PRECLINICAL SCREENING OF CNS STIMULANTS & CNS DEPRESSANTS

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CNS STIMULANTS

- These are those drugs whose primary action is to stimulates the CNS or to improve specific brain functions.
- CNS stimulants are drug that induce temporary improvement in either mental or physical functions.
- The CNS stimulants mostly produce a generalized action but, at high doses, result convulsions.

CNS STIMULANTS CLASSIFICATIONS

- **CONVULSANTS:-**
- Pentylenetetrazole
- Strychnine
- Bicuculline
- Picrotoxin
- **ANALEPTIC:-**
- Doxapram
- Nikethemide
- **PSYCHOMOTOR STIMULANTS:-**
- Amphetamine
- Methylphenidate
- Cocaine
- Atomoxetin

SCREENING MODEL OF CNS STIMULANTS

- **IN VIVO METHODS:-**

- Screening of Analeptics by actophotometer
- Rota-Rod test
- Sand-Displacement method
- Runway test
- Ptosis test
- Open field test
- Hole board test
- Strychinine induced test
- Jiggle cage test

SCREENING OF ANALEPTIC BY ACTOPHOTOMETER

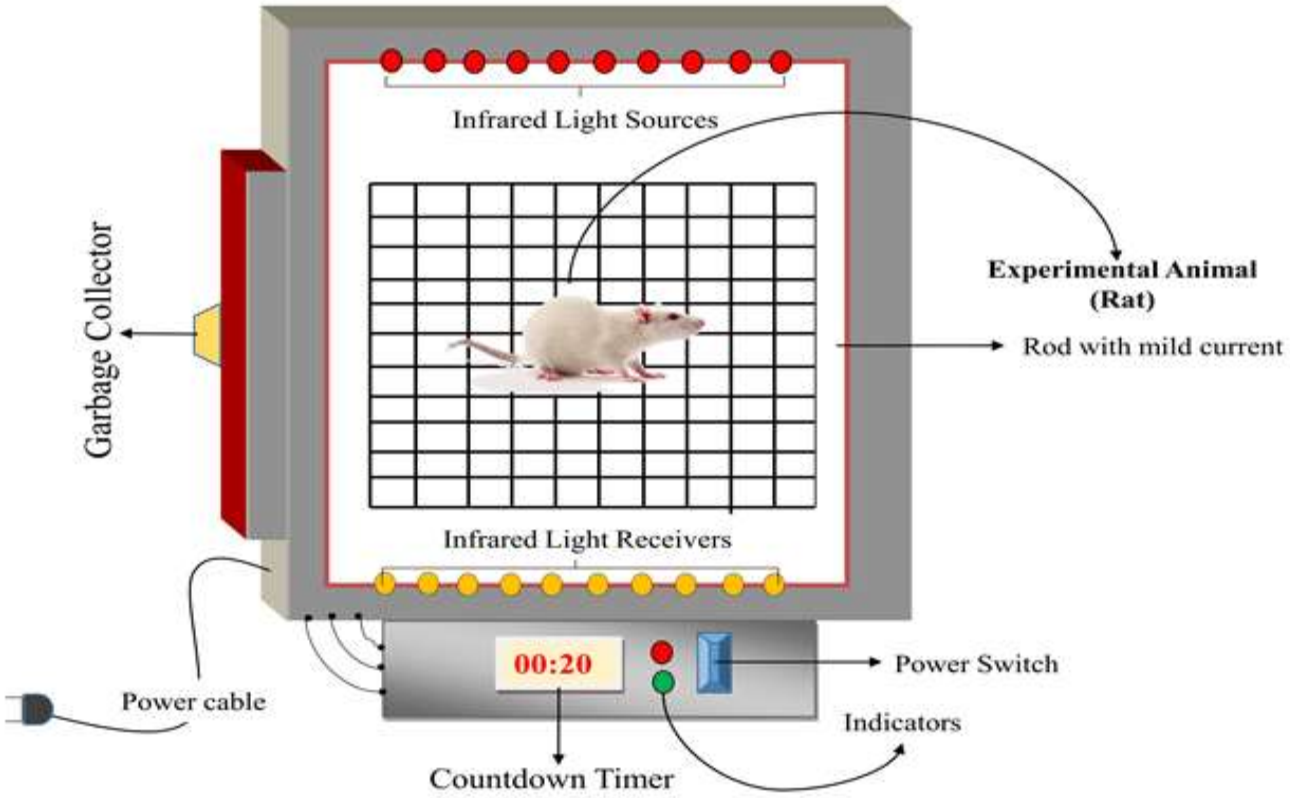
- **PURPOSE:-** CNS stimulants like Amphetamine increase the locomoter activity in animal.
- **PRINCIPLE:-** When the beam of light falling on the photocell is cut off by the animal , a count is recorded.
- **PROCEDURE:-** Mice weighing 20-50 gm are divided into 3 groups, each contain 4 animals.

Control: Saline, Standard: Amphetamine(1mg/kg I.P.)

Test: Drug to be calculated.

Mice from each groups, separately placed in actophotometer for 10 min. After every 30 min till the maximum effects of drugs observed

- **EVALUATION:-** No. of cut off is compared between the groups.
- More cut off:- CNS Stimulants
- Less cut off:- CNS depressants



RUNWAY TEST

- **PURPOSE:-** To study the spontaneous activity of cns stimulants.
- **PRINCIPLE:-** The Y-shaped runways is covered with paper that can indicate the footprints of rats which is counted afterwards for evaluation.
- **PROCEDURE:-** Wister rats of either sex weighing 250-300 gm are grouped.

Trained to run at runway apparatus for 3 days to achieve constant time and speed to pass runway.

CONTROL:- Saline, STANDARD:- Methamphetamine(2mg/kg I.P.) TEST:- Drug to be test.

After 30 min of administration of drug test is performed.

- **EVALUATION:-** The no. of foot prints on the maze path is measured.
- Higher no. of foot prints.:- CNS stimulants.

PTOSIS TEST

- **PURPOSE:-** Reserpine decrease the central sympathetic outflow and leads to ptosis in eye.
- **PROCEDURE:-** Albino mice are either sex weighing 18-24 gm are grouped.

Reserpine is given in all groups (4gm/kg I.P.). After 2hrs 45min.

Control:- saline , Standard:- Amphetamine, Test:- drug to be evaluated.

After 15 min ptotic rating is made.

- **EVALUATION:-** 4 for complete ptosis

  3 for 3/4 ptosis

  2 for 2/4 ptosis

  1 for 1/4 ptosis

Eyelid retraction
or
Eyelid ptosis

CNS DEPRESSANTS

- CNS Depressants is a type of drugs that slow down the brain activity, which causes the muscles to relax and calm and soothes the person.
- It also lower the neurotransmission levels, which is to depress or reduce the arousal or stimulation in various part of brain.
- It is used to treat insomnia, anxiety, panic attacks and seizures. They may also used to treat relieve anxiety and tension before surgery.

CLASSIFICATION OF CNS DEPRESSANTS

- **OPOIDS:-**
  - Narcotics- Opium, Morphine, Thebaine, Heroine, Fentanyl, etc.
- **NON-OPOIDS:-**
  - **Alcohol**
  - **Barbiturates-** Thiopental, Methohexital, Phenobarbital, Pentobarbital
  - **Benzodiazepines, -** Diazepam, Clonazepam, Alprazolam, Midazolam
  - **Non-benzodiazepines –** Zopiclone, Zolpidem

EVALUATION OF CNS DEPRESSANTS

- IN-VIVO METHODS

1. Despair Swim test
2. Muricidal behaviour in rats
3. Tail suspension test
4. Amphetamine Potentiation test
5. Benzodiazepines induced sleeping time

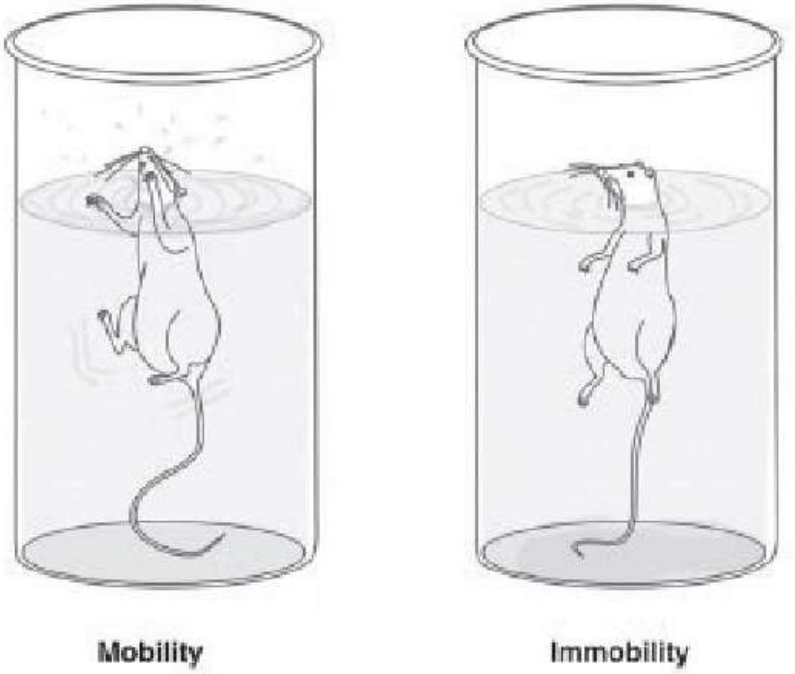
- IN-VITRO METHODS

1. Inhibition of NE uptake in rat brain.
2. Inhibition of dopamine uptake in rat striatal.

DESPAIRE SWIM TEST (FST)

- **Purpose:-**

- When a rat or mice are forced to swim in a restricted space from which they cannot escape are induced to a characteristics behaviour of immobility.
- The anti depressants drugs decrease the duration of immobility its most widely used method for screening of acute antidepressants.



PROCEDURE:-

- Adult rats are allowed to swim in a cylinder with no escape filled with water 25 degree C .

- When the rats are forced to swim in water initially it was hyperactive but approx 5 min later the activity slow down and the phase of immobility starts.

- After 15 min the rats were removed and allowed to dry. The duration of immobility was measured.

- The same activity was done for standard and test groups and drug was administered 1 hour earlier when test start.

EVALUATION:-

- The duration of immobility was measured for test control and std. groups treated with various drugs.
- The antidepressant drugs decreases the duration of immobility.

TAIL SUSPENSION TEST

- **PRINCIPLE:-**

This model is reflects behavioural despair, antidepressant drug reduce immobility time in tail suspension test.

- **PROCRDURE:-**

Male mice wt 20 to 30 g are used.

Animal are treated with test compound or the vehicle by IP injection 30 min prior to testing.

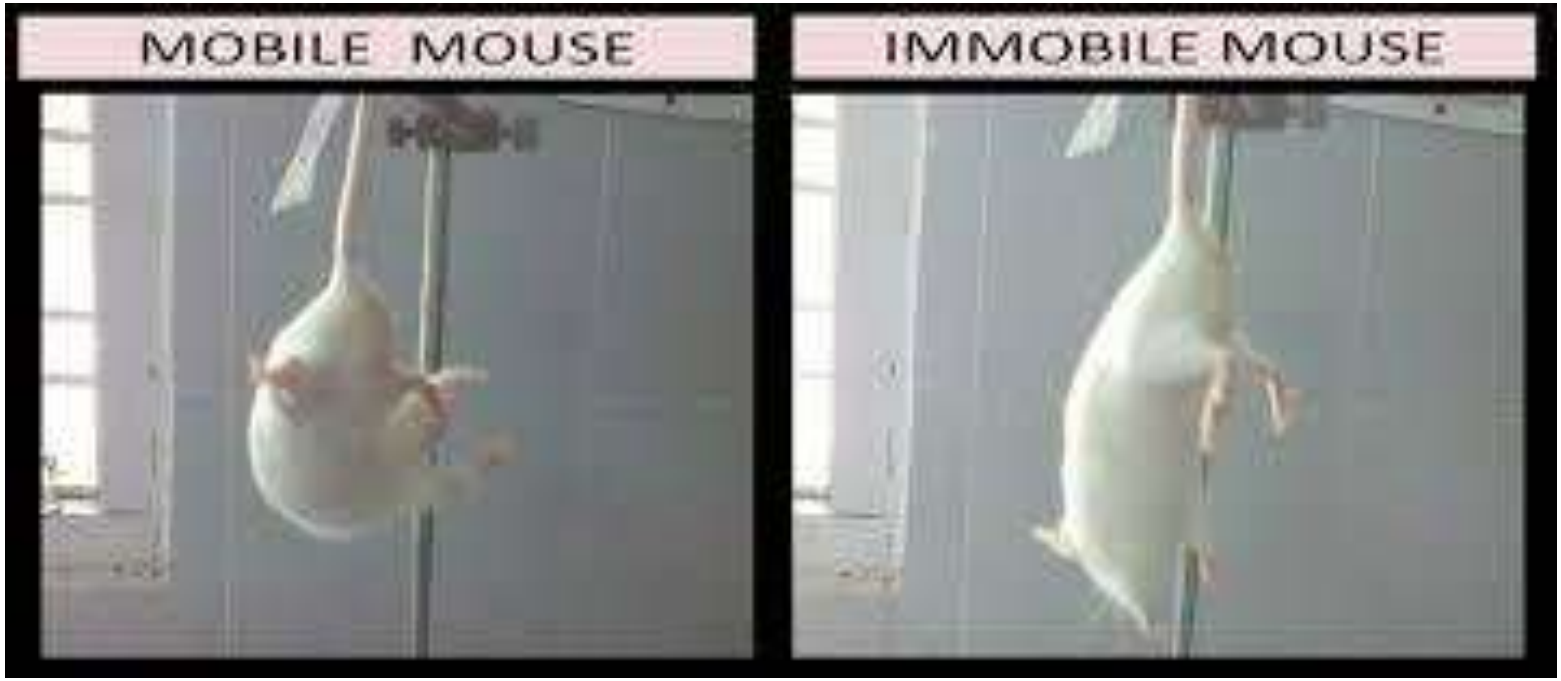
The mice are suspended upside down such that its nostril touches the water surface in container.

Initially, the animal tries to escape by making vigorously movements but it is unable to escape and becomes immobile.

The duration of immobility is recorded for a period of 5 min.

Evaluation:-

- The duration of immobility of standard and test was compared with control groups and the decrease of immobility was calculated.
- For different dose ED50 value was calculated.



AMPHETAMINE POTENTIATION TEST

PROCEDURE

- Rats male wister 250gm to 300gm are housed in a controlled environment with temperature 22 C for 12 hrs light/dark cycle and free access to food and water.

- The rat receives the test drug(antidepressants drug) in their home cage usually for 2 weeks.

- 90 mins after the last dose if the test drug, D-amphetamine (5-10 mg / kg) I.P is injected and 30 min later they are placed singly into cages with photocells to record their activity.

- Most antidepressants including TCA, MAOI potentiate amphetamine effects seen as increased locomotor activity.