whose floor was divided into 4 X 4 squares. They were allowed to explore for five minutes while their activities were being captured with a webcam(Sulaimon *et al.,* 2024). The grooming and rearing frequencies were evaluated from the videos by three trained individuals who were blinded to the study. The average of their readings was taken as the rearing and grooming frequencies.

Animal euthanization

On day eight post-MPTP administration, experimental mice were euthanized with the aid of isoflurane. The isoflurane was administered using the open-drop method and nose cone method to maintain the anesthesia while the mice were dissected. Transcardial perfusion was done by perfusing the mice with PBS followed by 10% neutral buffered formalin (NBF). The perfused cerebellar tissues (four per group) were excised for histological and immunohistochemical studies. The brain tissues that were not perfused with NBF (six from each group) were homogenized in 0.25M of sucrose solution for biochemical analysis.

Tissue processing for histological and immunohistochemical demonstration of the cerebellar tissue

The fixed cerebellar tissues were then dehydrated in increasing concentration of alcohol, cleared in xylene, embedded in paraffin wax and sectioned. For the hematoxylin and eosin (H&E staining), cerebellar sections were dewaxed in xylene, rehydrated through decreasing alcohol grades, and stained with hematoxylin and eosin. After rinsing and dehydration, they were cleared in xylene and mounted with DPX under a coverslip.

To immunohistochemically demonstrate nuclear factor erythroid 2-related factor 2(Nrf2) and B-cell lymphoma 2 (Bcl2) proteins. Antigen unmasking of sections was done by incubating in antigen retrieval solution at 60˚C for 50 minutes, which was followed by endogenous peroxidase inhibition, and then incubated in the primary antibodies (anti-Nrf2, or Bcl2 at 1:100 dilution) overnight at 10˚C. After rinsing, the sections were incubated in the secondary antibody (goat anti-rabbit mouse) for 30 min, and then reactivity was revealed with DAP + hydrogen peroxide.

Biochemical analysis

Six cerebellar tissues that were not perfused were subjected to homogenization followed by centrifugation for 10 minutes at a speed of 5000 rpm., from which supernatant was obtained to assay for antioxidant enzyme (glutathione peroxidase (GPx)), a marker of lipid peroxidation (malondialdehyde (MDA)), proinflammatory markers, (tumor necrosis factor-alpha (TNF α)), as well as a transcription factor involved in inflammation (nuclear factor kappa B (NF-κB)). ELISA kits used for TNF α (E-EL-R2856) and NF-κB (E-EL-R0673) assay were products of Elabscience Biotechnology Inc.USA was used for this study, and the protocol used was as described by the producer. MDA concentration assay was based on the reaction of 2-thiobarbituric acid with MDA at 25°C to produce a chromophore as described in our publication (Sulaimon *et al.,* 2024). The assay for GPx was based on the Ellman method, which involves using Ellman's reagent 5,5'-dithiobis-(2-nitrobenzoic acid (DTNB) to measure the

consumption of glutathione (GSH) during the GPx-catalyzed reaction (Ellman *et al.,* 1961).

Statistical Analysis

The data were analyzed with the 7.0 version of Graph Pad Prism using its unpaired Student's t-test tool. The bar charts were plotted with the mean ± SEM, and the statistical significance used was $p < 0.05$.

RESULTS

Sub-acute MPTP administration induced altered cerebellar function

It was observed that the grooming frequency was significantly higher in the control group compared to the MPTP group at $p<0.05$ (Fig. 1a). However, there was no significant difference in the rearing frequencies of the two groups because the p value was greater than 0.05 (Fig. 1b).

MPTP reduced glutathione peroxidase activity and Nrf2 expression in the cerebellum of adult male Balb/c mice

The result showed that MPTP reduced the cerebellum's Nrf2 expression (Fig. 2a) and significantly ($p<0.05$) inhibited cerebellar GPx (Fig. 2b). There was no significant difference ($p<0.05$) observed in the cerebellar MDA levels between the two groups. (Fig 2c).

MPTP up-regulated cerebellar TNFα in adult male Balb/c mice

The presence of oxidative stressors usually activates glial cells, particularly microglia, which in turn liberate proinflammatory factors such as TNFα and NF-κB. It was observed that the cerebellar TNF-α and NF-κB were significantly ($p<0.05$) higher in the MPTP group compared to the control (Fig. 3a).

Effect of MPTP on apoptosis of cerebellar neurons

Unchecked tissue oxidative stress and inflammation can lead to cell loss of both apoptotic and nonapoptotic types. The observed photomicrographs indicated the MPTP-induced depletion of cerebellar Bcl2 protein, making them prone to apoptosis. The loss of Purkinje cells was also confirmed in the cerebellar sections stained with H&E, where cell loss (Red oval) was observed, particularly in the Purkinje cell layer of the MPTP-administered mice Fig 4 (lower right photomicrograph).

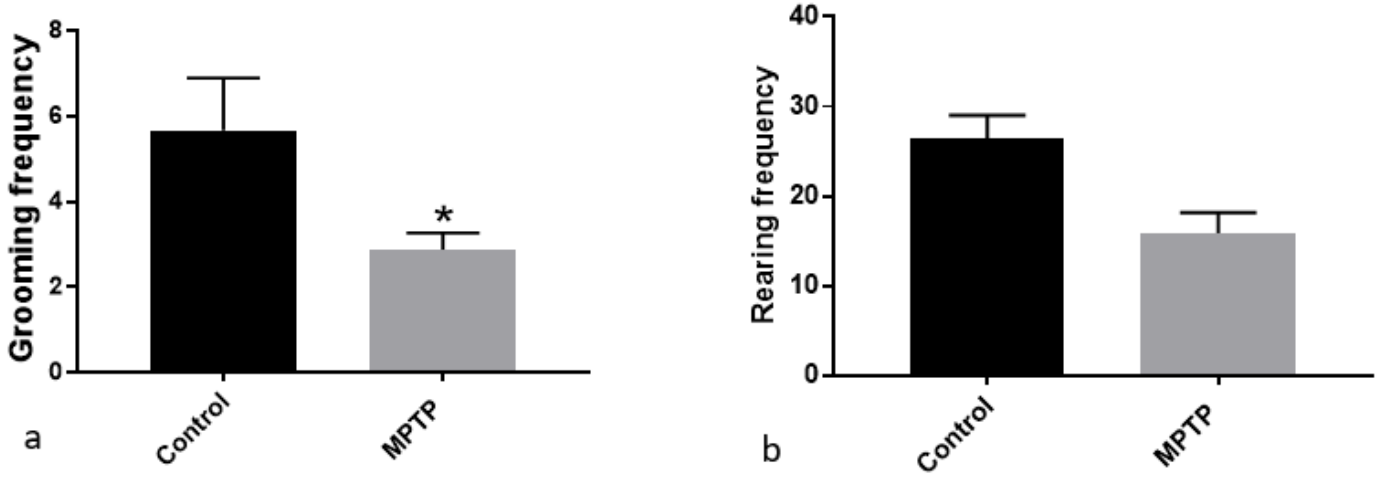

Fig.1: Impact of MPTP on cerebellar function. (a). grooming frequency, and (b). rearing frequency. * indicate significant difference at p<0.05.

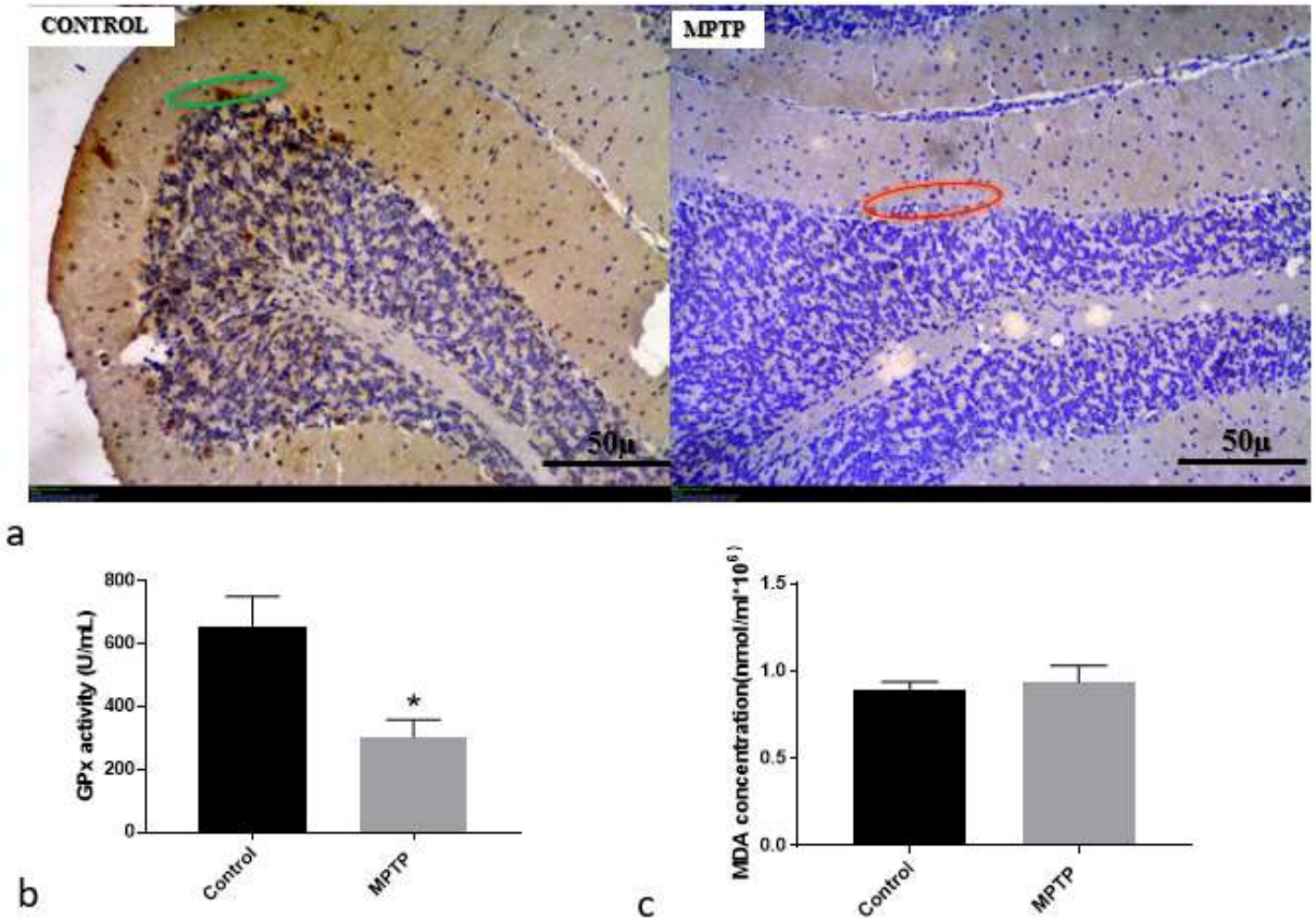

Fig. 2: MPTP depleted the cerebellar antioxidant factors. (a) Representative photomicrographs stained for Nrf2 protein show high Nrf2 expression, especially in the Purkinje cells (green oval) of the control, as against negligible Nrf2 expression observed in the MPTP group. (b) MDA concentration. (c) GPx activity of the experimental animals. * indicates a significant difference at p<0.05. photomicrographs were stained for Nrf2, x10 objective and 50µ scalebar.

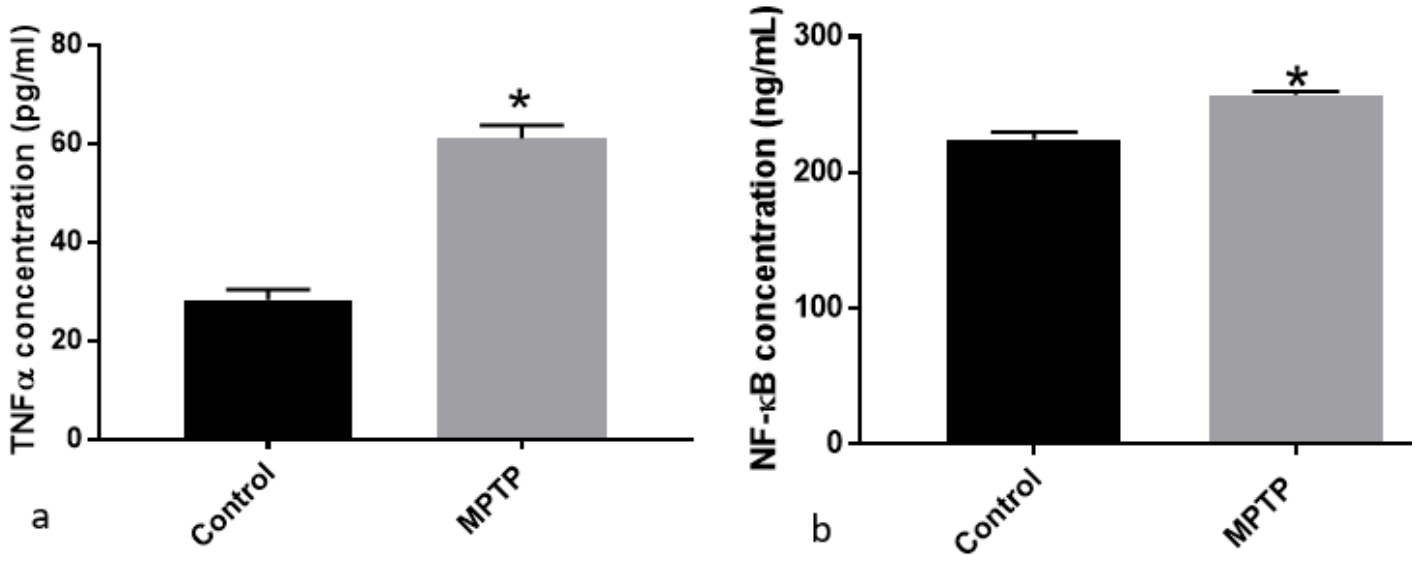

Fig.3. MPTP increased cerebellar proinflammatory markers * indicates a significant difference at p<0.05.

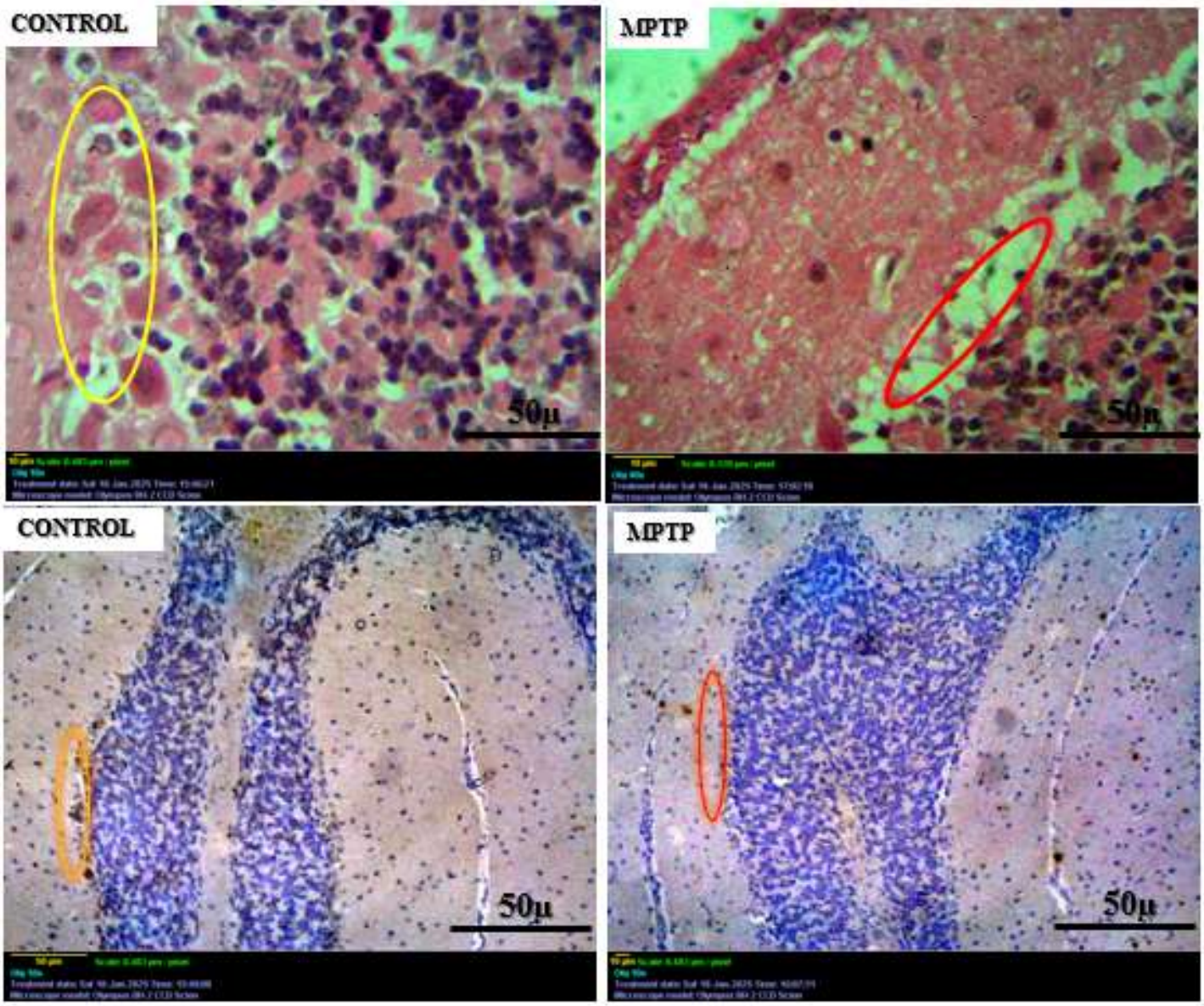

Fig 4. MPTP led to the loss of cerebellar Purkinje cells and Bcl2. The upper left slide shows the cerebellum of the control with intact Purkinje cells (yellow oval) as against their loss observed in the MPTP-administered animal (red oval) in the upper right photomicrograph: Lower photomicrographs were stained for antiapoptotic protein (Bcl2) which was prominently present in control (lower left slide (orange oval)) especially in the Purkinje cells, compared to the MPTP group lower left slide. Upper slides were stained with H&E, x40 objective and 10µ scalebar, lower slides stained for Bcl2 protein, x10 objective and 50µ scalebar

DISCUSSION

1-Methyl-4-phenyl- 1,2,3,6-tetrahydropyridine as a neurotoxin, selectively destroys the nigrostriatal dopaminergic neurons in humans, subhuman primates and lower animals (Mat Taib and Mustapha 2020 Dec 14). MPTP-induced PD mouse models have shed light on PD because they mimic vital aspects of PD, particularly the pathophysiology. Apart from the role of MPTP in the loss of SNpc dopaminergic neurons, some evidence also shows the loss of cerebellar Purkinje cells and some granule cells in mice treated with MPTP (Takada *et al.*, 1988) as high as those in the striatum and SNpc (Takada *et al.,* 1993). The sensitivity of MPTP is also strain-dependent which is why it is important to characterize the effect of MPTP administration on BALB/c strain which is available to researchers in this part of the world. This study characterized the effects of MPTP on oxidative stress, inflammation, apoptosis as well as the histomorphology of the cerebellum in adult male BALB/c mice. In this study, the Parkinsonian effect observed from the open-field test was reduced grooming frequency in the MPTP-administered mice compared to the control. This motor behaviour also happens to coincide with the role of the cerebellum. Hence, it can be deduced that MPTP did have a detrimental effect on the cerebellum function of adult male Balb/c mice. Execution of motor activities involves various parts of the brain, of which the cerebellum is inclusive. Additionally, even though they use different pathways to communicate with the cerebrum, the cerebellum and basal ganglia work together to ensure smooth

and coordinated movements, with the cerebellum focusing on fine-tuning and the basal ganglia initiating and regulating movements. Furthermore, evidence from virus tracing has reported communication between these important structures (Bostan and Strick 2010; Bostan and Strick 2018). Their route of communication involves the connection between the cerebellar dentate nucleus, the thalamus, and onward to the striatum, as well as the connection between the cerebellar cortex, pontine nuclei and the subthalamic nucleus which is a vital nucleus as far as PD is concerned(Bostan and Strick 2010; Bostan and Strick 2018), this is further corroborated by the fact that deep brain stimulation of the STN is highly effective in correcting the PD's motor symptoms(Rajamani *et al.,* 2024). Thus, the above connection explains why MPTP administration could alter motor coordination, one of the cardinal functions of the cerebellum.

Oxidative stress has been implicated in PD and MPTP-induced PD. Oxidation of MPTP to MPP+ by MAO-B in the brain was found to generate free radicals(Meredith and Rademacher 2011). Incubation of MPP+ with mitochondrial enzymes also induces free radical production, while the increased free radicals can further inhibit the function of complex I and induce oxidative stress, particularly in the basal ganglia (Adams *et al.,* 1993). However, given the connection between basal ganglia and cerebellum and their collective role in the movement, one could assume that the oxidative stress in the basal ganglia might spread to the cerebellum. To investigate this, we assayed for the level of oxidative stress markers in the cerebellum following systemic administration of MPTP. It was observed that MPTP was associated with the inhibition of antioxidant enzyme GPx activity and reduction in the antioxidant transcription factor Nrf2 expression. Glutathione peroxidase (GPx) is an important antioxidant factor as it protects cells from oxidative damage by reducing peroxides. Oxidative stress follows an imbalance between the level of free radicals and the antioxidants. Moreover, GPx has also been reported to be reduced in PD patients and MPTP-induced PD models (Johannsen *et al.,* 1991; Bai *et al.,* 2021). Nuclear factor erythroid 2-related factor 2 (Nrf2) activates the expression of several cytoprotective enzymes, including GPx. The activation of Nrf2 has been shown to protect against MPTP-induced neurodegeneration by enhancing the antioxidant defense system(He *et al.,* 2020); the above reports were mainly in the basal ganglia. However, the result from our study indicates that MPTP administration depleted the cerebellar endogenous antioxidant factors, thereby making the cerebellum prone to the detrimental effect of free radicals. A study by Zhang *et al* (2010) supported the fact that MPTP-induced oxidative stress in the cerebellum, which reported changes in cerebellar antioxidant proteins such as glutathione transferase following MPTP administration(Zhang *et al.,* 2010). Furthermore, they also reported that MPTP might predispose the cerebellum to nitrosative and oxidative stress as the level of cerebellar neuronal nitric oxide synthase (nNOS) was elevated following MPTP administration (Zhang *et al.,* 2010).

Cerebellar oxidative stress induced by MPTP could lead to neuroinflammation. To test this hypothesis, we assayed for proinflammatory factors TNFα and NF-κB, and we observed that MPTP induced inflammation by increasing the expression of these inflammatory markers. This inflammation could arise from a decrease in GPx activity and Nrf2 expression, which subsequently activates microglia that may release TNFα and NF-κB. The elevated NF-κB can further release other cytokines, including TNFα, which can exacerbate the ongoing cerebellar inflammation. Furthermore, TNFα can activate its receptors, which subsequently activate complex I. Complex I may then activate NF-κB and MAPKs, potentially leading to inflammation and tissue degeneration (Pasparakis and Vandenabeele 2015; Jang *et al.,* 2021). It has been previously reported that The treatment of MPTP causes an inflammatory reaction featured by infiltration of T cells into the SN and striatum, activation of the resident brain macrophages, microglia, and elevates gene expression tumour necrosis factor α (TNFα), proinflammatory cytokines interleukin-1 β (IL-1β), and interferon γ (INFγ)(Meredith and Rademacher 2011).

The human cerebellum plays a crucial role in coordinating movements rather than initiating them. It enhances precision and ensures accurate timing by processing information from sensory systems, including those in the spinal cord. Other parts of the brain. It integrates these inputs to fine-tune motor activity (Fine *et al.,* 2002). Hence, its histoarchitecture and cells must be intact to perform this vital motor function. Given that oxidative stress and neuroinflammation can ultimately lead to cell death, we assessed the level of Bcl2, an antiapoptotic protein. The findings from this study support the earlier discovery that associated MPTP with the depletion of antiapoptotic factors, consequently leading to cell death via apoptosis type(Langston 2017). Although these findings are largely in the basal ganglia, some studies have however also reported the reduction of cerebellar antiapoptotic protein in the cerebellum following MPTP exposure (Zhang *et al.,* 2010)The apoptosis was further supported by the cerebellum's histoarchitecture, where we observed a loss of Purkinje cells in the adult male Balb/c mice exposed to MPTP. The connection between oxidative stress and apoptosis that we reported from our findings is bolstered by the evidence that Bcl-2 overexpression protects against MPTP neurotoxicity through mechanisms that may involve both antioxidant activity and the inhibition of apoptotic pathways, as well as by the discovery that MPTP induces cerebellar DNA damage.

This study, therefore, concluded that MPTP neurotoxicity could spread to the cerebellum, possibly via its connections with basal ganglia or systemic oxidative stress and inflammation. Overall, cerebellar oxidative stress, inflammation, and apoptosis were observed following subacute MPTP administration on adult male Balb/c mice.

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