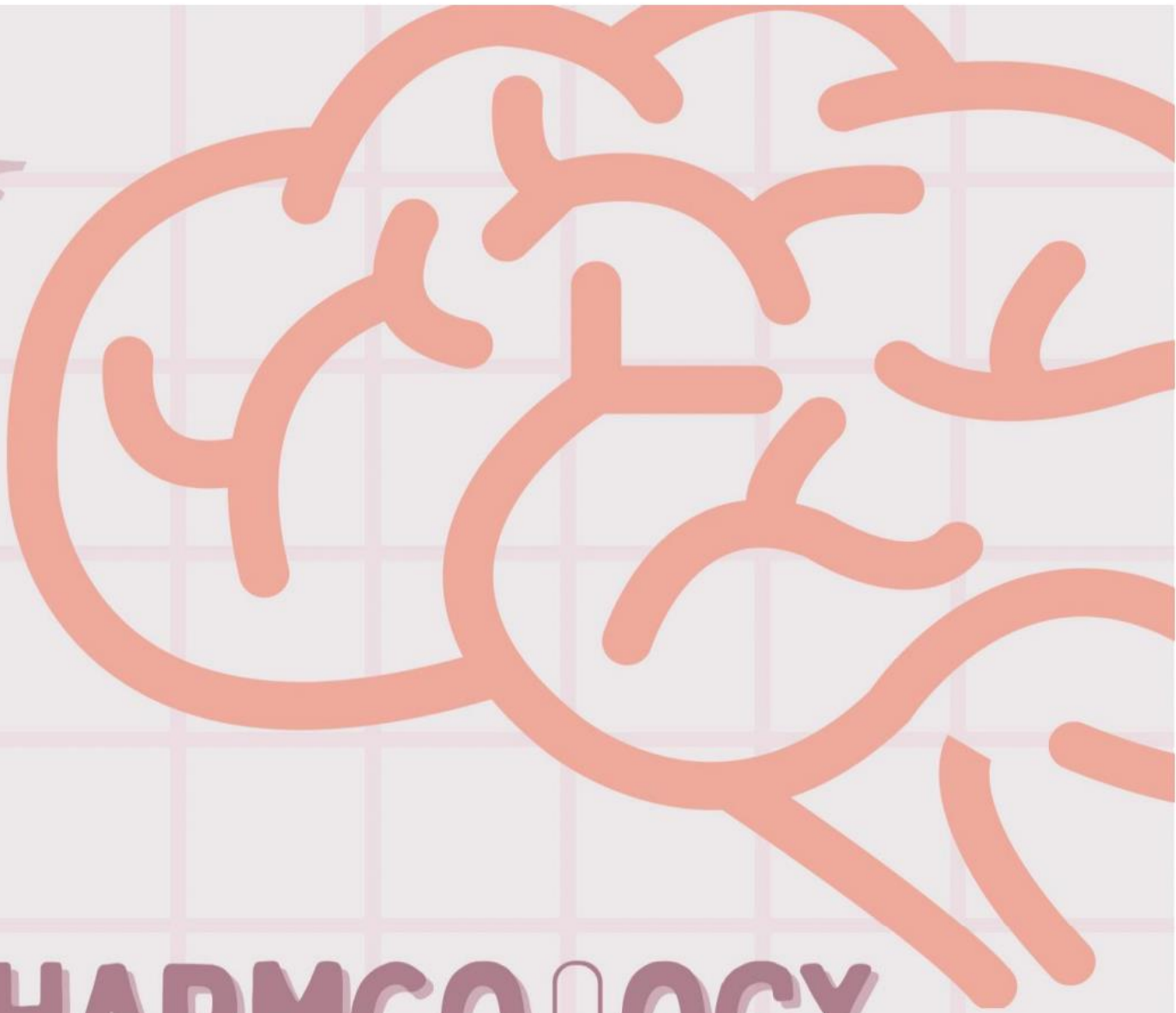

PHARMCOLOGY

SHEET NO. 1

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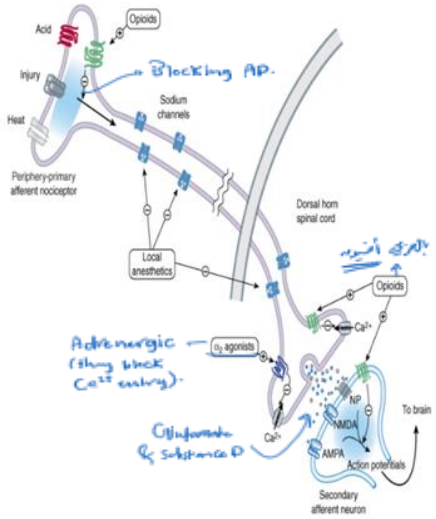
كلام الدكتور باللون البنفسجي* التوقيت بالاحمر*

Local Anesthetics:

(Anesthetics is an agent that stops pain impulses through nerves, Local in a specific area). (they block pain impulses in specific area, different than general anesthesia where the patient is sleeping)(Ex. local anesthetics applied around the nerve supplying the  not in the nerve).

• They **reversibly block impulse conduction** along nerve axons that **utilize sodium channels** as the primary means of action potential generation. (they enter the neuron and block sodium channels from the inside).
• Used to **block pain sensation from specific areas** of the body.
• Disadvantage: They also **block sympathetic vasoconstrictor impulses** (causing vasodilation and accelerate its elimination through blood circulation reducing the action of duration of the local anaesthetic) to specific areas of the body.

(10:00)



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.

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com
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The **ionotropic (related to ion channels) glutamate receptors**:

1. α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA for short) receptors:
• Present in ***all*** neurons.
• Majority of these receptors are permeable to Na+ and K+, but **NOT to Ca2+**. (they are ion channels).

2. Kainic acid (KA) receptors: ما اله دخل بالالم
• They are expressed at high levels in the hippocampus, cerebellum, and spinal cord.
• Permeable to Na+ and K+, and some can also be permeable to Ca2+.(not related to pain)

3. N-methyl-D-aspartate (NMDA) receptors: أهم واحد
• Present on essentially ***all*** neurons in the CNS (like AMPA receptors).
• All NMDA receptors are **highly permeable** to Ca2+ as well as to Na+ and K+.
*(we care about Na+ channels in propagating the pain impulses)

• **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 (which are the pain nerves) in the spinal cord and brain stem and causes a slow EPSP (excitatory post synaptic potentials) in target neurons → transmit noxious stimuli.
• **Glutamate**, which is released with substance P from these synapses plays an important role in transmitting pain stimuli.
*If we stop Substance P and Glutamate then we stop pain.

History of local anaesthetics

- **Cocaine** is the first local anesthetic introduced into clinical practice (for ophthalmic use, 1884).

Its chronic use was associated with **psychological dependence (addiction)**.

- **Procaine** was synthesized to improve upon the clinical properties of cocaine (1905) and became the dominant local anesthetic for ~ 50 years.
- **Lidocaine** (lignocaine) (1943) is the most widely used local anesthetic.

(20:00)

Chemistry of the drug

• 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, (drugs -in general- are weak acids or 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**.(when the drug enters through the aromatic ring(lipophilic group) across the cell membrane inside the cell and closes the Na+ channel from inside, it can not exit since it is charged (cationic form)).

• 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**. (abscesses and pus are acidic, so the drugs -which are weak bases- can't penetrate).

• Esters usually have a shorter duration of action (1-2 minutes) because they are more prone to hydrolysis than amides.

Classification end with caine

1. Amides:

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

2. Esters: (not commonly used)

Cocaine, Procaine, Tetracaine, Benzocaine.

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.

• When progressively **increasing** concentrations of a local anesthetic are applied to a nerve fiber, the threshold for excitation **increases**, impulse conduction **slows**, the rate of rise of action potential **declines**, the action potential amplitude **decreases**, **and finally, the ability to generate an action potential is completely abolished**.وهاد اللي بهمنا

• 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.

(smaller and more unmyelinated fibers are easier to block and more affected).

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					
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					
Dorsal root	Pain	0.4–1.2	None	0.5–2.3	++++
Sympathetic	Postganglionic	0.3–1.3	None	0.7–2.3	++++

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(30:00)

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**.
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 (because they are long acting drugs).

Pharmacokinetics:

- Ester-based local anesthetics are rapidly broken down in plasma (t½ < 1 minute).
- **Absorption** of the local anesthetic to 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.

• 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.

Adding a vasoconstrictor prolongs the action of anesthetic drugs and prevents cardiac and systemic toxicities.

• **Epinephrine**, when used in spinal anesthesia, **stimulates α2 adrenoceptors** which **inhibit release of substance P (neurokinin-1) and reduce sensory neuron firing** → enhancing and prolonging local anesthesia.

• **Clonidine** (not used anymore) and **dexmedetomidine** (α2-agonists substitute of Clonidine) augment local anesthetic effect in the subarachnoid space and peripheral nerves.

• **Vasoconstrictors are less effective in prolonging anesthetic action of the more lipid soluble, long acting drugs (bupivacaine, ropivacaine)** (they already have long action) possibly because they are highly tissue-bound.

• **Cocaine is peculiar in its sympathomimetic properties; it blocks catecholamine reuptake**.

(40:00)

• The distribution of the ester type local anesthetics has not been characterized because of the **extremely short half-lives**.
• Ester-type agents are hydrolyzed in the plasma by butyrylcholinesterase (pseudocholinesterase) to inactive metabolites.

• The amide agents are widely distributed after IV bolus administration (??!!). They can be sequestered in fat. **Caution!! (should be given IV infusion only for therapeutic use)**
• 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 (depends on the amount of the enzyme in the body)).
• Reduction in hepatic blood flow also decreases elimination of the amide agents.
• There is also a possibility of drug interactions with agents metabolized by the same isozyme resulting in reduced elimination of the local anesthetic.
(Drug that reduce hepatic blood flow: Beta Blockers, histamine (H2) receptor blocker – مهم 😊 please ctrl+c ctrl+p in your  😊)

Therapeutic Uses:

• To produce highly effective analgesia **in well-defined regions of the body**.
• **Routes of administration**:
1. Topical application: nasal, mucosa, wound margins.
2. Infiltration: injection in the vicinity of peripheral nerve ending **(Never ever inject the drug directly in the neuron).**
3. Nerve block: injection in the vicinity of major nerve trunks.
4. Injection into the epidural or subarachnoid spaces surrounding the spinal cord.
5. Intravenous regional anesthesia for short surgical procedures involving the upper and lower limbs. Explain! (more in orthopedic surgery)
• Repeated injection of the local anesthetic can result in **tachyphylaxis** (fast tolerance/loss of effectiveness) due to extracellular acidosis.
• Local anesthetics are commonly marketed as hydrochloride salts (pH ~ 4-6).

(52:07)

Other uses:

1. Neuropathic pain syndromes.
2. Cardiac arrhythmias.
a) Intravenous (infusion) (lidocaine).
b) Oral (mexiletine and tocainide) they are local drugs but used as lidocaine (antiarrhythmic).

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.

1. Central nervous system:
• At **low concentration:** all local anesthetics produce sleepiness, dizziness, visual & auditory disturbances and restlessness.
• An early symptom of local anesthetic toxicity is circumoral and tongue numbness and a metallic taste.

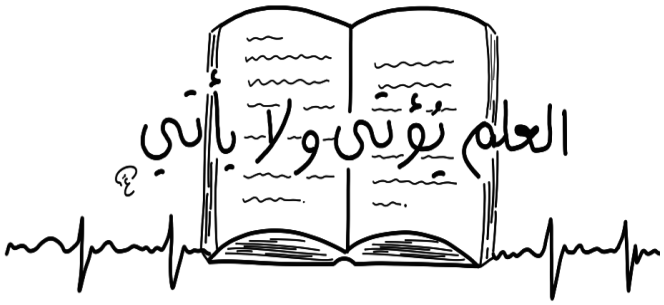
• At **higher concentration:** nystagmus and muscular twitching, followed by **overt tonic-clonic convulsions** (because they block the inhibitory neurons). They apparently cause **depression of cortical inhibitory pathways**.
*The stage of unbalanced excitation is followed by generalized CNS depression.
• Premedication with a parenteral **benzodiazepine** can provide prophylaxis against seizures.
• **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.
(a teen with MI → think of cocaine abuse).

2. Direct local neural toxicity:
• Transient neuropathic symptoms.
• More with **lidocaine** and **chloroprocaine**.

3. Cardiovascular toxicity:
• Results from effects on cardiac & smooth muscle membranes & indirect effects on ANS.
• Block cardiac sodium channels (antiarrhythmic).
• At **extremely high concentration:** they can block calcium channels.
• They **depress cardiac contraction** and produce **arteriolar dilation** (**except cocaine**) leading to systemic **hypotension**.
• Large doses of **bupivacaine** & **ropivacaine** have produced **cardiovascular collapse**.
• **Cocaine** produces **vasoconstriction** and **hypertension** as well as **cardiac arrhythmias**.
(remember **blocks catecholamine reuptake)**
Also, can lead to **local ischemia** & **ulceration** of mucosal membranes in chronic abusers who use the **nasal route**.

4. Hematologic effects: only with Prilocaine
- **Large doses** of **prilocaine** during regional anesthesia may lead to accumulation of the metabolite **o-toluidine;** an oxidizing agent capable of converting hemoglobin to methemoglobin.

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**.



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