Programme- D.pharm

Course- Pharmacology and Toxicology

Course code- DPH 213

Sem- 3rd sem

Year- 2nd

Topic- Drugs acting on CNS

Sub topic- Mechanism of drug action, general anaesthetic.

UNIT 1 (DPH 213)

GENERAL MECHANISM OF DRUG ACTION

In pharmacology, the term mechanism of action (MOA) refers to the specific biochemical interaction through which a drug substance produces its pharmacological effect. A mechanism of action usually includes mention of the specific molecular targets to which the drug binds, such as enzyme or receptor. Receptor site have specific affinities for drugs based on the chemical structure of the drug, as well as specific action.

Drugs that do not bind the receptors produce their therapeutic effect by simply interacting with chemical or physical properties in the body. E.g. Antacids and laxatives.

MOA describes functional or anatomical changes at the cellular level, resulting from the exposure of a living organism to a substance.

PRINCIPLES OF DRUG ACTION:- the basic types of drug action can be broadly classed as-

- Stimulation – increase in the activity of specialized cells.
- Depression – decrease in the activity of specialized cells.
- Irritation- it produces the changes in cellular structure and is producing inflammation.
- Replacement
- Anti-infective
- Modification of immune status
    - Drugs act by virtue of physical and chemical properties

e.g. Antacid – Neutralisation

Activated charcoal – adsorbent in heavy metal poisoning

$KMnO_4$ – Oxidising property

- Majority of drugs produce their effects by interacting with a discrete target biomolecule, usually a protein.
- Functional proteins that are targets of drug action can be grouped into four major categories, that is:

1. Enzymes:- almost all biological reactions are carried out under catalytic influence of enzymes.
   Levodopa – dopamine catalyzed by Dopa
   Stimulation of an enzyme increases its affinity for the substrate so that rate constant of the reaction is lowered. Apparent increase in enzyme activity can occur by enzyme induction i.e. synthesis of more enzyme protein.
2. Transporters:- several substrates are translocated across the membrane by binding to specific transporters which either facilitate diffusion in the direction of the

concentration gradient or pump the metabolite/ion against the concentration gradient using metabolic energy.
E.g. Furosemide inhibits the $Na+k+2cl^-$ co transporter in the ascending limb of loop of henle.
Hydrochlorothiazide inhibits the $Na+cl^-$ symporter in the early distal tubule.

3. Ion channels:- proteins which act as ion selective channels participate in the transmembrane signaling unregulate intracellular ionic composition. Drugs can affect ion channels either through a specific receptors, G-protein operated ion channels. Certain drugs modulate opening & closing of channels.
   e.g. Quinidine blocks myocardial Na^+ channels.
   Nicorandil open ATP sensitive K^+ channel.
4. Receptors:- Receptor is a macromolecule or a binding site located on the surface or inside the effector cell that serves to recognize the signal molecule but itself has no other function.

   The ability of the drug to give rise to a pharmacological response after its interaction with a receptor is termed as the intrinsic activity or efficacy of the drug.

   The ability of the drug to get bound to a receptor is termed as affinity of the drug for the receptor.

   A drug which initiates pharmacological action after combination with a receptor is termed as agonist.

   Drugs which binds to receptor but are not capable of producing a pharmacological response, produce receptor blockade. These compounds are termed as antagonists.

   A drug with an affinity equal to or less than that of a agonist, but with less intrinsic activity is termed as partial agonist.

DRUGS ACTING ON CENTRAL NERVOUS SYSTEM

Central Nervous System: - CNS primarily consists of the brain and the spinal cord. Unlike the autonomic nervous system it has a large number of nerve cells which are generally called neurons. Neurons send information to and receive it from other neurons and peripheral end organs such as muscle cells, glandular cells and receptors.

The information is transmitted from one neuron to another by nerve impulse. The meeting place of two neurons or their process is called the synapse. The depolarization of nerve terminal leads to the release of a specific chemical substance called neurotransmitter. A neurotransmitter diffuses across the synapse and cause a change in the ionic composition of the second neuron. This altered change in the potential difference is called postsynaptic potential. The postsynaptic potential could be excitatory or inhibitory to the second neuron.

GENERAL ANAESTHETICS

The term anaesthesia means loss of all modalities of sensation, particularly pain, along with a reversible loss of consciousness. Local anaesthetics abolish the pain sensation on localized areas without affecting the degree of consciousness. The first anaesthetic Nitrous Oxide (N_2O) was discovered by Priestly and Horacewells used it in 1884 for dentistry.

Classification:

1. Volatile general anaesthetics (inhalation anaesthetics)
   a) Liquids:- Diethyl ether, chloroform, halothane, enflurane, ethyl chloride, trichloroethylene, methoxyflurane, fluoroxene.
   b) Gases:- cyclopropane, nitrous oxide, ethylene.
2. Non volatile general anaesthetics (Intravenous Anaesthetics)
   a) Ultra short acting barbiturates:- Thiopental sodium, Methohexital
   b) Non-barbiturates
      i) Eugenol derivative:- Propandid
      ii) Phencyclidine derivative:- Ketamine
      iii) Steroid
      iv) Etomidate

Site of action of Anaesthetics

Ascending reticular activating system, which normally maintains a state of wakefulness. The administration of volatile or gaseous general anaesthetics demands an understanding of the fundamental laws of gases, which govern their behavior in the body.

The factors which control the transfer of the anaesthetic agents from the alveoli to the blood and from blood to the tissues are:

a) The solubility of the agent in the blood.
b) The rate of blood flow through the lungs and tissues.
c) The partial pressure of the agent in the arterial and mixed venous blood and the tissues.

Stages of Anaesthesia

There are four different stages of general anaesthesia and the third stage is divided into four planes.

1. Stage I or stage of Analgesia
   - This stage stretches from the beginning of inhalation of anaesthetic to loss of consciousness. With the continued administration of the anaesthetic agent the patient passes into second stage.
   - There is a gradual depression of the cortical centres in this stage.
   - Analgesia is produced before consciousness is lost.

2. Stage II or state of Delirium
    - This stage extends from loss of consciousness to the beginning of surgical anaesthesia.
    - It is associated with shouting, excitement, increased muscular activity, breath holding tachypnea and hyperventilation. These manifestations are due to release of the lower centres from the inhibitory control of higher centres as a result of cortical depression.
    - Pupils will dilate tachycardia and increase in blood pressure observed.
    - Struggling, increased tone of skeletal muscles, retching and vomiting are undesirable features of this stage. This can be prevented by pre-anaesthetic medication.
3. Stage of surgical anaesthesia

    It is characterized by a gradual loss of reflexes, regular respiration and relaxation of skeletal muscles. Reflex activity is lost. This stage is mostly employed for surgical innervation.

    - Plane I

    Pupils –normal, eyeballs-moving.
    Respiration regular and of thoraco-abdominal character.
    Blood pressure and pulse rate normal.
    Skeletal muscles are completely relaxed and eyelid reflex present.

    - Plane II

    Eye balls fixed.
    Respiration-amplitude decreased.
    Muscular relaxation- adequate

    - Plane III

    Asynchrony between thoracic and the abdominal respiratory movements.
    Intercostal muscles paralysed and respiration assumes an abdominal character, papillary light reflex and the corneal reflex are lost.
    Muscular relaxation- complete.

    - Plane IV

    Paralysis of intercostals muscles is complete.
    Pupils dilated, do not respond to light,
    Muscles flaccid and blood pressure is decreased.
    Secretions abolished from plane I to plane IV gradually.

    - State of respiratory paralysis

    Severe depression of vital medullary centres.
    Respiratory arrest accompanied by vaso-motor collapse and heart ceases to beat.

<u>VOLATILE GENERAL ANAESTHETICS</u>

a) Liquids

1. Diethyl ether: A concentration of 10 to 15% of ether in inspired air is usually required for induction, while concentration of 4 to 5 % may be used for maintenance.
   90 mg/100 ml of blood – Light anaesthesia
   110-130 mg/100 ml – surgical anaesthesia
   180/190 mg/100 ml – respiratory arrest
   Only minor portion of ether is oxidized within the body. 85 to 90% eliminated through lungs and the remainder through the skin, urine, milk and sweat. It crosses the placental barrier.

Advantages

- ✓ No pre-anaesthetic medication (PAM) required.
- ✓ Curarimimetic, so little or no need for skeletal muscle relaxant (SMR).
- ✓ Respiration is increased due to reflex action, does not modify blood pressure.
- ✓ Does not interfere with uterine contractility.
- ✓ No hepatotoxicity or nephrotoxicity.

Disadvantages

- ✓ Induction slow and increase secretions.
- ✓ Senstitation of baroreceptors may lead to inhibition of heart.
- ✓ Post anaesthetic symptoms like nausea and vomiting.
- ✓ Recovery is slow.

Preparations: (i) Ether I.P., Spirit of ether I.P. (1-4 ml)
(ii) Spirit of ether I.P. (1-4 ml)

Note- chloroform is no longer recommended due to hepatotoxicity and cardiotoxicity.

2. Halothane (Fluothane CHF_3)
   Loss of consciousness with 2 to 3% and maintenance with 1-2%. Retained for long time, dehalogenated, excreted through lungs.

Advantages

- ✓ Non-inflammable, potent and quick
- ✓ Post anaesthetic effects low.
- ✓ Inhibits secretions and it may be employed to induce controlled hypotension to provide a bloodless field during plastic surgery.

Disadvantages

- ✓ Skeletal muscle relaxant required.
- ✓ Respiration is depressed.
- ✓ CVS depressed and hence blood pressure decreased.
- ✓ Hepatotoxic, poor analgesic, expensive.

3. Ethyl chloride
   Induction in 1-2 minutes and recovery in 2 to 3 minutes.
   Muscular relaxation inadequate.
   Induces cardiac arrhythmias and cardiac arrest.

b) Gaseous anaesthetics

1. Cyclopropane
   1-2% analgesia without loss of consciousness. 6-8% loss of consciousness. 20-25% surgical anaesthesia. 35-50% respiratory failure and it is eliminated by exhalation.
   Advantages
   - ✓ Potent anaesthetic. No nausea and voiting.
   - ✓ Recovery rapid and smooth. Skeletal muscle relaxation is good.
   - ✓ Blood pressure, heart rate and cardiac contractivity well maintained.

   Disadvantages
   - ✓ Slow induction, danger of over dosage.
   - ✓ Eye ball movement reduced and depresses respiratory center.

4. Nitrous oxide
   N_2O +O_2 produces state of excitement & delirium and also produces amnesia(laughing gas).
   Nitrous oxide 35% to40% + air produces alagesia, 65% to 70% produces loss of consciousness. 80 % to 120% produces surgical anaesthesia and eliminated through lungs.
   Advantages
   - ✓ Non inflammable & non-irritating, rapid induction and recovery and safe.
   - ✓ Used for tooth extraction at sub anaesthetic concentration.
   - ✓ Nitrous oxide + oxygen to induce and ether to maintain known as GOE Technique (Gas-oxygen-ether).

   Disadvantages
   - ✓ Not potent and volatile excitement.

<u>NON-VOLATILE INTRAVENOUS ANAESTHETICS</u>

Ultra short acting barbiturates- these are administered intravenously to produce general anaesthesia are thiobarbiturates (thiopentone, thionyl and thiobarbitone) and methylated oxybarbiturates (hexobarbitone and methohexitone). The short duration of action is due to high lipid solubility and also due to the rapid destruction, by the liver, of these drugs.

Anaesthetic action

1) The subject passes through hypnosis and deep sleep or anaesthesia.
2) Consciousness is lost first, then the reflex activity and muscle tone and lastly the vital medullary centres are depressed.
3) Induction is very quick and pleasant.

4) Pupils react to light and remain contracted in light hypnosis. Corneal reflex remains active until deep anaesthesia is achieved.
5) A reliable sign of an adequate induction by thiobarbiturate is the absence of eye lid reflex.
6) The reflexes return in 10-30 minutes, but the patient remains disoriented for hours.

PRE- ANAESTHETIC MEDICATION

The term pre-anaesthetic medication refers to the use of drug prior to the administration of anaesthetics. This make anaesthesia safe and agreeable to the patient. Premedication aims at following effects:

1. Sedation to reduce anxiety of the patient before surgery. E.g. Barbiturates and morphine and their derivatives.
2. Analgesia to reduce pain, e.g. morphine and pethidine
3. Inhibition of parasympathetic activity so as to decrease the bronchial and salivary secretions induced by drugs like ether, e.g. Atropine.
4. Anti-emetics to avoid post anaesthetic nausea and vomiting. E.g. Prochlorperazine.

Reference - Dr. Suresh B., A text book of Pharmacology; published by birla publications Pvt. Ltd. 16th edition, Page no 15-19

2. en.m.wikipedia.org/wik