PHARMACOLOGY

LECTURE NO. 1

WRITER : Ruaa Hdeib

CORRECTOR:

DOCTOR: Yacoub M. Irshaid

Local Anesthetics

Specific area

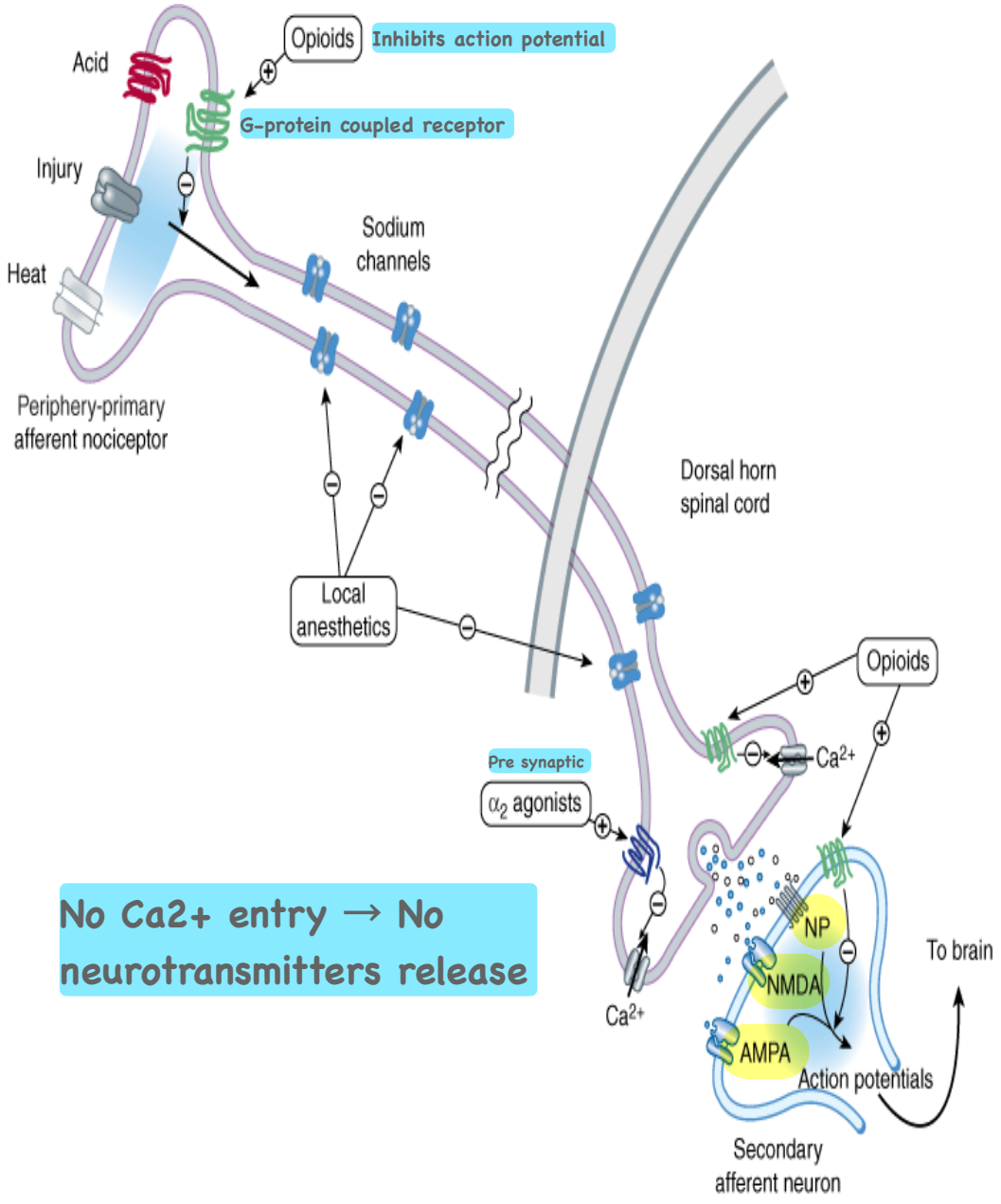
An agent that stops pain impulses

- They reversibly block impulse conduction along nerve axons that utilize sodium channels as the primary means of action potential generation.
- They are used to block pain sensation from specific areas of the body.
- They also block sympathetic vasoconstrictor impulses to specific areas of the body.

So they block Na+ channels

✓This effect is unwanted because as a result there will be vasodilation and this will accelerate the exit of the local anesthetic from the injection site → reduce the duration of action of the local anesthetic → need for more than one injection → bad consequences.

✓Na+ channels are important for pain sensation.



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Schematic diagram of a primary afferent neuron mediating pain, its synapse with a secondary afferent in the spinal cord, and the targets for local pain control. The primary afferent neuron cell body is not shown. At least three nociceptors are recognized: acid, injury, and heat receptors. The nerve ending also bears opioid receptors, which can inhibit action potential generation. The axon bears sodium channels and potassium channels (not shown), which are essential for action potential propagation. Synaptic transmission involves release of substance P, a neuropeptide (NP) and glutamate and activation of their receptors on the secondary neuron. Alpha2 adrenoceptors and opioid receptors modulate the transmission process.

Local Anesthetics

The ionotropic glutamate receptors:

1. **α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA) receptors:**

- **Present in all neurons.**
- **The majority of these receptors are permeable to Na^+ and K^+, but NOT to Ca^{2+}.** They are ion channels

2. **Kainic acid (KA) receptors:** (Not related to pain)

- **They are expressed at high levels in the hippocampus, cerebellum, and spinal cord.**

Local Anesthetics

- **Kainate receptors are permeable to Na^+ and K^+, and some can also be permeable to Ca^{2+}.**

3. ***N*-methyl-D-aspartate (NMDA) receptors:**

- **Are present on essentially all neurons in the CNS (like AMPA receptors).**
- **All NMDA receptors are highly permeable to Ca^{2+} as well as to Na^+ and K^+.**

Local Anesthetics

- Peptides often coexist with a conventional nonpeptide transmitter in the same neuron.
- Substance P is contained in and released from small unmyelinated primary sensory neurons in the spinal cord and brain stem and causes a slow EPSP in target neurons → transmit noxious stimuli. Noxious stimuli = Stimuli that cause pain.
- Glutamate, which is released with substance P from these synapses plays an important role in transmitting pain stimuli.

Local Anesthetics

- **Cocaine** is the first local anesthetic introduced into clinical practice (for ophthalmic use, 1884). Its chronic use was associated with psychological dependence (addiction).

Drug of abuse nowadays & it is not commonly used

- **Procaine** was synthesized to improve upon the clinical properties of cocaine (1905), and became the dominant local anesthetic for ~ 50 years.

Not commonly used nowadays

- **Lidocaine** (1943) is the most widely used local anesthetic.

(lignocaine)

Hydrophobic → penetrate the membrane

Hydrophilic → block the channel

Local Anesthetics

Hydrophobic

- Most agents consist of a lipophilic group (aromatic) connected via an ester or amide linkage to an ionizable group (tertiary amine). Base
- They are weak bases, and exist in the body as either uncharged base or a cation.
- The cationic form is the most active form at the receptor because it can not exit from the closed channels.

✓The aromatic ring improves the lipid solubility of the drug → ease the drug entrance through the membrane.
✓The tertiary amine play a pivotal role in the sequence of events leading to conduction block (block Na+ channel and because it is ionized it can't get back so the channel will be closed for a longer period of time.

Local Anesthetics

- **The uncharged form is important for rapid penetration of biologic membranes, since the receptor is not accessible from the external side of the cell membrane.**
- **They are much less effective when injected into infected tissue, because low pH cause ionization of the drug.** In cases of inflammation and pus formation (acidic) these drugs (bases) will get ionized → they can't penetrate the membrane → there will be no anesthetic effect.
- **Esters usually have a shorter duration of action because they are more prone to hydrolysis than amides.** ✓They have short half life ✓Hydrolyzed by pseudocholinesterase ✓We don't know much about its pharmacokinetics

Local Anesthetics

Classification:

1. **Amides:**

Most commonly used

Lidocaine (lignocaine), Mepivacaine, Bupivicaine, Levobupivicaine, Prilocaine, Ropivacaine.

They differ in their duration of action.. so they differ in their adverse effects

2. **Esters:**

Cocaine, Procaine, Tetracaine, Benzocaine.

Not commonly used

Local Anesthetics

Mechanism of Action:

- **The primary mechanism of action is blockade of voltage-gated sodium channels.**
- **Local anesthetics bind to receptors near the intracellular end of the sodium channel and block the channel in a time- and voltage-dependent fashion.**

Local Anesthetics

✓We give the anesthetics injection around the nerve NOT inside it (if you give it inside the nerve the nerve may got damaged).

- When progressively increasing concentrations of a local anesthetic are applied to a nerve fiber, ① the threshold for excitation increases, ② impulse conduction slows, ③ the rate of rise of the action potential declines, ④ the action potential amplitude decreases, ⑤ and finally, the ability to generate an action potential is completely abolished.

Local Anesthetics

- **Nerve fibers differ significantly in their susceptibility to block by local anesthetics on the basis of differences in size and degree of myelination.**
- **The smaller B and C fibers are blocked first, followed by other sensations, and motor function is the last to be affected.**

Local Anesthetics

TABLE 26–1 Susceptibility to block of types of nerve fibers.

Fiber Type	Function	Diameter (μm)	Myelination	Conduction Velocity (m/s)	Sensitivity to Block
Type A	Least susceptible				
Alpha	Proprioception, motor	12–20	Heavy	70–120	+
Beta	Touch, pressure	5–12	Heavy	30–70	++
Gamma	Muscle spindles	3–6	Heavy	15–30	++
Delta	Pain, temperature	2–5	Heavy	12–30	+++
Type B	Preganglionic, autonomic	<3	Light	3–15	++++
Type C	Most susceptible				
Dorsal root	Pain	0.4–1.2	None	0.5–2.3	++++
Sympathetic	Postganglionic	0.3–1.3	None	0.7–2.3	++++

Reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 12th ed. McGraw-Hill, 2012.

Local Anesthetics

Other Actions:

1. **Motor neurons are also affected and motor paralysis, which can be desirable during surgery, can limit the ability of the patient to cooperate during obstetric delivery and may impair respiratory activity.**
2. **Autonomic nerve block can result in hypotension and interfere with bladder function leading to urinary retention.**

In spinal anesthesia incontinence may happen

✓In GI evacuation constipation may occur

Local Anesthetics

3. **Some local anesthetics (lidocaine) have antiarrhythmic effects in the heart at concentrations lower than those needed to produce nerve block. Others (bupivacaine, ropivacaine) can cause lethal arrhythmias in high concentrations.**

✓Lidocaine is used in treating MI and it is safer to use than the others.

✓High dose of lidocaine causes arrhythmia.

✓Bupivacaine and ropivacaine are long acting drugs so they are more likely to cause arrhythmias than lidocaine.. because of that we use lidocaine to treat cardiac arrhythmias.

Local Anesthetics

Pharmacokinetics:

- Ester-based local anesthetics are rapidly broken down in plasma (t½ < 1 minute). Hydrolyzed very fast by pseudocholinesterase

Amides

- **Absorption** of the local anesthetic to the systemic circulation from the site of application depends on many factors including local blood flow.
- Application to a highly vascular area results in high blood levels of the local anesthetic.

✓Amides are metabolized by the liver.

Local Anesthetics

- **Vasoconstrictor substances such as epinephrine reduce the systemic absorption of the local anesthetic from the injection site, by decreasing blood flow, and prolong its local effect. Also, the systemic toxic effects of the local anesthetic are reduced.**

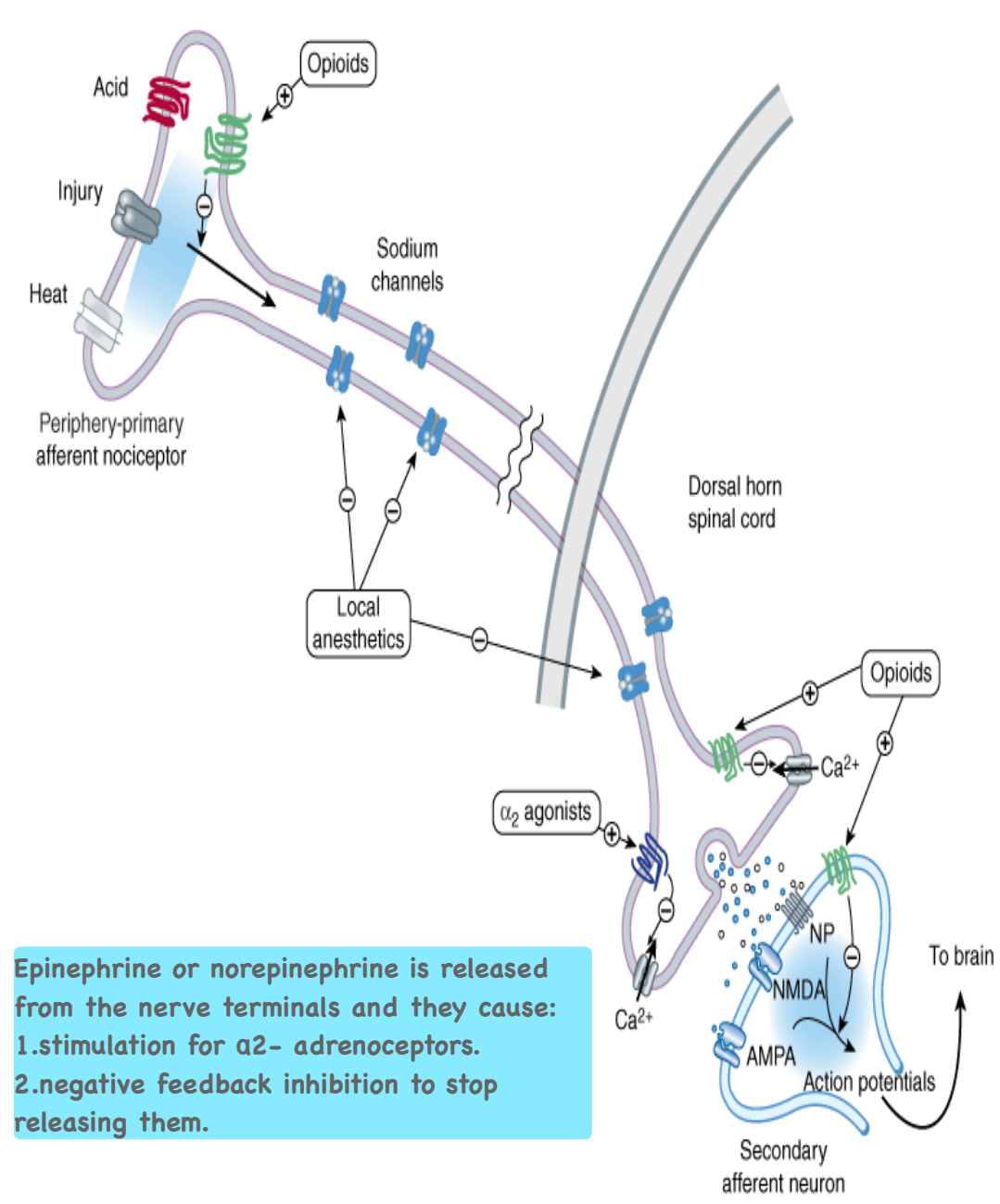
✓We don't want the local anesthetics to enter the circulation because they will cause toxic effects (cardiac arrhythmias and convulsions).

Local Anesthetics

It is not selective/ not used

- Epinephrine, when used in spinal anesthesia, stimulates α_2- adrenoceptors which inhibit release of substance P (neurokinin-1) and reduce sensory neuron firing → enhancing and prolonging local anesthesia.
- Clonidine and dexmedetomidine (α_2-agonists) have been used to augment local anesthetic effect in the subarachnoid space and peripheral nerves.

Has many bad adverse effects like depression



Epinephrine or norepinephrine is released from the nerve terminals and they cause:
1.stimulation for α2- adrenoceptors.
2.negative feedback inhibition to stop releasing them.

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Schematic diagram of a primary afferent neuron mediating pain, its synapse with a secondary afferent in the spinal cord, and the targets for local pain control. The primary afferent neuron cell body is not shown. At least three nociceptors are recognized: acid, injury, and heat receptors. The nerve ending also bears opioid receptors, which can inhibit action potential generation. The axon bears sodium channels and potassium channels (not shown), which are essential for action potential propagation. Synaptic transmission involves release of substance P, a neuropeptide (NP) and glutamate and activation of their receptors on the secondary neuron. Alpha2 adrenoceptors and opioid receptors modulate the transmission process.

Local Anesthetics

- **Vasoconstrictors are less effective in prolonging anesthetic action of the more lipid soluble, long acting drugs (bupivacaine, ropivacaine) possibly because they are highly tissue-bound.**
- **Cocaine is peculiar in its sympathomimetic properties. It blocks catecholamine reuptake.**

There will be high local concentration of catecholamine then no need for a vasoconstrictor.

In cocaine abusers, catecholamine reuptake inhibition can cause more vasoconstriction, high blood pressure, high cardiac contractility → more oxygen requirements & MI.

Local Anesthetics

- **The distribution of the ester type local anesthetics has not been characterized because of the extremely short half-lives.** Clinically, we don't give the amine agents as an IV injection
- **The amide agents are widely distributed after IV bolus administration (??!!). They can be sequestered in fat. Caution!!** This should not happen.
- **Ester-type agents are hydrolyzed in the plasma by butyrylcholinesterase (psuedocholinesterase) to inactive metabolites.**

Local Anesthetics

- The amide agents are metabolized in the liver by microsomal cytochrome P450 isozymes. Toxicity may result in patients with hepatic disease (lidocaine half-life increases from 1.6 to 6 hours). Variations depend on the concentration of cytochrome p450
- Reduction in hepatic blood flow also decreases elimination of the amide agents. Beta blockers / histamine h2 blockers they reduce the blood flow to the liver.
- There is also a possibility of drug interactions with agents metabolized by the same isozyme resulting in reduced elimination of the local anesthetic.

Local Anesthetics

Therapeutic Uses:

- To produce highly effective analgesia in well defined regions of the body.
- The usual routes of administration include:

1. Topical application: nasal, mucosa, wound margins. Spray
2. Infiltration: injection in the vicinity of peripheral nerve endings.

Infiltration local anesthesia

Local Anesthetics

3. Nerve block: injection in the vicinity of major nerve trunks. Around the nerve
4. Injection into the epidural or subarachnoid spaces surrounding the spinal cord. Spinal anesthesia

We use dexmedetomidine (α2-agonists) with them to enhance the anesthesia.

5. Intravenous regional anesthesia for short surgical procedures involving the upper and lower limbs. Explain!

Used in orthopedic surgeries

Refer to the lecture the doctor explained this point greatly!
From 46:35 to 51:05

Local Anesthetics

- **Repeated injection of the local anesthetic can result in tachyphylaxis (loss of effectiveness) due to extracellular acidosis.** Tachyphylaxis = fast Tolerance
- **Local anesthetics are commonly marketed as hydrochloride salts (pH ~ 4-6).**

Local Anesthetics

Other uses:

1. Neuropathic pain syndromes.
2. Cardiac arrhythmias. Given lidocaine as IV infusion

a) Intravenous (lidocaine)

b) Oral (mexiletine and tocainide)

They are local drugs like lidocaine, not used as local anesthetics, instead we use them as antiarrhythmic drugs in the same indication style of lidocaine.

Local Anesthetics

Adverse Effects:

- **Include systemic effects following absorption of the agent from the site of administration and direct neurotoxicity from the local effects when administered in close proximity to the spinal cord and major nerve trunks.**

Local Anesthetics

1. **Central nervous system:**

- **At low concentration, all local anesthetics are able to produce sleepiness, dizziness, visual and auditory disturbances and restlessness.**
- **An early symptom of local anesthetic toxicity is circumoral and tongue numbness and a metallic taste.** → Treat the patient with diazepam injection

Local Anesthetics

- At higher concentration, nystagmus and muscular twitching occur, followed by overt tonic-clonic convulsions. They apparently cause depression of cortical inhibitory pathways. The stage of unbalanced excitation is followed by generalized CNS depression.
- Premedication with a parenteral benzodiazepine can provide prophylaxis against seizures.

Local Anesthetics

- **Cocaine, a drug of abuse, may be abused to obtain a feeling of well-being. It can produce all the adverse effects of local anesthetics in addition to severe cardiovascular toxicity – hypertension, arrhythmias and myocardial failure.**

2. **Direct local neural toxicity:**

- **Transient neuropathic symptoms.**
- **More with lidocaine and chloroprocaine.**

Local Anesthetics

3. **Cardiovascular toxicity:**

- **Results from effects on the cardiac and smooth muscle membranes and indirect effects on the ANS.**
- **Block cardiac sodium channels (antiarrhythmic).**
- **At extremely high concentration, they can block calcium channels.**

Local Anesthetics

- They depress cardiac contraction and produce arteriolar dilation (except cocaine) leading to systemic hypotension. → Then cardiovascular collapse then death
- Large doses of bupivacaine and ropivacaine have produced cardiovascular collapse.
- Cocaine produces vasoconstriction and hypertension as well as cardiac arrhythmias. Also can lead to local ischemia and ulceration of mucosal membranes in chronic abusers who use the nasal route.

Local Anesthetics

4. **Hematologic effects: Administration of large doses of prilocaine** (An amide -type drug) **during regional anesthesia may lead to accumulation of the metabolite *o*-toluidine, an oxidizing agent capable of converting hemoglobin to methemoglobin.**

Local Anesthetics

5. **Allergic reactions:**

- **Ester-type agents are metabolized to *p*-aminobenzoic acid derivatives which seem to produce allergic reactions.**
- **Amide-type agents are extremely unlikely to produce allergic reactions.**

✓We don't commonly use ester-type agents so we don't expect allergic reactions much.
✓Amide-type agents are more commonly used.

"إنَّا كنا أصاغرَ قومٍ، ثم نحن اليومَ أكابرُ، وإنَّكم اليوم أصاغرُ قومٍ، وستكونون كبارًا، فتعلَّموا العلمَ تسودوا به قومَكم، ويحتاجون إليكم"

عروة بن الزبير