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Available online at: http://www.iajps.com ***Review Article***

A REVIEW ON ANIMAL MODELS INNEURODEGENERATIVE DISEASES

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Abstract:

Neurodegenerative diseases are among the leading cause of non-fatal disease burden in India. One in seven Indians was affected by neurodegenerative diseases. Although neurodegenerative agents is used for the management of neurodegenerative diseases like anxiety, psychosis, depression and mania it may side effects such as tardative dyskinesia, weight gain, weight loss, muscle cramps, dysphoria, gastrointestinal upset, eye problems or problems with blood tests. In this present review we made an exposure regarding many screening methods on evaluation of neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis, Huntington's disease, and Friedreich's ataxia, in the aspects of preclinical studies. These methods are very useful to evaluate the neurodegenerative agents like anti- Alzheimer's agents, anti- Parkinson's agents.

Keywords: *neurodegenerative diseases, preclinical studies, anti- Alzheimer's agents, anti- Parkinson's agents*

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I. INTRODUCTION:

Neurodegenerative diseases (NDs) are characterized by the progressive and irreversible loss of neurons in selective regions of the brain. In afflicted individuals, symptoms typically manifest as memory loss, anxiety, and depression, which evolve to severe motor dysfunction, profound cognitive deterioration, and loss of independent function. The risk of developing a ND rises sharply with age; the number of people with a neurodegenerative disease is low at younger ages, but the prevalence of people suffering from neurodegeneration doubles every 5 years after age 65.3 AD, the most common form of NDs, currently affects about 10 percent of the population over age 65 and 47 percent of adults aged over 85 years.3 NDs typically involve a slow decline in human function that results in an eventual need for constant care and assistance with the most basic activities of daily life, consequently generating a substantial social and financial burden.[(1)]

Examples:

Alzheimer's disease (AD),
Parkinson's disease (PD),
Amyotrophic lateral sclerosis,
Huntington's disease, and
Friedreich's ataxia,

They are devastating age-related conditions that have become one of the primary public health concerns of recent decades. [(1)]

1. Parkinson's Disease (PD)

Parkinson's disease (PD) is a slowly progressive neurodegenerative disease caused when a small group of brain cells that control body movements die. This disease was first described by **James Parkinson** in **1817**. It is characterised clinically by bradykinesia, resulting tremor, rigidity and postural instability. Pathological features of PD include loss of dopamine neurons in substantia nigra and presence of intracytoplasmic inclusions known as Lewy bodies in surviving dopamine neuron. It is not clear why Lewy body formation causes neuronal cell death. Among the available antiparkinson drugs, levodopa remains the most efficacious and still the mainstay of therapy. However, long term use of levodopa leads to wearing off phenomenon, on- off phenomenon, motor fluctuations and dyskinesia, which limit its further usage. Even though antiparkinson drugs are highly effective in alleviating the symptoms of Parkinsonism, but they do not give complete cure. Moreover, these drugs are often associated with frequent side effects like nausea, vomiting, depression, hallucinations, dizziness, dry mouth, sore throat, postural hypotension, diarrhea, mydraiasis, anxiety etc. The significance of many indigenous medicinal plants and their phytoconstitutents in the management of Parkinsonism with minimal side effect profile arise in this context. There has been an enormous demand for further scientific development of animal models that can mimic the progressive motor impairment as in PD. One such model is Haloperidol induced catalepsy i.e., a state of akinesia with muscular rigidity in animals. It is an established model for screening the drugs for antiparkinson effect. [(2)]

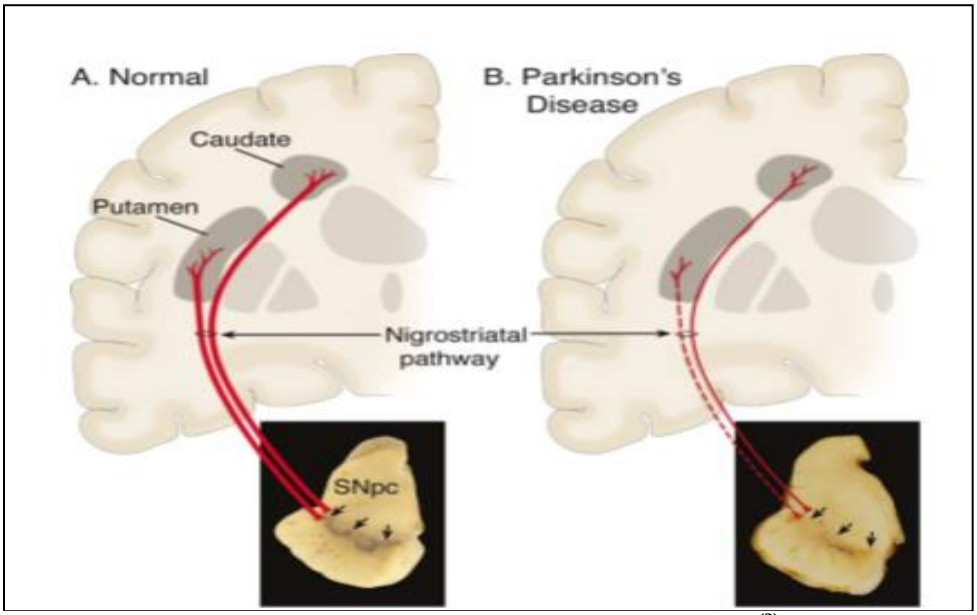

FIGURE 1: Neuropathology of Parkinson's disease [(3)]

(A) Schematic representation of the normal nigrostriatal pathway (in red):-It is composed of dopaminergic neurons whose cell bodies are located in the substantia nigra pars compacta (SNpc; see arrows).These neurons project (thick solid red lines) to the basal ganglia and synapse in the striatum (i.e. putamen and caudate nucleus).The photograph demonstrates the normal pigmentation of the SNpc, produced by neuromelanin within the dopaminergic neurons. [(3)]

(B) Schematic representation of the diseased nigrostriatal pathway (in red):- In Parkinson's disease, the nigrostriatal pathway degenerates. There is a marked loss of dopaminergic neurons that project to the putamen (dashed line) and a much more modest loss of those that project to the caudate (thin red solid line). The photograph demonstrates depigmentation (i.e., loss of dark-brown pigment neuromelanin; arrows) of the SNpc due to the marked loss of dopaminergic neurons. [(3)]

Causes of PD: [(4)]

Currently there is no known cause of understanding of why a person develops Parkinson's. There are many theories as to the causes and it is generally thought that multiple factors are responsible. Medical experts are not yet certain what destroys the dopamine producing nerve cells or what predisposes some people to develop Parkinson's and not others . Many researchers think that the condition may be caused by a combination of genetic and environmental factors and may vary from person to person. However, Parkinson's is not an infectious disease and it is not contagious.

- **Genetics:** Several genetic changes (mutations) have been identified as increasing a person's risk of developing Parkinson's disease, although exactly how these make some people more susceptible to the condition is unclear. Parkinson's disease can run in families as a result of faulty genes being passed to a child by their parents, however, inheriting the disease in this way is rare. Recent advances in genetic studies have identified mutations in a number of pathogenic genes (SNCA, Parkin, UCHL1, DJ-1, PINK-1, LRRK2 and ATP13A2 genes) that contribute to familial forms of PD.
- **Environmental factors:** Some researchers also feel that environmental factors may increase a person's risk of developing Parkinson's disease. It has been suggested that pesticides and herbicides used in farming and traffic or industrial pollution may contribute to the condition. However, the evidence linking environmental factors to Parkinson's disease is inconclusive. The potential environmental risk factors include farming activity, pesticide exposures, well-water drinking, and history of head trauma.
- **Other causes of Parkinsonism:** Parkinsonism' is the umbrella term used to describe the symptoms of tremors, muscle rigidity and slowness of movement. Parkinson's disease is the most common type of Parkinsonism, but there are also some rarer types where a specific cause can be identified. These include Parkinsonism caused by:
  i. **Medication (drug induced Parkinsonism):** where symptoms develop after taking certain medications, such as some types of antipsychotic medication, and usually improve once the medication is stopped.
  ii. **Other progressive brain conditions:** such as progressive supranuclear palsy, multiple systems atrophy and corticobasal degeneration.
  iii. **Cerebral infarction:** where a severe stroke causes several parts of the brain to die.

Symptoms:[(4)]

Parkinson's entails symptoms of many types – motor and non – motor. However, not every symptom affects every PwP, & the intensity of symptoms varies across individuals. In addition to these four cardinal motor symptoms there are many others which are also considered in the diagnostic process. Often the non-motor symptoms are more challenging for the person living with Parkinson's. Non-motor symptoms such as pain, depression and problems with memory and sleep can also occur and have an impact on the day to day life of the person with Parkinson's. The Four main symptoms of Parkinson's disease affect physical movement:

- **Tremor:** The most common symptom of Parkinson's disease is the unilateral, typically resting tremor in body parts, most commonly in the upper extremities. However, this finding can spread to the other parts of the body like lips, chin, jaw and tongue during the course of the disease. It is an early symptom and is seen in about 70% of people presenting with Parkinson's. The tremor of PD is a rest tremor- the shaking occurs when the patient is not trying to use the limb, and diminishes when the limb is in use. Tremor is related to an imbalance of neurotransmitters, dopamine and acetylcholine, for this reason, tremor may be the least responsive symptom to dopamine replacement therapy. This usually begins in the hand or arm and is more likely to occur when the limb is at rest .
- **Slowness of movement (bradykinesia):** Bradykinesia can be the most disabling symptom of the condition and refers to slowness,

decreased movement amplitude, and dysrhythmia. Physical movements are much slower than normal, which can make everyday tasks difficult and can result in a distinctive slow, shuffling walk with very small steps.

- **Muscles stiffness (rigidity):** Parkinson's disease can create greater tension in the tendon, leading to structural adjustment and an increase in tendon stiffness. Muscle rigidity may not be apparent to the person with Parkinson's but is felt by the medical practitioner in limb muscles when they are passively moved. Stiffness and tension in the muscles, which can make it difficult to move around and make facial expressions and can result in painful muscle cramps (dystonia).
- **Postural Instability:** Postural instability is one of the most disabling features of Parkinson's disease. Postural instability is often experienced in the late stages of PD and is a marker of disease progression. Little information is available on the role of visual inputs as an adaptive strategy to compensate for postural instability in PD. Postural instability and gait disturbances often develop later in the progression of the condition. If a loss of postural reflexes and resulting falls occur early, it is not suggestive of typical Parkinson's. Postural instability is a disabling feature of Parkinson's disease (PD), contributing to recurrent falls and fall-related injuries. In early Parkinson's the posture may show a slight flexion of the neck or trunk with a slight lean to one side.
- **Other Symptoms:** Anosmia, Anxiety, Constipation, Depression, Fatigue, Festination of speech, Postural hypotension and Micrographia.

Progression of PD:[4]

Parkinson's is a neurological disorder that progresses slowly with time. Symptoms normally begin on one side of the body and usually spread to the other side as Parkinson's progresses. It is difficult to estimate the rate of progression as every individual with Parkinson's may experience different symptoms. Symptoms present in the earlier stages of the condition may worsen and new symptoms may appear during the course of Parkinson's. Medications help in managing the symptoms but unfortunately, aren't implicated for slowing the progression of Parkinson's.

- **Early Parkinson's:** During the initial stages of Parkinson's, the symptoms may be mild and interfere with fine motor activities like buttoning a shirt, tying shoe laces, a change in handwriting and slowed movement. Tremor if present may appear on one side of the body, starting either with the finger/hand or toe/foot.
- **Advanced Parkinson's:** As Parkinson's progresses, the symptoms that appeared earlier tend to become more pronounced and problems with balance and change in posture become evident. After years of Parkinson's, a PwP tends to walk with a stooped posture with short steps.

Symptoms of Parkinson's develop slowly and gradually progress over time. Each person is affected differently and the rate of progression varies greatly between individuals. Parkinson's doesn't directly cause people to die and it is possible to live with Parkinson's for a long time, although symptoms do get worse over time.

Pathophysiology of PD:

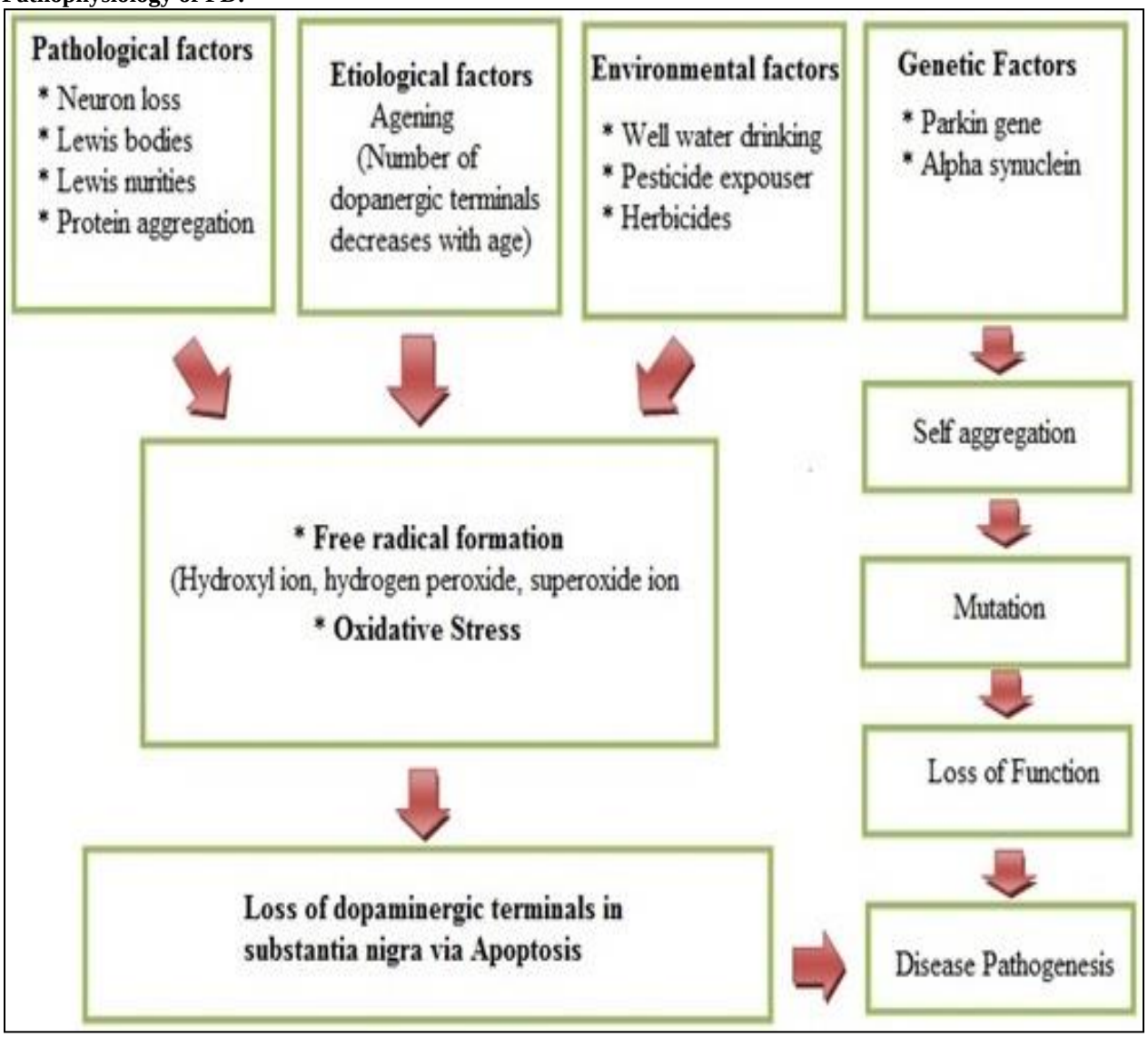

FIGURE 2: Pathophysiology of PD [5]

DRUGS USED IN PARKINSON'S

I. Drugs affecting brain dopaminergic system

1. Dopamine precursors: Levodopa (L-DOPA)
2. Peripheral decarboxylase inhibitors: Carbidopa,Benderizine
3. Dopaminergic agonist: Bromocriptine,Ropinirole,Pramipexole
4. MAO- B inhibitors: selegiline,Rasagiline
5. COMT Inhibitors: Tolcapone
6. Glutamate (NMDA) ANTAGONIST RECEPTOR: Amantadine

II. DRUGS ACTING ON BRAIN CHOLINERGIC SYSTEM:

1. Central anticholinergic: Trihexypheniyl, Procyalidine
2. Anti histamines:oxphenadrine, Promethazine

2 Alzheimer's Disease (AD)

The German psychiatrist and neuropathologist Dr. Alois Alzheimer is credited with describing for the first time a dementing condition which later became known as AD. In his landmark 1906 conference lecture and a subsequent 1907 article, Alzheimer described the case of Auguste D, a 51-year-old woman with a 'peculiar disease of the cerebral cortex,' who had presented with progressive memory and language impairment, disorientation, behavioural symptoms (hallucinations, delusions, paranoia), and psychosocial impairment.

Remarkably, many of the clinical observations and pathological findings that Alzheimer described more

than a century ago continue to remain central to our understanding of AD today. [6]

Alzheimer's disease is a form of brain degeneration in which abnormal particles called neurofibrillary tangles and neuritic plaques form in the brain and destroy healthy neurons (brain cells). These abnormalities tend to settle in brain areas that control the ability to learn a new fact and remember it 30 minutes, or a day later, a skill we refer to as "memory".[7]

(OR)

Alzheimer's disease is a chronic progressive neurodegenerative disorder characterized by three primary groups of symptoms. [8]

S.No	Groups	Symptoms
1	First group (cognitive dysfunction)	Memory loss, language difficulties, and executive dysfunction (i.e. loss of higher level planning and intellectual coordination skills).
2	Second group (psychiatric symptoms)	Depression, hallucinations, delusions, agitation—collectively termed non-cognitive symptoms.
3	Third group (difficulties with performing activities of daily living)	Deemed "instrumental" for more complex activities such as driving and shopping and "basic" for dressing and eating unaided.

FIGURE-3: Schematic representation of the healthy brain and AD patient brain [9]

The symptoms of Alzheimer's disease progress from mild symptoms of memory loss to very severe dementia (figure-4). [8]

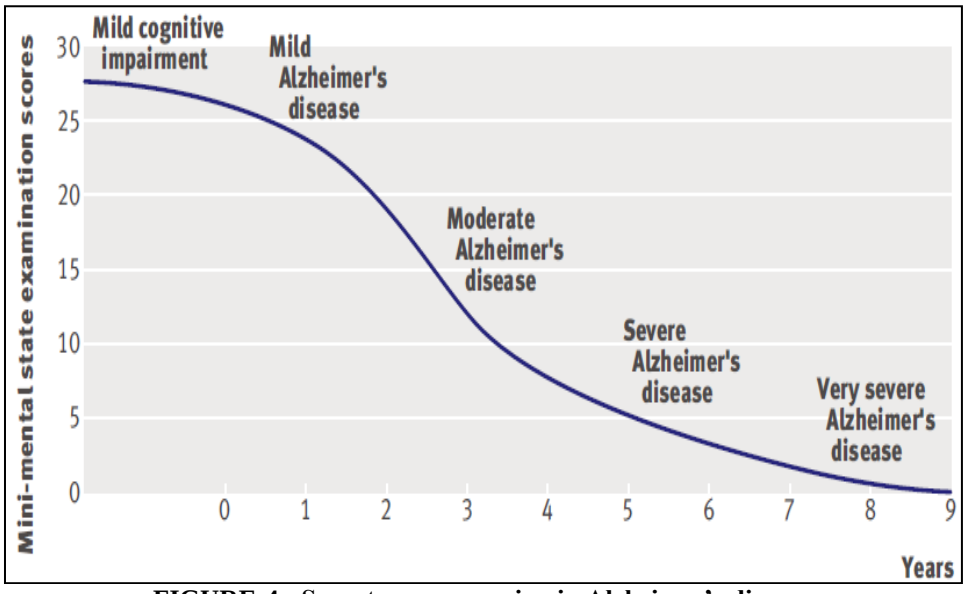

FIGURE-4: Symptom progression in Alzheimer's disease

Stages of AD: [10]

Stages	Name	Description
1	**Preclinical stage (No cognitive impairment)**	A newly defined stage reflecting current evidence that measurable biomarker changes in the brain may occur years before symptoms affecting memory, thinking or behavior can be detected by affected individuals or their physicians. While the guidelines identify these preclinical changes as an Alzheimer's stage, they do not establish diagnostic criteria that doctors can use now. Rather, they propose additional research to establish which biomarkers may best confirm that Alzheimer's-related changes are underway and how to measure them.
2	**Early stage (Very mild decline)**	Mild cognitive decline. • Difficulty in social or occupational settings • Friends or family may notice change
3	**Early stage (Mild cognitive decline)**	Mild cognitive impairment (MCI) due to Alzheimer's disease. In this stage, mild changes in memory and thinking are noticeable and can be measured on mental status tests, but are not severe enough to disrupt day-to-day life.
4	**Early stage [Moderate cognitive decline (Mild or early-stage Alzheimer's disease)]**	Probable Alzheimer's dementia. The differentiation of dementia from MCI rests of the determination of whether there is significant interference in the ability to function at work or in usual daily activities. This is a clinical judgment based on information obtained from the patient and from a knowledgeable informant.
5	**Middle stage [Moderately severe cognitive decline (Moderate or mid-stage Alzheimer's disease)]**	Moderate cognitive decline. • Difficulty performing simple tasks • May need assistance with activities of daily living such as bathing or dressing
6	**Middle stage (Moderately severe or mid-stage Alzheimer's disease)**	Severe cognitive decline.
7	**Late stage [Very severe cognitive decline (Severe or late-stage Alzheimer's disease)]**	Severe Impairment. • Supervision or complete assistance is required to complete all activities of daily living • Communication is severely impaired

SYMPTOMS: [11]

Typical early symptoms of Alzheimer's may include:

Symptoms	Description
Memory	Regularly forgetting recent events, names and faces.
Repetition	Becoming increasingly repetitive, e.g. repeating questions after a very short interval.
Misplacing things	Regularly misplacing items or putting them in odd places.
Confusion	Uncertainty about the time of day.
Disorientation	Disorientation, especially away from normal surroundings. Getting lost
Language	Problems finding the right words.
Mood and behavior	Some people become disinterested in what's happening around them, become irritable, or lose confidence.
Memory and thinking skills	People will find that their ability to remember, think and make decisions worsens
Communication	Communication and language become more difficult.
Behaviour	A person's behavior may change and some people can become sad or depressed. Anger and agitation become more common and people may

	develop anxieties or phobias
Hallucinations	People may experience hallucinations, where they may see things or people that aren't there.
Restlessness	Problems with sleeping and restlessness at night often occur.
Unsteadiness	People may become increasingly unsteady on their feet and fall more often
Daily activities	People gradually require more help with daily activities like dressing, toileting and eating.

Causes ofAD : [12]

While scientists know that Alzheimer's disease involves the failure of nerve cells, it's still Unknown why this happens. However, they have identified certain risk factors that increase the likelihood of developing Alzheimer's.

- **Age:** The greatest known risk factor for Alzheimer's is increasing age. Most individuals with the disease are 65 and older. One in nine people in this age group and nearly one-third of people age 85 and older have Alzheimer's.
- **Family history:** Another risk factor is family history. Research has shown that those who have a parent, brother or sister with Alzheimer's are more likely to develop the disease than individuals who do not. The risk increases if more than one family member has the illness.
- **Genetics:** Researchers have found several genes that increase the risk of Alzheimer's. APOE-e4 is the first risk gene identified and remains the one with strongest impact. Other common forms of the APOE gene are APOE-e2 and APOE-e3. Everyone inherits a copy of some form of APOE from each parent. Those who inherit one copy of APOE-e4 have an increased risk of developing Alzheimer's; those who inherit two copies have an even higher risk, but not a certainty.

Pathophysiology of AD : [13]

AD is characterized by progressive loss of brain tissue,extracellular plaques of β- amyloid protein, intracellular neurofibrillary tangles and neuronal degeneration.

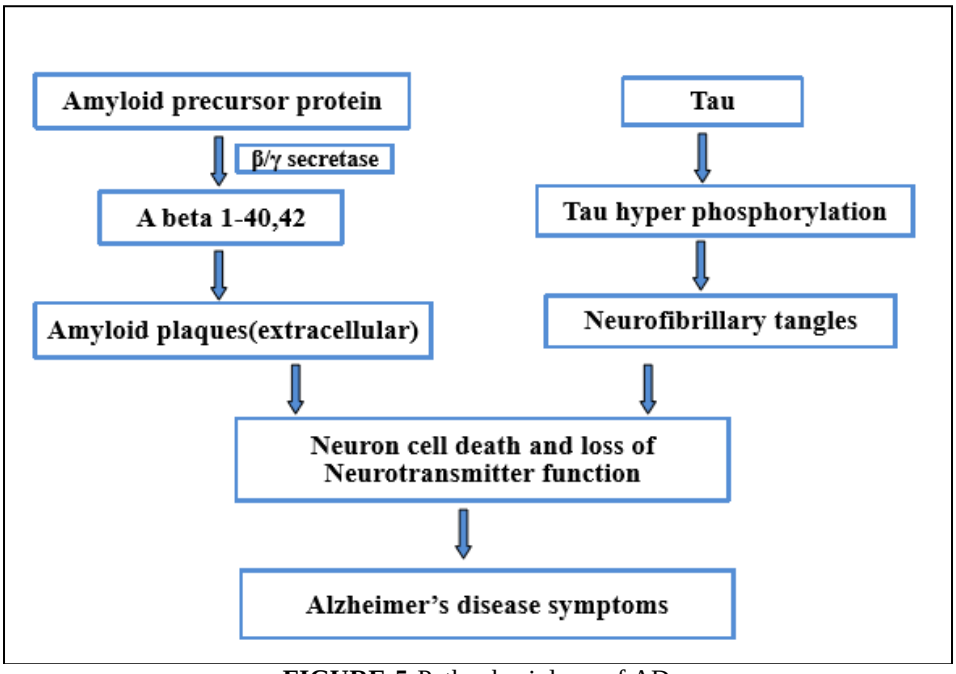

FIGURE-5: Pathophysiology of AD

DRUGS USED IN AD[14]

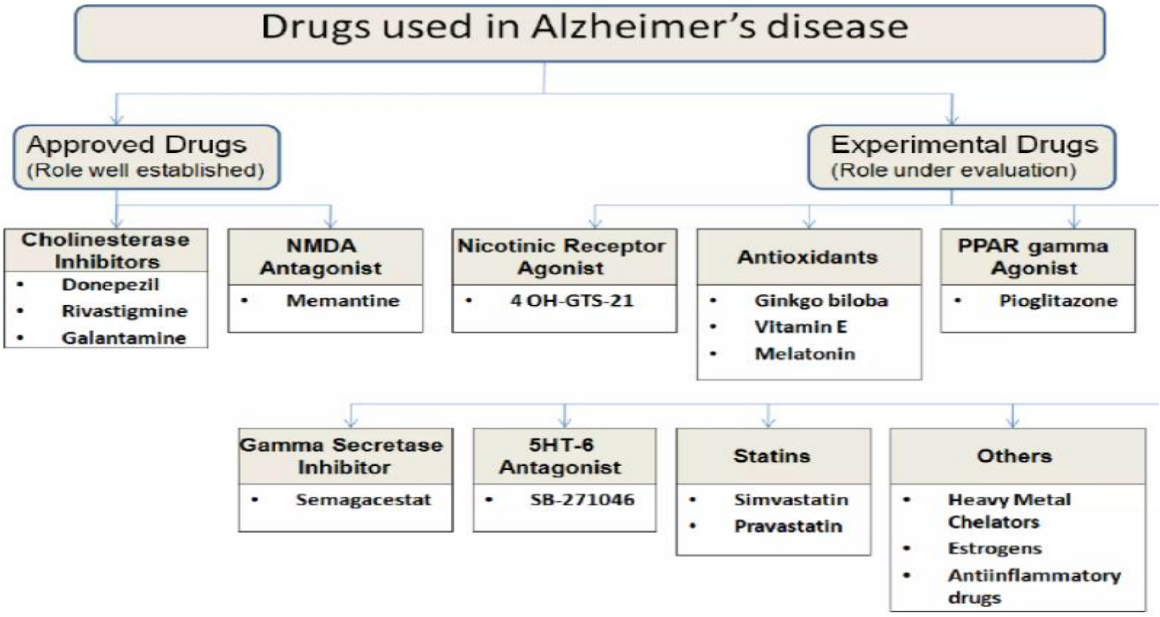

FIGURE-6: Drugs used in ad

II. ANIMAL MODELS PRECLINICAL SCREENING MODELS

ANIMAL MODELS FOR PARKINSON'S DISEASE

1.CIRCLING BEHAVIOUR IN NIGROSTRITAL LESIONED RATS[15]**:**

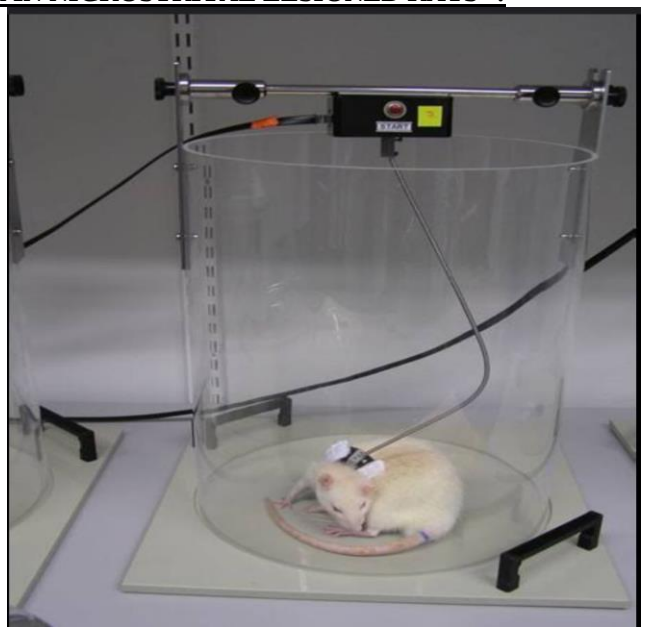

FIGURE-7:ROTAMETER

Principle:

- Unilateral lesion of the dopaminergic nigrostriatal pathway in the rat by the neurotoxin 6-hydroxydopamine (6-OHDA) induces hypersensitivity of the postsynaptic dopaminergic receptors in the striatum of the lesioned side .
- The rats rotate in a direction towards the lesioned side (ipsilateral) when an indirect acting compound such as amphetamine is administrated , but to the opposite direction (contralateral) when

a directly acting dopamine agonist,e.g ., apomorphine , or the dopamineprecursor L-dopaisgiven.

- ❖ Therefore, this test can be used for the study of central dopamine antgonists and agonist, particularly the activity of novel antiparkinsonian drugs.
- ❖ An imbalance of dompainergic activity with in the basal ganglia is associated with markedly asymmetric circling behaviour (Rotationturning) which measured by rota meter.
- ❖ This model is used in drug induced rotating behaviour and understanding of extra pyramidal disorder & of their treatment by dopaminergic agents.

Requriments:

Animal: male wister rats (200-250gm)
Dose : 6-OHDA neurotoxin 6- hydroxy dopamine & test drug.
Apparatus : Rotameter

Procedure:

- ❖ Male wister rats are taken.
- ❖ Rats are anesthetized with pentobarbital (60 mg/kg)
- ❖ Head is placed in stereotaxic device a sagittal cut is made in the skin of the skull, 2-mm wide hole is drilled with an electrical trepan drill.
- ❖ A 30- gaugestainless- steel cannula connected to a Hamilton syringe is aimed at the anterior zona compact of the substantia nigra
- ❖ A total of 8microgram of 6-OHDA in 4y/l of saline is injected at a rate of 1y/4min
- ❖ After the intracrainial injection the wound is closed. The animals allowed several weeks for recovery and for development of lesion
- ❖ Rats are divided in to groups:
  - ✓ Control groups for base value of ipsi lateral rotation-2.5mg/kg of damphetamine injected i.p. to rats.
  - ✓ Control groups for base value contra lateral rotation- 1mg/kg of Apomorphine injected i.p. to rats.
  - ✓ Test compounds are given i.p. or s.c and the animals placed in to the circling chambers. Circling is recorded over a1-h period.
  - ✓ Further studied test group as compared to control group.
  - ✓ No. of full turns (either ipsilateral Or contra lateral turning to lesion) are recorded an automatic print out counter every 15 min . for one or two hr. session.

Observation:

- ❖ For ipsi- lateral turning: administer 2.5 mg/kg Amphetamine & placed in circling chamber for 2hrs
- ❖ For contra- lateral turning: administer 1mg/kg& placed in .
- ❖ Circling chamber for 1 hour.
- ❖ Test compound are given i.p. or s.c & record reading with 15min. interval.

Evaluation:

- ❖ % change of drug turns from control turns is recorded.

2.STEPPING TEST IN RATS[16]

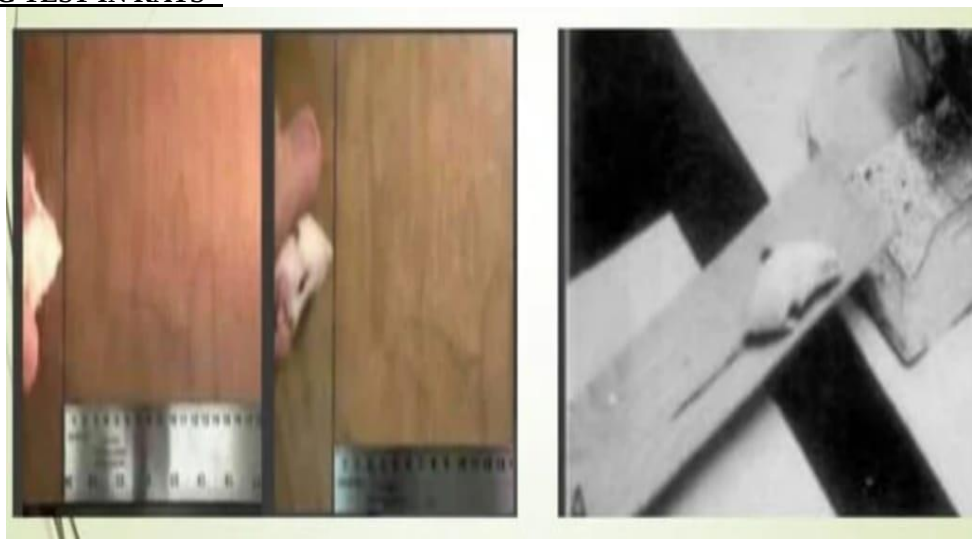

FIGURE-8 : RAT ON BENCH

Principle:

- This model is clinically relevant to unilateral model for parkinsonism akinesia.
- The 6 – OHDA lesion induced marked and long-lastingimpairments in the initiation of stepping movements with the contra lateral paw which can be ameliorated by application of drug.

Requirements:

- ANIMAL: Sprague Drawley rats,
- DOSE: 6 – OHDA (3.6 microgram/microliter in 0.2 microgram/ milliliter Ascorbate saline, test drug

Procedure:

- 6 – OHDA Lesion surgery female Sprague Dawley rats receive two stereotaxic injections of 6 -OHDA (3.6 microgram/ microliter in 0.2 microgram/milliliter ascorbate saline) in to the right ascending mesostriatal dopamine pathway using a 10-microliter Hamilton syringe.
- The cannula is left in place for an additional 5min before slowly retracted .
- The tests monitoring initiation time, stepping time and step length are performed using a wooden ramp with a length of 1m connected to the rats home cage.
- A smooth- surfaced tablets is used for measuring adjusted steps .
- During the first 3 days the rats are handled by the experimenter to familiarize them with the experimenter's sgrip.
- During the subsequent 1- 2 days the rats are trained to run spontaneously up the ramp to the home cage.
  1. The time to initiation of a movement of each forelimb, the step length, and the time required for the rat to cover a set distance along the ramp with each forelimb.
  2. The initiation of adjusting steps by each other forelimb when he animal was moved side ways along the bench surface.
- The stepping test comprises two parts:
- Each test consists of two test per day for three consecutive days and the mean of six subtests is calculated.

Evaluation parameter:

- Initiation time, stepping time , step length.
- Step length = length of ramp / no. of steps
- Sequence of testing in right
  - paw & followed by left paw testing, repeated twice.

ANIMAL MODELS FOR ALZHEIMER'S DISEASE[17]

1. **SCOPOLAMINE INDUCED AMNESIA IN MICE:**

Purpose and rationale:

Scopolamine is an antimuscarnic agent and inhibits the cholinergic transmission to induced amnesia or impair memory retention (Dilts and Berry, 1967; Glick and Zimmerberg., 1972: Schindler et al., 1984). Therefore, this test can be used to screen the cholinergic agonist drugs that can reverse the amnesic effects of scopolamine.

Method:

To test the amnesia induced by scopolamine, two-compartment test is employed.

⇩

Animals (mice) are administrated with scopolamine hydrobromide (3 mg/kg, i.p.) and five min later each mouse is individually placed in the bright part of the two-chambered apparatus for training as described above in the method of two-chambered test.

⇩

The scopolamine treated animal exhibits lesser latency time to enter the darker chamber on test day as compared to untreated control animals indicating amnesia for the (punishment) shock treatment applied during the acquisition in the dark chamber of the two-chambered test.

⇩

The animals are treated with vehicle or test or standard compounds 90 min before training or scopolamine treatment.

Interpretation:

Test drug increases the latency to enter the darker chamber on test day of the scopolamine treated animal indicating that the animal remembers (retention of memory) the punishment (shock) during trail and thus avoid the darker chamber.

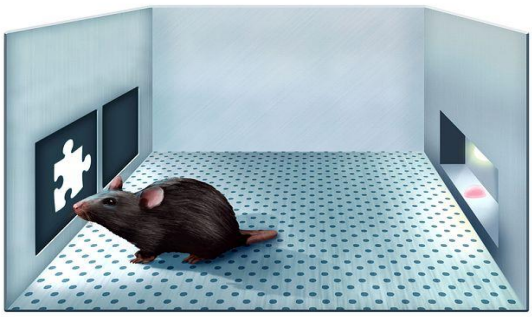

FIGURE-8: Two-chambered apparatus

2. RADIAL ARM MAZE:

The radial arm maze is employed to screen the spatial reference and working memory in the rat/mice. In the reference memory the information is useful for many sessions/day which is used during the entire experiment whilst working memory procedures, the information presented in the maze (arms baited) is useful for one session but not for subsequent ones: the rat has to remember the information during a delay interval (min to h Correct choices in the radial arm maze are rewarded by food.

Apparatus:

The radial arm maze is made up of Plexiglass painted black and is elevated 50 cm above the floor consists of an eight radial arm (43 cm long, 15 cm wide with 12 cm sides connected to a central area of 36 cm in diameter. Each arm has small black plastic cups (for food reward) placed at 30 cm from the central hub.

Method:

- Each mouse (maintained at 85% of its total diet) is subjected to the maze daily with the food pellet in a fixed arm followed by respective drug treatment for the period of 07 days and cleaned with damp cloth after each trial to avoid place preference or odor interference in the results.
- The test is conducted on 7 day by subjecting each mouse on the central hub after vehicle test or standard drug treatment and the food pellet is kept in a variable arm to screen the working memory.
- The time required by the animal (Latency) to find the food in the arms (baited arms) is recorded as a measure of working memory.
- The number of errors (entries to non-baited arms) are also counted during the test session.

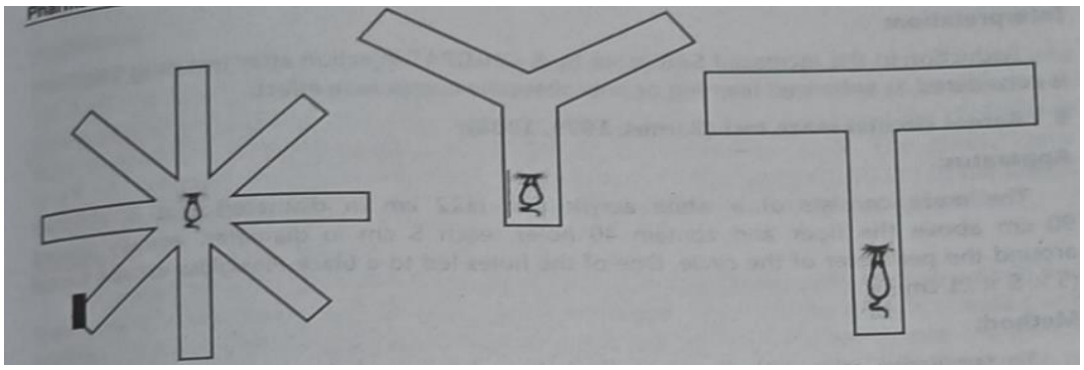

FIGURE-9:- depicting the radial , y, and t-maze (left to right)

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