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Proposed Neuromorphological Mechanism of Dopamine-2 Receptor Blocker Model of Parkinsonism

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ABSTRACT

Haloperidol is known to induce Parkinsonism by blocking dopamine-2 receptors (D_2R). However, the mechanism in which Parkinsonism is induced is not well known. In this study, the mechanism of D_2R inhibition model of Parkinsonism was proposed via neuromorphological findings observed in primary motor cortex and dorsal striatum. Sixteen female Wistar rats with average weight of 150 g were distributed into 4 groups (NS and -D2I, -D2II, -D2III). Parkinsonism was induced using 5 mg/kg, 10 mg/kg and 15 mg/kg of haloperidol for 21 days. Parkinsonism was accessed with the rotarod and parallel bar. Primary motor cortex (M1) and dorsal striatum (CPu) were processed and stained using haematoxylin and eosin (H&E) and Nissl stains. The density of Nissl bodies was examined with ImageJ software version 1.46. Data was analysed by one way analysis of variance and significant level was set at $p \leq 0.05$. The results showed that prolong inhibition of D_2R induces Parkinsonism by progressive deterioration of nuclear components, displacement and extrusion of nucleus leading to intracytoplasmic vacuoles in Betz cells of M1. This was projected to be associated with membrane damage. Neurofibrils were proposed to be lost following the numerous shrunken perikaryons observed in M1 and CPu. 70.6% of Nissl bodies were lost to high dose of haloperidol, this was purported to cause decline in protein synthesis and mitochondrial functions leading to decrease in synaptic plasticity and resulting in Parkinsonism.

Key words: *Haloperidol; Parkinsonism; Dopamine-2 receptor; Histology; Nissl bodies*

INTRODUCTION

Neuroleptics are known to have strong affinity for different subtypes of dopamine receptors (Mauri et al. 2014). Studies have shown that dopamine receptors have higher affinity for neuroleptics than dopamine (Howes et al. 2009; Berke 2018). For this reason, anti-psychotics binds to dopamine receptors even better than dopamine and without triggering G-protein. Binding of anti-psychotics to dopamine receptor disables dopamine from binding to its receptive site (Howes et al. 2009; Peng et al. 2016). The therapeutic action of anti-psychotics is their ability to bind to dopamine receptors without generating action potentials by opening ion channels (Lee et al. 2004; Lieberman et al. 2016). Anti-psychotic drugs alter dopaminergic neurotransmiss-ion system at both presynaptic and postsynaptic neuron level because dopamine-2 receptors are present on postsynaptic membrane, soma, dendrites and nerve terminals of presynaptic neurons (Vallone

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et al. 2000; Citrome 2015). Some neuroleptics interfere with the release of dopamine at the presynaptic terminal, while others block postsynaptic dopamine receptive site so that postsynaptic neuron cannot recognize dopamine (Hernádez-López et al. 2000; Rampino et al. 2019).

Regrettably, administration of typical anti-psychotics like haloperidol leads to the blockage of all dopamine-2 receptors including those that are present in regions involved in fine tuning of motor movements mainly substantia nigra pars compacta (SNpc), striatum (CPu) and primary motor cortex (M1) (Scherfler et al. 2004; Ishola et al. 2015; Sirajo et al. 2019). As a result, schizophrenic patients under the treatment of dopamine-2 receptor blocker over a period of time experience Parkinsonism (Pifl et al. 2014; Ishola et al. 2015; Sirajo et al. 2019). In this study, haloperidol; a member of neuroleptics was used not to treat schizophrenia but to induce Parkinsonism in Wistar rats and to deduce the possible mechanism in which the dopamine-2 receptor inhibitors acts to induce Parkinsonism, via neuromorphological findings observed in primary motor cortex and dorsal striatum.

MATERIALS AND METHODS

Ethical Approval Ethical Clearance

Ethical clearance was obtained from the Ethical Committee, Department of Anatomy, Faculty of Basic Health Sciences, Bayero University, Kano.

Drug Procurement

Haloperidol manufactured by Swiss Pharma Pvt. Ltd. Gujarat was re-suspended in normal saline. Haloperidol solutions were prepared weekly as needed and stored at 3 ℃.

Animal Treatment

Sixteen female Wistar rats with average weight of 150 g were procured from Biological Sciences Department Animal House, Bayero University Kano and assigned into four groups of four animals each in a cage sized 50 × 30 × 40 cm. Food and water were given *ad libitum* with 12-hour light and dark cycle. All animal handling was in line with the National Health Institute (NIH) and Institutional Animal Care and Use Committee (IACUC) guidelines (Anderson et al. 2002)

Behavioural Tests

At the end of the treatment phase, motor coordination of the animals was examined using the rotarod test. All animals were familiarized with the behavioural test room 72 h before the commencement of the tests (Sirajo et al. 2019).

Rotarod Test: The test involved three trials of 3 minutes each (T1, T2 and T3) separated by an inter-trial time of 90 min. The time spent on the rotarod in T1, T2 and T3 were obtained and the average determined the latency of fall (LOF) for each group (Ishola et al. 2015).

Parallel Bar Test: Motor coordination was accessed on two raised parallel bars of 1 m long and 3 cm apart, mounted on the 60 cm high wooden frame. The Wistar rats were placed at the 0.5 m mark (centre of the raised bars) and allowed to roam freely on the bar. The duration taken for the Wistar rats to make a 90˚ turn was recorded as the latency of turn (LOT) for a 3 min trial (Ishola et al. 2015).

Neurohistology

Animal Sacrifice

After the behavioural studies, animals were anaesthetized using 10 mg/kg ketamine. Three minutes later, the animals were transcardially perfused with normal saline to flush the blood followed by 10% formal saline to preserve the whole animal. Subsequently, the skull was opened and the whole brain was preserved using 10% formalin

Neural Tissue Procession

After fixation, the whole brain was dissected to expose the approximate primary motor cortex (M1) and dorsal striatum (CPu). The dissected brain tissues were processed using tissue transfer automated tissue processor (Leica, TP1020 model). Paraffin wax embedded tissue blocks were obtained for histology with the aid of embedding machine. Sections of 5 µm were obtained using the rotary microtome. Subsequently, the sections were put in water bath and picked up with glass slides. For haematoxylin and eosin (H&E) stains, the glass slides were dipped in haematoxylin solution for 5 min, and rinsed with tap water to remove excess stain for 3 min (Llewellyn, 2009). The slides were then put in acid alcohol for 5 min for differentiation and then washed in tap water again. The slides were then blued in Scott"s tap water for five minutes and counter stained with Eosin Y for 5 min. The sections

Table 1: Experimental design

Group	Treatment
NS	0.1 mL (intraperitoneal) of 0.9 % normal saline for 14 days
-D 2I	5 mg Haloperidol /kg of rats (intraperitoneal) for 21 days
-D2II	10 mg Haloperidol /kg BW of rats (intraperitoneal) for 14 days
-D2III	15 mg Haloperidol /kg BW of rats (intraperitoneal) for 14 days

NS- Norma saline; -D2I- Low dose of Haloperidol; -DII- Medium dose of Haloperidol; -D2III- High dose of haloperidol

were rinsed in tap water for 3 min, and then dehydrated in increasing concentration of alcohol, and then cleared in xylene. Tissues were then mounted with cover slips using DPX (Puchtler et al. 1986). Whereas for Nissl stain, sections were stained in 0.1% warm (40 ℃) cresyl violet solution for 5 min and rinsed in distilled water for 2 min, following which the sections were put in 95% ethyl alcohol for 5 min for differentiation (Puchtler et al. 1986). Subsequently, the sections were dehydrated in 100% alcohol for 5 min, cleared in xylene for 5 min (Llewellyn 2009) and mounted with DPX (Puchtler et al. 1986). The prepared slides were later evaluated for assessment of the mode of neural damages due to inhibition of dopamine receptors.

Stereology

At early stage of degeneration, there is dissociation of ribosome from the rough endoplasmic reticulum, thus, neurons with Nissl bodies were poorly stained. Such neurons in the primary motor cortex (M1) and dorsal striatum (CPu) were counted using the ImageJ software after applying threshold to depict the degenerating neurons (Peiying, 2012).

Statistical Analysis

Quantitative data were presented as mean ± standard error of mean (SEM); analysed using one way analysis of variance and Tukey's multiple comparison test. Statistical significant level was set at $p \leq 0.05$.

RESULTS

Motor Function

Rotarod Test

The rotarod test was conducted to examine motor function deficit, which was used to assess the induction of Parkinsonism. Low dose (5 mg/kg) of haloperidol (10.00 ± 0.40 sec) was found to have no significant loss of latency of fall when compared to the normal saline group (NS) (11.40 ± 0.87 sec) as seen in Figure 1. However, medium dosage (10 mg/kg) of haloperidol (7.60 ± 0.68 sec) caused significant ($p < 0.05$) loss of latency of fall when compared to NS. High dose of haloperidol (15 mg/kg) (6.00 ± 0.93 sec) also caused significant ($p < 0.05$) loss of latency of fall ($p < 0.01$) when compared to NS group as seen in Figure 1.

Parallel Bar Test

Parallel bar test was conducted to reaffirm the motor function deficit accessed in rotarod test. In this test, it was shown that both low dose (5 mg/kg) (50.00 ± 4.30 sec) and medium dose of Haloperidol (10 mg/kg) (52.50 ± 5.23 sec) have no significant loss of motor function when compared to NS (43.00 ± 3.39 sec) as seen in Figure 2. Significant ($p < 0.01$) motor deficit was found in high dose (15 mg/kg) of haloperidol group (-D2III) (69.50 ± 3.88 sec) as seen in Figure 2.

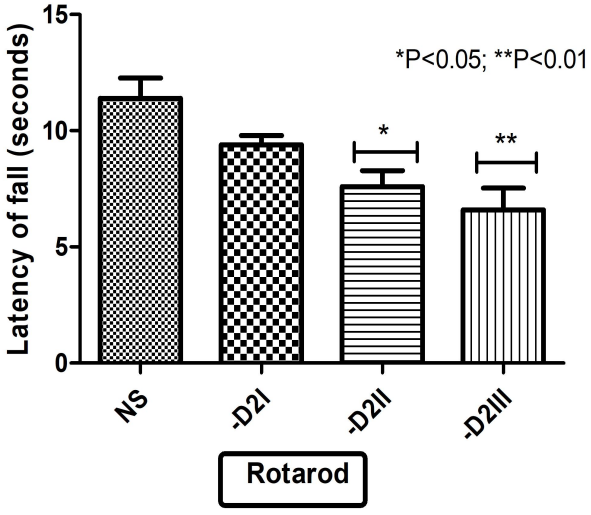

Figure 1: Motor function (rotarod) test for dopmine-2 blocker model of Parkinsonism. Latency of fall declined significantly in -D2II and -D2III group ($p < 0.05$; $p < 0.01$) respectively compared to the control group.

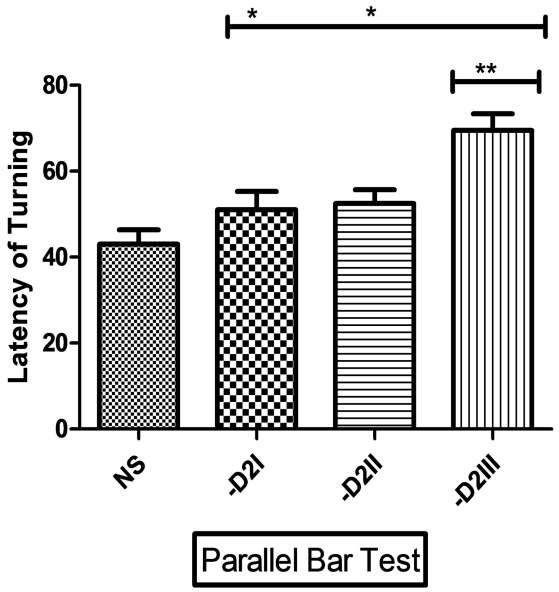

Figure 2: Motor function (parallel bar) test for dopmine-2 blocker model of Parkinsonism. Significant (**$p < 0.01$) increased in latency of turn was recorded in -D2III group compared to the control group.

Histomorphology

The Primary Motor Cortex

Photomicrograph of the fifth layer of the primary motor cortex (M1) of the norm saline (NS) group showed unremarkable neural organization of numerous Betz cells as seen in Figure 3. Low dose (5 mg/kg) of haloperidol treated group showed less density of Betz cells. Medium dose (10 mg/kg) of -D2R haloperidol treated (–D2II) group showed Betz cells with intracytoplasmic vacuoles High dose (15 mg/kg) of -D2R Haloperidol treated group (–D2III) showed distorted neural organization of Betz cells characterized by pyknosis, cavitations and extruded nuclear as seen in Figure 3.

The Dorsal Striatum

The dorsal striatum of the control, low dose of -D2R haloperidol (-D2I) and intermediate dose (10 mg/kg) of -D2R haloperidol (-D2II) treated groups showed unremarkable medium and small spiny neurons of striatum i.e. no striking difference (Fig. 4). However, high dose (15 mg/kg) of -D2R haloperidol (-D2III) treatment group showed enlarged medium and small spiny neurons of the dorsal striatum (Fig. 4).

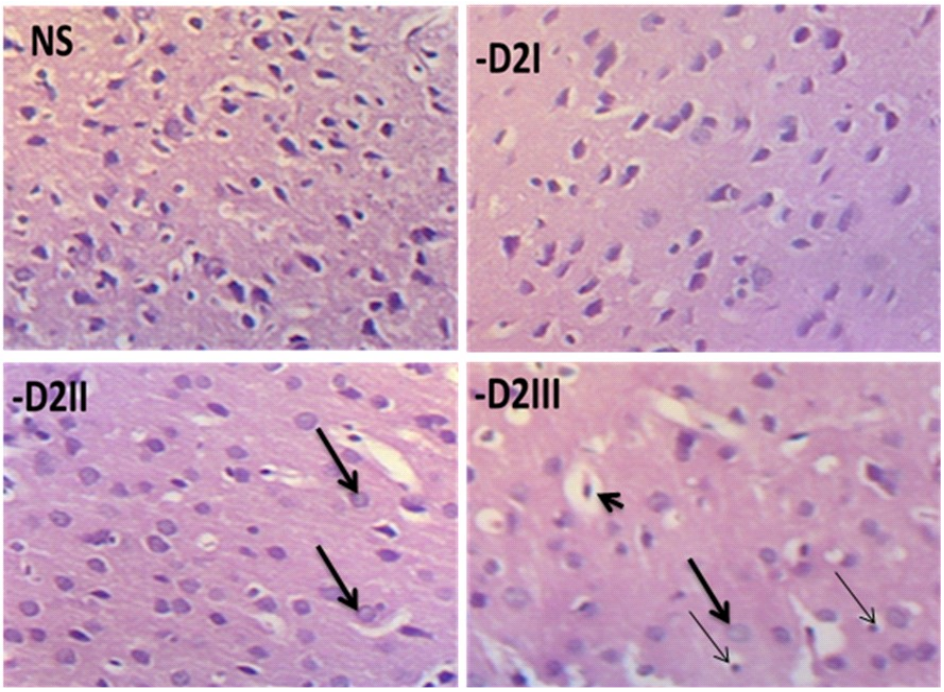

Figure 3: Overview of the fifth layer of primary motor cortex (M1); Control (NS) group shows unremarkable neural organization of numerous Betz cells. –D2I shows lesser density of Betz cells. –D2II group shows cavitated Betz cells (indicated by arrow). –D2III shows distorted neural organization of Betz cells characterized by pyknosis (Thin arrow), cavitations (Thick arrow) and extruded nuclear (arrow head) H&E ×400

Nissl Bodies Density Estimate

The degree of Nissl body degeneration was determined by the number of Nissl bodies lost. 14 days of administration of 15 mg/kg haloperidol (-D2 group) (178.8 ± 19.08) was found to cause significant ($p < 0.01$) loss of Nissl bodies compared to the control group (NS) (52.33 ± 3.33) as seen in Figure 5.

$$\text{Percentage loss} = \frac{Mean\ (NS) - Mean\ (-D2III)}{Mean\ (NS)} \times 100$$

$$\text{Percentage loss} = \frac{178.0 - 52.33}{178.0} \times 100 = 70.6\%\ Nissl\ body\ loss$$

DISCUSSION

It is well known that haloperidol is a dopamine D_2 receptors blocker (Bohlega and Al-Foghom 2013). It has been reported that prolong blockage of dopamine D_2 receptors leads to death of dopamine neurons (Jung et al. 2014; Berke, 2018; Sirajo et al. 2019) or its synaptic connection (Pifl et al. 2014) with the post synaptic neuron which eventually cause the manifestation of Parkinsonism (Karl et al. 2006; Booth et al. 2014). However, the mechanism in which this occurs is not well known. From the research findings, the mechanism in which dopamine-2 receptor blocker (haloperidol) induces Parkinsonism was proposed diagrammatically in Figure 6.1 and 6.2. The D_2R blocked by haloperidol is proposed to lead to loss of neurofibrils (microfilament and microtubule) which leads to the expression of several cell body shrinkages (Sirajo et al. 2019) as seen in Figure 3.

Although techniques to demonstrate neurofibrils were not employed, the presence of cell body shrinkage is a strong indication that neurofibrils were lost (Jai et al. 2000; Howard 2001; Sembulingam and Sembulingam 2012).

Many nuclei were found to be displaced toward the periphery (plasma membrane) of the perikaryon, this event was interpreted as pyknosis; a reversible hallmark of degeneration. In some very few instances, the nuclei were found to be displaced outside the membrane; those were read as extruded nucleus, which is an irreversible stage of degeneration (Jai et al. 2000; Castellani et al. 2007; Sembulingam and Sembulingam, 2012). This event results in expression of perikayron with intracytoplasmic vacuoles (Fig. 3). The progressive

deterioration of nuclear component suggests the neurons are undergoing necrosis or apoptosis (Stoica and Faden 2010).

About 70.6 % of Nissl bodies containing ribosomes which are responsible for the synthesis of proteins in the neurons were loss. This process is known as chromatolysis, usually resulting from neurotoxicity (McIlwain and Hoke 2005). When the D_2R are blocked, messenger RNA (mRNA) carries the genetic code from nucleus to the Nissl body, which produces more receptors to replace the loss. This process might not be effective in the haloperidol model of Parkinsonism due to the substantial loss of the protein producing machinery (Nissl bodies) (Pasternak 1971).

Even as mitochondrial has its own DNA and able to produce itself (Iborra et al. 2004; Martinez-Caballero et al. 2007), the amount of DNA however is insufficient to produce enough protein. As a matter of fact, studies have shown that most mitochondrial proteins are synthesized by cytoplasmic machinery and transported in to the mitochondria (Pasternak, 1971; Gabriel et al. 2001; Taylor and Turnbull 2005; Agnieszka et al. 2009). This suggests that, loss of Nissl bodies will eventually affect the mitochondria functions including synthesis of ATP and storage of calcium as illustrated in Figure 6.1 and 6.2 (Michael 2007; Thomas 2012). Due to the low ATP synthesis, intracellular level of cyclic adenosine monophosphate (cAMP) a derivative of ATP (Sadock et al. 2009) will be decreased, thereby affecting intracellular signal transduction at synaptic level. For dopamine to be released, action potential arrives at the synaptic bouton, resulting in a transient depolarization which opens voltage gated calcium ions channel resulting in to calcium influx. Increasing calcium in the synaptic bouton induces the secretion of dopamine from dopamine containing synaptic vesicle (Seeman 2002; Michael 2007). Significant loss of protein producing Nissl bodies projected to cause decline in mitochondria functions (Pasternak 1971) including calcium storage, the level of Ca^{2+} sufficient enough to bind to dopamine containing vesicle will decline as a result of poor mitochondria calcium storage. Furthermore, it is proposed that ribosome might plays an important role in the synthesis of tyrosine considering the fact that tyrosine is an amino acid as diagrammatically illustrated in Figure 6.1 and 6.2. Conclusively, the end result for these processes is proposed to cause decline in dopamine level, leading to Parkinsonism.

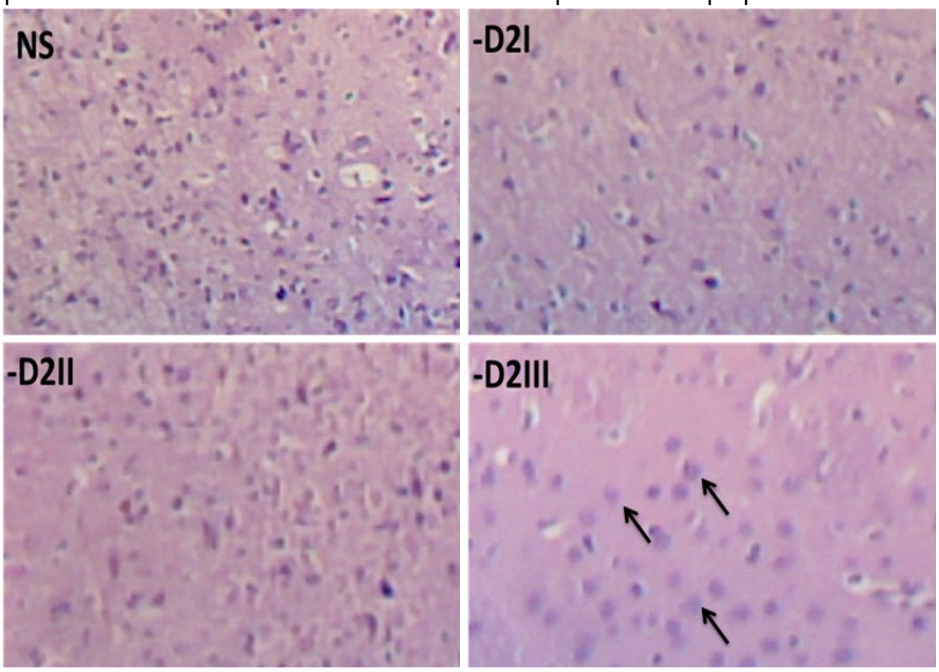

Figure 4: Overview of dorsal striatum; NS, -D2I,-D2II group show unremarkable medium and small spiny neurons of striatum, -D2III shows hypertrophied medium and small spiny neurons of the dorsal striatum (arrows) H&E ×400

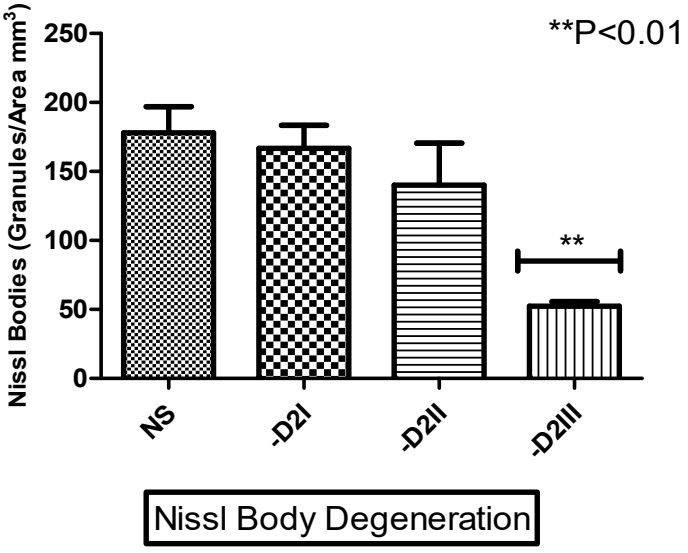

Figure 5: Nissl body density for Dopamine-2 receptor blocker induced Parkinsonism. Density of Nissl bodies declined significantly in Haloperidol administered groups when compared to the control group ($p < 0.01$).

Conclusion

Prolong inhibition of D_2R leads to the expression neuro-inflammatory hallmarks with the propensity to progress to neurodegenerative level. This process is proposed to induce Parkinsonism by inflicting neuronal membrane damage that resulted into nuclei extrusion. D_2R inhibition is also proposed to cause destruction of neurofibrils which might be the cause of cell shrinkages. Lastly, D_2R inhibition is proposed to cause loss of mitochondrial functions as result of significant chromatolysis recorded.

Conflict of Interest

None declared.

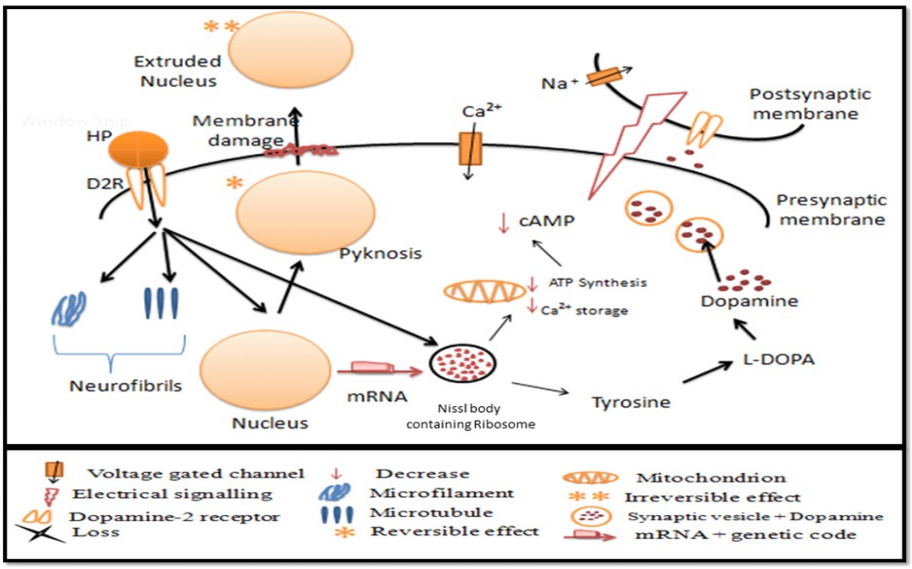

Figure 6.1. Schematic illustration of the mechanism of dopamine-2 receptor blocker Parkinsonian model

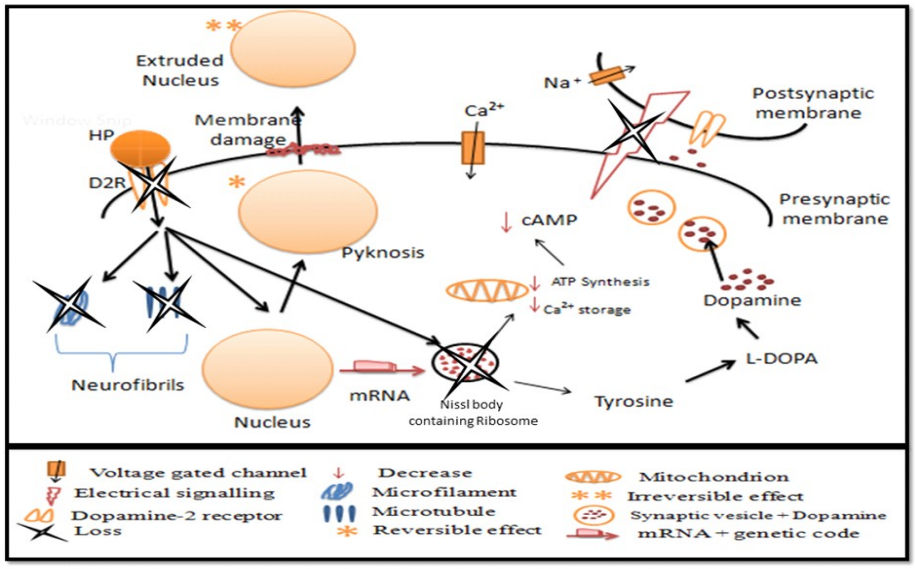

Figure 6.2: Schematic illustration of the mechanism of dopamine-2 receptor blocker Parkinsonian model

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