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Research Article

Neuroprotective effect of valsartan versus pramipexole on mouse model of MPTP-induced Parkinson's disease

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Abstract

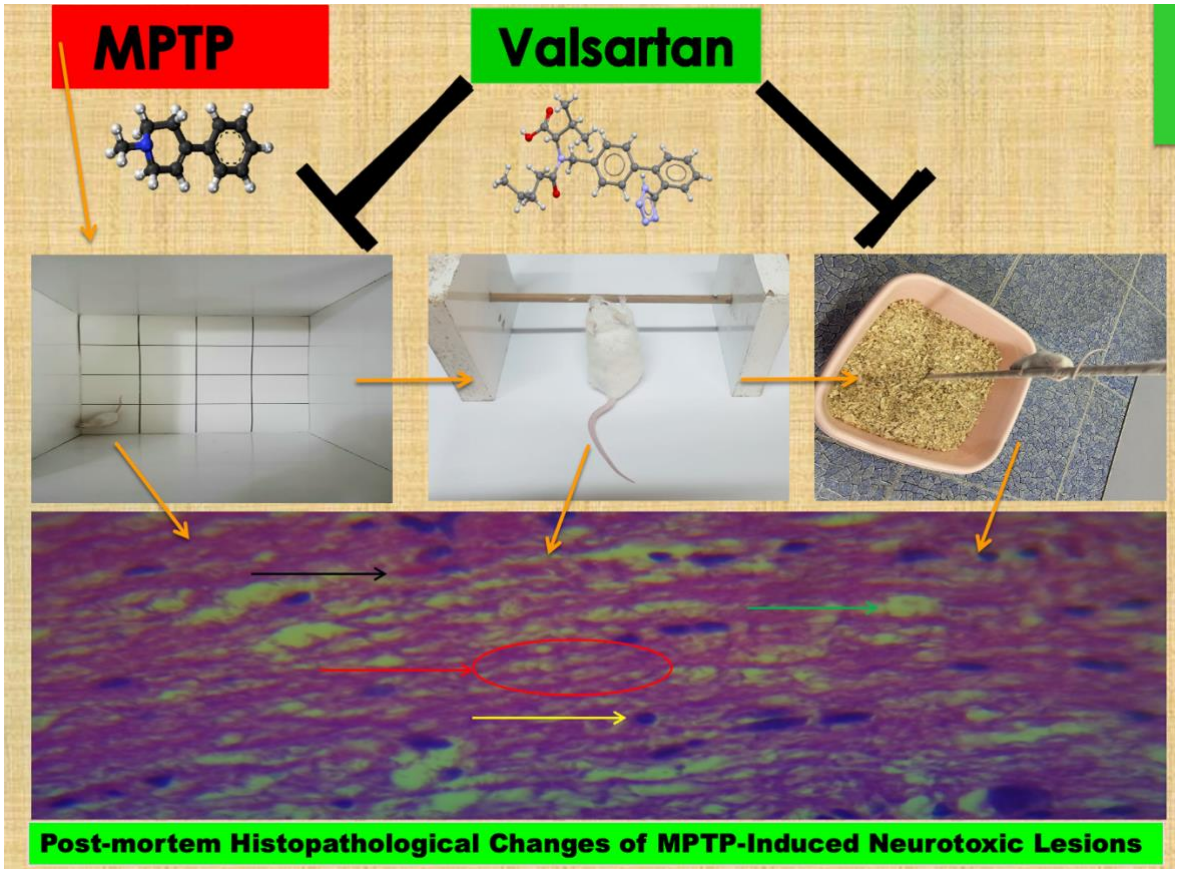
Introduction: Parkinson's disease is the second most common complex progressive neurodegenerative disease after Alzheimer's disease. Tremor, stiffness, and bradykinesia are common symptoms, additionally to postural instability as the condition advances. Valsartan is prescribed to treat hypertension and heart failure, and it mainly acts by antagonizing angiotensin II (Ang II) actions at the AT1 receptor. **Aim of the Study:** The present study aimed to investigate the neuroprotective effect of valsartan on experimentally induced Parkinson's disease in mice.

Materials and Methods: This study involved 40 male mice grouped into four groups (n=10). Group 1: The normal/healthy group obtained filtered water orally for 25 days. Group 2 got MPTP (30 mg/kg/day) intraperitoneally (IP) for 5 days, starting on day 15 to the close of day 19. Group 3 was given oral pramipexole (1 mg/kg/day) for 25 days, followed by an induction dose of MPTP (30 mg/kg/day) (IP) 60 minutes later. Group 4 received valsartan orally (30 mg/kg/day) for 25 days and then underwent induction with MPTP (30 mg/kg/day) (IP) 60 minutes after valsartan; on day 26, all animals were euthanized, and a biopsy of brain tissues was collected for examination.

Results and Discussion: Valsartan substantially decreased levels of MDA, IL-1β, and α-synuclein compared to those in the induction group. Valsartan also substantially increased dopamine levels while producing a non-significant decrease in caspase-3 levels. Moreover, histopathological examination of valsartan exerted good improvement as opposed to induction.

Conclusion: Valsartan produced neuroprotective effect through multiple mechanisms on MPTP exacerbated PD mouse model.

Graphical Abstract



Keywords

Parkinson's disease, MPTP, α-synuclein, AT1Rs, anti-hypertensive drugs, Valsartan

Introduction

Parkinson's disease (PD) starts with age-related symptoms (Santoro et al. 2023). It is a neurodegenerative condition caused mainly by the loss of dopamine neurons in the Substantia Nigra pars compacta (SNpc) and the development of Lewy bodies (LBs), made up of misfolded α-synuclein, that accumulate in several systems in PD patient with a heterogeneous pattern, comprising motor and non-motor symptoms (Rizek et al. 2016; van Munster et al. 2022; Cavarretta and Jaeger 2023). Motor symptoms such as tremor, akinesia, stiffness, and postural instability as well as several non-motor irregularities have been recorded, including excessive daytime sleepiness (EDS), insomnia, restless legs syndrome, and rapid eye movement sleep behavior disorder (RBD) (Tavora et al. 2014; Mekkey et al. 2020). The cause of PD is not completely known. However, there was certain proof that heredity and lifestyle factors, such as a decline in tobacco use and an increase in exposition to chemicals and pesticides, lead to the increased frequency of PD (Hantikainen et al. 2022; Bhidayasiri et al. 2024) There actually are numerous processes in the pathophysiology of Parkinson's disease, such as oxidative injury, neuroinflammation, irregular proteasome, mitochondrial synapses, and lysosomal malfunction, that are linked to the aberrant proteins in cortex and subcortex zones, with the subsequent disruption of several neurotransmitter networks (Avdeeva et al. 2016; Jellinger 2023).

Certain substances that harm neurons have been used to create animal models of PD is MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and its oxidation product, 1-methyl-4-phenylpyridinium ion (MPP+). Monoamine oxidase-B in astrocytes converts MPTP to MPP+, which is subsequently taken up by DA neurons via their dopamine transporter (DAT) and the

astrocyte dysfunction and decreased astrocyte proliferation, which is relevant in neurodegenerative disorders and critical for neuron survival. MPTP is neurotoxic promote cell death through mechanisms that include inflammation, ROS production, and inhibition of complex I in the mitochondrial electron transport chain (Campolo et al. 2017; Zhu and Gong 2020; Ahmed and Kadhim 2024).

α-Synuclein, a 140 amino acid protein present in presynaptic terminals in the brain, plays a role in neurotransmitter release, storage, circulation, and vesicle mobility during routine physiological situations (Limegrover et al. 2021; Gao et al. 2022). Growing proof shows that elevated α-synuclein levels are harmful and could play a role in the etiology of PD, and it has been investigated extensively as a disease marker, pathogenic trigger, and therapeutic target in synucleinopathies (Recasens et al. 2016; Majbour et al. 2022). The characteristic histopathology that describes PD is the presence of intracytoplasmic inclusions known as Lewy bodies, involving high quantities of the protein α-synuclein primarily beta sheet fibrillary structures (Limegrover et al. 2021). In addition, oxidative stress is brought about by an imbalance between the production of reactive oxygen species (ROS) and the availability of antioxidants or free radical detoxifiers (Abdelsalam and Safar 2015; Khaleel et al. 2025). MDA is a reactive end product of fatty acid peroxidation that drives free radical generation; hence, it serves as a measure of oxidative stress(Ardah et al. 2020; Raheem et al. 2025). Of note, oxidative damage may trigger inflammation, creating an endless cycle that leads to tissue destruction and a pro-inflammatory microenvironment (Aal-Aaboda et al. 2021b; Ali et al. 2025; Jaafar et al. 2025). However, many experimental trials demonstrate the beneficial effects of using agents with antioxidant activity in inflammatory and neurodegenerative diseases (Enogieru et al. 2018; Naji et al. 2022; Abdul-Majeed et al. 2025). Oxidative distress often develops in unexplained PD, and the byproducts of oxidative harm impair neuronal functions; nevertheless, these comprise just one aspect of a cycle, and they cannot be separated from various factors associated with dopaminergic cell destruction (Dias et al. 2013; Khan et al. 2025). Modifications in cytokine, neurotrophins, and apoptosis-associated protein concentrations in the nigrostriatal areas of PD could contribute to the breakdown and neurodegeneration of nigrostriatal dopamine-producing neuron connections (Nagatsu et al. 2000). Inflammatory cytokines play an important role in etiopathogeneses and destructive processes associated with cytokine storm, and the increased level in many cytokines such as IL-1, IL-2 and TNF-α are strongly correlated with inflammatory and immune–dysregulated conditions (Abbas et al. 2025; Shihab et al. 2025). Antihypertensive drugs which possess anti-inflammatory effects have been tried with success in many pathological condition, and their repurposing usage seems to be promising (Atarbashe and Abu-Raghif 2020; Abu-Raghif and Mahdi 2022; Dawood and Abu-Raghif 2024).

AT1Rs are G-protein coupled receptors or GPCRs which generated in several brain cells. The stimulation of AT1R signaling in the brain is all related with apoptosis, oxidative stress, and neuroinflammation. Therefore, AT1R signal attenuation helps with neuroprotection and cognitive enhancement. According to clinical research, administering ARBs can help prevent dementia and stroke. ARBs or angiotensin II type-1 (AT1) receptor blocker of various kinds, such as valsartan (VAL), which is an important medication for treating hypertension and heart failure, can cross the blood-brain barrier and affect brain tissue, and it can reduce neurodegeneration brought on by inflammatory reactions, reactive oxygen species (ROS), and apoptotic signals (Cai et al. 2021; El-din Hussein et al. 2023). However, many clinical and animal investigations conducted that ARBs have anti-inflammatory properties (Mohammed et al. 2022; Raheem et al. 2022). VAL lowers oxidative stress markers like malondialdehyde in the brain and boosts the activity of antioxidant defense enzymes like superoxide dismutase and catalase (Kaeidi et al. 2021).

Materials and Methods

Drugs and chemicals

A crystalline powder of MPTP hydrochloride was bought from Merere (China). Pramipexole medication was bought via Boehringer-Ingelheim Pharma-GmbH & Co. KG (Germany). Valsartan was bought from Sigma-Aldrich (USA). MDA, IL-1Beta, DA, and Cas 3 mouse ELIZA kits were bought via Elabscience (USA), while α-synuclein mouse ELIZA kits were acquired by Mybiosources (USA). Buffering phosphate solutions is sourced by Reagent-World (USA), and formaldehyde solutions 37% - via Fluka-Chemical (UK).

Animals

The study was an experimental randomized controlled study. A total of 40 albino male mice weighing 22-29 g, aged between 2-2.5 months, were employed in this study. Animals were

gathered via the Al-Razi-Center at the Ministry of Industry and Minerals and housed within circumstances of supervised relative humidity, temperature, and light-dark cycle conditions in the animal house at the Biotechnology Research Center (Al-Nahrain University, Iraq). Throughout the experiment, mice were given conventional laboratory pellets and unlimited access to water. The study was conducted upon approval by the Institutional Review Board at the College of Medicine (Al-Nahrain University, Iraq).

Study design

Group 1: Healthy/normal control group, all the mice in this group received DW by oral gavage tubes once daily for a period of 25 days.
Group 2: Induction group, all mice were administered MPTP (30mg/kg/day) IP for 5 continuous days (Zhang et al. 2017), starting on day 15 through the completion of day 19.
Group 3: In the positive-control group, all mice were treated with pramipexole (1 mg/kg/day) orally via gavage tube for 25 days, (ElHak et al. 2010), accompanied by an induction with MPTP (30 mg/kg/day, IP) 60 minutes after pramipexole through days 15 to 19 (Hu et al. 2018).
Group 4: All mice got treated with valsartan (30 mg/kg/day) orally by gavage tube for 25 days (Abbassi et al. 2016). Next, throughout the treatment, the induction was carried out with MPTP (30 mg/kg/day), IP, 60 minutes following valsartan from day 15 to 19 (Asmaa Abdulwahab and Haitham Mahmood 2025).

Induction design of Parkinson's disease

MPTP crystallized powder was pulverized, weighed (60 mg), and mixed into 40 mL of 0.9% saline solution (Nazif et al. 2020). Mice were administered a daily IP dosage of 30 mg/kg of MPTP for five consecutive days (Zhang et al. 2017). Since the clear solution was only stable for a day at 25°C, it was utilized soon after preparation.

Preparation of drugs

To make the valsartan solution, 25 mg of pure powdered valsartan dispersed in 2 drops of triethanolamine after being weighed using an electronic balance. The amount was then completed to 8 mL with DW to obtain a clear solution, which was then administered by gastric gavage at a dose of 30 mg/kg/day (Abbassi et al. 2016). Pramipexole was supplied as oral tablets weighing 0.18 mg; approximately 12 tablets dissolved in 20 milliliters of DW (Taravini et al. 2016). The obtained solution (2.16 mg/20 mL) was administered by gastric gavage at a dose of 1 mg/kg (ElHak et al. 2010).

Biochemical analysis

On day 26, all animals were killed by cervical dislocation after being anesthetized by diethyl ether anesthesia, then brain tissue homogenates were prepared by immediately exercising the brain, which was then cleaned and cleansed with PBS (7.5, 4´C) to get rid of every remnant blood. Once dried by using filter paper, slices were divided into little pieces. PBS and chopped tissues were combined in tubes to create a brain tissue homogenate for every mouse (Jawad et al. 2014; Alhussien et al. 2022). Following that, homogenates were performed for a single minute utilizing a tissue homogenizing device (Karl-Kalb, Germany). Every procedure mentioned previously required storing samples on ice (Sraibit Abbod et al. 2014; Abdulhameed and Kadhim 2024). The supernatants were extracted by centrifuge (Cypress-Diagnostics, Belgium), and the residual portion was permitted to naturally settle and frozen until getting utilized for bio-indicator evaluations. Using a glass homogenizer on ice, tissue was homogenized in accordance with the supplier's directions based on tissue specimen weight. The supernatant was collected by centrifuging the homogenates at 4°C for 5–6 minutes at 5000Xg (Aljawad et al. 2015; Aal-Aaboda et al. 2021a; Luty et al. 2025). Preserved tissue homogenates were used for estimation of MDA, IL-1 beta, caspase 3, DA, and α-synuclein using ELIZA kits according to manufactures procedures.

Histopathological analysis

Small slices of the mid-brains were preserved in 10% formaldehyde solution using the paraffin section procedure in order to assess for histological alterations in all groups (Hassan et al. 2023; Thammer et al. 2025). Brain tissues were dried in an increasing alcohol grades, then fixated, and wax embedded. After cutting paraffin slices to a thickness of 5-7 µm, hematoxylin-eosin staining was done (Habbas et al. 2025).

Statistical analysis

The Kolmogorov-Smirnov testing of normalcy was applied, and a portion of the information contained in every variable was not assigned to a typical distribution; non-parametric statistical

computation was adopted in the present research. When analyzing 6 groups, a Kruskal-Wallis analysis was employed to determine the level of significance. Pairwise comparisons were performed using Benjamini, Krieger, and Yekutieli's two-stage linear step-up approach. A p-value of ≤0.05 indicated statistical significance. All studies utilized GraphPad Prism edition 10.0.0 for Windows (Abdullah et al. 2021; Herez et al. 2022).

Results

Effect of tested agents on dopaminergic parameters

Effect of tested agents on dopamine (DA) marker

Firstly, mean of induction (group 2) demonstrated a considerable suppression (p-value ≤0.05) in DA level as contrasted to healthier control (group 1). On the other hand, valsartan (group 4) demonstrated a considerable rise (p-value ≤0.05) in the level of DA as contrasted to induction (group 2) as shown in Table 1 and Figure 1A.

Effect of tested agents on neuro-inflammatory parameters

Effect of tested agents on interleukin (IL)-1β marker

Regarding neuro-inflammatory markers, mean of induction (group 2) demonstrated a marked increment (p-value ≤0.05) in IL-1β level as opposed to normal control (group 1). On the other hand, valsartan (group 4) demonstrated a marked decrease (p-value ≤0.05) in the level of IL-1β as opposed to induction (group 2) as illustrated in Table 1 and Figure 1B.

Effect of tested agents on oxidative stress parameters

Effect of tested agents on malondialdehyde (MDA) marker

There was a significant increase in MDA level in the brain of induction (group 2) (p-value ≤ 0.05) as matched to healthy controls (group 1). While valsartan (group 4) demonstrated a significant decrease (p-value ≤ 0.05) as matched to induction (group 2), as clarified in Table 1 and Figure 1C.

Impact of studied agents on apoptotic parameters

Impact of studied agents on Caspase 3 (Cas 3) marker

There was a significant rise in the apoptotic marker like Cas 3 level in brain tissue of induction (group 2) (p-value ≤0.05) as opposed to healthy controls (group 1). While the concentration of this marker decreases among valsartan group (group 4), but it did not reach the degree of significances as compared to induction (group 2) as shown in Table 1 and Figure 1D.

Table 1. Impact of studied agents on different dopaminergic, neuro-inflammatory, oxidative, and apoptotic parameter.

Parameters	Groups			
	Group 1 (Normal control)	Group 2 (Induction)	Group 3 (positive control)	Group 4 (Valsartan)
DA (pg/mL)	1,217.27±73.05[a]	213.37±81.73[b]	1,243.59±72.07[a]	906.28±189.46[c]
IL-1β (pg/mL)	84.75±29.56[a]	244.23±134.92[b]	112.45±21.61[a]	118.53±16.54[c]
MDA (ng/mL)	121.80±44.6[a]	732.05±176.94[b]	396.09±179.06[c]	260.22±125.91[a]
Cas3 (ng/mL)	0.90±0.24[a]	6.69±1.76[b]	2.18±1.22[c]	3.35±0.58 [d]

Note: Every data point reflects the mean ± SD (SD: standard deviation). Panels with identical letters represent no considerable differences (p-value > 0.05), whereas distinct letters represent considerable differences (p-value ≤ 0.05), indicating that comparing a to b and c is significant at p ≤ 0.05 and comparing b to c is significant at p < 0.05.

Impact of studied agents on diagnostic parameters

Impact of studied agents on α–synuclein marker

Regarding α–synuclein, there was a significant rise in the level of this protein in the brain of induction (group 2) as compared to normal control (p-value≤0.05), while valsartan (group 4)

demonstrated a significant suppression of this protein (p-value≤0.05) when contrasted to induction (group 2) as clarified in Table 2 and Figure 2.

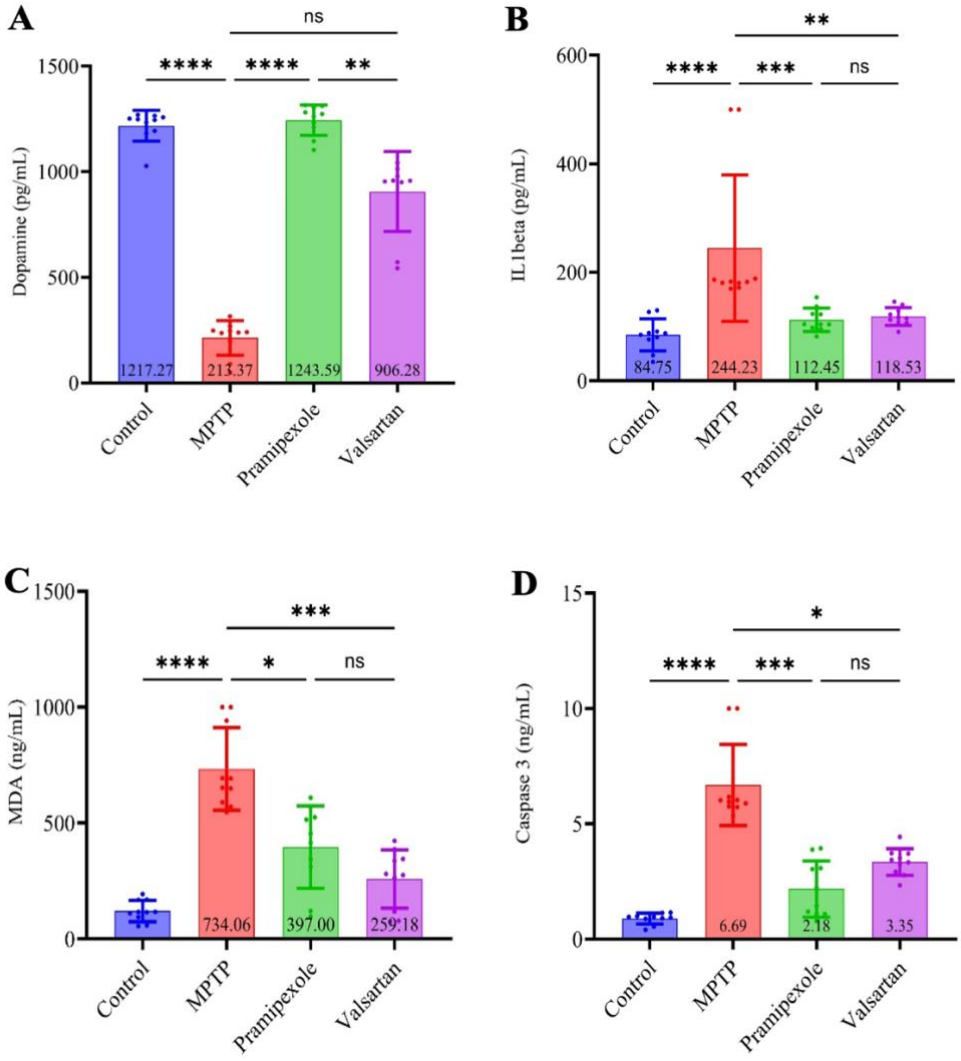


Figure 1. Impact of studied agents on different dopaminergic, neuro-inflammatory, oxidative, and apoptotic parameters. **A:** Impact of studied agents on dopamine (DA) marker**. B:** Impact of studied agents on interleukin (IL)-1β marker. **C:** Impact of studied agents on malondialdehyde (MDA) marker. **D:** Impact of studied agents on Caspase-3 (Cas-3) marker. ***Note:*** Group 1 represents the healthy/normal control mice; Group 2 represents the induction/MPTP mouse model; Group 3 represents the positive-control/pramipexole-treated mice; and Group 4 represents the valsartan-treated mice. The data points reflect the mean ± SD, indicating that the comparison of a to b and c is significant at $p \leq 0.05$, and that the comparison of b to c is significant at $p < 0.05$.

Table 2: Impact of studied agents on α-synuclein level

Parameters	Groups			
	Group 1 (Normal control)	**Group 2 (Induction)**	**Group 3 (positive control)**	**Group 4 (Valsartan)**
α -synuclein (ng/ml)	10.98±6.29[a]	24.66±4.52[b]	11.24±2.04[a]	11.56±1.89[a]

Note: Each value represents mean ± SD (SD: standard deviation). Columns with similar letters indicate no significant difference (p-value > 0.05), while different letters indicate a significant difference (p-value ≤ 0.05), suggesting that comparing a to b and c is significant at $p \leq 0.05$, and comparing b to c is significant at $p < 0.05$.

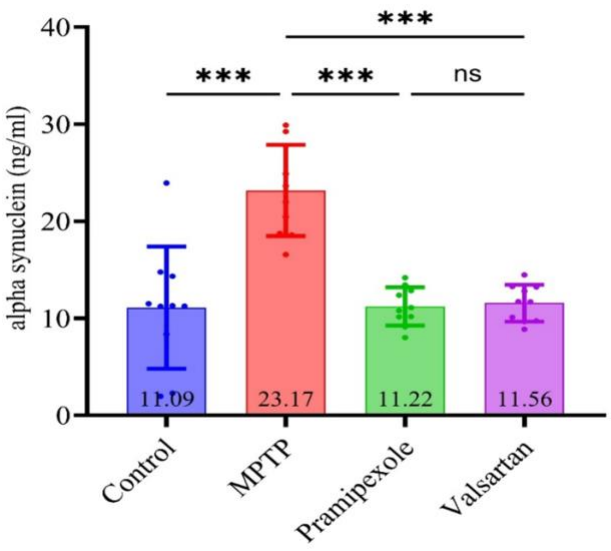


Figure 2. Impact of studied agents on α-synuclein level. Group 1 represents the healthy/normal control mice; Group 2 represents the induction/MPTP mouse model; Group 3 represents the positive-control/pramipexole-treated mice; and Group 4 represents the valsartan-treated mice. ***Note:*** The data points reflect the mean ± SD, showing that the comparison of a to b and c is significant at $p \leq 0.05$, and that the comparison of b to c is significant at $p < 0.05$.

Histopathological examination

The histopathological picture of mid-brain tissue from ostensibly healthy controls (group 1) revealed typical substantia nigra, no neuronal loss, no vacuolated outer space, no Lewy body structures, and melanin-rich neurons. Meanwhile, the mid-brain region of induction (group 2) demonstrates severe vacuolated space, profound loss of neurons, marked pyknotic nuclei, and an abundance of Lewy body structures. In the context of the positive controls (group 3), the mid-brain tissue biopsy displayed minor improvements, involving minor vacuolated space, minimal decline in neurons, limited pyknotic nuclei, and no Lewy body structures. As shown in Figure 3, valsartan mid-brain specimens showed moderate improvement, characterized by moderate loss of neurons, moderate vacuolated area, frequent pyknotic nuclei, and no Lewy body formation as indicated in Figure 3.

Discussion

Parkinson's disease is a neurological degenerative condition with complicated processes. Its pathogenesis and etiology are still unknown, but it has now placed a significant burden on society. The MPTP murine prototype is a traditional animal prototype of PD that captures the disease's key pathological features. MPTP is a fast-acting lipid-soluble substance that crosses the blood brain barrier. It is absorbed through the dopamine transporters and destroys dopamine-producing neurons by inhibiting mitochondrial respiratory chain complexes and oxidative damage. This leads to a reduction in dopaminergic neurons and problems that are similar to PD in both motor and non-motor phases. Following an IP injection, monoamine oxidase B (MAO-B) transforms MPTP into the positive-charged poisonous byproduct 1-methyl-4-phenylpyridine (MPP+). It has been suggested that MPTP causes neurotoxicity by selectively blocking mitochondrial complex I activity, which lowers ATP production and increases reactive oxygen species as well as a variety of processes, including chronic inflammation, apoptosis, and mitochondrial oxidation, may be involved in the effects of MPP+ (Lee et al. 2009; Lv et al. 2021). In the current research, MPTP (30 mg/kg/d, IP) is administered sub-acutely to the mice for 5 successive days (Zhang et al. 2017). This work aligns with earlier research which demonstrated that mice which were administered with MPTP alone show a noteworthy decrease in the number of dopaminergic neurons in addition to striatal DA and TH expression levels. TH is the enzyme that limits the rate of dopamine production, storage, and release. On the other hand, the dopamine transporter (DAT) is important in controlling synaptic dopamine concentrations. Shutting down TH and DAT expression in the striatum and SNpc in PD results in impaired L-DOPA synthesis and reduced dopamine neuronal transport, resulting in dopaminergic dysfunction and ensuring motor deficits (Nazif et al. 2020; Rehman et al. 2022).

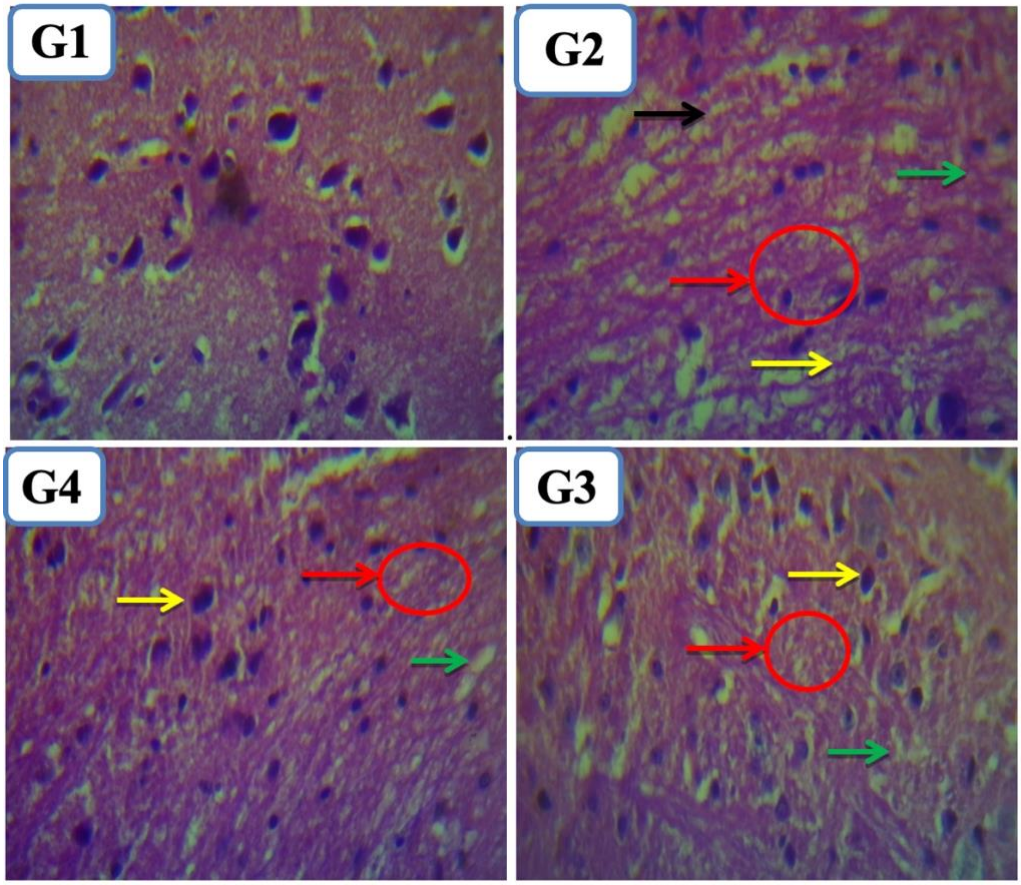


Figure 3: Haematoxylin and eosin-stained histopathological mid-brain sections from groups of mice at 40X.magnifcation. ***Note:*** G1 represents the healthy/normal control mice; G2 represents the induction/MPTP mouse model; G3 represents the positive-control/pramipexole-treated mice; and G4 represents the valsartan-treated mice. Normal control group showed normal picture of mid brain. Induction, positive control, and valsartan groups showed various changes. The black arrow denotes Llewy body structures, while the red arrow and circles reflect neuronal loss. The yellow arrow denotes pyknotic nuclei, and the green arrow denotes vacuolated space.

Concerning the impact of MPTP on oxidative stress marker (MDA) which indicated that MPTP cause significant rise in MDA level in brain tissue when opposed to normal control group is consistence with prior study (Ardah et al. 2020). The primary site of oxidative stress is the mitochondria, where it can cause more damage to the organelles and could result in additional tissue damage. Oxidative stress, which is damaging to the SN area, occurs when antioxidant molecules found in cells, such as superoxide dismutase (SOD) and glutathione peroxidase (GSH), are not able to eliminate dangerous substances, like reactive oxygen species (ROS), in an effective way when exposed to different dangerous stimuli, such as toxins. Oxidative damage can cause lipid peroxidation (LPO) and MDA, a sign of LPO. As previously mentioned, failure of mitochondria leading to oxidative stress also leads to apoptosis of dopaminergic neurons (Chen et al. 2018). In the present study, regarding the effect of MPTP on caspase-3 levels in brain tissue, it is demonstrated that a significant increase in apoptotic markers seems to agree with the previous study, which indicated that the injection of MPTP causes a noteworthy elevation in cytochrome-C, Bax, Apaf-1, fragmented caspase-9, and fragmented caspase-3 production and a diminution of Bcl-2 in the striatum region (Wang et al. 2018). When MPP+ is absorbed by dopamine-releasing neurons, which causes disruptions to mitochondrial respiratory activities, a decrease in ATP generation and an increase in intracellular ROS generation within the mitochondria result in hyperpolarization of the membrane and the opening of permeability transition pores. Cytochrome c, a pro-apoptosis polypeptide, is liberated into the cytoplasm when the mitochondrial membrane breaks down. Thus far, the build-up of cytochrome c results in the formation of apoptosome complexes including procaspase-9 and Apf, which in turn initiates the activation of caspase-9 and the caspase cascade. Moreover, cytosolic cytochrome c interacts with the Bcl-2 family proteins to activate the Bax proteins, which promote apoptosis (Shen et al. 2017; Liu et al. 2021).

The current study's findings concerning the impact of MPTP on inflammatory marker such as IL-1β are consistent with previous research showing that MPTP possess a robust action on

microglia, stimulating them and inducing alterations in their morphological and phenotypic features (microgliosis), which leads to the release of substantial amounts of ROS. It is well known that ROS trigger the activation of the NF-κB pathway, which phosphorylates a Kappa inhibitor and increases the synthesis of pro-inflammatory cytokines such interleukin-1beta, interleukin-6, and tumor necrosis factor (San Miguel et al. 2019). Finally, influence of MPTP on α-synuclein is consistent with a previously suggested rise in this protein. When MPTP is delivered, degeneration of the neurons develops. This occurs when α-synuclein migrates from its synaptic location to accumulate in deteriorating neural cell structures, the initial stage of Lewy body synthesis. In pathological events, α-synuclein shifts from monomers to inclusions, creating soluble oligomer species that harm neuron cells (Campolo et al. 2017).

Unfortunately, there is currently no treatment plan for PD patients. Conventional treatments, including levodopa, simply relieve symptoms and seriously impair motor function. Furthermore, the disease's progression cannot be stopped or reversed by these treatments (Xu et al. 2017). Furthermore, treatment over an extended period of therapy with PD medication can cause drug-resistance symptoms or a range of side effects. It is necessary to develop novel safe medicines with an array of therapeutic strategies in order to minimize adverse reactions and boost patient-specified care. Repurposing medications is a useful strategy for reducing development costs and accelerating timeframes (Pariyar et al. 2022).

As far as we are aware, no prior work has been conducted on the mitigative effects of valsartan on Parkinson's disease. Several studies have investigated the biological effects of AT1R antagonists (ARBs) other than valsartan on Parkinson's disease. In the current study, groups treated with valsartan shown a range of improvements in biochemical parameters and histological examinations as compared to groups that received induction, which resulted in a noteworthy rise in the dopaminergic neuronal marker, such as DA in the brain tissue. Additionally, there was a notable decrease in the oxidative stress marker, MDA, and considerable downregulation of neuro-inflammatory indicators, such as IL-1β. A drop in apoptotic marker, such as Cas 3, was also seen; however, it did not achieve statistical significance. Furthermore, there was a good improvement in histopathological analysis and a significant drop in α-synuclein, a diagnostic protein that is a key marker of PD progression. As will be discussed later, all of the results mentioned above are in line with the findings of numerous previous studies.

Angiotensin II receptor blockers (ARBs) such as valsartan (VAL) are potent and selective medications used for the management of hypertension and chronic heart failure (Mil et al. 2021). Wakai et al. demonstrated that VAL reduces the production of reactive oxygen species and cytochrome C release, providing neuroprotective advantages against transient forebrain ischemia. VAL reduces neuronal damage, boosts the brain's antioxidant defense system (catalase and superoxide dismutase), and lowers oxidative indicators like MDA (Kaeidi et al. 2021). Valsartan administration has been shown in two different studies to increase antioxidant defense, decrease chemotactic and adhesive component levels, and lessen neuronal damage in an Alzheimer's disease model. The potential of AT1R antagonists (ARBs) have neuroprotective effects on brain diseases by reducing inflammation, improving life expectancy, and treating comorbid disorders (Saavedra et al. 2011; Cai et al. 2021; Mil et al. 2021). Therefore, sartans are neuroprotective both directly by inhibiting AT1R and indirectly by reducing the levels of inflammation and reactive oxygen species that follow injury (Villapol et al. 2015). Therefore, ARB protection against dopaminergic cell death induced by dopaminergic neurotoxins is essentially dependent on reduction of microglial activation. Prior studies have indicated that microglia is a probable source of dopaminergic neuronal cell death in PD (Zawada et al. 2011; Garrido-Gil et al. 2012). Furthermore, decreased Bax expression and increased Bcl-2 expression were caused by candesartan-induced AT1R blockade, which consequently decreased caspase 3 activities and the number of apoptotic cells in LPS-treated SHRs. This discovery was corroborated by earlier studies that demonstrated that Ang II promotes apoptosis in human endothelial cells and alveolar epithelial cells in both rats and humans (Goel et al. 2018). It has been reported in recent times that other ARBs, such as Telmisartan (TEL), can control key pathological features of PD proteins, such as α-synuclein, neurotrophic elements (BDNF and GDNF), dopamine transporters (DAT), tyrosine hydroxylase (TH), vesicle monoamine transporter 2 (VMAT2), and glial fibrillary acidic proteins (GFAP), in animal models of the disease. In several neurodegenerative illnesses, these specific proteins promote the onset of dopaminergic degeneration (Thakur et al. 2015).

Pramipexole (PPX) is a direct dopaminergic agonist, acts as a first line of treatment in delaying the initiation of levodopa medication and is essentially neuroprotective against MPTP-induced striatal DA depletion in mice. It is generally well tolerated and effective in treating motor symptoms in both early and severe stages of PD. Additionally, it is about 30 times more selective for D3R than D2R (Joyce et al. 2004; Constantinescu 2008; Rokosik et al. 2012). Nevertheless, certain investigations have determined that PPX links to the internal portion of the mitochondrial

cell membrane and regulates the opening of transitional pore spaces, hence inhibiting mitochondrial permeability.

This indicates that PPX, along with its dopamine-agonizing actions, has an influence on mitochondrial activity. Though at low doses, pramipexole displays antioxidative, anti-apoptotic, and neuroprotective properties that have been connected with mitochondrial functions (Kosmowska et al. 2020).

Conclusion

Treatment with VAL (30 mg/kg/day) substantially improves MPTP-induced Parkinson's disease. Nevertheless, the outcomes indicate that VAL possesses the most prospective neuroprotective impacts via hampering oxidative damage, inflammatory responses, apoptotic pathways, and α-synuclein amplification. Additionally, VAL encompasses an advantageous influence on histopathological changes in the PD mouse model. Therefore, VAL could offer chances for the development of innovative treatments for Parkinson's disease.

Additional information

Conflict of interest

The authors declare the absence of a conflict of interests.

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Ethics approval

The research project was permitted by the Institutional Review Board (IRB) of the College of Medicine, Al-Nahrain University (Iraq), after thorough examination for ethical concerns according to document number. UNCOMIRB07052024 on 12/11/ 2022. The Declaration of Helsinki's ethical standards were followed when doing the study project.

Data availability

Data corroborating the results of this study may be acquired by the corresponding author upon reasonable request.

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Author Contribution

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