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Screening Models for Alzheimer's Disease

{Pharmacological & Toxicological Screening Method -1}

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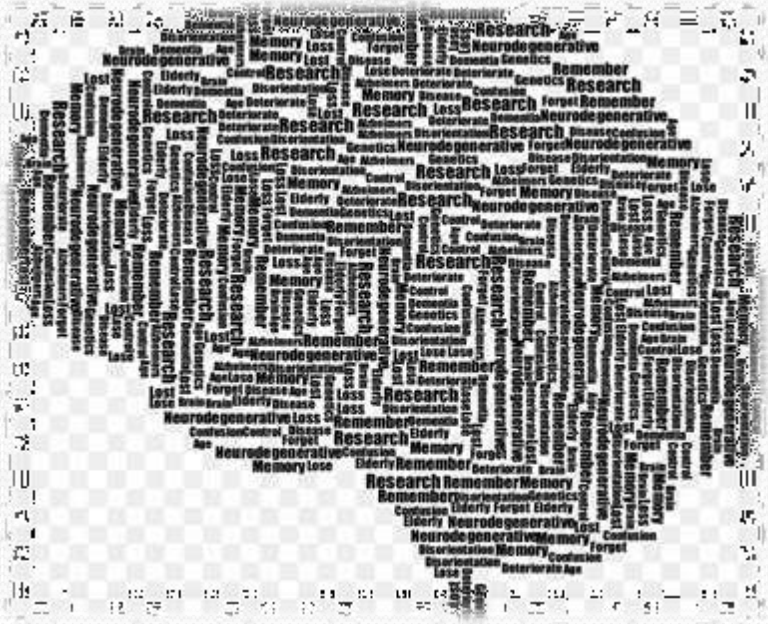


INTRODUCTION

- Alzheimer disease is a chronic , irreversible , Neurodegenerative disease that can effect the cell of the brain and causes impairment of intellectual functioning .
- It is also called as Senile Dementia or Ageing Disease .
- It is a brain disorder in which patients slowly lose their memory , thinking Ability and Eventually the ability to carry easiest tasks.

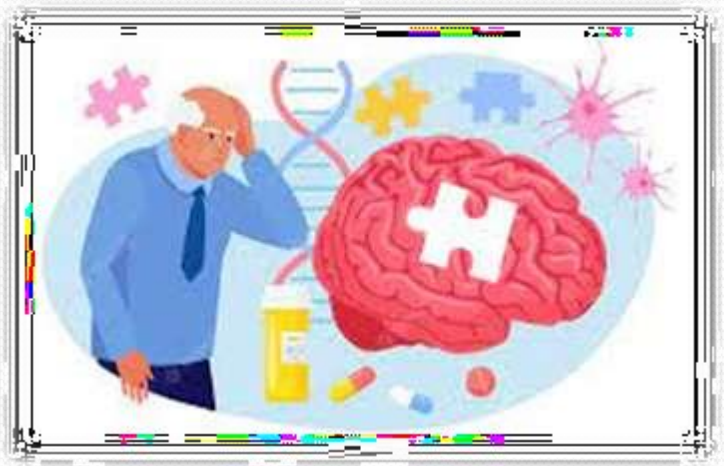
ORIGIN OF ALZHEIMER'S DISEASE

- The disease was first described by Dr. Alois Alzheimer , a German Physician in 1906 .
- Alios Alzheimer conducted research on a patient named Auguste Deter , who exhibited sever memory loss , language problems and behavioral changes .
- After her death he examined her brain and identified the characteristics abnormal protein deposits , known as Amyloid Plaques and Tau Tangles , which are hallmark Features of the Disease .
- Thus the condition was named “Alzheimer’s Disease” in honor of Dr. Alois Alzheimer's .

INCIDENCE

- About 3% of men and women ages 65 to 74 have Alzheimer disease and nearly half of those age 85 and older may have the disease .

- About 3,60,000 new cases of Alzheimer ‘s are diagnosed each year.



TYPE OF ALZHEIMER'S DISEASE

1. **Early – Onset Alzheimer's** – This refers to cases where symptoms appears before the age of 65 .

- Early onset Alzheimer's is relatively rare and may have stronger genetic links .

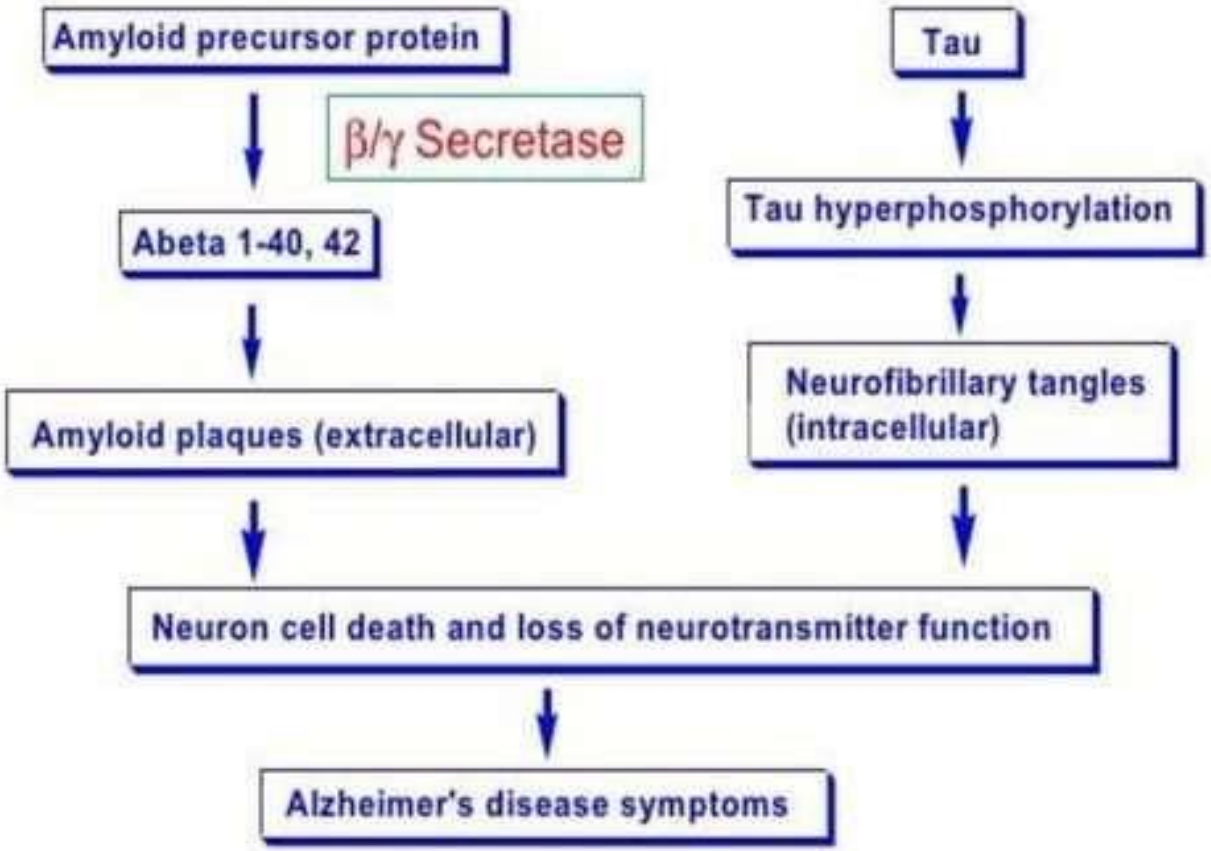
2. **Late – Onset Alzheimer's** – This is the more common form where symptoms typically develop after the age of 65 .

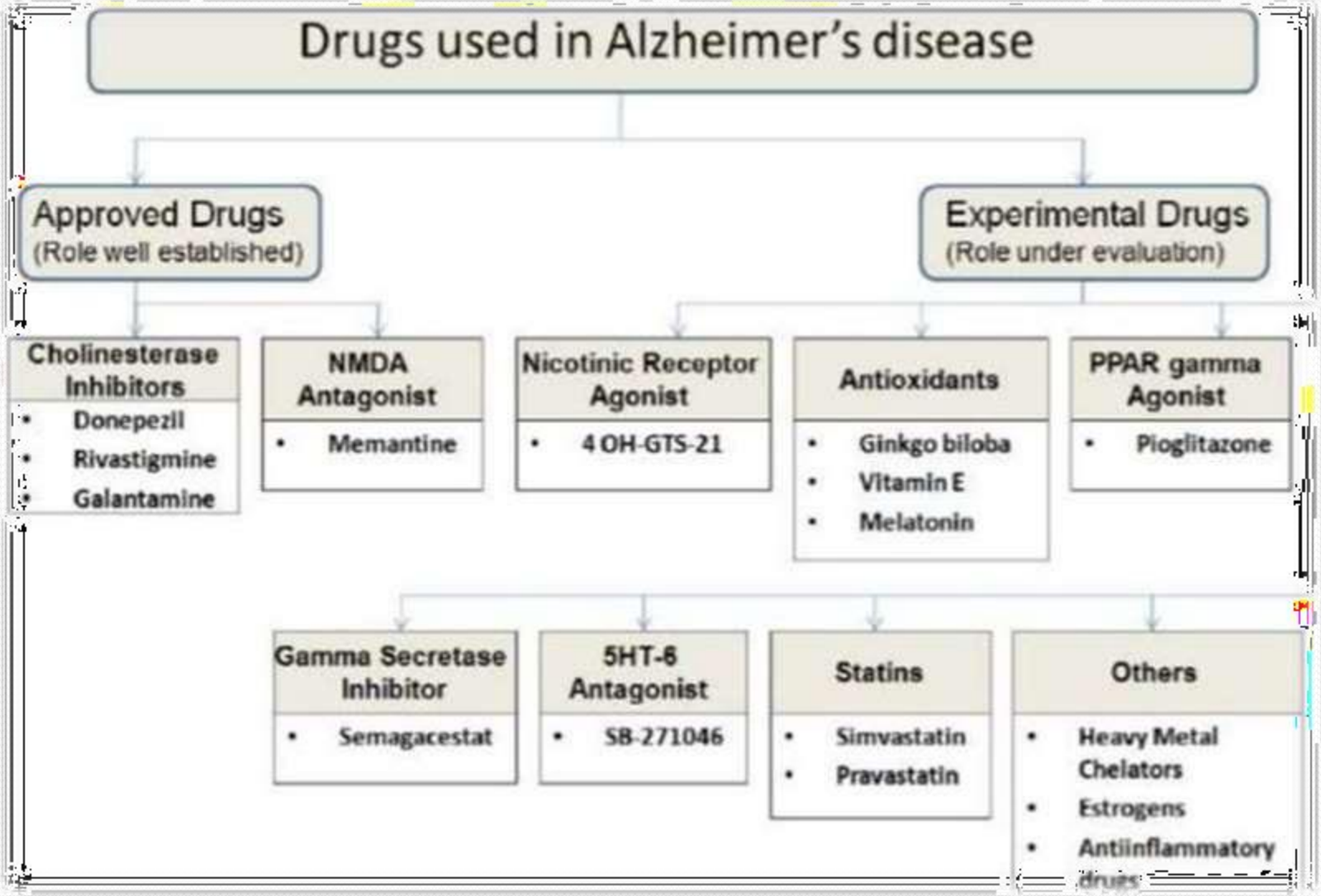
- It is influenced by a combination of genetic , Environmental and lifestyle factors .

SIGN & SYMPTOMS

- Apraxia { Difficulty with skilled movement }
- Aphasia {inability to speak or understand }
- Anomia { inability to find work }
- Agnosia { loss of sensory organs }
- Behavior and Personality Change
- Memory loss
- Confusion

Alzheimer's Disease Pathophysiology




Drugs used in Alzheimer's disease
Approved Drugs
(Role well established)
Experimental Drugs
(Role under evaluation)
Cholinesterase Inhibitors
Donepezil
Rivastigmine
Galantamine
NMDA Antagonist
Memantine
Nicotinic Receptor Agonist
4 OH-GTS-21
Antioxidants
Ginkgo biloba
Vitamin E
Melatonin
PPAR gamma Agonist
Pioglitazone
Gamma Secretase Inhibitor
Semagacestat
5HT-6 Antagonist
SB-271046
Statins
Simvastatin
Pravastatin
Others
Heavy Metal Chelators
Estrogens
Antiinflammatory drugs

SCREENING Models Of Alzheimer's Disease

IN-VITRO METHOD

- Inhibition of Acetylcholine esterase activity in Rat straitum .
- Inhibition of Butyrly Choline esterase activity in Human Serum .

IN-VIVO MODELS

- Passive Avoidance Method
- Step Down Method
- Step Through Method
- Two Compartment Test
- Uphill Avoidance Test
- Scopolamine induced Amnesia in Mice

STEP DOWN METHOD

Purpose and Rationale

- An animal(mouse or rat) in an open spends most of the time close to the walls and in corners.
- When placed on an elevated platform in the centre of a rectangular compartment , it steps down almost immediately to the floor to explore the encloser and to approach the wall.
- This technique is employed in different modifications.

PROCEDURE

REQUIREMENTS

a) Mice or rats of either sex are used.

b) A rectangular box (50x50) with electrifiable grid floor 35 fits over the block.

c) Grid floor is connected to shock device .

A typical paradigm consists of :

a) Familiarization

b) Learning

c) Retention test

Familiarization: *The animal is placed on the platform, released after raising the cylinder, and the latency to descend is measured. After 10 s of exploration, it is returned to the home cage.*

Learning: *Immediately after the animal has descended from the platform an unavoidable footshock is applied (Footshock: 50 Hz; 1.5 mA; 1 s) and the animal is returned to the home cage*

Retention Test: 24 h after the learning trial the animal is again placed on the platform and the stepdown latency is measured. The test is finished when the animal steps down or remains on the platform (cutoff time: 60 s).

EVALUATION

- The time of descent during the learning phase and the time during the retention test is measured .
- A prolongation of the step-down latency is defined as learning.

STEP -THROUGH METHOD

PURPOSE AND RATIONALE

- This test uses normal behavior of mice and rats.
- These animals avoids bright light and prefer dim illumination .
- When placed into a brightly illuminated space connected to a dark enclosure , they rapidly enter the dark compartment and remain there .
- The standard techniques was developed for mice by Jarvik and Kopp {1967} and modified for rats by King and Glasser {1970}

PROCEDURE:

Step-Through
Passive Avoidance

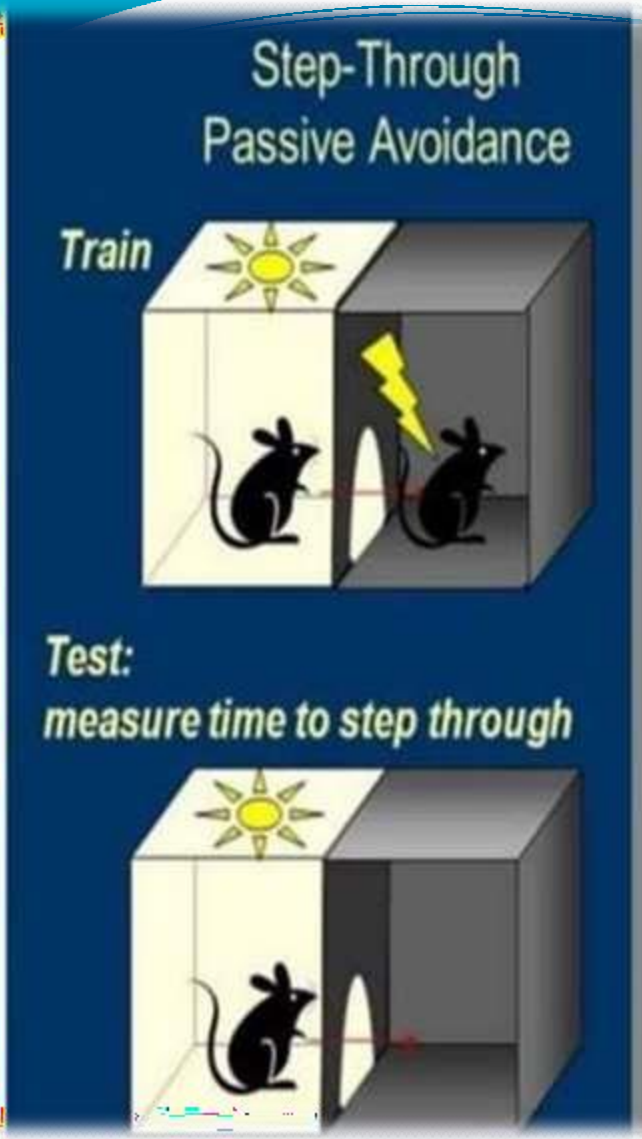
Train

Test:
measure time to step through

Mice and rats of either sex are used. The test apparatus consists of a small chamber connected to a larger dark chamber via a guillotine door.

The test animals are given an acquisition trial followed by a retention trial 24 h later. In the acquisition trial the animal is placed in the illuminated compartment at a maximal distance from the guillotine door, and the latency to enter the dark compartment is measured.

Animals that do not step through the door within a cut-off time: 90 s (mice) or 180 s (rats) are not used.



- *Immediately after the animal enters the dark compartment, the door is shut automatically and an unavoidable footshock (Footshock: 1 mA; 1 s – mice; 1.5 mA; 2 s – rat) is delivered.*
- *The animal is then quickly removed (within 10 s) from the apparatus and put back into its home cage.*
- *The test procedure is repeated with or without*

EVALUATION

- The time to Step -through Method during the learning phase is measured and the time during the retention test is measured .
- In this test a prolongation of the step- through latencies is specific to the experimental situation .
- An increase of the step- through latency is defined as learning .

SCOPOLAMINE -INDUCED AMNESIA IN MICE

PURPOSE AND RATIONALE

- The administration of anti- muscuranic agent scopolamine to young human volunteers produces transient memory deficits.
- Similarly, scopolamine impairs memory retention when given to mice.
- The ability of different cholinergic drug agonist to reverse the amnesic affects of scopolamine is now well documented in animal and human volunteers.

PROCEDURE

- The scopolamine test is performed in groups of 10 male NMRI mice weighing 26-32 g in one trail.
- Five min after i.p administration of 3mgl/kg of scopolamine hydrobromide.
- Each mouse is placed invidually in bright part of two chambered apparatus.
- After brief orientation period,mouse enters the second or darker chamber.
- Once inside second chamber ,the doors are closed to avoid escape.
- A 1 mA, 1-sec foot shock is applied through grid floor.The mouse then return to home cage.

- 24 hrs later , testing is performed by placing the animal again in the bright chamber.
- The latency in entering the dark chamber within 5 min test session is measured electronically.
- Whereas, untreated control animals enter the darker chamber in second trail with the latency of about 250sec.
- Treatment with scopolamine reduces the latency to 50 sec.
- Test compounds are administered 90 min before training.
- The prolonged latency indicates that animal remembers that it has been punished and therefore , avoids darker chamber .

EVALUATION

- After treatment with various doses of test drug latencies obtained were expressed as % latencies .
- In some cases, straight dose-response curve is obtained whereas with other drugs inverse U-shaped dose responses are observed.