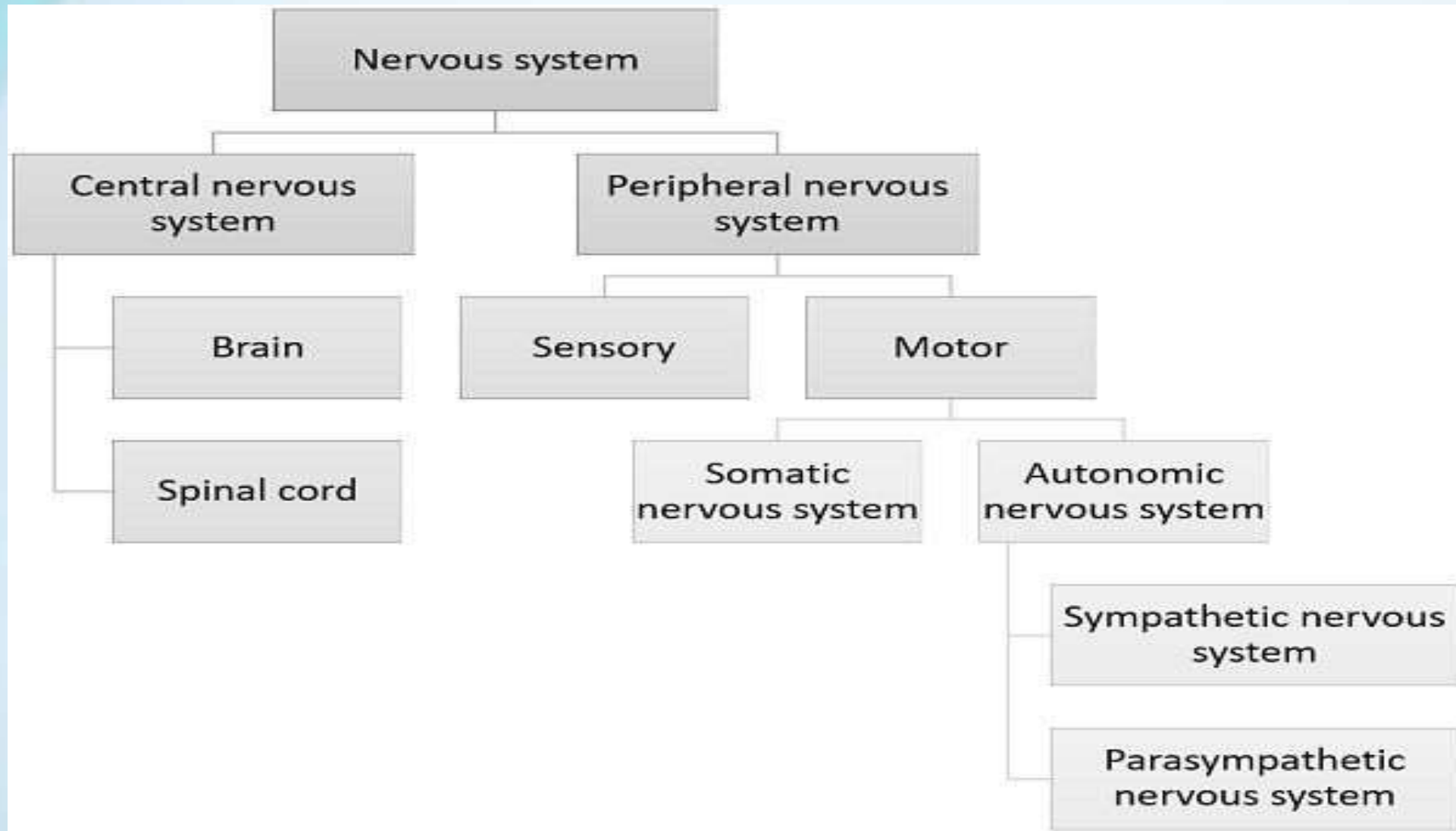




**PRECLINICAL SCREENING MODELS FOR DRUG ACTING ON
AUTONOMIC NERVOUS SYSTEM
(PHARMPCOLOGICAL AND TOXICOLOGICAL SCREENING)**

CONTENT :-

1. Introduction
2. Organization of ANS
3. Sympathetic Nervous system
4. Animal model used for screening sympathomimetics
IN-VIVO
IN-VITRO
5. Animal model used for screening of sympatholytics
6. Animal model used for screening of Parasympathomimetics
7. Animal model used for screening of parasympatholytics



ORGANIZATION AND FUNCTION OF AUTONOMIC NERVOUS SYSTEM

ORGANIZATION OF ANS

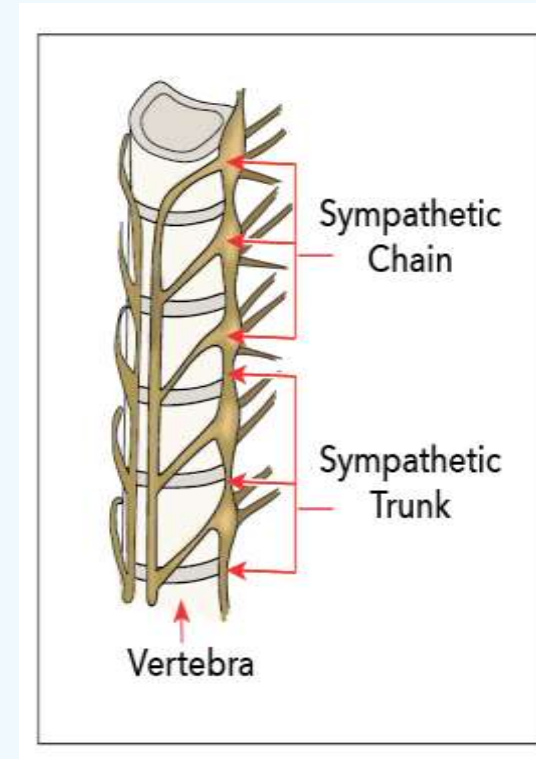
- ❖ In ANS, a nerve **Originating from brain/spinal cord** first enters ganglia and then reaches the effector organ.
- ❖ The nerve – fibre coming up to ganglia is termed as **pre-ganglionic fibre**.
- ❖ Nerve coming from ganglia to effector organ is called as **Post ganglionic fibre**.
- ❖ The part of the nervous system that **controls muscles of internal organs** (such as the heart , blood vessels, lungs, stomach, and intestines and **glands** (such as salivary glands and sweat glands).

Sympathetic Nervous System (SNS) or (Adrenergic Division)

- ❖ The sympathetic nervous system (SNS) is also another divisions of ANS.
- ❖ The sympathetic nervous system consists of many nerve cells found in the peripheral and central nervous systems.
- ❖ The allows organisms the ability to activate many different responses at once , leading to a coordinated flight or fight response.

The Sympathetic Nervous System is made up of the Following parts :-

1. Sympathetic Trunks
2. Preganglionic Sympathetic fibres
3. Postganglionic Sympathetic Fibres
4. Collateral ganglia



Animal models used for screening sympathomimetics

- **In Vivo Models**

- Bioassay of adrenaline by monitoring blood pressure in dogs
- Rabbit eye model
- Cat spleen model
- Spinal cat model

- **In Vitro model**

- Bioassay of adrenaline using rabbit intestine
- Isolated frog heart preparation



IN VIVO MODELS

1. Rabbit eye model:-

- Method :-

Healthy young rabbit (2-3kg) are used in this model.



Animals are divided into different groups: control, standard and test.



0.1% adrenaline HCL solution is used as a standard



Eyes of rabbits are washed with distilled water and left for five minutes.



Adrenaline /test drug is applied topically respective group & measured the pupil diameter.

calculate the mean diameter in each group.

INTERPRETATION

- Mean pupil diameter of standard and test groups are compared with the control group.
- The topical administration of adrenaline or other sympathomimetics increases the pupil diameter and produce mydriasis effect in the eye.

2. Cat spleen model :-

Method :-

Healthy cats (2-4kg) are used in this model. Cats are anesthetized by a suitable anesthetized agent .



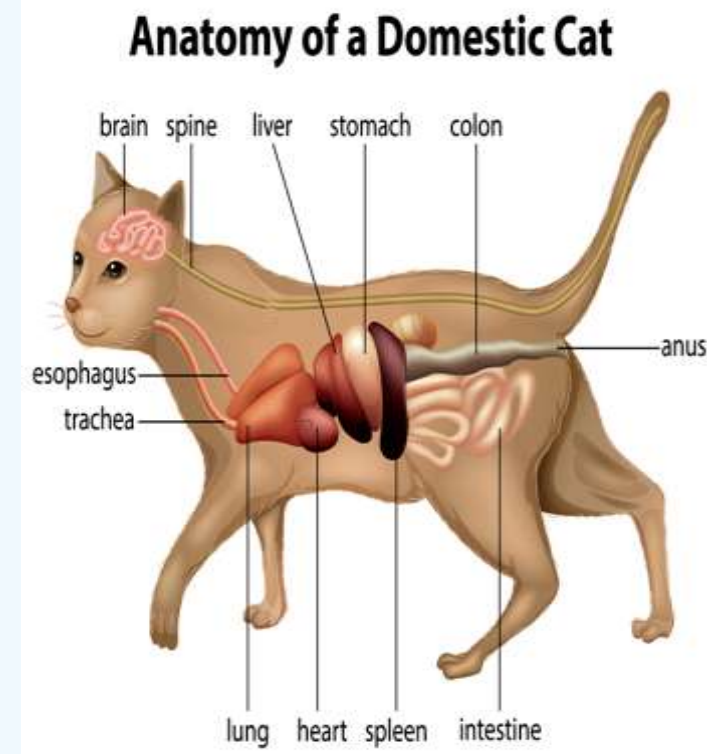
The animal is dissected to expose spleen.



THE splenic nerves are cut to avoid the release of catecholamine from other site.



The adrenal gland are also removed to avoid the release of press amine.



Heparin is administered I.V to prevent blood clotting.



The abdominal region is filled with warm paraffin & aerated with a carbogen (a mix. Of 95% O₂ & 5% CO₂)



Adrenaline is inj. Into the splenic artery to contract spleen & and release the transmitter.



Non adrenaline is measured by scintillation counter for radioactivity measurement.

INTERPRETATION

- The sympathomimetic increase the release of nonadrenaline .
- The different doses of the test compound are used to compare with standard.

Animal models used for screening sympatholytics

In Vivo Models

1. Adrenergic antagonism in the rodent's eye
2. Blood pressure response in dogs
3. Cardiovascular response in rats
4. Nictitating membrane prolapses in cats

In Vitro Models

1. Isolated frog heart Preparation
2. Isolated aortic muscle strips
3. Isolated guinea pig tracheal chain

In vivo model:-

1. Adrenergic antagonism in rodent:-

- METHOD:-
- Albino rats (120-150g) or albino mice(25-30g) are employed in the model.
- Experimental animal are divided into control, test having 4-6 animals in each .
- Drugs are administered subcutaneously to the respective groups.
- After 30 min. of test drugs administration , nonadrenaline (0.1mg/kg, i.v) are injected.

- The pupil diameter of each animal is measured.
- The mean value of each group is reported.

INTERPRETATION:-

- The sympatholytic drug antagonize the mydriasis effects of sympathomimetics.
- Therefore, the pupil diameter of test groups is lesser than control group.

PARASYMPATHETIC /CHOLINERGIC SYSTEM

- ACH is the principal neurotransmitter in the cholinergic system.
- ACH is synthesized locally in cholinergic nerve ending.
- ACH is quaternary ammonium compounds and is rapidly hydrolysed by cholinesterase's hence no therapeutic application .

Animal model used for screening parasympathomimetic:-

- ***IN VIVO MODELS***

- Blood pressure response in anesthetized animals
- Miosis effect on rabbit eye

- ***IN VITRO MODELS***

- Isolated heart preparation
- Isolated ileum preparation
- Frog's rectus abdominis muscle preparation
- Isolated tracheal chain preparation



IN VIVO MODELS

1. Blood pressure response in anesthetized animals :-

- Method:-

1. Animals are anesthetized with a suitable anesthetic agent and prepared for blood pressure monitoring.
2. Animal are kept on artificial respiration.
3. The carotid artery is cannulated for recording blood pressure.
4. The femoral vein is cannulated for injecting ACH or test drug .
5. After stabilization ,ACH (1-6mg) test drug is injected and BP recorded.

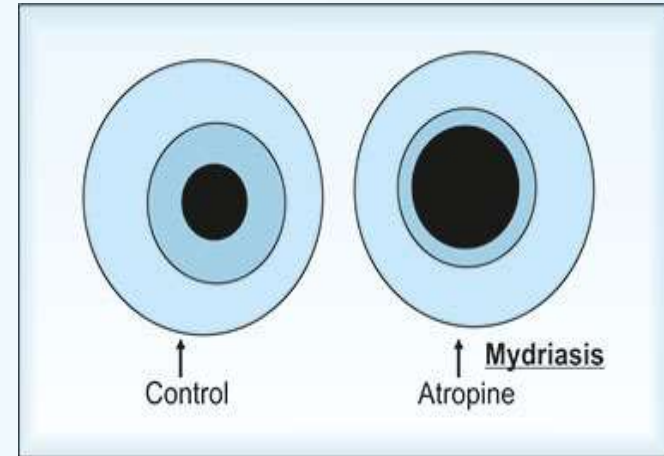
❖ INTERPRETATION:-

The fall in BP after administration is compared with the Fall by the standard ACH preparation.

2. Miosis effect on rabbit eye:-

- Method:-

1. Male rabbits are generally used in this model
2. Animals are divided into different groups.
3. 0.5-2% pilocarpine or 0.25-0.5% physostigmine ophthalmic solution is used as a standard.
4. Eyes of rabbits are washed with distilled water and left for 5 min.
5. TEST/VEHICLE/Standard drug is applied topically to their respective groups and measured the pupil diameter.
6. Calculate the mean pupil diameter in each group.



❖ INTERPRETATION:-

1. Mean pupil diameter of std. and test groups are compared with control group.
2. The topical administration of standard or other parasympathomimetics decrease the pupil diameter and produce miotic effect.



• *IN VITRO MODEL*

1. Isolated heart preparation :-

- Isolated heart preparation model is also used for evaluation of parasympathetic system similar to the sympathetic system.
- Para-sympathomimetics like ACH (2ug) decreases the force of contraction and heart rate by activation of receptor on heart, while parasympatholytic (atropine 20ug) administration has little effect on the heart but opposes the effect of parasympathetic stimulation .
- In this model, frog's or rabbit's heart is used .
- The detailed methodology is similar as describe in chapter animal model for screening symapathomiemtic.