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PARKINSON'S DISEASE: ADVANCES IN PRECLINICAL SCREENING MODELS

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ABSTRACT: About 1.5% of the world's population is suffering from Parkinson's disease, mostly above 55 years of age. It is identified by dopaminergic neuron loss in the striatum's *Substantia nigra* & dopamine loss (DA). The disease of Parkinson is the second most widespread neurodegenerative disorder. It adversely affects the motor system as the disease increases the destruction of the motor system. It is also known that it also affects almost other components of the brain, but slowly. By using these animal models, we got to know the process of PD, its etiology, its pathology, molecular mechanisms, and numerous other disorders. Experimental models are carried out using theses different agents such as reserpine, 6-hydroxydopamine, haloperidol, 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine, and rotenone when used to produce particular PD characteristics. In addition, genetic models are also used to understand the processes in multicellular organisms such as drosophilia and zebrafish. Behavioral studies have been conducted mainly using these multicellular organisms.

INTRODUCTION: Parkinson's disease (PD) is the second most chronically progressive neurodegenerative disorder that affects over 1.5% of the world's population over 55 years of era [1, 2]. In some cases, tremor, stiffness, bradykinesia and postural instability recognize this disease [3, 4, 5, 6, 34, 35]. Loss of dopaminergic neurons in the substantia nigra & loss of dopamine (DA) in the striatum identify the pathological. Lewy bodies (LB), another significant identification of the pathology. Lewy bodies can be discovered in the brain that is present in the substantia nigra or in the cortex during the disease of Parkinson.

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A Lewy body is an eosinophilic cytoplasmic inclusion composed of a thick nucleus encircled by halo of 10 nm broad radiating fibrils and its primary structural component is alpha-synuclein [7, 36]. Some trials show that PD is caused by alpha-synuclein but has not yet been proven. There was also a study of oxidative stress and mitochondrial dysfunction. These reactive free radicals include reactive oxygen species as well as peroxynitrite, as shown by the research in enhanced production or reduced detoxification of reactive free radicals.

Proteins, lipids, and DNA undergo oxidative damage when reacted with these free radicals. It has been found that alike to the binding site for rotenone, MPP+, a site of electron leak within the complex I of electron transport chain (ETC) [3, 4]. More studies have found that MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) acts as a neurotoxin that in substantia nigra affects dopaminergic cells.

Because MPTP demonstrates toxicity, it is transformed into MPP by MAO enzyme [8]. Taking all these parts into account, the finest animal models for PD study would be chosen, showing some pathophysiological symptoms and only after some authentication of the symptoms will be chosen which drug or chemical agent to test their efficacy [9, 10]. Yeast [11], worms [12], zebrafish and fruit flies [13] are helpful for the study of basic PD-related cellular procedures such as apoptosis, autophagy, oxidative stress, protein misfolding and degradation, vesicle-mediated transport, and protein function.

Some trials demonstrate tumor formation using zebrafish. Rodents have been commonly used to study the disease since years of PD studies because they are readily accessible, genetically comparable to humans, and comparatively low price compared to other large pets. Dopamine loss has been corrected through the use of animal model by using L-DOPA as L-DOPA is the primary drug for treating PD as it crosses the blood-brain barrier.

Pharmacological Models:

Reserpine Model: Reserpine was the first agent to be given to rodents in Parkinson's disease studies. Although we are still uncertain about pharmacological and neurochemistry of PD, this model has been used to first demonstrate the therapeutic efficacy of Parkinson's disease therapy, L-DOPA or levodopa drug remains the golden standard drug for PD treatment. The peripheral portion that belongs to the adrenergic system does not work as it was seen in reserpine-treated animals that lack transmitter. In addition, to what extent reserpine CNS action can be allocated to modifications in brain catecholamines or 5-hydroxytryptamine it last to be proven [14]. This agent, reserpine, also screens compounds for antioxidant and anti-inflammatory medicines that assist avoid motor impairments such as dyskinesia [15, 16, 17, 18, 19, 37, 38].

Methodology and Evaluation: Animals can be tested for 5 days back to back with reserpine. It is possible to test animals for induction of tremors after 24 h of last therapy by providing them the results as follows:

No tremors-0, occasional twitches-1, intermittent or mild twitches-2, continue tremors-3.

The amount of tremors can be counted for approximately 5 min. Akinesia can be determined by keeping the animal's tail and placing the front paws on the platform and allowing the animal to walk with the front paws for 3 min approx. Muscular stiffness can be determined by putting the animal with forelimbs in the center of the horizontal glass rod at the height of approx. 30 cm above the table, and time of falling was noted [20].

Locomotor activity, by using an actophotometer, can be assessed. The device consists of photoelectric cells linked to a counter in the circuit. The animal is cutting the light beam falling on the photocell as they move, this can be recorded for about 10 min. Grip strength, rotarod devices can be used to evaluate. The rod has a length of 75 to 80 cm and a diameter of about 3 to 5 cm, split into four to six parts. Each animal is then put on rotating rod and it can be observed that each group of animals has a latency to break down.

Haloperidol Model: Haloperidol is another experimental PD model. Haloperidol treated animals show little construct activity. Postsynaptic dopamine receptors moderate haloperidol-induced catalepsy. Haloperidol is used for the treatment of psychosis as it is a neuroleptic drug. It functions by disrupting receptors of dopamine D2 and D1 in medium spiny neurons, which include motor circuit indirect and direct pathways. This leads to blockage of striatal dopamine transmission, which causes abnormal downstream firing in the basal ganglia as symptoms of muscle stiffness, locomotive activity, and catalepsy [21].

Methodology and Evaluation: After 30 min of haloperidol administration, the catalepsy duration can be measured at an interval of 30, 60, 90, and 120 min for about 5 min. Catalepsy duration can be assessed by putting an animal at a height on the horizontal metal bar so that the forelimbs of the animal should be on the horizontal bar while the hindlimbs are on the ground [22]. The animals may be handled with extract or L-dopa-carbidopa 60 min prior to haloperidol administration [23]. It should be observed when the animal removes its paw from the bar.

Scoring for catalepsy was provided as follows:

Step I: The rat was separated from the home cage and put on a table. A score of 0.5 can be provided if the rat does not respond when touched or pushed.

Step II: The rat's front paws were held on a block of 3 cm approx. If the rat fails to respond within 15 sec, it can give a score of 0.5.

Step III: The rat's front paws were held on a block of 9 cm approx. If the rat does not respond within 15 sec, it is possible to score 1 [24].

6-OHDA Model: 6-Hydroxydopamine (6-OHDA) was the first chemical to be found to create a model of animals with particular neurotoxic impacts on catecholaminergic pathways [25]. The 6-OHDA systemically given cannot cross the blood brain barrier.

Methodology and Evaluation: 6-OHDA is injected into SN or the nigrostriatal tract, within 24 h, dopaminergic neurons begin to degenerate and striatal dopamine is depleted within 2 to 3 days. The size of the lesion depends on the quantity of 6-OHDA injected, the location of the injection, and the sensitivity differences between animal species. 6-OHDA causes a slow, retrograde degeneration of the nigrostriatal system over a period of weeks when injected into the striatum [26, 27]. The 6-OHDA structure is comparable to dopamine, while the existence of an extra hydroxyl group makes it toxic to dopaminergic neurons. There is significant proof of oxidative stress participation in neurotoxic impacts induced by 6-OHDA. 6-OHDA-induced lesions occurred in mice, cats, dogs, and monkeys, rats are most frequently used due to the precise positioning of the samples in the body and low maintenance costs. The 6-OHDA model does not mimic all the distinctive clinical and pathological characteristics of PD. 6-OHDA does not influence other brain areas, such as locus coeruleus, nor does it lead to cytoplasmic inclusions (Lewy bodies) such as those seen in PD.

In addition, the nature of the experimental model varies from the progressive degeneration of dopaminergic nigral neurons in PD. Even with all of these constraints, the 6-OHDA lesion model was used to determine the efficiency of antiparkinsonic compounds. This experimental model has also been useful in assessing the effectiveness of cell transplantation and in testing neurotrophic factors, compounds that promote the survival of degenerating nigral neurons in PD [26, 27, 28]. 6-OHDA is often used as a unilateral model because this compound's bilateral injection into the striatum results in serious adipsia, aphagia, and death.

Rotenone: A rotenone, natural compound, is widely used as an organic insecticide and in ponds to kill irritating fish. It stops the electron transport chain's complex I, also causes mitochondrial dysfunction and contributes to cell loss in the nigrostriatal pathway. Rotenone is a lipophilic compound that crosses the blood-brain barrier readily [26, 28]. Chronic exposure to low rotenone levels led in a consistent inhibition of complex I through the rat brain. Rotenone exposure varies from MPTP exposure, which selectively inhibits complex I in dopaminergic neurons because of its dopamine transporter activity. In spite of this uniform inhibition of the complex, rotenone-induced selective degeneration of the nigrostriatal dopaminergic pathway, selective striatal oxidative damage, and the formation of beneficial inclusions of ubiquitin and alpha-synuclein in nigral cells comparable to Lewy PD bodies [39, 40].

This model's significant drawbacks are its labor-intensive nature and variability, with some animal displaying lesions and some not. Furthermore, it is hard to keep bilaterally lesioned animals as they are addressed bilaterally with 6-OHDA or MPTP. In addition, complex I deficiency can cause excitotoxicity and oxidative damage to neurons, both of which have been associated with PD [72, 73]. The rotenone model appears to be a credible model resulting in particular, progressive and chronic degeneration of the nigrostriatal pathway comparable to human Parkinson's disease in this systemic complex I inhibition. It also reproduces PD's neuronal inclusions and oxidative damage. Thus, in PD pathogenesis, the rotenone model repeats most of the processes believed to be essential. In this model, studies of neuroprotective drug therapy may be more applicable to PD than other model systems.

Methodology: It is possible to divide animals randomly into four distinct groups (8–10 animals). Group I can be administered as a control for 35 days, and Group II animals can be administered with rotenone for 35 days. Group III may be given

for 35 days with other sample drugs. Group IV can be treated for 35 days in combination with other test drugs and rotenone. Behavioral studies were performed after the last dose of 24 h and before animal sacrifice. For biochemical research, neurochemical studies, and histological analysis, animals have been randomly split.

Different brain areas can be separated and weighed in one set of animals. A 10% (w/v) homogeneous tissue prepared in a phosphate buffer of 0.1 M (ph 7.4). It is possible to use homogenates to estimate biochemical research.

The midbrain may be removed and stored at 80 °C for HPLC research in the other set of animals. Cortex, midbrain, and cerebellum can be separated and stored in formal calcium at room temperature for histological research.

MPTP Model: It has been shown that N-MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) causes Parkinson's disease symptoms in exposed people. This compound, when given to primates, causes partial destruction of basal ganglia and a syndrome analogous to Parkinson's disease.MPTP is metabolized by the enzyme MAO-B to 1-methyl-4-phenyl-2, 3-dihydropyridium (MPDP+) which then generates the respective pyridium species MPP+. Endothelial cells contain monoamine oxidases; several studies associated monoamine oxidase concentrations with neuronal loss induced by MPTP [29, 41].

Methodology and Evaluation: Taking 8 adult rhesus monkeys weighing 5-8 kg over a 5-8 day period with N-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (N-MPTP) cumulative intravenous doses up to 10-18 mg/kg. These animals had a parkinsonism such as a disease (akinesia, stiffness, postural tremor, flexed posture, eyelid closure, drooling), which may be overturned by L-dopa administration. N-MPTP pathological and biochemical modifications are comparable to well-established modifications in patients with Parkinsonism [30]. Marmosets were used to estimate N-MPTP intoxication [31, 32, 33]. Scale 0 (standard) to 17 (max) is used to rate the incidence.

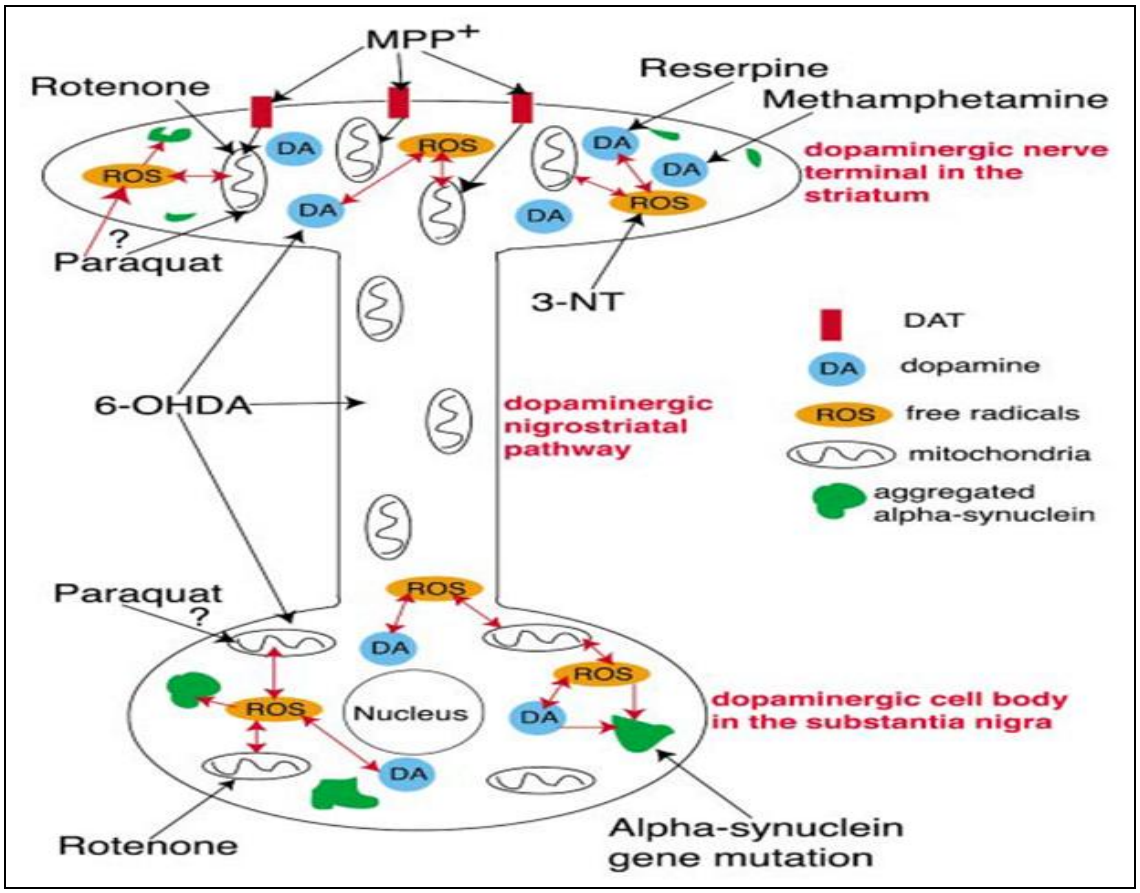

FIG. 1: SCHEMATIC DIAGRAM SHOWING THE PHARMACOLOGICAL AGENT'S LOCATION OF ACTION RESULTING IN NIGROSTRIATAL DEGENERATION AND STRIATAL DOPAMINE DEPLETION [7]

TABLE 1: SCORING ACCORDING TO INCIDENCE

Observation	Scoring
1. Movement	
Normal	0
Reduced	1
Sleepy	2
2. Checking movement	
Present	0
Reduced	1
Absent	2
3. Attention & blinking	
Normal	0
Abnormal	1
4. Balance & co-ordination	
Normal	0
Impaired	1
Unstable	2
Falls	3
5. Vocalization	
Normal	0
Reduced	1
Absent	2

Emerging Genetic Models in Multicellular Model Organisms

Drosophila Melanogaster: The most widely used fruit fly (Drosophila melanogaster) is one of the most well-understood models. The length of Drosophila fruit flies is about 3 mm. The Drosophila feeds and breeds on fermenting fruit or other fermenting sugar sources such as drainage waste. Many human genes, including PD genes such as parkin, UCH-L1, PINK1, DJ-1, and LRRK2, in Drosophila have extremely sustained homologues [42]. The fly has a very quick cycle of life. Within 10 to 12 days at room temperature, mating pairs can generate hundreds of genetically identical descendants. This is the traditional distinction between rodents and models, in which only a few offspring are formed every 3 to 4 months. The fly can be regarded as multiple model organisms, each with its own specific advantages, defined by stage of development: the embryo, the larva, the pupa, and the adult. The adult fly conducts the functions of the mammalian heart, lung, kidney, intestine, and reproductive tract. The adult fly's brain is quite noteworthy. There are more than 1,00,000 neurons that form discrete circuits and neuropil that mediate complicated behaviors including circadian rhythms, sleep, teaching and memory, courtship, feeding, aggression, grooming, and flight navigation. The reaction of flies to many drugs in the CNS is comparable to that of mammals [43-50]. Lewy bodies such as structures in the fly demonstrate favorable signs for α-synuclein and consisted structurally of filaments and granular material comparable to human Lewy bodies [51]. In dopaminergic neurons, two other family mutant forms (A30P and A53 T) were demonstrated together with human α-synuclein. α-synuclein expression resulted in age-related loss of dopaminergic cells, accumulations of Lewy bodies, and cognitive deficits [51, 52]. It leads to sensitivity to oxidative stress as well as abnormal wing phenotype due to dysfunction of the parkin gene in flies [53, 54]. Recently, the microarray method has shown upregulation of oxidative stress elements and innate immune response genes upon dysfunctioning of parkin gene in flies, but no significant change in stress-induced endoplasmic reticulum or component of the cell cycle [55]. Treatment with rotenone has been shown to cause flying impacts, loss of dopaminergic neurons and locomotive defects, showing that environmental and genetic mechanisms on PD can be useful [56].

Methodology and Evaluation: Flies may be subjected to rotenone [ROT] chronically. Adult dietary exposure with ROT for 7 days can be determined afterward, its capacity to modulate locomotive behavior, selective loss of dopa-minergic neurons in the brain, and critical dysfunction of the locomotive [57]. It is possible to use fly vials without sample compound and ROT as control. Flies (male adult, 7-8 days old) can be divided into six groups: (1) Control (2) ROT (3) ROT plus extract (0.05% w/v) (4) ROT plus extract (0.1% w/v). It is possible to study climbing activity for 60 sec by tapping at the bottom. Locomotor behavior can be conveyed as a percentage of flies fleeing in 60 sec over a minimum range of 10 cm. The flies treated with plant extract (0.05% w/v & 0.1% w/v) can be contrasted for locomotive operation with ROT-treated flies. Models of Drosophila may be a helpful way to look into the future infused consequences of genetic and environmental toxins.

Zebrafish: It is estimated that zebrafish as a vertebrate model have comparable human genes to flies [58, 59]. It also develops an understanding of human diseases such as neurodegeneration and cancer [60, 61]. Due to the transparent embryo body that matures outside the mom, zebrafish was

extremely informative in research and researching developmental processes. Zebrafish system includes fast early embryonic development of the existence of some human-like bodies (*e.g.*, liver, kidney, heart), full immune system (innate and adaptive), ease of administration of drugs, and reduced maintenance costs than rodents [62]. An authorized fish seller gave Zebrafish (*Danio rerio*). Those subjects were 3–4 months old, and the research chose the same size fish. Proper conditions were retained, and bubble sparger was used to supply fish with internal oxygen. Fishes have been fed twice. The pH was maintained at a water temperature of 27 °C - 29 °C at 7.0–8.0. Tanks are produced of a glass of high quality [63].

Some Behavioral Parameters Studied in Fish:

Latency to Travel from One Point to Another: Catalepsy reduces fish velocity owing to muscle stiffness [64, 65, 66]. Following catalepsy induction, fins rigidity was observed due to which difficulties were observed in swimming. That's why it took them longer to move from one tank point to another.

Complete Cataleptic Time: The time the fish was used as an index of locomotive activity in fish shows the state of full catalepsy when subjected to haloperidol [67]. This was the parameter used to estimate zebrafish model effectiveness by studying bromocriptine and pramipexole's protective impact.

Time Spent Near The Bottom Of The Tank: Zebrafish swim on the water surface. When they are moved to a fresh tank, they primarily spend more time at the bottom of the tank, and sometime after they come to the surface, this is ascribed to their exploration and most often because of their anxiety [67, 68, 69]. Here, the time spent by the fish below the line drawn on the test tank was calculated. Haloperidol is a well-known model in rats and is widely used [24, 70, 71]. Zebrafish tend to swim on the surface of water from one side of the tank to the other. But haloperidol removed those behaviors. Fishes began to swim erratically, *i.e.* upside-down, arrow-like, or circle-like, and spent more time near the tank bottom. All these erratic behaviors were reversed by bromocriptine and pramipexole. Bromocriptine and pramipexole also regained reduced swimming velocity owing to haloperidol.

This indicates that the zebrafish dopaminergic system operates like the mammalian dopaminergic system. For PD, it can, therefore, be an ideal model organism.

CONCLUSION: Animal modeling systems are the nearest we could study to humans. A number of animal PD models were developed to understand this disease's pathogenesis and potential test medication. There are advantages and disadvantages to each model. Further research is needed to generate the ideal PD model that shows readily detectable parkinsonian motor deficits, selective and gradual loss of aging DA neurons, and cytoplasmic inclusions similar to Lewy-body.

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