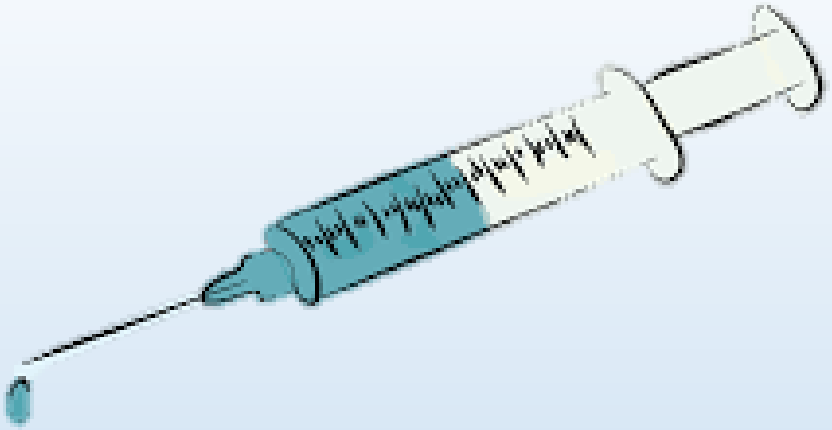


Local Anesthetics

by:

Dr Soodeh Tavakoli

DVM-PhD Candidate in pharmacology

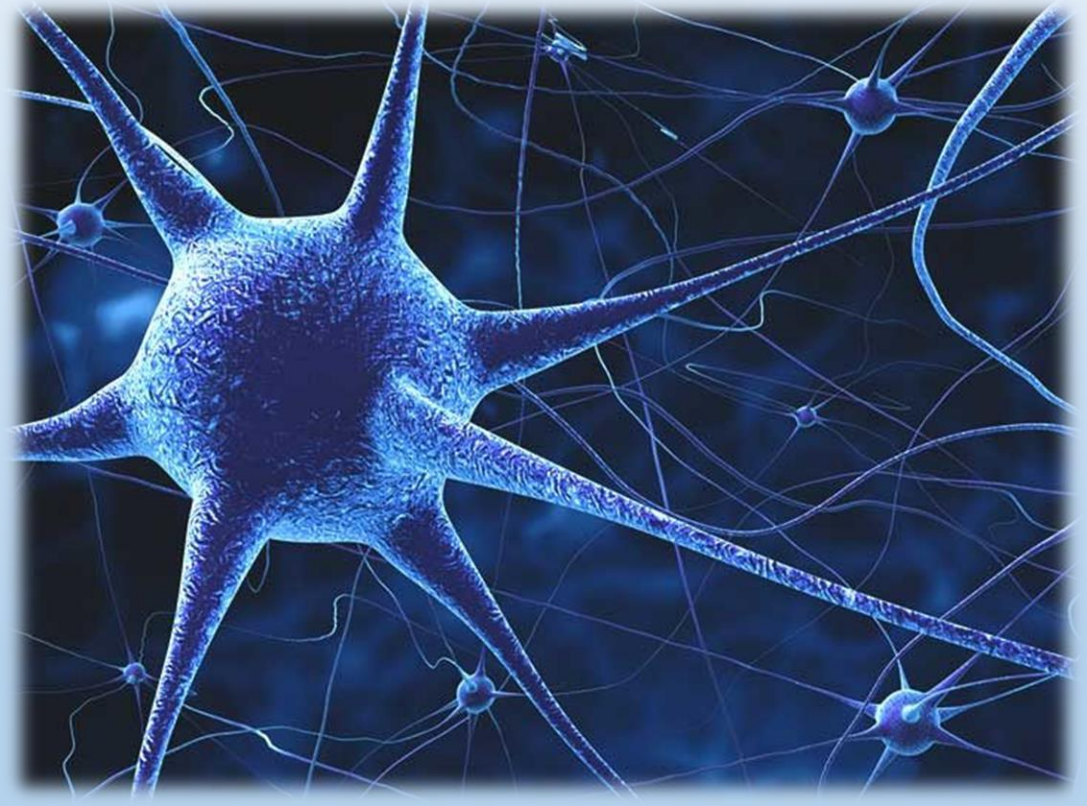
Soodeh.tavakoli@ut.ac.ir

Pharmacology of Nervous system

- **Drug acting on ANS include:**

Local anesthetics

- **Drugs acting on CNS**
  1. **Anesthetic Drugs**
  2. **Sedative**
  3. **Tranquilizers**
  4. **Drugs modifying behavior**



Difference between LA and GA?

GA is associated with physiological changes and unconsciousness

- The first local anesthetic to be used was cocaine
- It was introduced into human clinical practice in the 1880s as an ophthalmic anesthetic.
- But its addictive actions were soon discovered
- It was still used until procaine was synthesized in the early 1900s
- Lidocaine (lignocaine) is probably the agent most commonly used today.
- Other agents used include mepivacaine, bupivacaine, proxymetacaine and prilocaine.
- Procaine is still used occasionally

Clinical applications

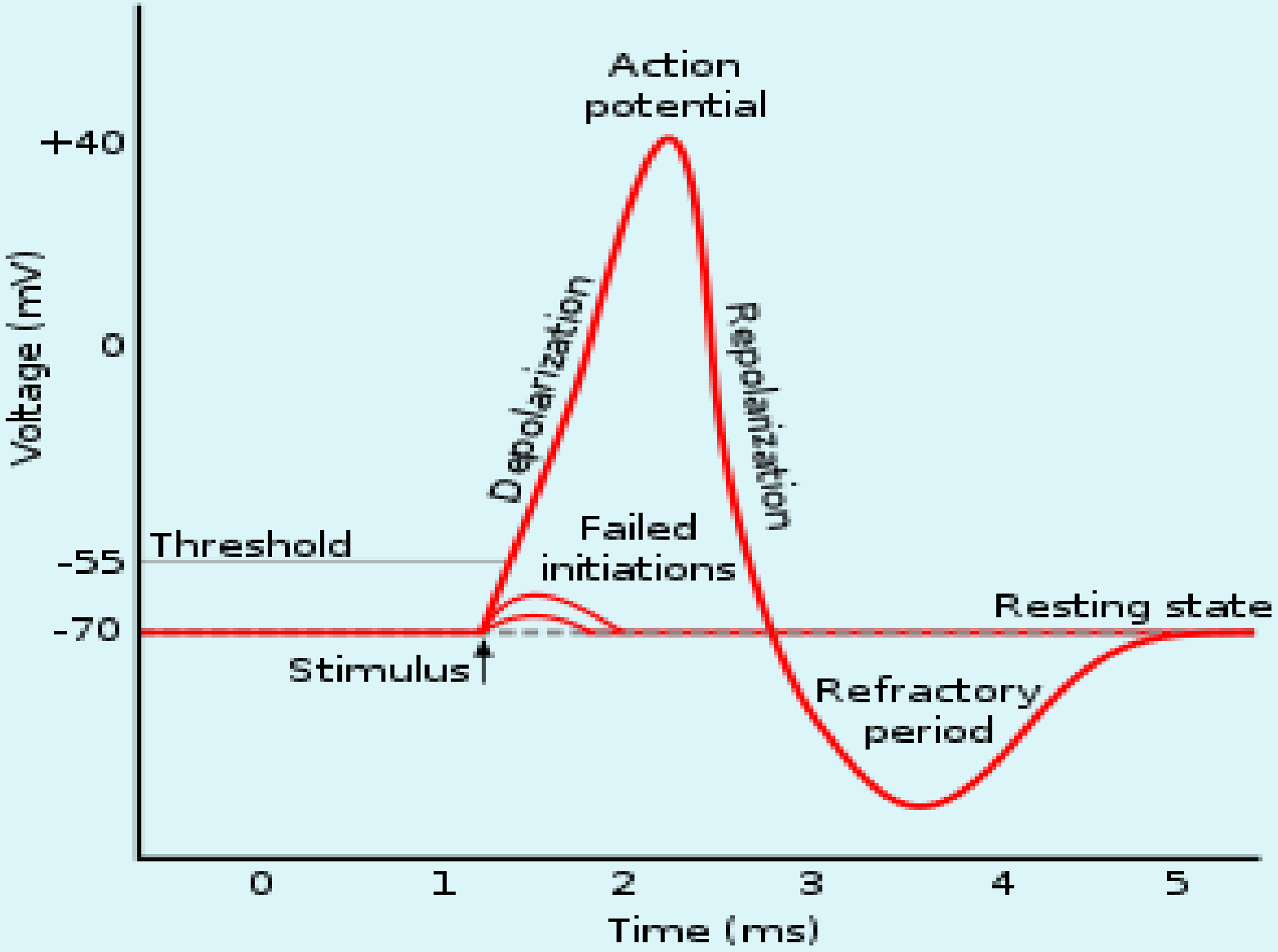
- Local anesthetics are used to desensitize a localized or regional area.
- They may be administered topically (spray, ointment) or infiltrated subcutaneously, around nerves, into joints or into the epidural space
- In veterinary medicine they are often used to provide additional analgesia in anesthetized patient
- They have a sparing effect on the MAC of volatile anesthetics and used as an adjunct to general anesthesia

- ***Examples of local anesthetic uses include:***
  - ✓ topical anesthesia of the larynx for intubation, particularly in cats
  - ✓ topical anesthesia of the eye remove foreign bodies
  - ✓ SC infiltration to provide analgesia for minor procedures including suturing, removal of small skin tumors and skin biopsies
  - ✓ peripheral nerve blocks for regional analgesia of the head or limbs
  - ✓ Interapleural administration via a chest for analgesia after thoracic trauma or surgery

- ✓intra-articular administration to provide analgesia prior to or following surgery of joints
- ✓epidural administration for regional analgesia of the caudal, abdomen, hindlimb etc undergoing major surgery
- ✓Intravenous regional administration to provide analgesia for surgery of the distal limbs
- ✓Interathecal (spinal) administration for large area of anesthesia and deep operation

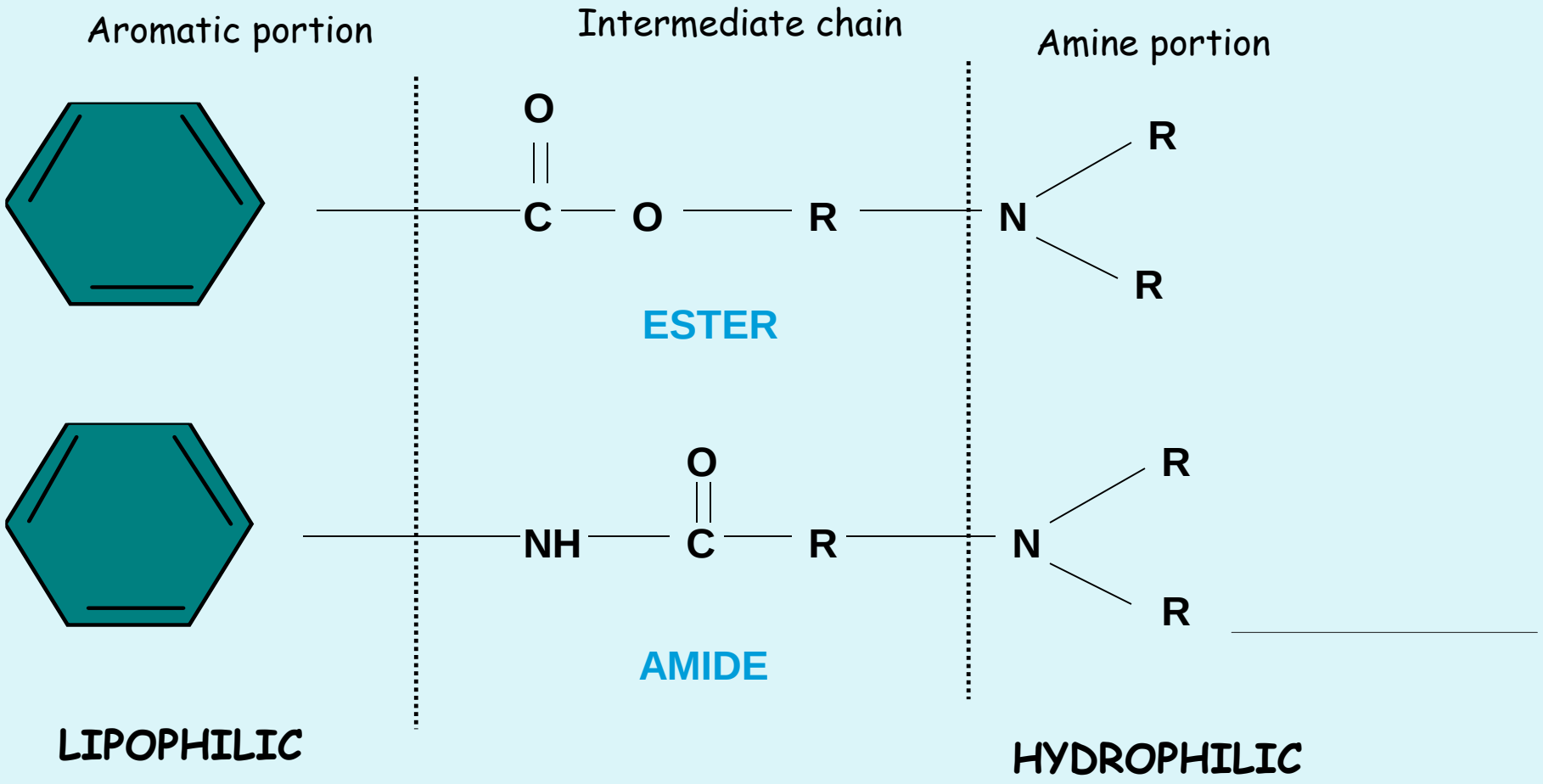
Mechanism of action

- LA inhibit both the initiation and conduction of action potentials by preventing the inward sodium current.
- They bind to receptors within the sodium channel to block the flow of ions.
- The local anesthetic must first diffuse through the axon membrane and then enter the ion channel via the opening on the internal surface of the membrane.
- LAs can potentially block impulse conduction in all types of nerve fiber but differences in sensitivity exist.
- Small-diameter fibers are more sensitive than large-diameter fibers
- Myelinated neuron will block more readily than an unmyelinated neuron of similar size.
- Thus nociceptive afferents (C fibers and Aδ) are more susceptible than motor neurons
- Autonomic nerve fibers are also very sensitive to the LAs


Action potential
+40
0
-55
-70
Voltage (mV)
Depolarization
Repolarization
Threshold
Failed initiations
Resting state
Stimulus
Refractory period
0
1
2
3
4
5
Time (ms)

تمامی بیحس کننده های موضعی بازهای ضعیفی هستند که تحت عنوان بازهای سه ظرفیتی طبقه بندی می شوند

دارای ساختمان ۳ قسمتی هستند



ترکیبات آمینواستری

- Hydrolyzed in plasma by pseudo-cholinesterase.
- Para Amino Benzoic Acid is the by-products of metabolism is: the common cause of allergic reactions seen with these agents

- PROCAINE
- procaine (Novocaine)
- tetracaine (Pontocaine)
- benzocaine
- cocaine

Distribution is low due to short $T_{1/2}$

Hydrolyzed quickly by plasma butyrylcholinesterases

ترکیبات آمینوآمیدی

- They are metabolized in the liver to inactive
- Most dependent on liver blood flow due to the high extraction
- True allergic reactions are rare, especially with lidocaine

1. Lidocaine
2. Mepivicaine,
3. Prilocaine,
4. Bupivacaine,
5. Etidocaine and
6. Ropivacaine

Widely distributed after IV

Liver metabolism by Cyto c P450

Most dependent on liver blood flow because of high extraction ratio

The liver toxicity is more

for topical anesthesia include

- EMLA cream (eutectic mixture of local anesthetic) contains a mixture of lidocaine (2.5%) and prilocaine (2.5%).
- It is used to provide topical anesthesia of the skin and sixty min may be required for the maximum effect to develop.
- A clear solution of 2% lidocaine as spray is available for topical anesthesia of the larynx. Each spray contains 2–4 mg of lidocaine.
- Lidocaine is also available as a 1% gel to facilitate procedures such as urethral catheterization.

Aqueous solutions for injection:

5% procaine, 2% lidocaine, 2% mepivacaine, 0.5% bupivacaine, 0.2% ropivacaine).

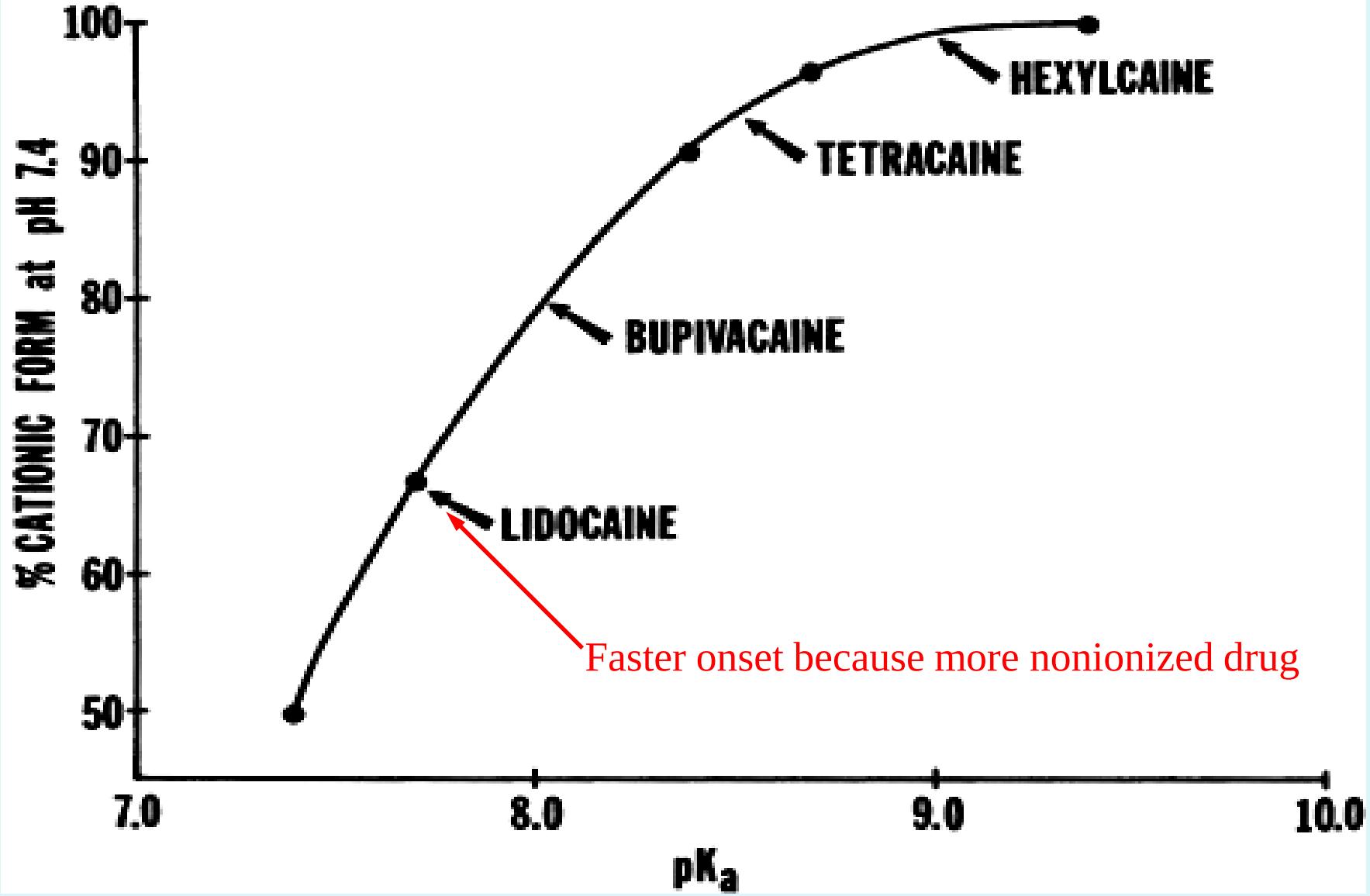
Lidocaine plus low concentrations of adrenaline (epinephrine)

- ✓It causes a localized vasoconstriction plus ansethesia that prolong its duration of effect and reducing the risk of systemic toxicity.
- ✓Such preparations should not be used for IV regional analgesia.
- ✓Neither are they recommended for desensitization of an extremity such as a digit

- LAS in solution exist in a chemical equilibrium between the basic uncharged form (B) and the charged cationic form (BH^+).
- At a certain hydrogen concentration which is specific for each drug, the concentration of local anesthetic base is equal to the concentration of charged cation.
- This hydrogen concentration is called the pKa.
- This relationship is expressed as,

$$pH = Pka + Log\ [B]/[BH+]$$

رابطه بین pKa و میزان یونیزاسیون و شروع بیحسی



- Lower pKa means greater fraction of the molecules exist in the unionized form, so more easily cross nerve membranes leading to faster onset.
- The pKa of currently used local anesthetic compounds lies between 7.7 and 8.5.
- Acidosis environment (as is present in an infected, pus tissue) further increases the ionized fraction of drugs.
- It is associated with slower onset and poor quality of local anesthesia when a local anesthetic is injected into an acidic infected area.
- Local anesthetics with a higher degree of protein binding have a prolonged duration of action.

فاکتورهای مؤثر در عملکرد بیحس کننده ها

عواملی چون pH، حلالیت در چربی ، منقبض کننده های عروقی، میزان گردش خون و حساسیت فیبرها و نورونهای عصبی مؤثر هستند

۱- اثرات pH

- In the body they are as charged (cationic) or uncharged
- Charged form binds to receptor site
- But uncharged form penetrates membrane
- Infected tissues can change the penetration
- Efficacy of drug can be changed by altering extra cellular or intracellular pH

۲- حلالیت در چربی و پتنسی

- Lipid solubility is the primary determinant of anesthetic potency.
- The highly lipophilic agents penetrate more into the nerve membrane; less molecules are required to block conduction
- **More lipophilic agents are more potent as local anesthetics**
- **Drugs with vasodilator properties (lidocaine) have more rapid vascular uptake and fewer potency**

۳- اثرات گردش خون

- Absorption depends on the speed of administration and doses.
- Distribution allows absorption to occur in three phases:
  1. **Drug occurs at highly vascular tissues (lungs and kidneys)**
  2. **It appears less in vascular muscle and fat.**
  3. **Then the drug is metabolized.**
- Metabolism involves in the chemical structure based on two classes, amide and ester as discussed earlier.
- Rapid metabolism decreases potential toxicity

نسبت حلالیت در چربی و قدرت بیحس کنندگی

Drug	Relative potency	Lipid solubility
Procaine	=1	100
Prilocaine	1.8	129
Lignocaine	2	366
Bupivicaine	8	3420

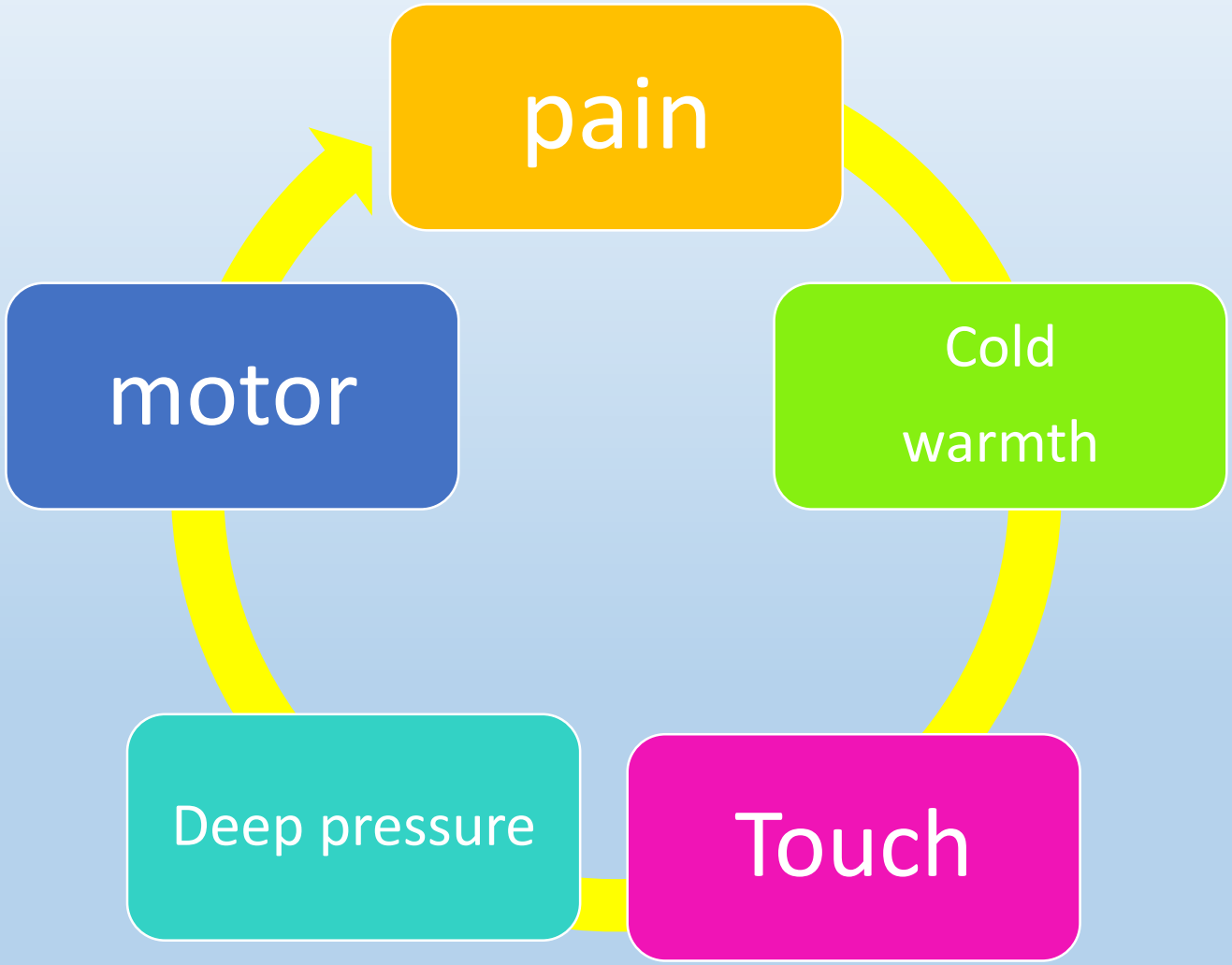
4- اثرات منقبض کننده های عروقی

- Vasoconstrictors decrease the rate of vascular absorption;
- more anesthetic to reach the nerve membrane, ↑depth of anesthesia.
- Combination of of vasoconstrictors increase duration of action.
- 1:200,000 epinephrine appears to be the best vasoconstrictor.

5- میزان حساسیت فیبرها و نورونهای عصبی به دارو

- In general, small nerve fibers are more susceptible than large fibers; however, susceptibility depends on:
  - the type of fiber
  - degree of myelination
  - fiber length and
  - frequency- dependence

ترتیب اثرگذاری



Toxicity

- To reduce the risk of systemic toxicity, total doses of 6 mg/kg lidocaine, 5 mg/kg mepivacaine or 2 mg/kg bupivacaine should not be exceeded in dogs
- Toxic doses may be lower in cats and doses should not exceed 4 mg/kg lidocaine, 2.5 mg/kg mepivacaine or 1.5 mg/kg bupivacaine. Toxicity is additive and if combinations of local anesthetics are used the dose of individual drugs should be reduced accordingly.

If absorbed systematically in excessive amounts, Las can cause CNS excitement,

- If be absorbed in even higher amounts, can cause CNS depression.

The excitement is due to inhibition of inhibitory activities

اثرات قلبی عروقی

1. Depression of the cardiovascular system.
2. Dilation of peripheral vascular (**except cocaine** that induce vasoconstrictive)
3. Hypotension and a certain type of abnormal heartbeat (atrioventricular block) characterize such depression
4. May ultimately result in both cardiac and respiratory arrest.