STRUCTURAL CHANGES IN THE PREFRONTAL CORTEX OF THE ALBINO RAT IN EXPERIMENTALLY INDUCED PARKINSON’S DISEASE

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Abstract:
In Parkinson’s disease models, Rotenone, a popular pesticide and mitochondrial complex I inhibitor, causes dopaminergic neuron loss (PD). Nonetheless, the rotenone neurotoxicity mechanisms are still poorly defined. In this study, we used rotenone to induce Parkinson’s disease and investigate its effect on medial prefrontal cortex (mPFC). Thirty rats were divided into two groups (control and Rotenone (n=15) each). Rats in rotenone group received a daily dose of 2 mg/kg of rotenone dissolved in 1 ml of sunflower oil by subcutaneous injection for 5 weeks. Rotenone group showed both motor dysfunction as evaluated by rotaroad (RRT) and open field tests (OFT) and non-motor changes (depression) as evaluated by forced swimming test (FST). Histologically, the rotenone group has shown layer I widening and layer II and layer IIII condensation with marked apoptotic changes and neuropil showed decrease distribution and absence of nerve fibers compared to control group in the mPFC. Immunohistochemically, rotenone group showed depletion of dopaminergic cells in the midbrain (MB) and dopaminergic nerve fibers in the mPFC and aggregation of Lewy bodies (LB) in both tissue together these changes were associated with significant increase in the optical density (OD) of caspase-3 immune expression and significant decrease of OD of GFAP immune expression in the rotenone group compared with control group. Also, rotenone group demonstrated significant increase in the lipid peroxidation and nitric oxide as well as significant reduction in the glutathione level in the MB and mPFC compared with control group. In conclusion rotenone induced PD model in rats caused behavioral, neurochemical, histological, and immunohistochemical changes in the mPFC.

Keywords: Rotenone, Medial Prefrontal Cortex (mPFC), Parkinson's disease (PD).

INTRODUCTION:
Parkinson’s disease (PD) in the elderly population is an increasingly crippling neurodegenerative disorder that affects about 6 million individuals worldwide (Chaudhuri et al., 2006). The mean age of onset of symptoms is 60 to 65, but about 10% of patients with PD experience motor symptoms before 40 years of age (Paul, 2011). PD results from dopamine depletion in the limbic pathways of substantia nigra pars compacta (SNpc) and ventral tegmental area (VTA), leading to motor and non-motor disease symptoms, including cognitive and behavioral disorders (Sgambato-Faure et al., 2005; Aarsland et al., 2010; Li et al., 2017). Anatomically, the prefrontal cortex (PFC) forms the frontal pole of the cerebral hemisphere. It is divided into the medial prefrontal cortex (mPFC) and the orbitofrontal cortex (oFC). The mPFC is subdivided into infralimbic cortex, prelimbic cortex, and dorsal anterior cingulate cortex (Akkoc and Ogeturk, 2017). The mPFC is predominantly innervated by MB VTA dopaminergic nerve fibers (Spencer et al., 2015) which is named...
VTA mPFC fibers. These fibers are projected mainly to layer IV (inner granule cell layer) (Li et al., 2017).

Rotenone is an insecticide; it causes inhibition of the mitochondrial electron transport chain and nigro-striatal degeneration. Chronic rotenone exposure can induce PD in humans (Kamel, 2013). Many studies have addressed the adverse effects of PD on the midbrain but, little is known about the possible corresponding changes in the mPFC. After establishment of rat model of PD, this study aimed to investigate the hypothesis that the development of PD has an impact on the mPFC as it is innervated by dopaminergic nerve fibers from the MB VTA.

MATERIALS AND METHODS:

Experimental animals:

This research used thirty adult male albino rats weighing 200-250 grams. Male rats were used because it had been shown that rotenone is more toxic to the females and that the mortality rate is higher in the females than in males (Gupta, 2014). Before the start of the experiment, the rats were kept in metal cages with soft wood bedding chips and fed two weeks of standard rat chow diet and water ad libitum for acclimatization and to insure normal growth and behavior. The study was carried on at the research lab of faculty of medicine of Mansoura University. The experiment was performed in compliance with the guidelines of the National Institutes of Health (NIH) for the maintenance and use of animals from the science laboratory; NIH Publication 1986 (86/609/EEC). The research has been accepted by the local institutional research committee (MDP.18.11.14).

The rats were divided into two groups:

1. **Control group**: (n=15) received a daily dose of 1 ml of sunflower oil for a period of five weeks by subcutaneous injection.
2. **Experimental group**: (n=15) received a daily dose of 2 mg/kg of rotenone dissolved in 1ml of sunflower oil by subcutaneous injection for five weeks (Sharma & Nehru, 2013).

Rotenone was obtained in powder form from Sigma –Aldrich (Germany), while sunflower oil obtained from El-Gomhorya Company for pharmaceuticals, Egypt. The behavioral locomotor activity of the rats was assessed after the last injection to evaluate the success of the PD rat model.

1- Evaluation of behavioral locomotor activity, three tests was evaluated in the animals to assess the PD model and examine its effect on the MB and mPFC.

i- Rotarod Test (RRT): (You et al., 2019)

By testing the capacity of rats to stay on a rotating rod, the Rotarod test was used to assess motor coordination. Three day training of the rotarod test was performed before injection of rotenone. The apparatus is attached to the variable-speed motor by a horizontal rough metal rod with a diameter of 3 cm. This 70cm long rod was split by wooden partitions into four parts. To discourage the animals from jumping from the revolving rod, the rod was positioned at a height of 50cm. The rotation rate has been adjusted to permit the normal rats to remain on it for 5 minutes. Five trials were given to each rat before the actual reading was taken. With the rotation of the rod, each trial begins and finishes with the drop of the rat. The rotational speed was steadily increased to 10 rpm over 1 minute till the rats fell off the rotating rods. Latency until fall was detected. (A score was given to each rat as follow; score 1= fall from 1-5 sec, score 2= fall from 6-10 sec, score 3= fall from 11-20 sec, score 4= fall from 21-30 sec, score 5= fall after 30 sec).
ii- **Spontaneous Activity in the Open Field** (Shallie et al., 2017):
The open field apparatus, measuring 72 x 72 cm with walls measuring 36 cm, was made of white plywood. There was a transparent one of the walls, so rats could be seen in the apparatus. On the floor, blue lines were drawn with a marker and were visible through the translucent floor. The lines break the floor into sixteen squares measuring 18 x 18 cm. In the middle of the open field, a central square (18 cm x 18 cm) was drawn. Rats were put in one of the open field's four corners and permitted the apparatus to be explored for five minutes. Rats were returned to their home cages after the five-minute test and the open field was washed with 70% ethyl alcohol and allowed to dry among tests. The number of line crosses and the frequency of rearing have been used as measures of locomotor activity. As measurements of exploratory behavior and anxiety, the number of central square entrants and the length of time spent in the central square were also used. Every rat was then given a score that was calculated as the sum of line crosses and number of rears for total locomotor activity.

iii- **Forced swimming test (FST)**: (Campos et al., 2005)
In a glass jar (40 x 25 cm) comprising 15 cm of water held at 24 ° ± 2 °C, the rats were individually forced to swim. Total immobility duration was measured in seconds over a span of 6 minutes. When it stopped struggling and stayed floating in the water with minimal motion, the rat was considered to be immobile. Before being brought back to their home cages, the rats were permitted to dry for 15 minutes in a heat enclosure (32˚C). For Two weeks, the test was performed once a day.

**Specimen Collection:**
After the last injection, chloral hydrate (300 mg/kg, intraperitoneal) was used to anaesthetize all rats. Then, half of the rats were sacrificed by intracardiac perfusion through the left ventricle with 10% buffered neutral formalin. Midbrain was dissected out and processed for TH+ and α-synuclein immunohistochemistry and the mPFC was dissected out and processed for histological studies (cresyl and silver staining) and immunohistochemical studies (Anti TH+, Anti α synuclein antibodies, Anti Caspase 3, and Anti GFAP antibodies immunohistochemistry). The MB and prefrontal cortex of the other half of the rats were used for neurochemical study.

**II- Neurochemical Study (ELISA of MB and mPFC homogenate).**
For processing of homogenates, the fresh samples of MB and prefrontal cortex were weighted and transported to a glass homogenizer and homogenized following the addition of 10 phosphate buffer volumes in an ice bath (pH 7.4). At 3000 rpm for 10 minutes at 4°C, the homogenate was centrifuged utilizing a refrigerated centrifuge. Levels of malondialdehyde (MDA) (Leão et al., 2017), nitric oxide (Bhidwaria, & Ashwlayan, 2017) and reduced glutathione (Subramaniam and Ellis, 2013) for assessing ROS (oxidizing activity in the MB and mPFC).

**III- Histological and immunohistochemical Study:**
Specimens of the MB and the prefrontal cortex were kept in 10% buffered neutral formalin then processed for paraffin sections and stained with:

i- **Nissl stain**: for examining the histology of the mPFC (Pilati et al., 2008).
ii- **Silver stains**: for detecting the nerve fibers of the mPFC (Pilati et al., 2008).
iii- **Tyrosine Hydroxylase (TH) immunohistochemistry**: for detecting TH positive cells in the MB and dopaminergic nerve fibers in mPFC respectively (Li et al., 2017).
iv- **α-synuclein immunohistochemistry**: for detecting lewy bodies in the MB and the mPFC (Acosta et al., 2015).

v- **Caspase 3 immunohistocemistry**: for assessing of apoptotic activity inside the mPFC(Omara et al., 2014).

vi- **GFAP immunohistochemistry**: for evaluating astrocytes activity inside the mPFC (Liu et al., 2017).

<table>
<thead>
<tr>
<th>Antibodies</th>
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<tr>
<td>TH +</td>
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<td>ABclonal, USA</td>
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Iv-Morphometric study:
Images were captured using Olympus CX41 light microscope and photographed with a Nikon CP5000 digital camera. Image analysis was performed using ImageJ 1.51j8 program. Images were captured with 40× and 100× objective lenses. TH positive neurons were counted manually by image J program (Huang et al., 2017). For brightness modification, ImageJ v2.35 (NIH) has been used to identify the existence and degree of TH positivedopaminergic nerve fibers, GFAP and caspase3 immunostaining in the DAB images. To analyze the cytoplasmic staining, an ImageJ plug-in was operated by assigning a histogram profile to the deconvoluted DAB image utilizing the H-DAB vector to generate three distinctly colored images: green, brown, and blue. DAB image calibration (brown-colored) was performed by measuring the average intensity of five non-overlapping stained tissue regions. For legitimate contrasts utilizing this method, the uniformity of section thickness has been considered. To prevent bias in the results, the empty areas were excluded from the measurements. We used the following formula to convert the intensity numbers into Optical Density (OD): OD = log (Maxintensity|mean intensity):
where the maximum intensity = 250; mean intensity = mean grey value (EL-Tarhounyet al., 2014).

Statistical Analysis:
Data was tabulated, coded and analyzed utilizing version 25.0 of the computer software SPSS (Statistical package for social science). For the statistical comparison among the two groups, the significance groups of parametric data of behavioral changes, neurochemical changes and immunohistochemical changes. *P* ≤ 0.05 was deemed statistically significant.

RESULTS:
I- Confirmation of Parkinson's Rat Model:

i- Behavioral tests:

- The rotaroad test revealed a highly significant reduction in latency before the rotary rod dropped by the rotenone rats (2.8±1.5) compared to control rats (4.6±1.1) (*p*<0.001).
- The open field test showed highly significant decrease in the total score measured in the rotenone rats (11.2±6.7) compared to control rats (32.6±6.69) (*p*<0.001).
- The forced swimming test revealed a highly significant increase in the duration of the rotenone rat immobility (44.7±24.4) compared to control rats (11.8±3.3) (*p*<0.001) suggesting that rotenone treated rats showing behavioral despair (depression). Histogram (1)
ii- Neurochemical results:
The mid brain specimen showed highly significant increased levels of MDA (2.87±1.5) and NO (1.1±.22) and highly significant decreased levels of GSH (0.73±0.12) in the rotenone group compared to control group, (71±13), (1.34±0.71), (1.33±0.1) p < 0.001), respectively (Histogram 2, 3 and 4).

iii- Immunohistochemical results in the mid brain:
- TH immune stained sections showed highly significant decrease in number of dopaminergic cells in rotenone treated rats (2.01±0.72) compared to control rats (14.51±1.199) (p<0.001). Histogram (5), Fig (1)
- α synuclein stained sections showed Lewy bodies appeared as rounded brown stained vesicle surround by perivascular space in rotenone treated rats however, absence of Lewy bodies in control rats. Fig (1).

II- Results of medial prefrontal cortex:
i- Neurochemical results:
The medial prefrontal cortex specimen showed highly significant increased levels of MDA(2.05±26) and NO (2.12±25) and highly significant decreased level of GSH (0.8±071) in rotenone treated rats compared to control rats (1.36±0.55), (0.863±0.2669), (1.397±0.38) (p<0.001). (Histogram 2.3.4)

ii- Histological results:
-Cresyl violet stained sections:
Control rats showed normal distribution of mPFC layers which were arranged in six layers (molecular, outer granular, pyramidal, inner granular, ganglionic and multiform, respectively). Layer one is the molecular layer, layer two is the outer granular layer, layer three is the pyramidal cell layer, layer four is the inner granular layer, layer five is the ganglionic layer and layer six is the multiform layer. There are big rounded vesicular nuclei and prominent nucleoli in the granule cells. Vesicular nuclei and Long peripheral processes are owned by the pyramidal cells. The glial cells, with dark nuclei, are small in size. There are neuronal and glial cellular processes in the neuropil. (Fig 2 A & B) Treated rats with Rotenone revealed a widening of layer one and a condensation of layer two and layer three. There are shrunken pyknotic nuclei and broad pericellular space in several neurons that appear odd, shrunken, darkly stained (Fig 2 C & D)

-Silver stained sections:-
Control rats showed normal cells with long processes and neuropils containing neuronal and glial cellular processes and less beaded blood vessels. The other hand, rotenone group showed short processes of neuronal cells and presence of more beaded blood vessels (Fig 2 D & E).

iii- Immunohistochemical results:
TH immune stained sections of Control rats showed highly positive reaction in the nerve fibers of mPFC but in the sections of the rotenone treated rats there was a mild reaction. In all examined sections TH immune reaction was more obvious in lower three layers than upper three layers. (Fig 3A, B, C & D)
By image analysis, rotenone treated group showed highly significant decrease (0.26±0.14) in the OD of TH immune stain compared to control group (0.52±0.11) (p < 0.001). Histogram (5)
-α- synuclein immune stained sections showed presence of Lewy bodies in rotenone treated rats moreover, there is no detection of Lewy bodies in control rats (Fig 3 E & F).

-Caspase-3 immune stained sections of control rats showed moderated positive reaction to caspase 3 but in sections of rotenone treated rats there is highly positive reaction (Fig 4 E & F).

By image analysis, rotenone treated group showed highly significant increase in the OD of caspase 3 immune stain (0.9±0.03) compared to control group (0.22±0.08) (p<0.001). Histogram (6)

-GFAP immune stained sections of rotenone treated rats showed decreased positive reaction of GFAP activated astrocyte compared to control group (Fig 4 A, B, C & D).

By image analysis, rotenone treated group showed significant decrease (1.3±0.1) in the OD of GFAP immune stain compared to control group (1.4±0.1) (p≤0.004). Histogram (6)

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**Histogram (1):** Behavioral changes (RRT, OFT and FST).
RRT: Rotarod test, OFT: Open field test, FST: Forced swimming test, P is significant to control, P < 0.001 is highly significant, P < 0.05 is significant.

**Histogram (2):** Tissue levels of MDA in the mid brain and the medial prefrontal cortex of the studied group. P is significant to control, P < 0.001 is highly significant, P < 0.05 is significant.
Histogram (3): Tissue levels of NO in the mid brain and the medial prefrontal cortex of the studied group. 
P is significant to control, \( P < 0.001 \) is highly significant \( P < 0.05 \) is significant.

Histogram (4): Tissue levels of GSH in the mid brain and the medial prefrontal cortex of the studied group. 
P is significant to control, \( P < 0.001 \) is highly significant \( P < 0.05 \) is significant.

Histogram (5): Number of TH positive dopaminergic cells in the mid brain and the mean optical density (OD) of dopaminergic nerve fibers of the studied group: 
P is significant to control, \( P < 0.001 \) is highly significant \( P < 0.05 \) is significant.
Fig (1): Photomicrographs of the midbrain sections of adult rat: (A): Control rat shows deeply stained positive TH+ dopaminergic neurons (arrows). (B): Rotenone treated group shows decreased number of TH+ dopaminergic neurons (arrow). (C): Control rat illustrates normal spindle shaped dopaminergic neuron (arrow) and absence of α-synuclein aggregated protein. (D) Rotenone treated group shows positive α-synuclein aggregated protein (Lewy body) (LB). (A,B: Th+ immunohistochemistry x 400; C,D: α-synuclein immunohistochemistry x400).

Fig (2): Photomicrographs of sections of adult rat mPFCs: (A,B) Control rat illustrates the organized layers of mPFC; the molecular layer (LI), the outer granular layer (LII), the pyramidal cell layer (LIII), the inner granular layer (LIV), the ganglionic layer (LV) and the multiform layer (LVI). There are large rounded vesicular nuclei and prominent nucleoli in the granule cells (Dotted arrow). Pyramidal cells (black arrow) have vesicular nuclei and long peripheral processes and nissl granule (g). Neuropil showing neuronal and ganglionic processes (n). (C,D) Rotenone treated rat illustrates: widening of the layer I (LI) and condensation of layer II (LII) and layer III (LIII). Several neurons containing shrunken pyknotic nuclei and broad pericellular space are irregular, shrunken, darkly stained (black arrow), neuropil (n) showing vacuols (v). (E) Control rat illustrates: pyramidal shaped cells with long processes (black arrows) and neuropil (n) showing interconnecting nerve fibers. (F)
Rotenone treated rat illustrates: degenerated nerve cells (dotted arrow) and depletion of interconnected nerve fibers (black arrow) and increased beaded blood vessels (blue head arrows). (A, C: CVx100; B, D: CVx400; E, F SV x400).

**Fig (3):** Photomicrographs of sections in adult rat mPFC: (A, B) Control rat (A) upper three layers illustrates: less localization of TH positive immunoreactive dopaminergic nerve fibers, (B) lower three layers showing more localization of TH positive immunoreactive dopaminergic nerve fibers of cerebral cortex (black arrows). (C&D) Rotenone treated rat illustrates: decreased expression of TH positive immunoreactive dopaminergic nerve fiber in upper and lower layers . (E) Control rat illustrates normal rounded granular cells (black arrow) absence of α-synuclein aggregated protein (Lewy body) (LB). (F) Rotenone treated rat illustrates: +ve α-synuclein aggregated protein (Lewy body) (LB). (A, B, C, D; TH x 400; E, F; α-synuclein immunohistochemistry x400).

**Fig(4):** Photomicrographs of sections in adult rat mPFC: (A, B) Control rat illustrates: highly positive reaction of GFAP positive astrocytic cells reaction (black arrow). (B) showing processes of astrocytic cells and connection in between (head arrow). (C, D) Rotenone rat illustrates: Mild GFAP positive astrocytic cells reaction (black arrow). (A, B, C, D; GFAP x400; E, F; GFAP x1000; E, F; Casp3 x400).
(D) showing absence of astrocytic processes and decreased interconnection in between (black arrows). (E) Control rat illustrates: mild positive caspase 3 reaction (black arrows). (F) Rotenone treated rat illustrates: highly positive caspase 3 reaction (black arrows). (A: GFAP x400; B: GFAP x1000; E,F: Casp 3 immunohistochemistry x 400).

Histogram (6): The mean optical density (OD) of Caspase 3 and GFAP immunostaining of the studied group:
P is significant to control, P < 0.001 is highly significant P < 0.05 is significant.

DISCUSSION:

A rotenone-induced Parkinsonian model in albino rats displayed histological alternations in mPFC neurons in the current study. The histological changes were associated with increased OD of dopaminergic nerve fibers and CASP-3 immunostaining and decreased OD of GFAP immunostaining.

Here, we found that daily subcutaneous administration of rotenone produces degenerative lesion of dopaminergic neurons in SNpc of MB with aggregation of α-synuclein protein (Lewy bodies), thus a PD model was established and this was associated with apoptotic and degenerative lesions of nerve cells and fibers with decreased activation of astrocytes in mPFC.

In the present study there is highly significant decrease in locomotor activity that proved by rotarod and open field test and this result was reported in previous recent studies, (Moreira et al., 2011, Liu et al., 2015 and Wrangel et al., 2015). Owing to changes in locomotor activity induced by central nervous system stimulants, behavioral changes and immobility can be caused. As rotenone administration causes degeneration of dopaminergic neurons of SNpc of MB and basal ganglia (striatum), it could lead to decreased dopamine secretion which is responsible for inducing mobility (Tremblay et al., 2015). Moreover rotenone treated rats showed a significant increase in the floating time of forced swimming test that may indicate a depressive behavior as reported by (Santiago et al., 2010 and McDowell & Chesselet, 2012). The observed immobility in this test model signifies ‘behavioral despair which may be due to affection of VTA-dopaminergic pathway to mPFC leading to depletion of dopamine and affecting function of frontal cortex (personality center) that its affection causing depression (Santiago et al., 2010 and Beaudoin-Gobert et al., 2015).

In the present study, Lipid peroxidation (MDA) and NO were showing highly significant increase and there was highly significant decrease in GSH in rotenone treated group in mPFC.
and MB in rotenone treated rats and that was agreed with (Subramaniam and Ellis, 2013, Abdel-salam et al., 2014, González-Burgos et al., 2015, and Xiong et al., 2015).

By compromising the integrity of weak neurons, oxidative stress is thought to play a significant role in neuronal degeneration and death of nigral cells in PD; mitochondrial dysfunction, enhanced metabolism of dopamine which can generate excessive hydrogen peroxide and other reactive oxygen species (ROS) and impaired antioxidant function are potential causes of excess oxidative stress output (i.e. decreased levels of reduced glutathione) (Jenner 2003) in the SNpc (Schapira et al., 1990) and other locations (Parker et al., 1989 and Krige et al., 1992, Sherer et al. 2002; Moore et al. 2005). However, Swarnkar et al., 2010 showed no association among decreased GSH and increased MDA except in MB, GSH was reduced in striatum without MDA change whereas MDA was increased in hippocampus without GSH change and the frontal cortex stayed unaffected in terms of oxidative stress caused by rotenone in the area (Mbiydzenyuy et al., 2018).

Histological finding of the present study revealed degeneration of cell bodies of nerve cells of the mPFC that result was reported by Abdel-Salam, et al., (2014) and Abdel-Salam, et al., (2018). Silver staining methods in rodent models of acute and chronic neurodegeneration may define damaged or degenerating neurons (Tenkova and Goldberg, 2007). Silver staining revealed loss of nerve fibers and synapses between nerve cells that was agreed with Schulz-Schaeffer, 2010 and Sonia Angeline et al., 2012). The outcomes of the number of TH (+) dopaminergic neurons in the MB revealed highly significant decrease in rotenone treated group and this result was demonstrated by Galhom et al., (2017) and Liu et al., (2015) and this is due to degeneration of dopaminergic neurons due to inhibition of the mitochondrial electron transport chain and nigro-striatal degeneration and decreased GSH generation as a protective mechanism to dopaminergic cells. Due to its lipophilic nature, Rotenone promotes the formation of alpha-synuclein fibrils and crosses both the blood-brain barrier and the cell membrane (Allam and Schmidt, 2002). The findings of this experiment showed that TH+ nerve fibers were scattered in the control group across the cortical layers, mainly in layer IV that is substantiated by a prior anatomical study (Liu et al., 2015) that there was a decline in OD of TH+ nerve fibers compared to the rotenone group, suggesting a decline in TH+ nerve fibers. This finding showed that VTA damage caused by rotenone injection could trigger anterograde nerve damage to the projected fibers of the nerve. This result was supported by earlier studies by Sweet et al. (2014), which found that damage to SNpc and VTA in a broad range of brain regions was correlated with a reduction in nerve fibers.

Compared with the control group in the present research, the OD of caspase 3 activity increased in the mPFC of the rotenone treated group and apoptotic cells were increased and scattered throughout the cortical layers and that was agreed with (Norazit et al., 2010 and Sonia Angeline et al., 2012). Other studies have shown that the activity of caspase-3 in the PD brain (Mogi et al. 2000) and levels (Tatton 2000; Jiang et al. 2012) in the SN and temporal cortex have increased. Hartmann et al. (2000) found, in comparison to these findings, a substantial decline in caspase-3-positive pigmented neurons in PD patients’ SNpc relative to controls, which may be due to changes in the distribution of caspase 3 within the dopaminergic neurons in SNpc, as it is increased in dorsal part than ventromedial part. Accumulation of α-synuclein in dopaminergic neurons results in decreased mitochondrial complex I activity and increased generation of reactive oxygen species, as well as degradation of dopamine products undergoing autoxidation, leading to increased generation of reactive oxygen species that may reflect a potential significant mechanism contributing to dopaminergic neuronal death via apoptosis (Erekat, 2018).
The present study have showed that significant decrease in the OD of GFAP immunohistochemistry of the mPFC in rotenone treated group compared with control group and this result was detected by (Abdel-Salam et al., 2018), van den Berge et al., 2012 and Tong et al., 2015) due to accumulation of α syncline in astrocytes causing degeneration of astrocytes (Halliday and Stevens 2011) and decreased GFAP activity. However, other studies were showed that astrocytes activity increased and increased GFAP expression in mid brain (Abdel-Salam et al., 2018) and striatum (Ojha et al., 2016). Nonetheless, many findings suggest that an inflammatory response in the Parkinsonian brain is ongoing (Orr et al., 2005). Halliday and peers (Halliday and Stevens, 2011) speculate that α-synuclein accumulation in astrocytes is the primary etiopathological factor in PD and other synucleinopathies, could damage SN astrocytes and thus promote dopamine neuron degeneration. Overexpression of α-synuclein in astrocyte culture induced glial cell death (Stefanova et al., 2001).

CONCLUSION:

Rotenone induced a rat model of PD proofed by behavioral changes, neurochemical changes, decreased number of TH+ dopaminergic neurons and presence of Lewy bodies in mid brain followed by studying of structural and neurochemical changes in mPFC which showed increase in MDA and NO and decrease in GSH. Histopathological study showed degeneration of neuronal cells bodies and disconnection of nerve fibers synapses. Caspese-3 showed increased activity while GFAP showed decreased activity and this is the first study to collecting data about changes in mPFC in a model of PD induced by rotenone subcutaneous injection.

REFERENCES:


