LOCAL ANAESTHETICS AGENTS

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CONTENT

- Introduction
- Pharmacology of local anaesthetics
- Molecular mechanism of action
- Pharmacokinetics
- pharmacodynamics
- Systemic toxicity and
- Recent developments

HISTORY

All LA originated from COCAINE (alkaloid in leaves of Erythroxylum coca), first used as LA by KOLLER, an ophtalmic surgeon in Vienna

In 1884, he used the first local anesthetic on a patient with glaucoma

General formula: aromatic group joined to an amine by an intermediate group with either ESTER or AMIDE link

PROCAINE (Ester) first used 1904

LIDOCAINE (Amide) introduced 1940s

INTRODUCTION

Local anaesthetics are drugs which cause

- Reversible local anaesthesia and a loss of nociception. Without loss of conciousness when they are used on specific nerve pathways,
- Effects such as analgesia and paralysis can be achieved.

Analgesic drugs that suppress action potentials by blocking voltage-activated sodium ion (na+) channels in excitable tissues.

Local anaesthetics do not diminish consciousness when administered correctly.

The blockade of voltage activated Na+ channels accounts for both their

- analgesic effects, mediated through inhibition of action potentials in nociceptive neurones, and their systemic effects.

inhibition of action potentials in the heart

- contributes to local anaesthetic toxicity and also accounts for the antiarrhythmic actions of intravenous lidocaine (a class 1b antiarrhythmic)

Other drugs which can inhibit voltage activated Na+ channels, ...also have local anaesthetic properties

- diphenhydramine (a first-generation histamine H1 receptor antagonist) and
- amitriptyline (a tricyclic antidepressant)

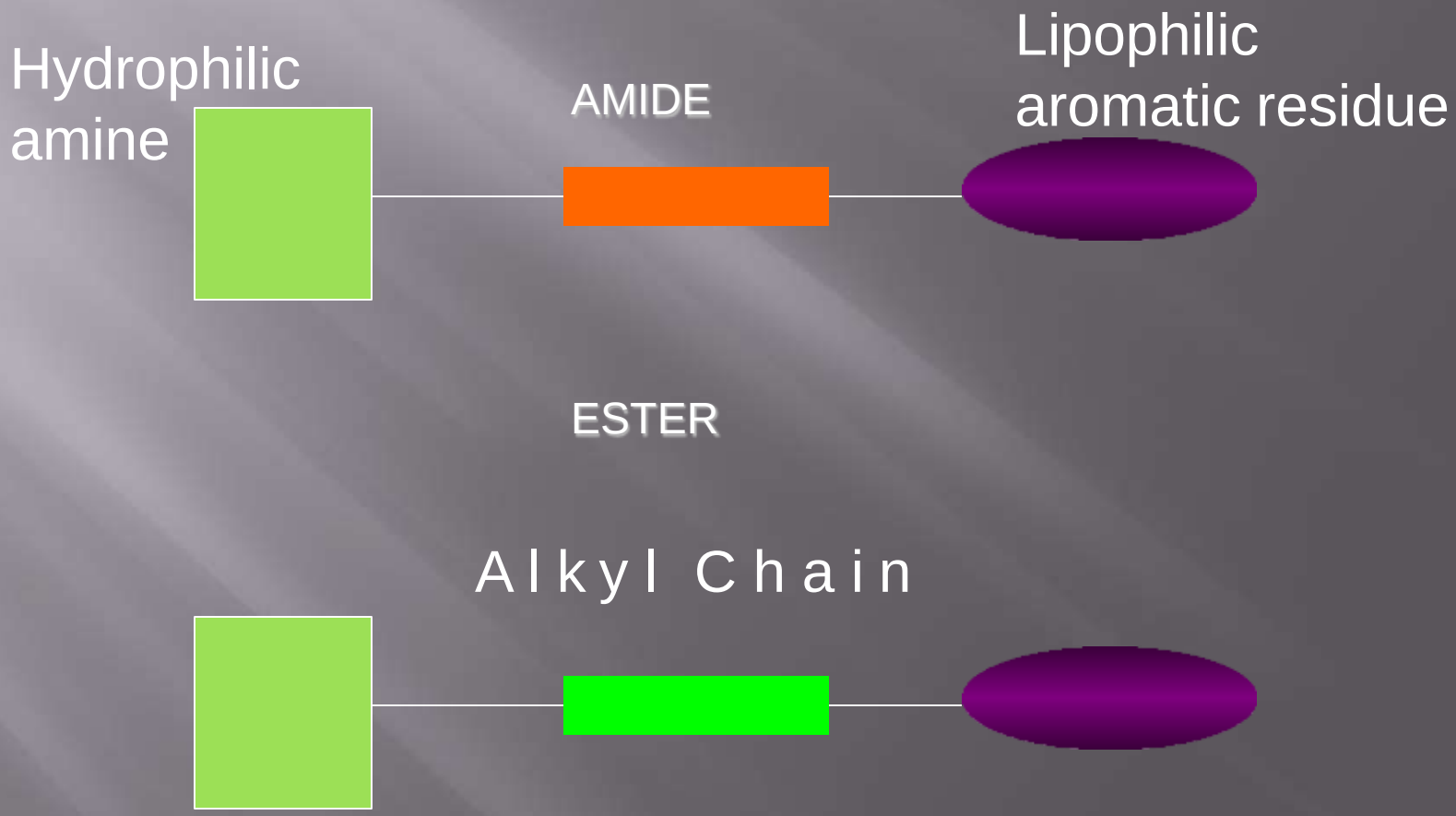
Prosperities of ideal LA

- Reversible action.
- Non-irritant.
- No allergic reaction.
- No systemic toxicity.
- Rapid onset of action.
- Sufficient duration of action.
- Potent.
- Stable in solutions.
- Not interfere with healing of tissue.
- Have a vasoconstrictor action
- Not expensive

Definition

A local anaesthetic can be defined as a drug which reversibly prevents transmission of the nerve impulse in the region to which it is applied, without affecting consciousness

Chemistry


Hydrophilic amine
AMIDE
Lipophilic aromatic residue
ESTER
Alkyl Chain

LOCAL ANAESTHETIC STSTRUCTURE

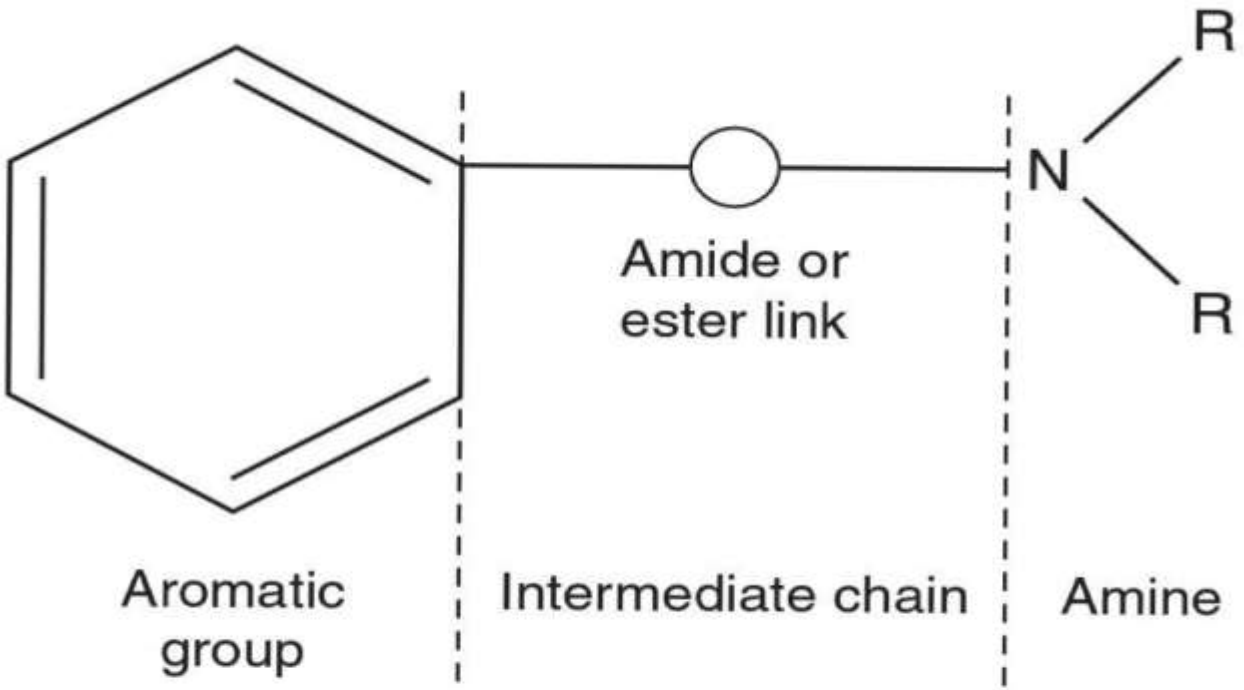


FIGURE 4.4 ■ General formula for local anaesthetic drugs.

LOCAL ANAESTHETIC STRUCTURE

1. aromatic benzene ring portion,....

- lipophilic moity

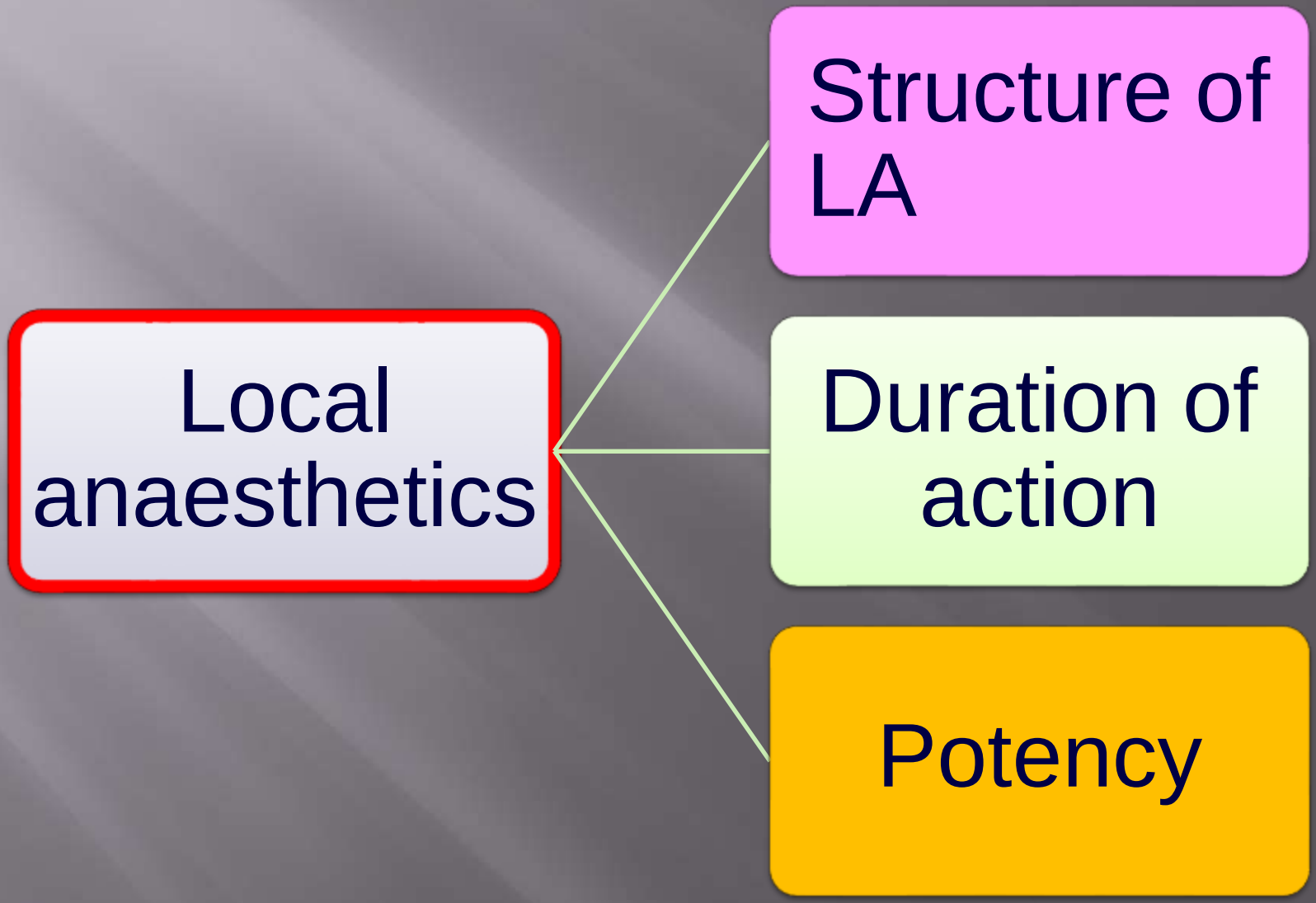
2. intermediate chain .....Amide and ester…basis of classification

- anaesthetics are so named because of their distinctive bonds within the intermediate chain

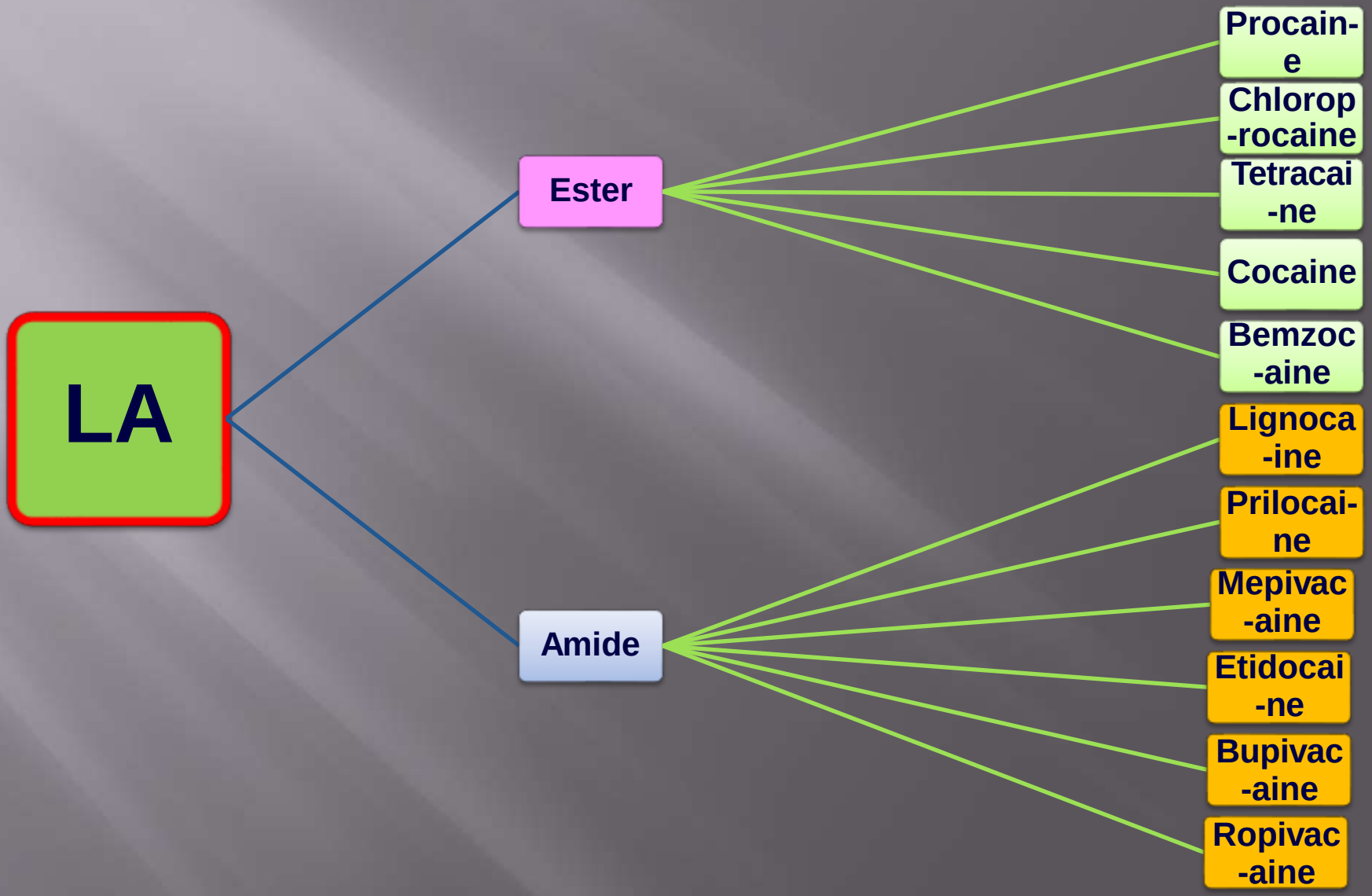
3. amine group.....

- hydrophilic group…hydrocarbon chain
- (usually a tertiary amine) proton acceptor
- providing the potential for both charged and uncharged isoforms (i.e. the source of the *amphipathic nature* of local anaesthetics)

CLASSIFICATION



Classification based on structure



Differences

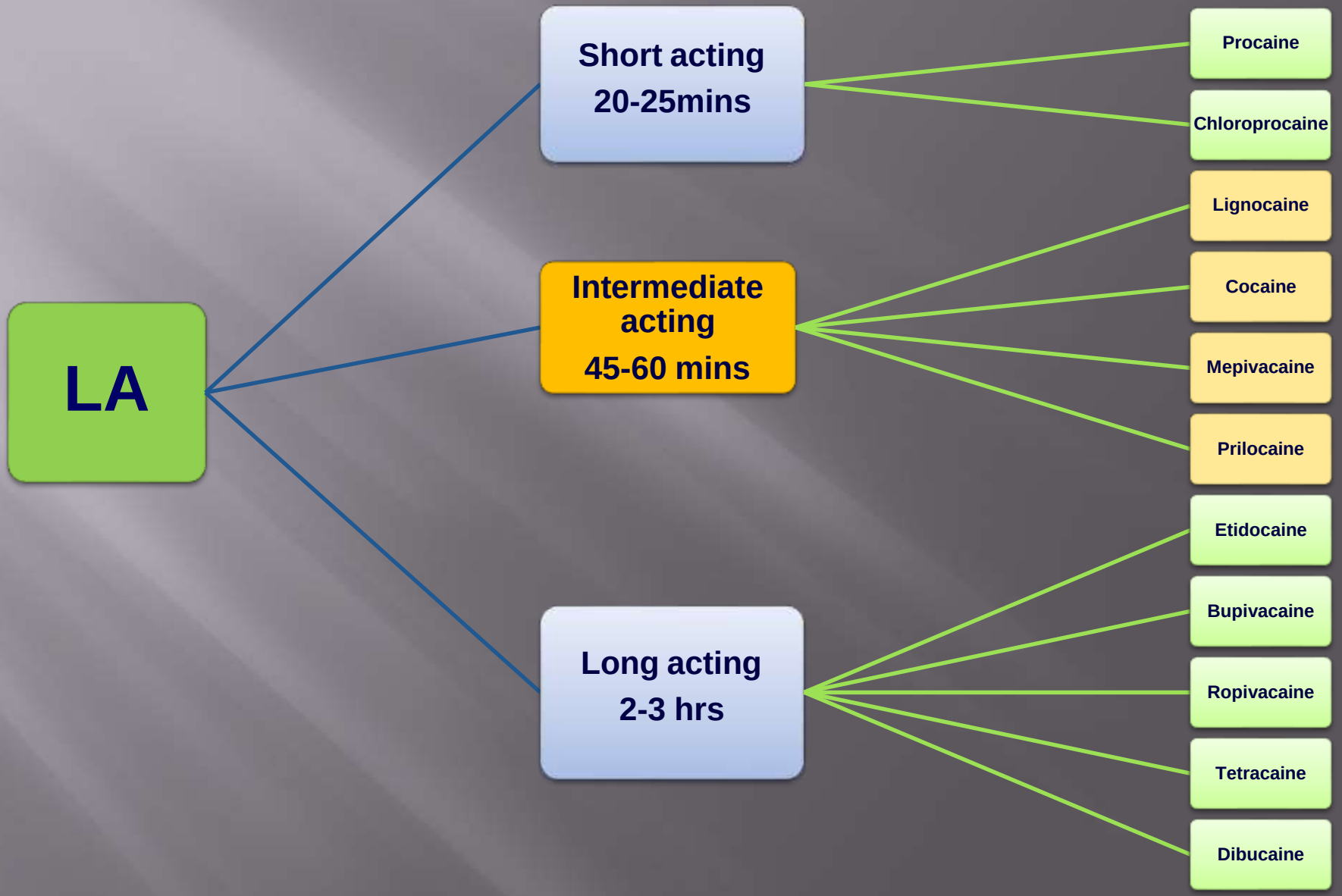
E S T E R S

- Short duration of action
- Less intense analgesia
- Higher risk of hypersensitivity ESTER linked LA s are rarely used.
- Hydrolyzed by Plasma Cholinesterase in blood.
- Rarely used for Infiltration anesthesia
- But useful for topical use mucous membranes.

A M I D E S

- Produce more intense and longer lasting
- Bind to alpha1 acid glycoprotein in plasma
- Not hydrolyzed by Plasma Cholinesterase, but in liver
- Rarely cause hypersensitivity reactions- no cross reactivity with ESTER L A s.

Classification-Duration of action



Drug	Plain Solution			Epinephrine-Containing Solution	
	Concentration (%)	Max Dose (mg)	Duration (min)	Max Dose (mg)	Duration (min)
Short Duration					
Procaine	1-2	500	20-30	600	30-45
Chloroprocaine	1-2	800	15-30	1000	30
Moderate Duration					
Lidocaine	0.5-1	300	30-60	500	120
Mepivacaine	0.5-1	300	45-90	500	120
Prilocaine	0.5-1	350	30-90	550	120
Long Duration					
Bupivacaine	0.25-0.5	175	120-240	200	180-240
Ropivacaine	0.2-0.5	200	120-240	250	180-240

Classification-Potency

Drug	Relative Conduction-Blocking Potency*	Physiochemical Properties	
		pK_a†	Hydrophobicity‡
Low Potency			
Procaine	1	8.9	100
Intermediate Potency			
Mepivacaine	1.5	7.7	130
Prilocaine	1.8	8.0§	129
Chloroprocaine	3	9.1	810
Lidocaine	2	7.8	366
High Potency			
Tetracaine	8	8.4	5822
Bupivacaine	8	8.1	3420
Etidocaine	8	7.9	7320

STRUCTURE ACTIVITY RELATIONSHIPS

Local anesthetics are weak bases

- that usually carry a positive charge at the tertiary amine group at physiological pH

Physicochemical properties of local anesthetics depend on the

- Substitutions in the aromatic ring
- The type of linkage in the intermediate chain
- And the alkyl groups attached to the amine nitrogen

Potency

- Correlates with octanol solubility, which in turn reflects the ability of the local anesthetic molecule to permeate lipid membranes
- Potency is increased by adding large alkyl groups to a parent molecule

The minimum concentration of local anesthetic that will block nerve impulse conduction is affected by

- 1.Fiber size, type, and myelination
- 2.pH
  - (acidic ph antagonizes block)
- 3.Frequency of nerve stimulation and
- 4.Electrolyte concentrations
  - (hypokalemia and hypercalcemia antagonize blockade).

Onset of local anesthetic action depends on many factors, including

- lipid solubility
- relative concentration of the **nonionized lipidsoluble form (B) and the ionized water-soluble form (BH +), expressed by the p Ka** .
  - The p Ka is the pH at which the fraction of ionized and nonionized drug is equal.

Less potent, less lipid-soluble agents generally have a faster onset than more potent, more lipidsoluble agents.

Local anesthetics with a **pKa closest to physiological pH** will have (at physiological pH) a greater fraction of nonionized base (B) that more readily permeates the nerve cell membrane, generally facilitating a more rapid onset of action

Local anesthetic solutions are prepared **commercially as water-soluble hydrochloride salts (pH 6–7)**.

Because **epinephrine** is unstable in alkaline environments,

- commercially formulated, epinephrine- containing, local anesthetic solutions are generally more acidic (pH 4–5).....**slower onse**t than when the epinephrine is added by anesthetist at time of injection

when local anesthetics are injected into **acidic (eg, infected) tissues**

- onset is delayed
  - Because extracellular base(B) to-cation (BH+) ratio is decreased

Tachyphylaxis—

- the decreased efficacy of repeated doses of LA—could be partly explained by
  - the eventual consumption of the local extracellular buff ering capacity by repeat injections of the acidic local anesthetic solution

alkalinization of local anesthetic solutions … increasing the amount of free base available.

- (particularly commercially prepared, epinephrine-containing ones)
- by the addition of **sodium bicarbonate** (eg, 1 mL 8.4% sodium bicarbonate per 10 mL local anesthetic)
- **speeds the onset** and
- improves the quality of the block by....
- also decreases pain during subcutaneous infi ltration.

Duration of action

- correlates with potency and lipid solubility.
  - Highly lipid-soluble local anesthetics have a longer duration of action, presumably because they more slowly diffuse from a lipid-rich environment to the aqueous bloodstream.
  - Lipid solubility of local anesthetics is correlated with plasma protein binding.

Differential block of sensory rather than motor function would be desirable. Unfortunately,

- only bupivacaine and ropivacaine display some selectively

MECHANISM OF ACTION

The **primary target of local anaesthetics**, the voltage- activated Na+ channel **(VASC)** is one of numerous membrane proteins which reside in the phospholipid bilayers encapsulating **neurones**

Local anaesthetics applied either topically to the skin or by infiltration **inhibit action potentials in primary afferent nociceptive** neurones

Pain transmission begins as a depolarization in the nerve ending of the primary afferent neurone initiated by the activation of cation channel

CONDUCTION BLOCK

MECHANISM OF ACTION OF LOCAL ANESTHETICS

A. Anatomy of Nerves

B. Electrophysiology of Neural Conduction and Voltage-Gated Sodium Channels

C. Molecular Mechanisms of Local Anesthetics

D. Mechanism of Nerve Blockade

A. Anatomy of Nerves

1. Nerves in both the central nervous system (CNS) and peripheral nervous system are differentiated by the

- pres-ence or absence of a myelin sheath that is interrupted at short intervals by specialized regions called nodes of Ranvier.

2. Nerve fibers are commonly classified according to their

- size,
- conduction velocity
- function

Table 30-3 Classification of Peripheral Nerves According to Anatomy, Physiology, and Function

Fiber Class	Subclass	Myelin	Diameter (μm)	Conduction Velocity (msec)	Location	Function	Susceptibility to Local Anesthetic Block
A	α	+	6-22	30-120	Efferent to muscles	Motor	++
	β	+	6-22	30-120	Afferent from skin and joints	Tactile, proprioception	++
	γ	+	3-6	15-35	Efferent to muscle spindles	Muscle tone	+++
	δ	+	1-4	5-25	Afferent sensory nerves	Pain, cold temperature, touch	+++
B		+	<3	3-15	Preganglionic sympathetic	Various autonomic functions	++
C	sC	–	0.3-1.3	0.7-1.3	Postganglionic sympathetic	Various autonomic functions	++
	dC	–	0.4-1.2	0.1-2.0	Afferent sensory nerves	Various autonomic functions Pain, warm temperature, touch	+

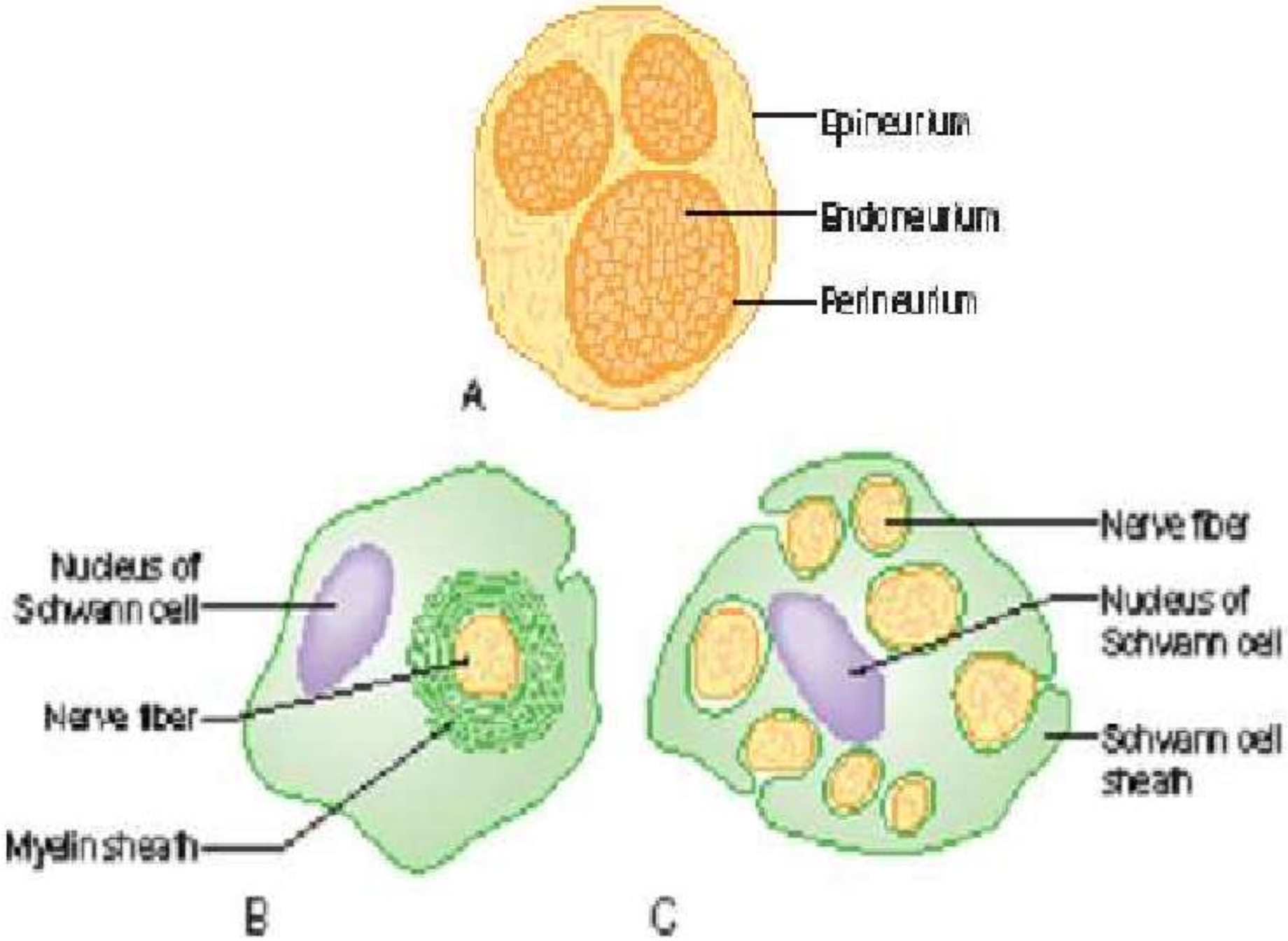

Epineurium
Endoneurium
Perineurium
A
Nucleus of Schwann cell
Nerve fiber
Myelin sheath
B
Nerve fiber
Nucleus of Schwann cell
Schwann cell sheath
C

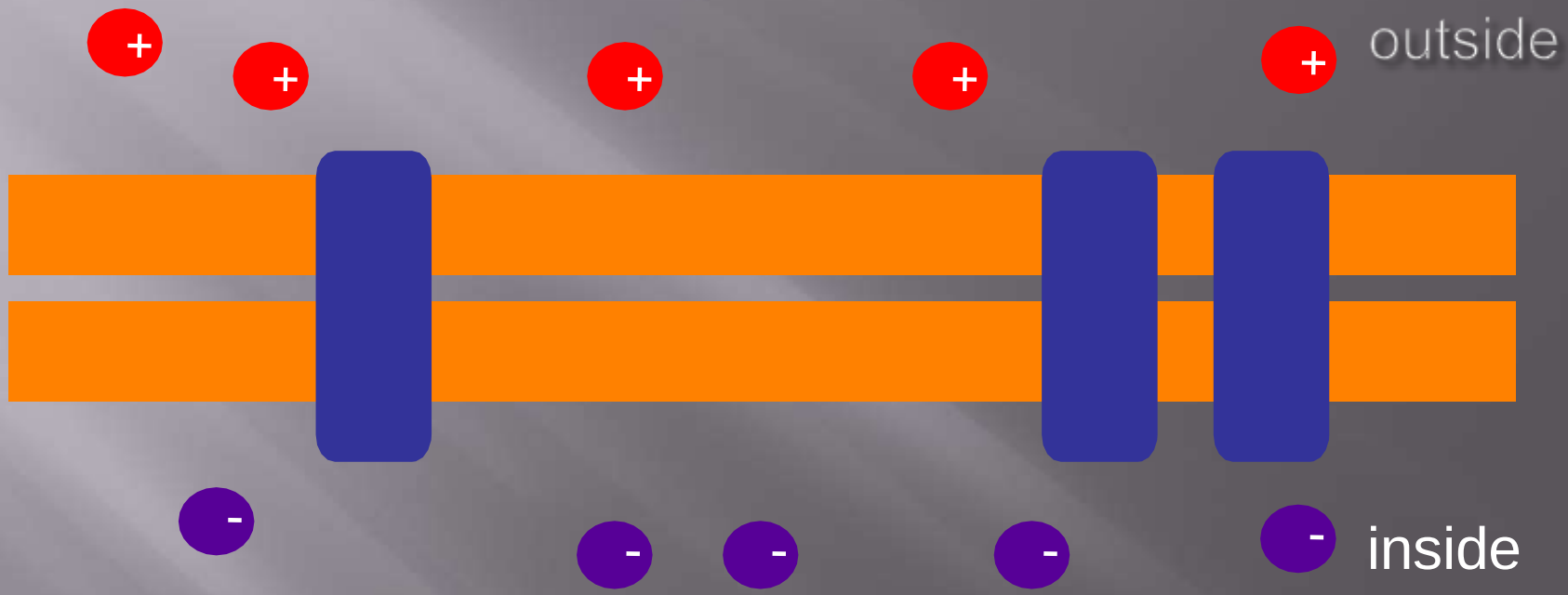
TABLE 21-1 CLASSIFICATION OF NERVE FIBERS

Classification	Diameter (μ)	Myelin	Conduction (m/sec)	Location	Function
A-α	6–22	+	30–120	Afferents/ efferents for muscles and joints	Motor
A-β					Proprioception
A-γ	3–6	+	15–35	Efferent to muscle spindle	Muscle tone
A-δ	1–4	+	5–25	Afferent sensory nerve	Pain, touch, temperature
A					
B	<3	+	3–15	Preganglionic sympathetic	Autonomic function
C	0.3–1.3	–	0.7–1.3	Postganglionic sympathetic	Autonomic function
				Afferent sensory nerve	Pain, temperature

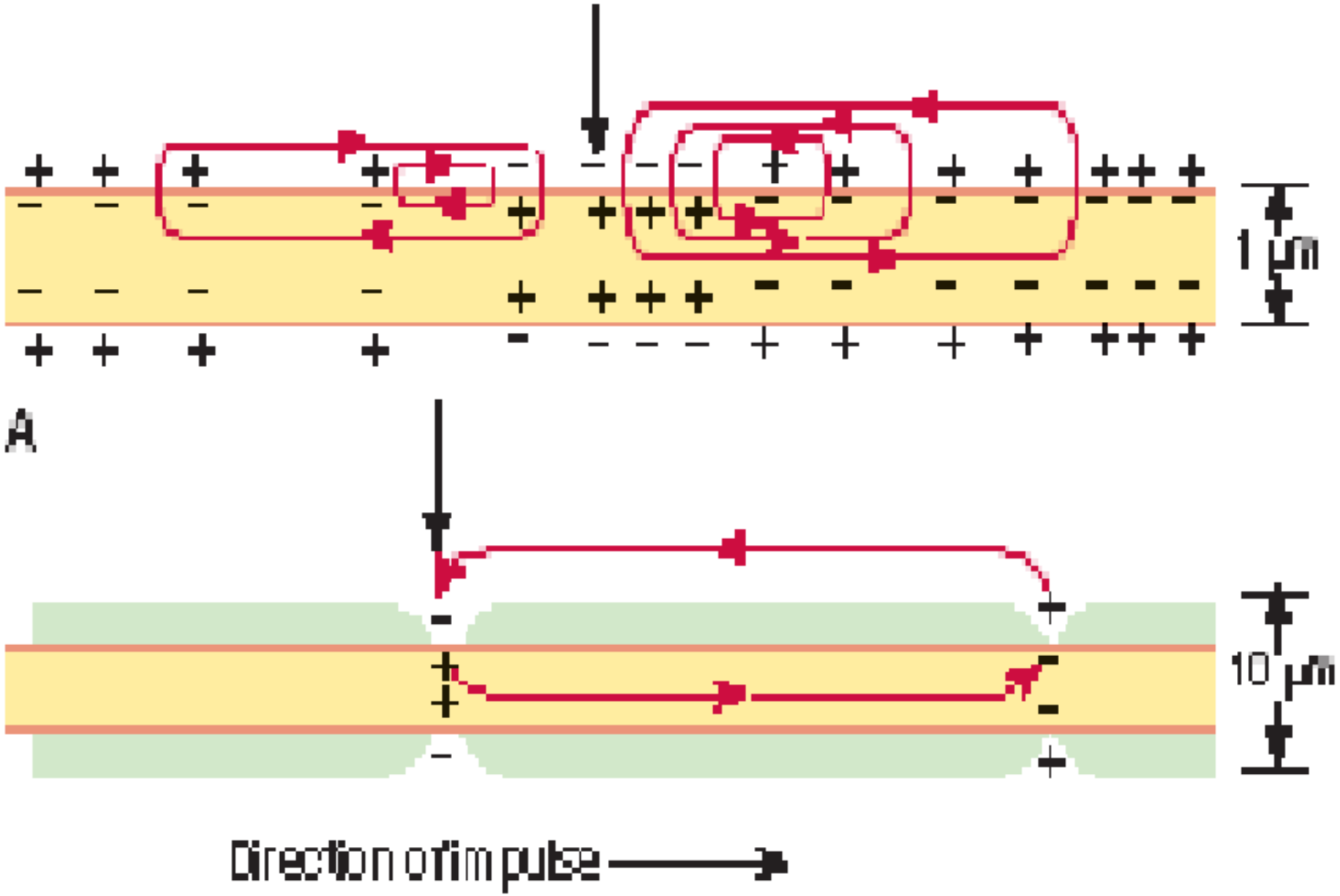
B. Electrophysiology of Neural Conduction and Voltage-Gated Sodium Channels

1.Transmission of electrical impulses along cell membranes is the basis of signal transduction.

- Energy neces-sary for the propagation and maintenance of the electric potential is maintained on the cell surface by ionic dis-equilibrium across the permeable cell membrane.
- The **resting membrane potential** (about –60 to –70 mV) is predominantly attributable to a difference in the intracellular and extracellular concentrations of potas-sium and sodium ions.



Resting potential of neuron = -70mV


1 µm
A
10 µm
Direction of impulse
B

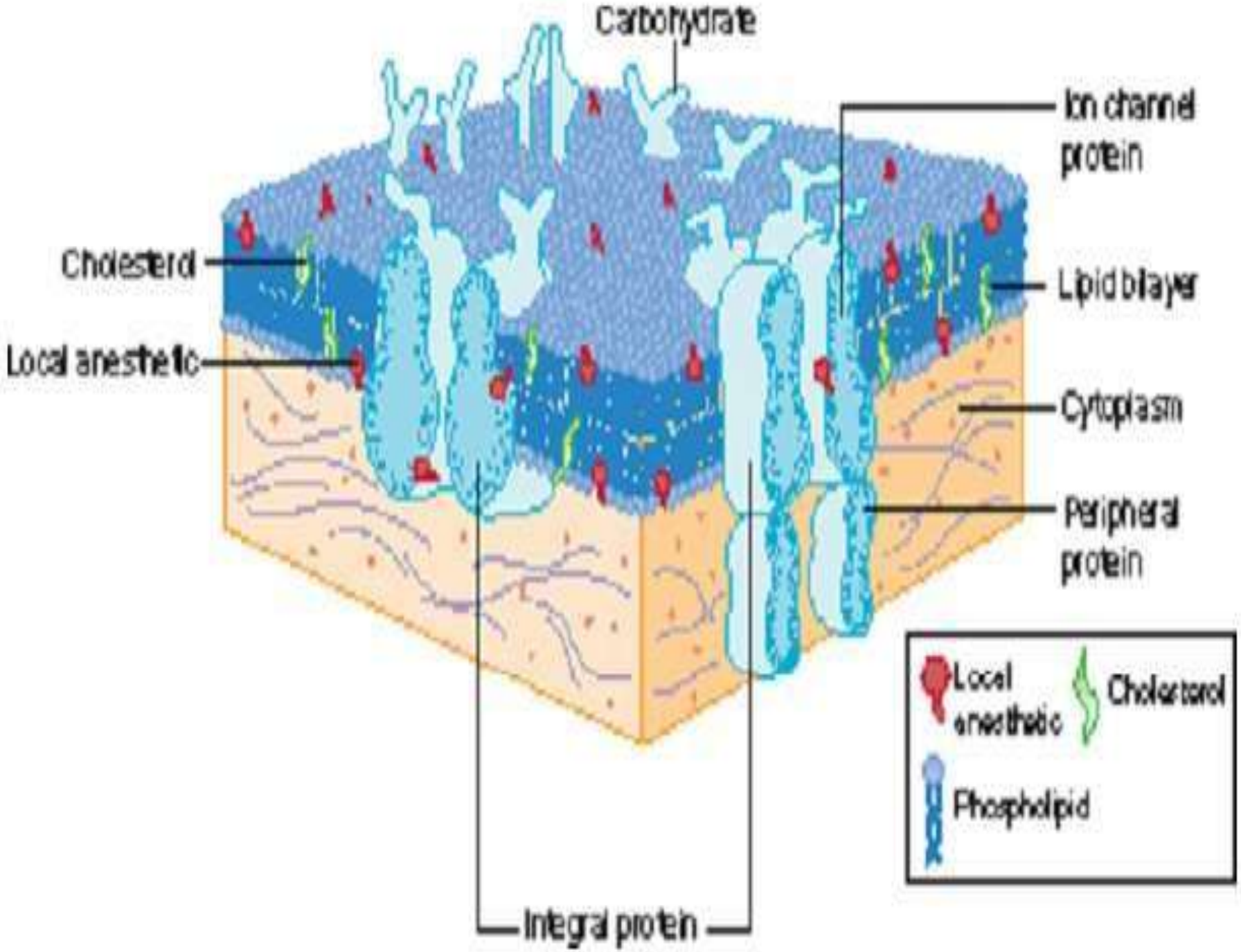
C. Molecular Mechanisms of Local Anesthetics

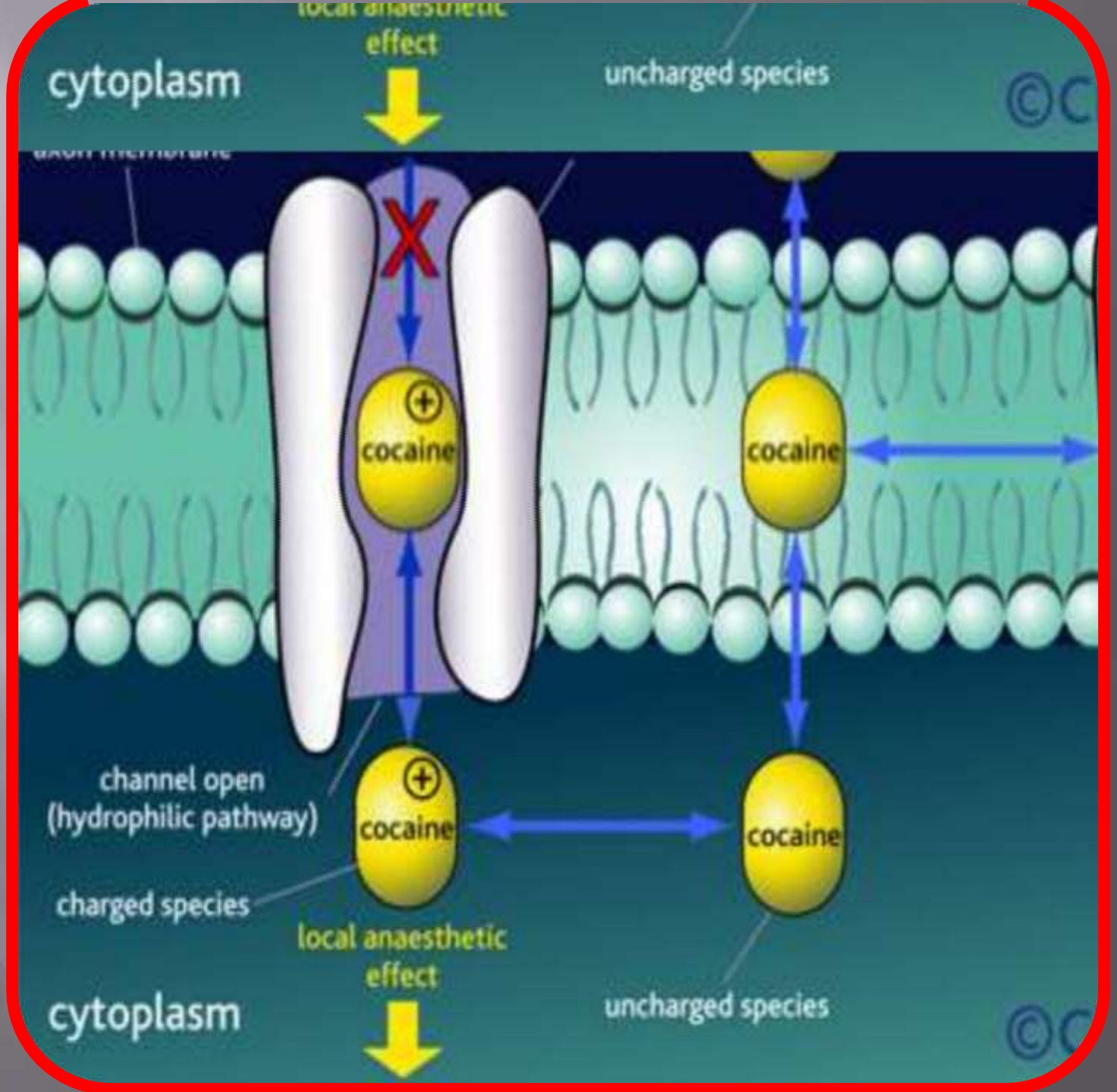
1.local anesthetics induce anes-thesia and analgesia through

- direct interactions with the sodium channels.
- They reversibly bind the intracellular portion of voltage-gated sodium channels.

2.Application of local anesthetics typically produces

- concentration-dependent decrease in the peak sodium current.


Carbohydrate
Ion channel protein
Cholesterol
Lipid bilayer
Local anesthetic
Cytoplasm
Peripheral protein
Local anesthetic
Cholesterol
Phospholipid
Integral protein


effect
cytoplasm
uncharged species
cocaine
cocaine
channel open
(hydrophilic pathway)
cocaine
cocaine
charged species
local anaesthetic
effect
cytoplasm
uncharged species

D. Mechanism of Nerve Blockade

1.Local anesthetics block peripheral nerves by disrupting the transmission of action potentials along nerve fibers…Conduction block

- Only about 1% to 2% of the injected local anesthetics ultimately penetrate into the nerve to reach the site of action (voltage-gated sodium channels).

2.The degree of nerve blockade depends on the local anes-thetic's concentration and volume

- needed to suppress the regeneration of nerve impulses over a critical length of nerve fiber

3. Differential Block…. Not all sensory and motor modalities are equally blocked by local anesthetics

- (sequential disappearance of temperature sensation, proprioceptio--→ motor function-→sharp pain-→and last light touch).
  - This differential blockade had been thought to be simply related to the
    - diameter of the nerve fiber (smaller fibers are inherently more susceptible to drug blockade than large fibers),
    - but this does not appear to be universally true. In this regard, small nerve fibers require a shorter length (<1 cm) exposed to local anesthetic for block to occur than do large fibers

Q.....What is frequency-dependent blockade? How does frequency-dependent blockade relate to the activity of local anesthetics?

1.According to the modulated receptor model

- sodium ion channels alternate between several conformational states, and
- local anesthetics bind to these different conformational states with different affinities.

During excitation

- sodium channel moves from a **resting-closed state** to an **activated-open state**, with passage of sodium ions and consequent depolarization. After depolarization, the channel assumes an **inactivated-closed conformational state.**
- Local anesthetics bind to the ***activated and inactivated states more readily*** than the resting state, attenuating conformational change.

- **Drug dissociation** from the inactivated conformational state is slower than from the resting state.

- **Thus, repeated depolarization produces more effective anesthetic binding.**
  - Progressive enhancement of conduction blockade with repetitive stimulation….. use-dependent or frequency-dependent block.

2. The flow of ions responsible for action potentials is mediated by a variety of channels and pumps

- the most important of which are the voltage-gated sodium chan-nels.
- Nine isoforms of voltage-gated sodium channels have been identified.

Local anaesthetics **inhibit VASC** activity by gaining access to the **open channel** from the ***inside of the cell*** and binding to specific amino acids lining the channel **lumen** .

- They bind preferentially to the open channel and are therefore said to be ***use-dependent (or open channel) blockers***.

local anaesthetic must cross the cell membrane, a passage which requires lipid solubility. The molecule must then diffuse into the aqueous environment within the ion channel.

- Amide and ester local anaesthetics posses both lipophilic and hydrophilic properties and are described as ***amphipathic***
- They exist in basic (uncharged) and cationic (charged) forms and the ***relative proportion of each*** (determined using the Henderson–Hasselbalch equation) is dependent upon the
  - pH of the solution
  - pKa of the local anaesthetic

An alkaline solution speeds the onset of analgesia by increasing the proportion of ***uncharged (B)*** local anaesthetic on the outside of the nerve, resulting in more rapid access to the inside of the cell

infected and inflamed tissue has a relatively low (acidic) pH leading to an increase in the proportion of the membrane-impermeant ***cationic (BH+)*** local anaesthetic component and the requirement for higher doses to achieve analgesia

PHARMACOLOGICAL PROPERTIES OF LOCAL ANAESTHETICS

pKa

- the pH at which the ionized and nonionized form of a compound is present in equal amounts.
- For basic drugs such as local anaesthetics, the greater the pKa, the greater the ionized fraction.
- As diffusion across the nerve sheath and nerve membrane requires non-ionized drug, a local anaesthetic with a low pKa has a fast onset of action while a high pKa causes a slow onset of action.
- lidocaine (pKa 7.6) has a fast onset in comparison with bupivacaine (pKa 8.2)

LA with pKa closest to physiological pH…

- Will have a greatest fraction of non-ionized (B) base …that more rapid penetration in to the nerve cell membrane

Onset of LA action directly correlates with pKa…..**..NOT SUPPORTED BY ACTUAL DATA.**

- Eg ,2 Chloroprocaine…agent of FASTEST ONSET has greatest pKa (9.1) of all clinically used LA.
- Other factors such a ease of diffusion through connective tissue effect the onset in vivo

Molecular weight

- influences the rate of transfer of drug across nerve membranes and through the dura mater. The lower the molecular weight the more rapid is the transfer.

Lipid solubility,

- often expressed as the partition coefficient, influences potency.
- The partition coefficient is the ratio of aqueous and lipid concentrations when a local anaesthetic is introduced into a mixture of oil- and water-based solvents.

Protein binding

- including local anaesthetic attachment to **protein components of the nerve membrane**, ***increases the duration*** of action of a local anaesthetic
- In plasma
  - amide anaesthetics bind predominantly to **α-acid glycoprotein** (AAG), a high-affinity limited capacity protein, and albumin, a low-affinity large capacity protein.

The bioavailability of anaesthetic is

- determined by the availability of plasma proteins; the greater the AAG availability, the greater the binding of anaesthetic, and the lower the free plasma concentration.
- **After surgery, trauma or malig-nancy**,
  - AAG concentrations increase significantly and
    - protect patients receiving local anaesthetic epidural or perineural infusions from anaesthetic toxicity by curbing increases in the free fraction of local anaesthetics.

Vasoactivity

- influences **potency and duration of action**.
- The vasoactivity of commonly used local anaesthetics is **biphasic** with dilatation occur-ring with anaesthetic concentrations ≥0.25% and vasoconstriction at concentrations <0.25%.
- When measured by **Laser Doppler flowmetry** in the forearm, the vasoactive potencies occur in the order:
  - ***lidocaine > bupivacaine > levobu-pivacaine > ropivacaine.***
- **Adrenaline** at a dose of 1.25 µg provides significant vasoconstric-tion when administered with bupivacaine and levobupivacaine.

TABLE 21-2 PHYSIOCHEMICAL PROPERTIES OF CLINICALLY USED LOCAL ANESTHETICS

Local Anesthetic	pKa	% Ionized (at pH 7.4)	Partition Coefficient (Lipid Solubility)	% Protein Binding
Amides				
Bupivacaine*	8.1	83	3420	95
Etidocaine	7.7	66	7317	94
Lidocaine	7.9	76	366	64
Mepivacaine	7.6	61	130	77
Prilocaine	7.9	76	129	55
Ropivacaine	8.1	83	775	94
Esters				
Chloroprocaine	8.7	95	810	NA
Procaine	8.9	97	100	6
Tetracaine	8.5	93	5822	94

TABLE 4.1

The Features of Individual Local Anaesthetic Drugs

Proper Name/ Formula	*% Equivalent Concentration*[a]	*Relative Duration*[a]	*Toxicity*	*pK_a*	*Partition Coefficient at 36 °C*	*% Protein Bound*	*Main use by Anaesthetists in the UK*
Cocaine	1	0.5	Very high	8.7	?	?	Nil
Benzocaine	NA	2	Low	NA	132	?	Topical
Procaine	2	0.75	Low	8.9	3.1	5.8	Nil
Chloroprocaine	1	0.75	Low	9.1	17	?	Not available
Tetracaine	0.25	2	High	8.4	541	76	Topical
Lidocaine	1	1	Medium	7.8	110	64	Infiltration Nerve block Epidural
Mepivacaine	1	1	Medium	7.7	42	77	Not available
Prilocaine	1	1.5	Low	7.7	50	55	Infiltration Nerve block IVRA
Ropivacaine	0.25	2–4	Medium	8.1	230	94	Epidural Nerve block
Bupivacaine	0.25	2–4	Medium	8.1	560	95	Epidural Spinal Nerve block

PHARMACOKINETICS

- Absorption
- Distribution
- Metabolism
- Clearance
- Placental transfer

Absorption

Absorption is determine by ……

- absorption site,
- dose and
- rate of injection, and
- pharmaco-logical properties of LA
- with or without addition of adren-aline

plasma concentration after injection at various sites is:

- intrapleural > intercostal > lumbar epidural > brachial plexus > sciatic > femoral

First-pass pulmonary metabolism limits the concentra-tion of local anaesthetic which reaches the systemic circulation.

TABLE 21-6 DETERMINANTS OF THE RATE AND EXTENT OF SYSTEMIC ABSORPTION OF LOCAL ANESTHETICS

Site of injection (intercostal > caudal > brachial plexus > sciatic or femoral)
Dose
Physiochemical properties (lipid solubility, protein binding)
Addition of epinephrine

Distribution

Tissue distribution of local anaesthetics is proportional to the

- lipid solubility of the drug and the
- blood supply.

Local anaesthetic drugs are distributed **rapidly** to

- Brain
- heart,
- liver
- lungs

but **more slowly** to …… which have a lower blood supply

- muscle and
- fat,.

The patient's **age**, **car-diovascular** status and **hepatic** function **influence tissue blood flow.**

Metabolism

Amide

- metabolism is dependent on hepatic blood flow.
- Toxicity of amides is more likely with
  - prolonged infusions in sick, elderly patients,
- postoperative increase in AAG attenuates the rise in plasma concentrations

Esters

- hydrolysed rapidly in plasma by pseudocholinesterase to the metabolite
  - para-aminobenzoic acid (PABA), which can generate an allergic reaction.

Clearance

Clearance of amide local anaesthetics is dependent on

- hepatic metabolism

metabolites may accumulate in

- renal failure.

Metabolism is fastest in the rank order:

- prilocaine > lidocaine > bupivacaine.

Placental Transfer

Protein binding

- determines the rate and **degree of diffusion** of local anaesthetics across the placenta.

fetal toxicity is dependent primarily on

- **free fraction of local anaesthetic**, which is the same in mother and fetus.

Effects on Organ Systems

inhibition of voltage-gated Na channels from circulating local anesthetics might affect

- action potentials in neurons **throughout the body**
- as well as impulse generation and conduction in the **heart**

Mixtures of local anesthetics should be considered to have additive toxic eff ects; therefore,

- a solution containing 50% of the toxic dose of lidocaine and 50% of the toxic dose of bupivacaine if injected by accident intravenously will produce……. toxic eff ects.

A. Neurological

Central nervous system is vulnerable to local anesthetic toxicity and is the site of premonitory signs of rising blood concentrations in awake patients.

- **Early symptoms** include circumoral numbness, tongue paresthesia, dizziness, tinnitus, and blurred vision.
- **Excitatory signs** include restlessness, agitation, nervousness, garrulousness, and a feeling of "impending doom." Muscle twitching heralds the onset of tonic–clonic seizures.
- **Still higher** blood concentrations may produce central nervous system depression (eg, coma and respiratory arrest).

Potent, highly lipid-soluble local anesthetics

- produce seizures at lower blood concentrations than less potent agents.

Infused local anesthetics have a variety of actions.

- Systemically administered local anesthetics such as lidocaine (1.5 mg/kg) can decrease cerebral blood flow and attenuate the rise in intracranial pressure that may accompany **intubation**
- Infusions of lidocaine and procaine have been used to supplement general anesthetic techniques, as they are capable of **reducing the MAC** of volatile anesthetics by up to 40%.
- Infusions of lidocaine inhibit inflammation and reduce postoperative pain. Infused lidocaine reduces postoperative opioid requirements

Cocaine

- **stimulates** the central nervous system
- and at moderate doses usually causes a sense of euphoria.
- An **overdose** is heralded by restlessness, emesis, tremors, convulsions, arrhythmias, respiratory failure, and cardiac arrest.

Chlorprocaine

- unintentional injection of large volumes of chloroprocaine into the subarachnoid space (during attempts at epidural anesthesia), produced
  - total spinal anesthesia
  - and marked hypotension, and caused
  - prolonged neurological deficits....cause of this neural toxicity may be direct neurotoxicity or a combination of the low pH of chloroprocaine and a preservative, sodium bisulfite.

neurotoxicity following repeated intrathecal injection is

- **lidocaine = tetracaine > bupivacaine > ropivacaine**.

B. Respiratory

Lidocaine **depresses hypoxic drive** (the ventilatory response to low Pa O 2

Apnea can result from

- phrenic and intercostal nerve paralysis or
- depression of the medullary respiratory center following direct exposure to local anesthetic agents (as may occur after retrobulbar blocks;
- after administration of a “high” spinal or epidural anesthetic is nearly always the result of hypotension, rather than phrenic block

relax bronchial smooth muscle

Intravenous lidocaine (1.5 mg/kg) may be effective in blocking the reflex bronchoconstriction sometimes associated with **intubation**.

C. Cardiovascular

All local anesthetics **depress myocardial automaticity**

Myocardial **contractility and conduction** velocity are also depressed at higher concentrations.

Mechanism of cardiac effects

- direct cardiac muscle membrane changes (ie, cardiac Na channel blockade) and
- in intact organisms from inhibition of the autonomic nervous system

Effect on blood vessels

- at **higher concentrations**.....All local anesthetics except cocaine produce smooth muscle relaxation ,may cause some degree of **arteriolar vasodilation**
- at **low concentrations** all local anesthetics inhibit nitric oxide, causing vasoconstriction

Major cardiovascular toxicity

- usually requires about three times the local anesthetic concentration in blood as that required to produce seizures

At increased blood concentrations...cardiac arrest due to the combination of

- arrhythmias,
- heart block,
- depression of ventricular contractility,
- and hypotension

signs of local anesthetic overdose during general anesthesia..

- Cardiac arrhythmias or
- circulatory collapse

in awake subjects,

- signs of transient **cardiovascular** stimulation
  - (tachycardia and hypertension) may occur **with**
- **central nervous** system excitation at local anesthetic concentrations producing central nervous system toxic side effects.

Lidocaine

- hypertension associated with **laryngoscopy and intubation** is attenuated in some patients by intravenous administration of lidocaine (1.5 mg/kg) 1–3 min prior to instrumentation.
- overdoses of lidocaine can lead to marked left ventricular contractile dysfunction.

Bupivacaine...Unintentional intravascular injection of bupivacaine during regional anesthesia

- **severe cardiovascular toxicity**.
  - including left ventricular depression,
  - atrioventricular heart block, and
  - life-threatening arrhythmias such as
    - ventricular tachycardia and fibrillation.
  - predisposing risk factors.
    - Pregnancy, hypoxemia, and respiratory acidosis and Young children

Levobupivacaine, the S(−) isomer of bupivacaine

- **fewer cardiovascular and cerebral side effects** than the racemic mixture; studies suggest its cardiovascular effects may approximate those of ropivacaine.

Bupivacaine….continued

- is associated with more pronounced changes in conduction and a greater **risk of terminal arrhythmias** than comparable doses of lidocaine
- The R(+) optical isomer of bupivacaine blocks more **avidly and dissociates more slowly** from cardiac Na channels than does the S(−) optical isomer

Ropivacaine

- Onset time and duration of action are similar,
- but ropivacaine produces **less motor block** when injected at the same volume and concentration as bupivacaine (which may reflect an overall lower potency as compared with bupivacaine)
- **greater therapeutic index** than bupivacaine.
  - This improved safety profile likely reflects its formulation as a pure S(−) isomer—that is, having no R(+) isomer—as opposed to racemic bupivacaine.

Cocaine

- cardiovascular reactions are unlike those of any other local anesthetic
- Adrenergic nerve terminals normally reabsorb norepinephrine after its release. Cocaine inhibits this reuptake, thereby potentiating the effects of adrenergic stimulation.
- hypertension and ventricular ectopy.....contraindicated its use in patients anesthetized with halothane.
- Cocaine-induced arrhythmias have been successfully treated with adrenergic and Ca channel antagonists.
- **vasoconstriction** when applied topically and is a useful agent to reduce pain and epistaxis related to nasal intubation in awake patients.

D. Immunological

True **hypersensitivity reactions** to local anesthetic agents—as distinct from systemic toxicity .....

- are uncommon.

Esters appear more likely to induce a true **allergic reaction** (due to IgG or IgE antibodies) especially if they are derivatives (eg, procaine or benzocaine) of p -aminobenzoic acid

Commercial multidose preparations of amides often contain **methylparaben** , which has a chemical structure vaguely similar to that of PABA….

- responsible for most of the apparent allergic responses to amide agents.

E. Musculoskeletal

local anesthetics are mildly **myotoxic**

- When directly injected into skeletal muscle (eg, trigger-point injection treatment of myofascial pain)
- Regeneration usually occurs 3–4 weeks

Concomitant **steroid or epinephrine** injection worsens the **myonecrosis**.

F. Hematological

Lidocaine

- mildly **depresses normal blood coagulation**
  - (reduced thrombosis and decreased platelet aggregation) and
  - enhances fibrinolysis
  - reduced efficacy of an epidural autologous blood patch shortly after local anesthetic administration
  - lower incidence of embolic events in patients receiving epidural anesthetics

Clinical Uses of LA

- Local infiltration
- Topical anesthesia
- Peripheral nerve blocks
- Spinal,epidural & caudal anesthesia
- Arrhythmia therapy
- Pain management
- To suppress sympathetic response during endotrachial intubation


Akorn
NDC 17478-711-30
Lidocaine Hydrochloride Jelly USP, 2%
℞ only
Sterile 30 mL
Akorn
NDC 17478-711-10
Lidocaine Hydrochloride Jelly USP, 2%
℞ only
Sterile 5 mL

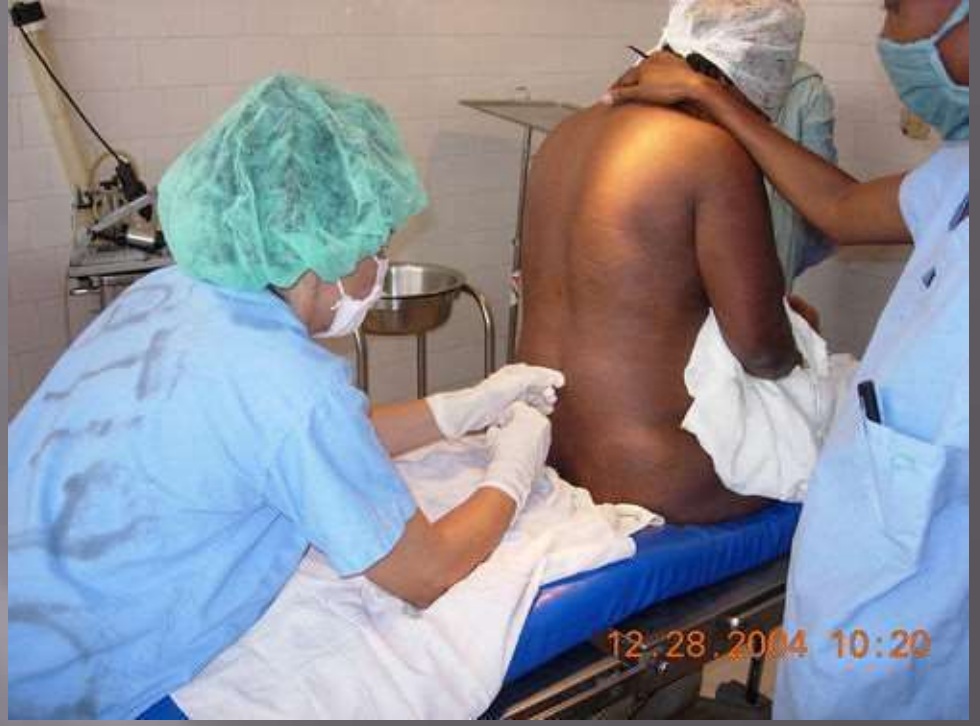

30 g cream
emla 5%
lidocaine prilocaine
AstraZeneca
emla 5%
lidocaine prilocaine
30 g cream
AstraZeneca


Afrin
Nasal Decongestant
Sinus
with Vapomase
#1 Doctor Recommended Brand
a unique formula for fast relief of sinus congestion and painful pressure.
12 Hour Spray
1/2 FL OZ (15 mL)
Afrin


Xylometazoline
Otrivin
1 mg/mL (0.1%)
METERED DOSE
NASAL SPRAY


Xylocaína Spray
AstraZeneca


5 mL
Cocaine 10%
HCl Topical Solution topique
100 mg/mL
SANDOZ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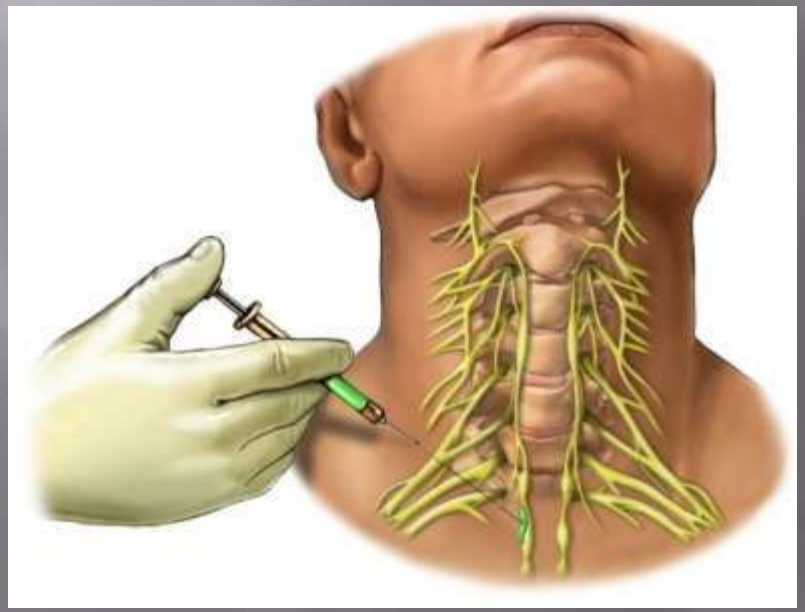

Lignocaine

- Intravenous lidocaine (1.5 mg/kg) may be effective in blocking the **reflex bronchoconstriction** sometimes associated with intubation
- lidocaine (1.5 mg/kg) can decrease cerebral blood fl ow and attenuate the rise in i**ntracranial pressure** that may accompany intubation in patients with decreased intracranial compliance
- Infusions of lidocaine **inhibit infl ammation and reduce postoperative pain.** Infused lidocaine reduces postoperative opioid requirements suffi ciently to reduce length of stay aft er colorectal or open prostate surgery.
- **to supplement general anesthetic** techniques
  - Infusions of lidocaine and procaine have been used to supplement general anesthetic techniques, as they are capable of reducing the MAC of volatile anesthetics by up to 40%.

Agent	Techniques	Concentrations Available	Maximum Dose (mg/kg)	Typical Duration of Nerve Blocks[1]
Esters				
Benzocaine	Topical[2]	20%	NA[3]	NA
Chloroprocaine	Epidural, infiltration, peripheral nerve block, spinal[4]	1%, 2%, 3%	12	Short
Cocaine	Topical	4%, 10%	3	NA
Procaine	Spinal, local infiltration	1%, 2%, 10%	12	Short
Tetracaine (amethocaine)	Spinal, topical (eye)	0.2%, 0.3%, 0.5%, 1%, 2%	3	Long
Amides				
Bupivacaine	Epidural, spinal, infiltration, peripheral nerve block	0.25%, 0.5%, 0.75%	3	Long
Lidocaine (lignocaine)	Epidural, spinal, infiltration, peripheral nerve block, intravenous regional, topical	0.5%, 1%, 1.5%, 2%, 4%, 5%	4.5 7 (with epinephrine)	Medium
Mepivacaine	Epidural, infiltration, peripheral nerve block, spinal	1%, 1.5%, 2%, 3%	4.5 7 (with epinephrine)	Medium
Prilocaine	EMLA (topical), epidural, intravenous regional (outside North America)	0.5%, 2%, 3%, 4%	8	Medium
Ropivacaine	Epidural, spinal, infiltration, peripheral nerve block	0.2%, 0.5%, 0.75%, 1%	3	Long

Adverse effect/toxicity of LA

Adverse effect/toxicity of LA

Toxicity.....with large dose

- CNS
- CVS

Transient neyrological symptoms..**TNS**

- transient pain & sensory abnormalities in back,buttocks or lower limbs
- Risk factors
  - lidocaine SA
  - lithotomy position
  - Outpatient anesthesia

Cauda equina syndrome...in continuous spinal anesthe by hyperbaric 5% lignocaine through microcatheters

- diffuse injury to cauda equina nerve roots by lignocaine direct neurotoxicity....bladder, bowl dysfunction & paraplegia

Allergic reaction.....mostly in Esters due to PABA

TABLE 21-14 POSSIBLE CAUSES OF TRANSIENT NEUROLOGIC SYMPTOMS

Concentration-dependent neurotoxicity
Patient positioning
Early ambulation
Needle trauma
Neural ischemia
Pooling secondary to maldistribution

Allergic Reactions to Local Anesthetics

1. True allergic reactions to local anesthetics, especially aminoamides, are rare.

2. Increased allergenic potential with ester local anesthetics may be caused by metabolism to para-aminobenzoic acid, which is a known antigen.

3. Preservatives such as methylparaben and metabisulfite can also provoke an allergic response.

4. Evaluation with skin pricks, intradermal injections, or subcutaneous provocative dose challenges are recommended for individuals with suspected local anesthetic allergy

LOCAL ANAESTHETIC TOXICITY

Each LA has **maximum safe doses** .....But it must be recognized that the maximum safe dose depends on

- The patient pathophysiology
- The specifi c nerve block
- The rate of injection
- Other factors.

Systemic toxicity still remains a problem in clinical practice. **Reasons** for this include

- An increase in the practice of upper limb block,
- Increased surgical use of local anaesthetics in high volumes for procedures such as
- Tissue infiltration
- Tumescent anesthesia
- Use of high-concentration compound local anaesthetic mixture
- Inappropriate use of medical devices
- Administration of levobupivacaine and ropivacaine at doses greater than those recommended by the manufacturers.
- Unintentional intravascular injection

Maximum safe

TABLE 4.2

Maximum Doses of Local Anaesthetics Administered as a Bolus

	Plain (mg)	*Plain per kg (mg kg^{-1})*	*With Adrenaline (mg)*	*With Adrenaline (mg kg^{-1})*	*Maximum Dose Over 24 h (mg)*
2-Chloroprocaine	800	11	1000 mg	13	
Prilocaine	600	8	600 mg	8	
Lidocaine	200	3	500 mg	7	
Mepivacaine	400	6	500 mg	7	
Bupivacaine	150	2	225 mg	3	400
Levobupivacaine	150	2			400
Ropivacaine	225	3			800

Adapted from McLeod GA, Butterworth JF, Wildsmith JAW (2008) Local anesthetic systemic toxicity. In: Cousins, Bridenbaugh, Horlecker, Carr (eds) Neural blockade. Lippincott, Williams & Wilkins, Ch 5 pp 114–132.

Mechanisms of Systemic Toxicity

Direct injection into the vasculature (especially **arterial injection** in the head and neck)

- Blindness
- Aphasia
- Hemiparesis
- ventricular arrhythmias including fibrillation,
- convulsions,
- respiratory depression,
- coma
- cardiac arrest

The most potent local anaesthetics have the highest tendency to cause systemic toxicity.

Cardiovascular effects are caused by **blockade of cardiac VASCs and K+ channels.**

Levobupivacaine and ropivacaine are thought less likely to interact with cardiac VASCs.

CNS...mechanism

Convulsions may be caused by the

- **blockade of GABAA** receptors in the CNS and
- respond to positive modulators of GABAA receptor function (barbiturates, propofol and benzodiazepines).

local anaesthetics interfere with
mitochondrial energy functions

- Involvement of mitochondria in local anaesthetic toxicity was proposed when a patient with carnitine deficiency showed marked sensitivity to a low dose of bupivacaine,

Clinical Manifestations of LA toxicity

Toxicity involves CNS & CVS

- CNS more sensitive to toxic effects of LA.... So involves first usually

CNS toxicity

- Light-headeness,
- Tinitis
- perioral numbness,confusion
- Muscle twitching
- auditory & visual hallucinations
- Tonic-clonic seizure
- Unconciousness
- respiratory arrest

CVS toxicity….less common but can be fatal

- Hpertension
- Tachycardia
- Decreased contractality & cardiac output…hypotension
- Sinus bradycardia
- ventricular dysrhythmias
- circulatory arrest

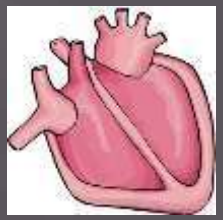

TABLE 21-10 DOSE-DEPENDENT SYSTEMIC EFFECTS OF LIDOCAINE

Plasma Concentration (μg/mL)	Effect
1–5	Analgesia
5–10	Lightheadedness
	Tinnitus
	Numbness of tongue
10–15	Seizures
	Unconsciousness
15–25	Coma
	Respiratory arrest
>25	Cardiovascular depression

1	Recognition	Sudden alteration in mental status, severe agitation or loss of consciousness, with or without tonic-clonic convulsions Cardiovascular collapse: sinus bradycardia, conduction blocks, asystole and ventricular tachyarrhythmias	
2	Immediate management	Stop injecting the LA Call for help Maintain the airway and, if necessary, secure it with a tracheal tube Give 100% oxygen and ensure adequate lung ventilation (hyperventilation may help by increasing plasma pH in the presence of metabolic acidosis) Confirm or establish intravenous access Control seizures: give a benzodiazepine, thiopental or propofol in small incremental doses Assess cardiovascular status throughout Consider drawing blood for analysis, but do not delay definitive treatment to do this	
3	Treatment	**In circulatory arrest** Start cardiopulmonary resuscitation (CPR) using standard protocols Manage arrhythmias using the same protocols, recognising that arrhythmias may be very refractory Consider the use of cardiopulmonary bypass if available **Consider lipid emulsion** Continue CPR with lipid emulsion Recovery may be >1 hour	**Without circulatory arrest** Use conventional therapies to treat: hypotension, bradycardia, tachyarrhythmia **Consider lipid emulsion** Propofol is not a suitable substitute for lipid emulsion
4	Follow-up	Arrange safe transfer to a clinical area with appropriate equipment and suitable staff until sustained recovery is achieved Exclude pancreatitis by regular clinical review, including daily amylase or lipase assays for two days Report cases as follows: in the United Kingdom to the National Patient Safety Agency (via www.npsa.nhs.uk) in the Republic of Ireland to the Irish Medicines Board (via www.imb.ie) If lipid has been given, please also report its use to the international registry at www.lipidregistry.org. Details may also be posted at www.lipidrescue.org	

Reproduced with permission from AAGBI Safety Guideline Management of severe local anaesthetic toxicity http://www.aagbi.org/publications/guidelines/docs/la_toxicity_ 2010.pdf.

Management of systemic toxicity

Management of systemic toxicity

- Recognition of the prodromal symptoms
- Treatment
- Follow up

1.Recognition of the prodromal symptoms

CNS	• Sudden alteration in mental status • severe agitation or • loss of consciousness • with or without tonic-clonic convulsions
Cardiovascular collapse:	• sinus bradycardia • conduction blocks • asystole and • ventricular tachyarrhythmias

2.Immediate management A-B-C

Stop injecting the LA

Call for help

Maintain the **airway** and, if necessary, secure it with a tracheal tube

Give 100% oxygen and ensure **adequate lung ventilation** (hyperventilation may help by increasing plasma pH in the presence of metabolic acidosis)

Confirm or establish **intravenous access**

Control seizures: give a benzodiazepine, thiopental or propofol in small incremental doses

Assess cardiovascular status throughout

Consider drawing blood for analysis, but do not delay definitive treatment to do this

3.Treatment

In circulatory arrest

- Start cardiopulmonary resuscitation **(CPR)** using standard protocols
- Manage **arrhythmias** using the same protocols, recognising that arrhythmias may be very refractory
- Consider the use of **Cardiopulmonary bypass** if available
- Consider **lipid emulsion**
- Continue CPR with lipid emulsionemulsion
- Recovery may be > 1 hour

arrest

Use conventional therapies to treat:

hypotension,

bradycardia

tachyarrhythmia

Propofol is not a suitable substitute for lipid emulsion

- Use conventional therapies to treat:

4.Follow-up

Arrange **safe transfer** to a clinical area with appropriate equipment and suitable staff until sustained recovery is achieved

Exclude **pancreatitis** by regular clinical review, including daily amylase or lipase assays for two days

Report cases

Intralipid doses

Immediately

- Give an initial intravenous **bolus** injection of 20% lipid emulsion 1.5 mL/kg over 1 min
  - **AND**
- Start an intravenous **infusion** of 20% lipid emulsion at **15** mL/kg/hr

After 5 mins

- Give a maximum of **two repeat boluses** (same dose) if:
  - cardiovascular stability has not been restored
  - or an adequate circulation deteriorates
- Leave **5 min between boluses**
- A **maximum of three boluses** can be given (including the initial bolus)
  - **AND**
- Continue i**nfusion** at same rate, but
- double the rate to **30** mL kg−1 h−1 at any time after 5 min, if: *cardiovascular stability has not* been restored or an adequate circulation deteriorates
- Continue infusion until stable and adequate circulation restored or maximum dose of lipid emulsion given

Prevention of Severe Local Anaesthetic Toxicity

Regional blocks should always be performed in an area equipped to deal with cardiorespiratory collapse, such as an **anaesthetic room or block room** within the theatre suite.

The age, weight and condition of the patient should be taken into account, and **doses adjusted** accordingly.

Syringes of local anaesthetics and perineural and epidural infusions should be **labelled** clearly. Use of premixed sterile solutions is encouraged.

Gentle aspiration of the syringe should precede every injection, but anaesthetists should be aware that negative aspiration does not guarantee extravascular positioning of the needle tip – false negatives do occur.

Both during and after drug administration, the anaesthetist must **keep talking to the patient.**

An appropriate **test dose** should be given depending on the situation. For example, a test dose of 3 mL of 'epidural' bupivacaine 0.5% (15 mg) injected accidentally into the intrathecal space will provide a definitive outcome – spinal anaesthesia. In contrast, injection of 0.5 to 1 mL during a perineural block under ultrasound is usually sufficient to differentiate between intraneural and extraneural injection.

Ultrasound allows visualization of the position of the needle or catheter, their relationship to other structures – both nerves and large blood vessels – and the spread of local anaesthetic solution, although no definitive evidence exists yet that its use reduces overall complication rates.

CLINICAL PREPARATION OF LOCAL ANAESTHETICS

Local anaesthetics are presented clinically as **hydrochloride salts with pH 5–6** .... enable them to be dissolved in water (resulting in an acidic solution..... because an alkaline pH destabilizes local anaesthetic solutions.

Alteration of **pH influences the rate of onset**.

carbonated lidocaine favours the un-ionized molecule and has a faster onset of action

acidic tissue enhances ionization and reduces the onset and efficacy of local anaesthetics.

Local anaesthetics are available as solutions for

- Injection
- Sprays
- creams
- gels.

Most local anaesthetic preparations contain a preservative agent such as

- 0.1% sodium metabisulphite, with or without a fungicide.
- Multidose vials contain 1mg/ml of the preservative methyl parahydroxybenzoate.

Drug may also be combined (by the manufacturer or in some cases the clinician) with

- **Other local anaesthetics** (e.G. EMLA cream - eutectic mixture of local anaesthetics) or
- Additives designed to enhance their effects. These include
- **Adrenaline** 1/200,000 or phenyephrine
- **Bicarbonate** (eg 0.15ml of 8.4% solution added to 10ml 0.5% bupivacaine)....Increases the ph of the environment when administered. Consequently more drug is present in its unionised form and speed of onset
- **Glucose** (usually 80mg/ml)....To increase the baricity of the solution

TABLE 16–3 Clinical use of local anesthetic agents.

Agent	Techniques	Concentrations Available	Maximum Dose (mg/kg)	Typical Duration of Nerve Blocks[1]
Esters				
Benzocaine	Topical[2]	20%	NA[3]	NA
Chloroprocaine	Epidural, infiltration, peripheral nerve block, spinal[4]	1%, 2%, 3%	12	Short
Cocaine	Topical	4%, 10%	3	NA
Procaine	Spinal, local infiltration	1%, 2%, 10%	12	Short
Tetracaine (amethocaine)	Spinal, topical (eye)	0.2%, 0.3%, 0.5%, 1%, 2%	3	Long
Amides				
Bupivacaine	Epidural, spinal, infiltration, peripheral nerve block	0.25%, 0.5%, 0.75%	3	Long
Lidocaine (lignocaine)	Epidural, spinal, infiltration, peripheral nerve block, intravenous regional, topical	0.5%, 1%, 1.5%, 2%, 4%, 5%	4.5 7 (with epinephrine)	Medium
Mepivacaine	Epidural, infiltration, peripheral nerve block, spinal	1%, 1.5%, 2%, 3%	4.5 7 (with epinephrine)	Medium
Prilocaine	EMLA (topical), epidural, intravenous regional (outside North America)	0.5%, 2%, 3%, 4%	8	Medium
Ropivacaine	Epidural, spinal, infiltration, peripheral nerve block	0.2%, 0.5%, 0.75%, 1%	3	Long

Drug Interactions

Local anesthetics potentiate **nondepolarizing muscle relaxant** blockade

Succinylcholine and ester local anesthetics depend on **pseudocholinesterase** for metabolism. Concurrent administration might conceivably increase the time that both drugs

Dibucaine, an amide local anesthetic, inhibits pseudocholinesterase, and the extent of inhibition by dibucaine defi nes one family of genetically abnormal pseudocholinesterases

Pseudocholinesterase inhibitors (eg, organophosphate poisons) can prolong the metabolism of ester local anesthetics

Histamine (H 2) receptor blockers and β blockers (eg, propranolol) decrease hepatic blood fl ow and lidocaine clearance.

Opioids potentiate epidural and spinal analgesia produced by local anesthetics.

α 2 -adrenergic agonists (eg, clonidine) potentiate local anesthetic analgesia produced aft er epidural or peripheral nerve block injections.

THANKS