Preclinical screening models for CVS activity

Preclinical Screening Models for Antihypertensives



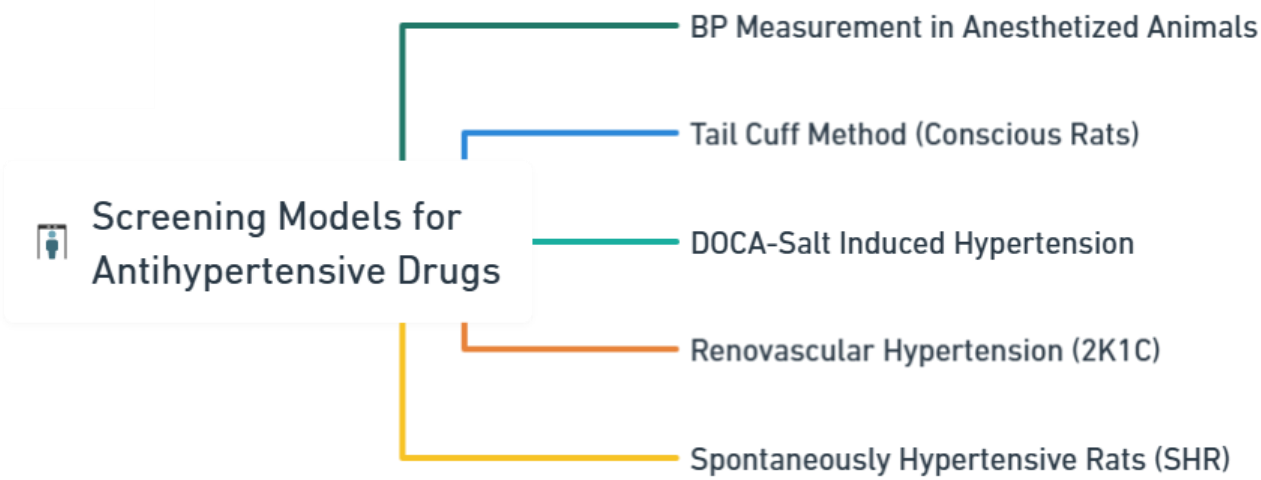
What are antihypertensives?

- Antihypertensive drugs are used to lower high blood pressure (hypertension).
- High blood pressure increases the risk of heart attack, stroke, and kidney damage.
- **These drugs act by:**
  - Relaxing blood vessels (vasodilation)
  - Reducing heart rate or force of contraction
  - Decreasing blood volume (by increasing urine output)
  - Modifying hormones involved in blood pressure control
- **Examples:**
  - ACE inhibitors (e.g., enalapril)
  - Beta-blockers (e.g., atenolol)
  - Calcium channel blockers (e.g., amlodipine)
  - Diuretics (e.g., hydrochlorothiazide)

Why is screening needed?

- Before giving any new drug to humans, we must test:
  - How effectively it lowers blood pressure
  - How fast it works
  - Whether it has side effects on heart, kidneys, or brain
  - What mechanism it uses (e.g., ACE inhibition, calcium channel blocking)

Common Preclinical Screening Models for Antihypertensive Drugs



A. Blood Pressure Measurement in Anesthetized Animals

- Animals like rats, rabbits, or dogs are anesthetized.
- A cannula is inserted into the carotid artery to measure mean arterial blood pressure (MAP).
- The test drug is injected, and blood pressure changes are recorded using a pressure transducer and polygraph.
- If blood pressure drops, it suggests antihypertensive action.
- Heart rate is also monitored to check for reflex tachycardia or bradycardia.

B. Tail Cuff Method (Non-invasive Blood Pressure in Conscious Rats)

- Used in awake animals, mainly rats.
- A cuff is placed on the tail; it inflates and deflates like a human BP monitor.
- Blood flow is detected using a sensor.
- This method is used for screening over days or weeks, especially in chronic treatment models.

C. DOCA-Salt Induced Hypertension Model

- DOCA (deoxycorticosterone acetate) is a steroid that, when combined with high salt intake, causes chronic hypertension in rats.
- It mimics volume-dependent hypertension, similar to humans with kidney-related high blood pressure.
- Antihypertensive drugs are tested for their ability to reduce and maintain lower blood pressure over time.

D. Renovascular Hypertension (2K1C Model – Two Kidney, One Clip)

- In this model, one of the two renal arteries in a rat is partially blocked (clipped).
- This reduces blood flow to one kidney, causing renin-angiotensin system activation, leading to high blood pressure.
- Drugs like ACE inhibitors or angiotensin receptor blockers (ARBs) are tested here.

- This model is useful to screen drugs that act on the renin-angiotensin-aldosterone system (RAAS).

E. Spontaneously Hypertensive Rats (SHR)

- These are genetically modified rats that naturally develop high blood pressure as they age.
- No surgical intervention is needed.
- This model closely mimics essential hypertension in humans.
- Useful for long-term drug studies, side effects, and organ protection effects.

Preclinical Screening Models for Diuretics

What are diuretics?

- Diuretics are drugs that increase urine output, helping to remove excess salt and water from the body.
- **They are used to treat:**
  - Hypertension (by reducing blood volume)
  - Edema in heart failure, kidney disease, or liver disease
- **Types include:**
  - Thiazide diuretics (e.g., hydrochlorothiazide)
  - Loop diuretics (e.g., furosemide)
  - Potassium-sparing diuretics (e.g., spironolactone)

Why is screening needed?

- **To test:**
  - How effectively the drug increases urine volume
  - How fast it acts
  - Whether it increases excretion of sodium, potassium, or chloride
  - Potential risks like electrolyte imbalance

Common Screening Models for Diuretics

A. Saluretic Activity in Rats (Natriuretic/Diuretic Effect)

- Rats are placed in metabolic cages that allow separate collection of urine.
- They are given a salt load (usually saline orally or intraperitoneally).
- Then, the test drug is administered.
- Urine is collected at fixed intervals (e.g., 2, 4, 6 hours).

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