General and Local Anesthetic Agents

- **ANESTHESIA**: reversible reduction or loss of sensation mainly pain and other responses including muscle movements and consciousness during surgeries or any invasive procedures that cause pain

- **General Anesthesia** renders the patient:
  - amnesic
  - unconscious while causing muscle relaxation
  - suppression of undesirable reflexes

- **Local Anesthesia**

Theories of anesthesia

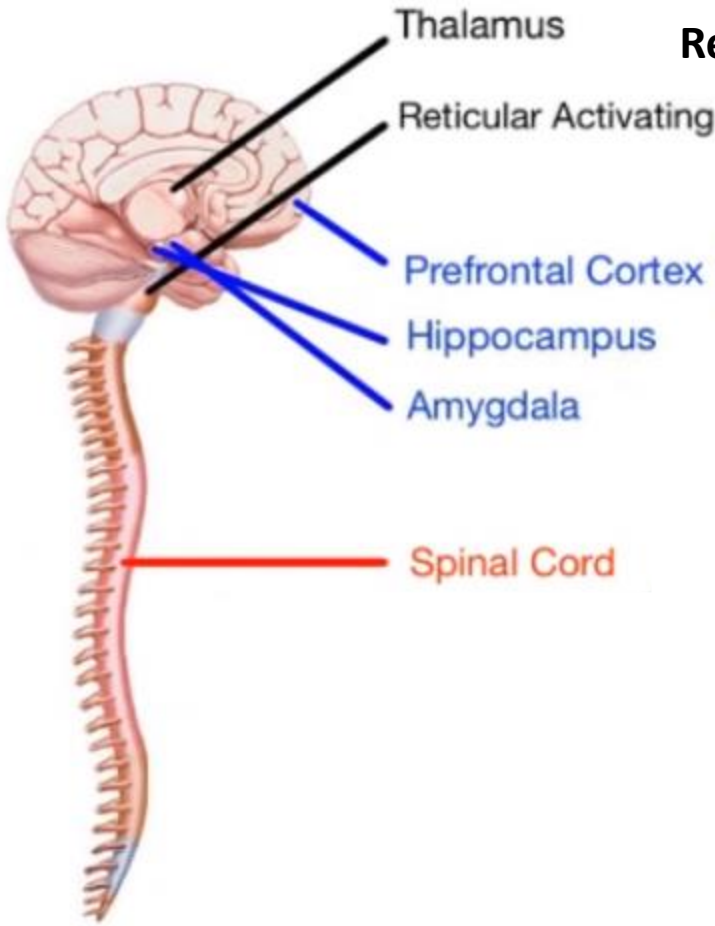
- Most anesthetics enhance the activity of inhibitory GABA A-receptors

- Many inhibit activation of excitatory receptors, such as glutamate and nicotinic acetylcholine receptors

Stages of Anesthetic Activity

- ***Stage I - Induction***
  - conscious but drowsy
  - responses to painful stimuli reduced
- ***Stage II - Excitement***
  - lose consciousness
  - no longer responds to non-painful stimuli
  - responds in a reflex fashion to painful stimuli
- ***Stage III - Surgical anesthesia***
  - movement ceases and respiration becomes regular
- ***Stage IV - Medullary paralysis***
  - respiration and vasomotor control cease
  - death occurs

Mechanism of action of GAs



Reversible loss of consciousness

Amnesia

Immobility and analgesia

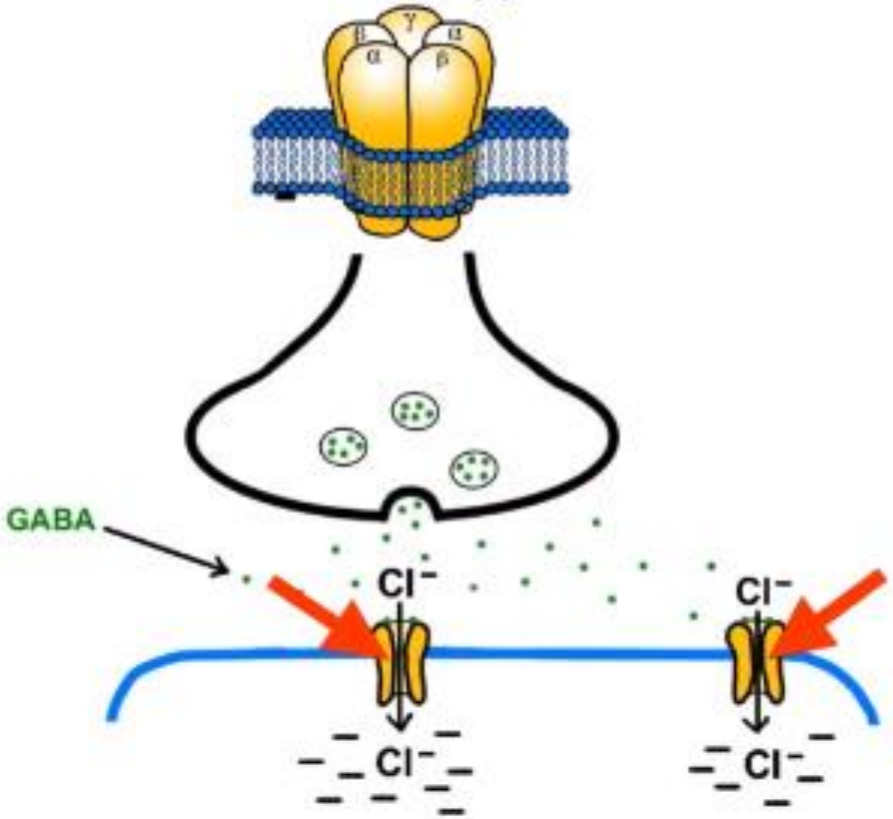
Classification

- General anesthetics are divided into two groups on the basis of their route of administration
  - inhalation anesthetics
  - Intravenous anesthetics

1st Group

Etomidate Propofol Barbiturates

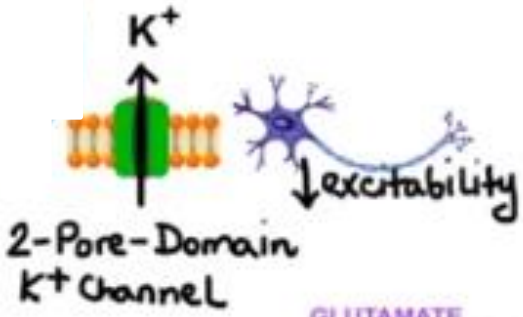
GABA$_A$

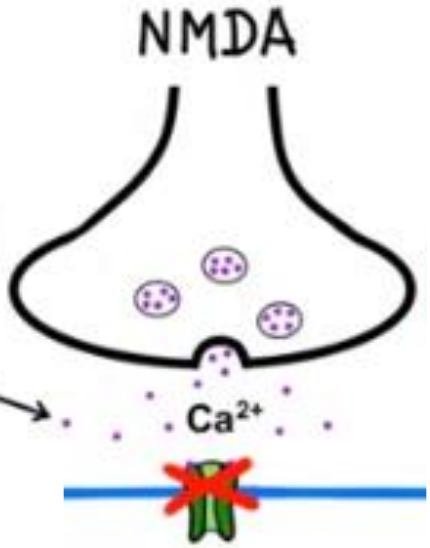


2nd Group

Ketamine

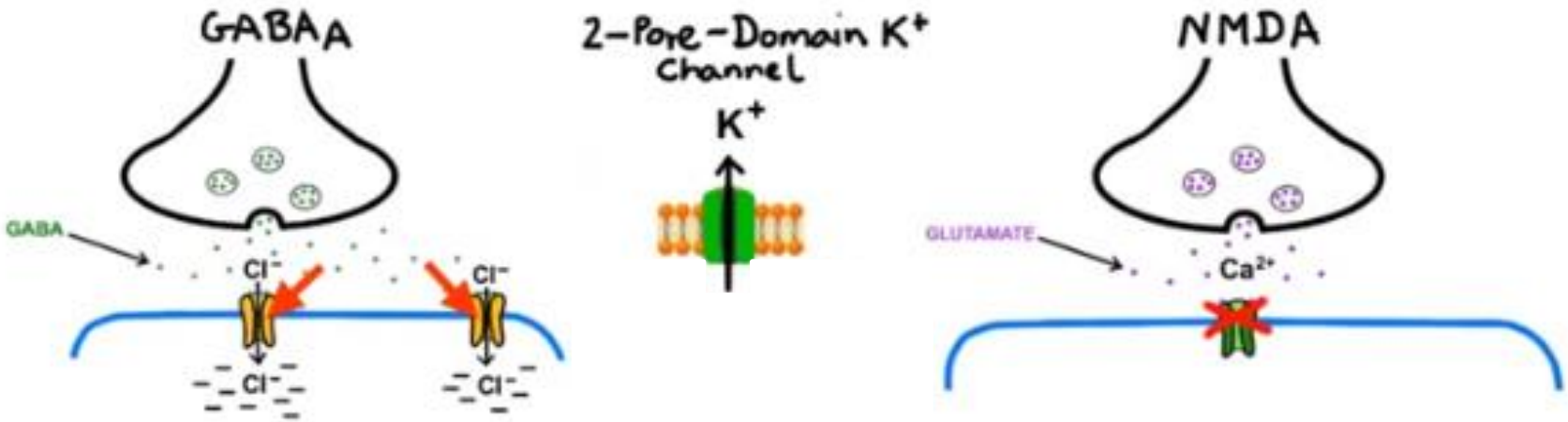
Nitrous Oxide
Xenon
Cyclopropane





3rd Group

Halothane Enflurane Isoflurane Sevoflurane Desflurane



Neuronal Nicotinic Acetylcholine Receptors

Serotonin Type 3 Receptors

Mitochondrial ATP-Sensitive Potassium Channels

Sodium Channels

Hyperpolarization-Activated Cyclic Nucleotide-Gated Channels

Anesthesiology

Inhalational anesthetics :

Non-halogenated gas:

- Nitrous oxide (NO)

Halogenated hydrocarbons:

- Halothane
- Enflurane
- Isoflurane
- Desflurane
- Sevoflurane
- Methoxyflurane – nephrotoxicity.

Properties of Ideal Inhalational Anesthetics

- Rapid, pleasant anesthetic induction and recovery
- Rapid changes in anesthetic depth
- Adequate relaxation of skeletal muscles
- Wide margin of safety
- Absence of toxic effects or other adverse properties in normal doses

Anesthesiology

The important characteristics of Inhalational anesthetics which govern the anesthesia are :

- Solubility in the blood (blood : gas partition co-efficient)
- Solubility in the fat (oil : gas partition co-efficient)

Anesthesiology

Blood : gas partition co-efficient:

- It is a measure of solubility in the blood.
- It determines the rate of induction and recovery of Inhalational anesthetics.
- Lower the blood : gas co-efficient – faster the induction and recovery – Nitrous oxide.
- Higher the blood : gas co-efficient – slower induction and recovery – Halothane.

Solubility to blood

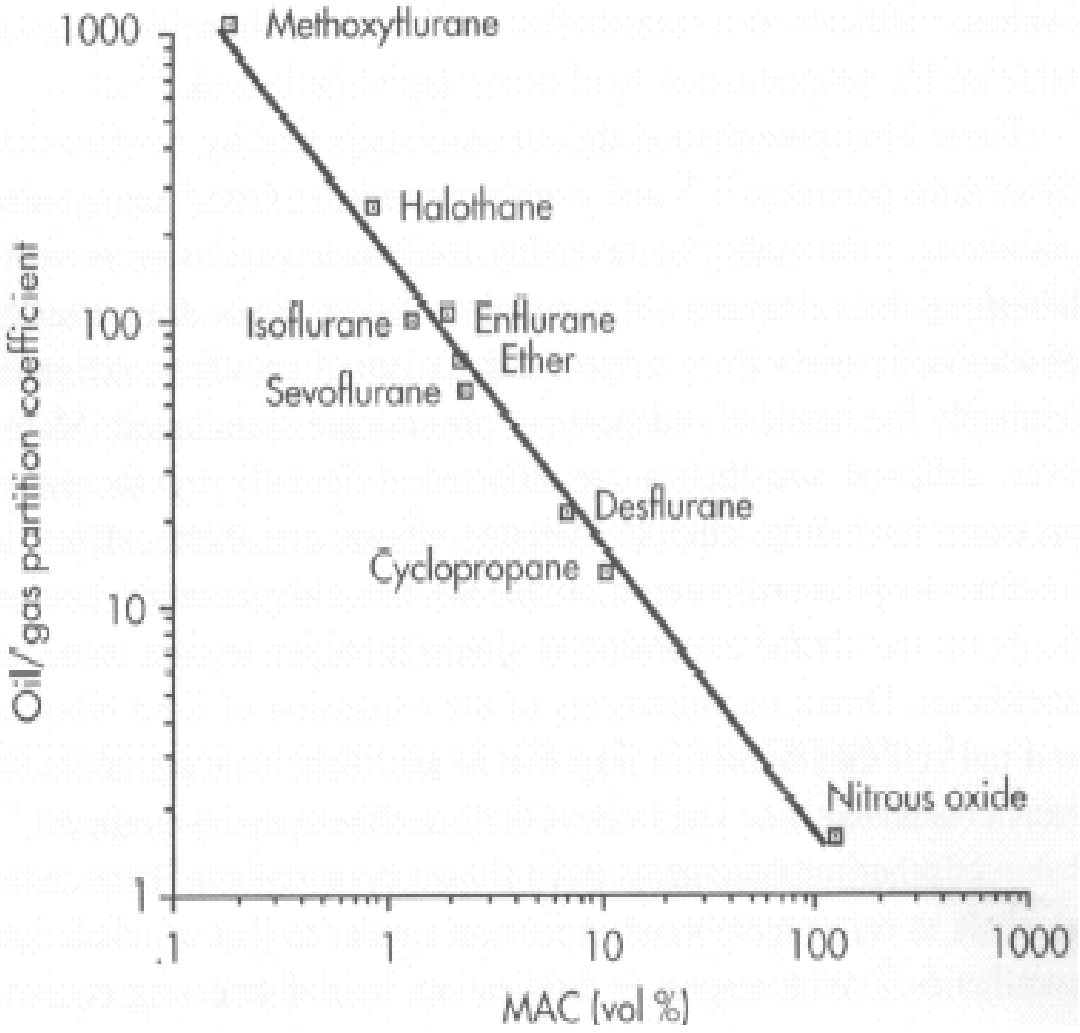
- Based on blood/gas partition coefficient
- Lowest to highest
- NO
- Isoflurane
- Enflurane
- halothane

POTENCY

- Defined by MAC
  - Clinical potency can’t be predicted by chemical structure
  - Potency correlates w/ lipid solubility

Volatile Anesthesia

- Potency of an anesthetic is directly correlated with its lipid solubility. The more lipid soluble, the more potent



Volatile Anesthesia Terminology

- ***MAC or minimum alveolar concentration***
  - The percent of gas in a mixture required to achieve the effect.
  - A method to compare relative potencies of inhalational anesthetics
    - Smaller the MAC, the more potent the anesthetic
- ***Partition coefficient***
  - Relative solubility of a substance in two immiscible phases
    - Blood: Gas partition coefficient
    - Blood: Brain partition coefficient

Pharmacokinetics of Inhalational Anesthetics

At equilibrium:

- The tensions of the gas are equal in the
  - Inspired air
  - Alveolar air
  - Arterial blood
  - Body tissue
  - Venous blood
- The *amount* of gas in a particular tissue is a function of its solubility (partition coefficient concept)

The minimum alveolar concentration

- Is an index of inhalation **anesthetic potency**
- The **MAC** is defined as the minimum concentration of drug in the alveolar air that will produce immobility in 50% of patients exposed to a painful stimulus
- **A low MAC indicates high anesthetic potency**

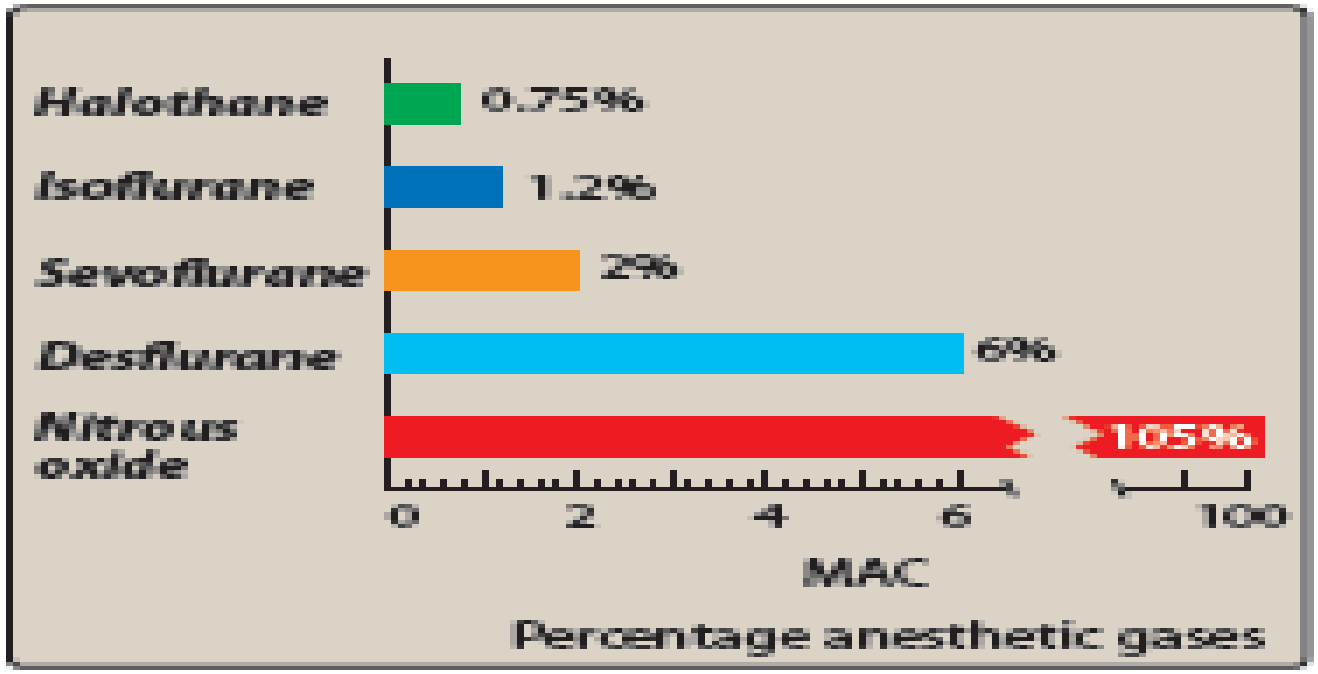


Figure 11.4
Minimal alveolar concentrations (MAC) for anesthetic gases.

Highest to lowest MAC

- NO
- Ether
- Enflurane
- Isoflurane
- halothane

Prototypic Inhalational General Anesthetics

- According to MAC:

1. Halothane [MAC 0.75]
2. Isoflurane [MAC 1.2]
3. Enflurane [MAC 1.7]
4. Ether [MAC 3.2]
5. Nitrous oxide [MAC 104]

Pharmacokinetics of Inhalational Anesthestics: Elimination and Metabolism

- Most inhalational anesthetics are marginally metabolized by the liver
  - < 10% metabolized in the liver and 90% excreted unchanged in the expired air
  - Halothane is the notable exception
    - > 40% metabolized in the liver
- Elimination via the lungs: Dictated by the blood: gas and blood: tissue partition coefficients

Malignant Hyperthermia

- Rare event with genetic basis, 70% lethal if untreated
  - 1:50,000 risk in adults; 1:15,000 risk in children
- Halothane, Isoflurane, Desflurane
- Hypercatabolic reaction
  - Muscle rigidity
  - Tachypnea
  - Cardiac dysrhythmias, electrolyte imbalance
  - Massive increase in core body temperature
  - due to increased mobilization of intracellular Ca^{++} in muscles, increased skeletal muscle metabolic activity
- Treat with Dantrolene to inhibit Ca^{++} transport

Individual Inhalation Anesthetics

Nitrous oxide:

- low potency, therefore must be combined with other agents
- rapid induction and recovery
- good analgesic, WEAK anesthetic properties
- can cause diffusion hypoxia
- Safest and least hepatotoxic
- risk of bone marrow depression with prolonged administration.
- laughing gas
- can retard O_2 uptake during recovery, thus 20% of O_2 is always needed

Inhalational anesthetics

Halothane:

- It is a potent anesthetic.
- Induction is pleasant.
- It sensitizes the heart to catecholamines.
- It dilates bronchus – preferred in asthmatics.
- It inhibits uterine contractions.
- Halothane hepatitis and malignant hyperthermia can occur.

HALOTHANE

- **Prototype**
- **Weak analgesic; POTENT anesthetic**
- **Usually co-administered w/ N_2O, opioids, or local anesthetics**
- **Metabolized to tissue-toxic hydrocarbons (trifluroethanol) & bromide ion**

HALOTHANE

- **Disadvantages:**
- Reduced myocardial contractility & causes hypotension
- Arrhythmias
- Increase arterial pressure
- Atropine sensitive **bradycardia**

Inhalational anesthetics

Enflurane:

- Sweet and ethereal odor.
- Generally do not sensitizes the heart to catecholamines.
- **Seizures occurs at deeper levels – contraindicated in epileptics.**
- Caution in renal failure due to fluoride.

Inhalational anesthetics

Isoflurane:

- It is commonly used with oxygen or nitrous oxide.
- It do not sensitize the heart to catecholamines.
- Its pungency can **irritate the respiratory system.**

ISOFLURANE

- Disadvantages:
  - More pungent odor than halothane
  - Progressive respiratory depression & hypotension

Inhalational anesthetics

Desflurane:

- It is delivered through special vaporizer.
- It is a popular anesthetic for day care surgery.
- Induction and recovery is fast, cognitive and motor impairment are short lived
- **Malignant hyperthermia**
- It **irritates the air passages** producing cough and laryngospasm.

METHOXYFLURANE

- potent, high lipid solubility
- Used in child birth
- Disadvantages: Metabolized to flouride; Respiratory and circulatory depression

IV Anesthetics

- **Thiopental**
  - barbiturate with very high lipid solubility
  - GABA- mimetic
  - rapid action because of rapid transfer across blood-brain barrier
  - Potent anesthetic, weak analgesic effect
  - Little muscle relaxation
  - **Laryngospasm, not for asthma pt,not w/ porphyria**

Anesthesiology

Thiopental

- It is an ultra short acting barbiturates.
- *Consciousness regained within 10-20 mins by redistribution to skeletal muscle.*
- It do not increase ICP.
- It is eliminated slowly from the body by metabolism and produce hang over.
- It can be used for rapid control of seizures.

IV anesthetics

Etomidate:

- It is a short acting anesthetic.
- **It suppress the production of steroids from the adrenal gland and no repeated injections.**
- It is a pro-convulsant and emetic.
- **CVS stability** is the main advantage over anesthetics.

IV Anesthetic Agents

Ketamine

- analogue of phencyclidine, w/ similar properties (psychotic reactions)
- effect on NMDA-type glutamate receptors
- onset of effect is relatively slow (2-5 minutes)
- produces “dissociative” anesthesia, in which patient may remain conscious and insensitive to pain
- can increase intracranial pressure
- Causes cardiovascular stimulation but not respiratory depression

IV anesthetics

Ketamine:

- ⚠ Emergence delirium, hallucinations and involuntary movements occurs in 50% cases during recovery.
- It is useful for burn dressing and trauma surgery
- Dangerous for hypertensive and IHD.

IV anesthetics

Propofol:

- Most commonly used IV anesthetic
- Unconsciousness in ~ 45 seconds and lasts ~15 min
- **Anti-emetic in action**
- Suited for day case surgery - residual impairment is less marked.

Anesthetic Adjuvants

- **Benzodiazepines** (midazolam, diazepam)
  - Anxiolytic
  - Amnesia
  - Sedation
  - Administered prior to induction (preoperatively)
  - Used to provide conscious sedation
- **Opioids** (fentanyl, remifentanil, meperidine, morphine)
  - Analgesia (preoperatively and intraoperatively)
  - Sedation
  - Muscle rigidity with large doses
  - Increased nausea, vomiting and itching on recovery

Local anesthetics (LAs)

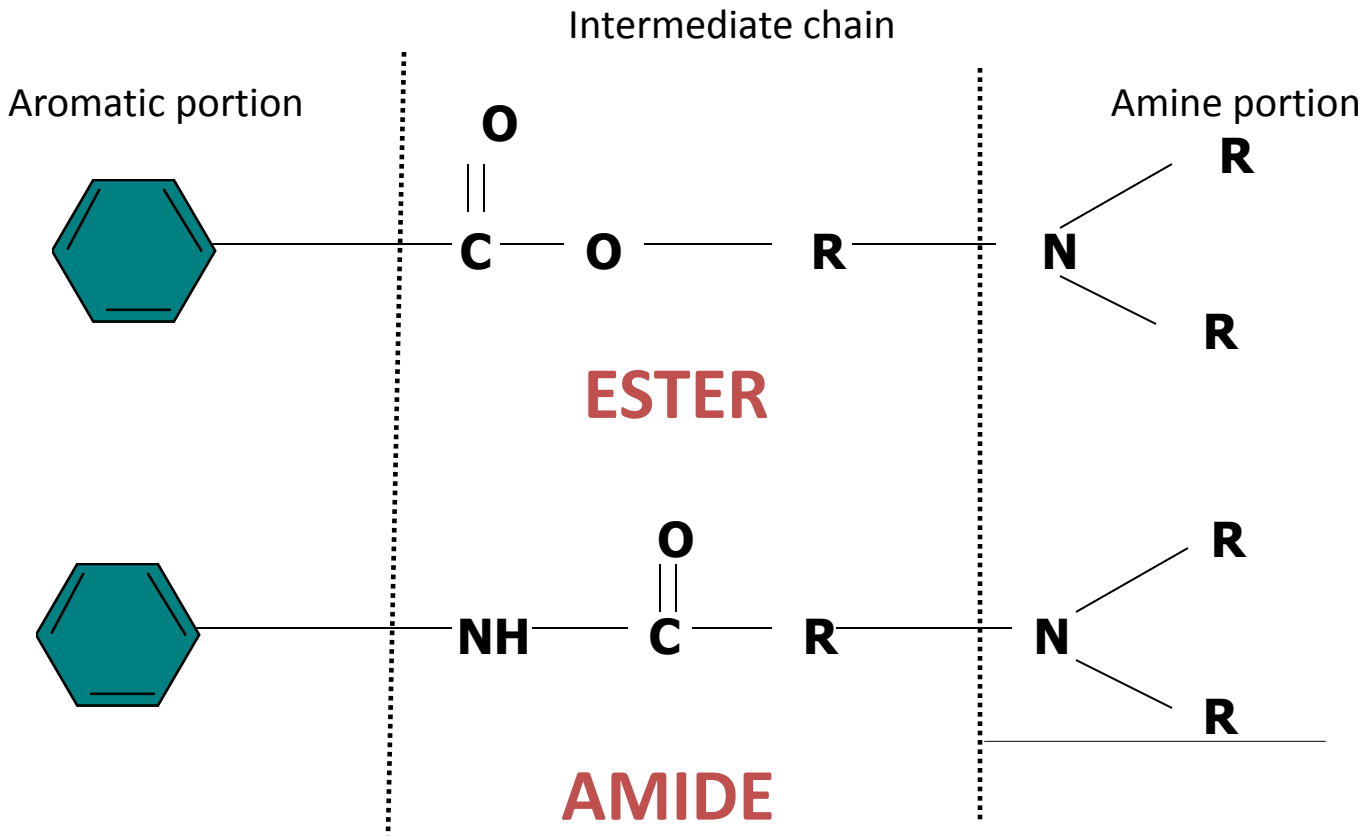
The esters

Local Anesthetics

Clinical Significance of chemical classification

- Biotransformation/duration of action
  - ESTERS are rapidly metabolized in the plasma by a cholinesterase
  - AMIDES are more slowly destroyed by liver microsomal P450 enzymes.

LAs are Weak Bases



LIPOPHILIC

HYDROPHILIC

Local Anesthetics

DESIRABLE CHARACTERISTICS

- Rapid onset of action
- Brief, reversible block of nerve conduction
- Low degree of systemic toxicity***
- Soluble in water and stable in solution
- Effective on all parts of the nervous system, all types of nerve fibers and muscle fibers

- NONE totally meets these optimally yet!!

Local Anesthetics

MECHANISM OF ACTION

- LA have greatest affinity for sodium channel in inactivated state and slows its reversion to the resting state.
- Administration:
- Topical, injected into nerves, epidural or subarachnoid space (spinal)
- Notes:
- Reduced pH, as in inflamed tissues reduces effectiveness (cationic form predominates)
- Co-administered with vasoconstrictor epinephrine (1:100,000)

The esters

- Benzoic acid derivatives
- P-aminobenzoic acid derivatives
- Acetanilide- lidocaine
- Toluidine - prilocaine
- thiophene - ultracaine

Benzoic Acid Derivatives

- Co**caine**
- Cyclomethi**caine**
- Hexyl**caine**
- Isobu**caine**
- Mepryl**caine**
- Pipero**caine**

P-aminobenzoic acid Derivatives

- Benzo**caine**
- Buta**caine**
- Propoxy**caine**
- Pro**caine**
- Propara**caine**
- Chlorpro**caine**
- Tetra**caine**

SELECTIVE PHARMACOLOGICAL PROPERTIES OF SOME ESTER - type LA

Cocaine

- medical use limited to surface or topical anesthesia (corneal or nasopharyngeal)
- avoid epinephrine because cocaine already has **vasoconstrictor** properties (EXCEPTION!!!)
- A toxic action on heart may induce rapid and lethal **cardiac failure**
- A marked **pyrexia** is associated with cocaine overdose

SELECTIVE PHARMACOLOGICAL PROPERTIES OF SOME ESTER - type LA

Benzocaine

- Used to produce anesthesia of mucous membranes and to **suppress gag** reflex during endoscopy
- methemoglobinemia

SELECTIVE PHARMACOLOGICAL PROPERTIES OF SOME ESTER - type LA

Procaine

- Used for *infiltration* because of low potency and short duration but most commonly used for **spinal anesthesia**
- Short local duration -produces significant vasodilation. Epinephrine used to prolong effect
- **DOC** for patients with liver disease

SELECTIVE PHARMACOLOGICAL PROPERTIES OF SOME ESTER - type LA

Tetracaine

- topical, infiltration and spinal anesthesia
- Frequently used **for topical ophthalomogical anesthesia**
- slow onset and more prolonged effect than procaine (**longest duration of the esters**)

Local anesthetics (LAs)

The AMIDES

The amides

- Lido**caine**
- Mepiva**caine**
- Bupiva**caine**
- Prilo**caine**
- Etido**caine**
- Ropiva**caine**
- Levobupiva**caine**
- Arti**caine**

SELECTIVE PHARMACOLOGICAL PROPERTIES OF SOME AMIDE - type LA

LIDOCAINE:

- most widely used LA
- effective by **all routes**
- faster onset, more intense, longer lasting, than procaine
- good alternative for those allergic to ester type
- more potent than procaine but about equal toxicity
- more sedative than others

SELECTIVE PHARMACOLOGICAL PROPERTIES OF SOME AMIDE - type LA

Mepivicaine:

- effective by **all routes except topical**
- similar onset and duration as lidocaine
- more toxic to neonates so not used in obstetrical anesthesia
- fetus poorly metabolizes mepivicaine

SELECTIVE PHARMACOLOGICAL PROPERTIES OF SOME AMIDE - type LA

Bupivacaine:

- no topical effect
- slower onset and one of longer duration agents
- unique property of sensory and motor dissociation
- can provide sensory analgesia with minimal motor block
- has been popular drug for analgesia during labor

SELECTIVE PHARMACOLOGICAL PROPERTIES OF SOME AMIDE - type LA

Ropivacaine:

- enantiomer of bupivacaine **(S stereoisomer)**
- no topical effectiveness
- clinically ~ equivalent to bupivacaine
- similar sensory versus motor selectivity as bupivacaine
- significantly less cardiotoxicity than bupivacaine at equipotent doses.
- Long-acting LAs are very potent and may cause cardiac arrest with a misplaced injection or relative overdose

THANK YOU

s.hunaiti@ju.edu.jo