Loss of function from LAs: temperature/pain → touch → proprioception → motor control

- Different sized nerve fibers have different functions (thin = more sensitive to LA)
- To block conduction, several nodes of Ranvier need to be affected (larger nerves = further apart nodes are)

Local anesthetics SAR

- Lipophilic group (usually aromatic ring) and hydrophilic group (1^o, 2^o, 3^o amine) linked by an amide or ester group
- pKa = 8 (acidic form predominates at physiological pH and is in its soluble form)

MOA of LAs:

1. Acidic form is soluble
2. Basic form to cross membrane
3. Acidic form in cytosol to block Na^+ channel from inside out (use-dependent – need AP to block it)

Delivery of LAs: topical, infiltration, nerve block, epidural, subarachnoid (into CSF)

Factors that affect onset and duration of LAs

pH:

Uncharged (basic) form crosses the membrane

Charged (acidic) form blocks the channel

Redistribution → systemic circulation (protein bound)

Esters: broken down by pseudocholinesterase (in plasma) – short $t_{1/2}$

Amides: broken down in liver by N-dealkylation & hydrolysis

LA	pKa	Lipid sol	Block duration (min)	Toxicity
Esters				
Procaine	8.7	Very low	60	Low
Benzocaine	2.5	Moderate	While in contact	Methemi-globinemia
Amides				
Lidocaine	7.9	Moderate	90-200	Moderate
Bupivacaine	8.1	High	180-600	High (cardiotoxicity)

Side effects of LAs

CNS:

- Initial: nervousness, dizziness, blurred vision & tremors (transient)
- Later: drowsiness, convulsions, unconsciousness, respiratory arrest
- Direct effect on neuronal sodium channels

CV:

- Hypotension, CV collapse, bradycardia, cardiac arrest

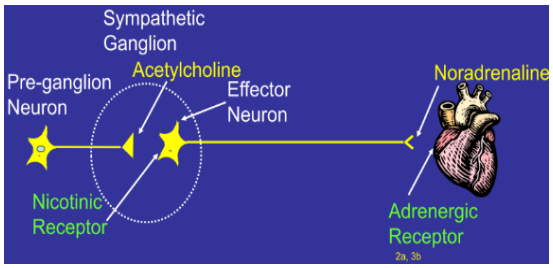
➢ Direct effect of LAs on cardiac & arteriolar sodium channels

➢ Indirect effect due to sympathetic blockade & CNS

Local:

- Hypersensitivity (dermatitis to breathing difficulties) → esters more common
- Prolonged anesthesia may last for several weeks post injection

SNS



α1 selective agonists

- Phenylephrine: mydriatic, decongestant, raises BP (used IV)
- Xylo & oxy-metazoline: topical decongestants (promote constriction of nasal mucosa, ↓ mucus production)
  - ➔ Oxymetazoline may cause hypotension (affinity for α2 receptors)

α2 selective agonist: clonidine

- Antihypertensive (central action to reduce sympathetic output)
- Reduces sx of nicotine & alcohol withdrawal
- Analgesic (epidural)
- Vasoconstriction (local application)

Causes dry mouth, drowsiness & sedation, constipation
→ decreased sympathetic tone may reduce salivation
→ blockade of release of acetylcholine

β selective agonist: isoproterenol

- Positive chronotropic & inotropic actions (β1 effect)
- Potent vasodilator (β2 effect)
- Increased in cardiac output → fall in DBP & decrease/slight increase in SBP

β2 selective agonist: salbutamol

- Treatment of asthma (bronchodilator)

β3 selective agonist: mirabegron

- Relaxes bladder detrusor muscle

Causes hypertension & tachycardia (monitoring) & inhibits CYP2D6

Epinephrine (adrenaline): non-selective agonist (α & β)

CNS	• Doesn't cross BB • Fear, anxiety, restlessness, tremor, HA (indirect) • Mydriasis (pupil dilation)
CV	• Vasoconstriction • ↑ ionotropy & chronotropy • Vasodilates skeletal muscle blood vessels (↑SBP but ↓ DBP)
RESP	• Bronchodilation (relaxation of bronchial smooth muscle)
GI	• Decreased motility and secretion
GU	• Decreased voiding pressure
Glands	• Sweating (indirect) • Pallor (variable)

Used for: reduction of regional blood flow (LA); cardiac arrest; bronchial asthma; anaphylaxis

α1	Vascular smooth mscl	Contraction
	Pupillary dilator muscle	Contraction (pupil dilates)
	Prostate	Contracts
	Bladder sphincter	Contracts
α2	Adrenergic & cholinergic	Inhibit NT release
	Vascular smooth mscl	Contraction
	GI smooth muscle	Relax (indirect)
	Fat cells	Inhibits lipolysis
β1	Heart	Positive chonotrope & inotrope
β2	Respiratory & vascular smooth muscle	Relaxation (dilate)
	Ciliary epithelium	Production of aqueous humor
β3	Fat cells	Activates lipolysis
	Bladder	Mediates relaxation

α1 selective antagonist: prazosin (low bioavailability)

- Hypertension (2nd); mild benign prostatic hypertrophy

ADRs: reflex tachycardia & postural hypotension; mioisis & nasal stuffiness; ↓ bladder sphincter tone

1st dose effect (dizziness to syncope) in elderly

Non-selective β blocker: propranolol (low bioavailability)

- Hypertension, angina, migraine, essential tremor, decrease sudden death after MI, severe hyperthryroidism

ADRs: fatigue, dizziness, depression, nightmares, bradycardia, increases triglyceride levels