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Local anesthetics

Department of Pharmacology MU

Local anesthetics (LA)

- cause temporary loss of sensation in a limited area by local reversible inhibition of sensory neurons

- sensitivity of nerve fibers to LA:
  vegetative > sensory > motoric nerve fibers

- in sensory fibers the perception of heat is blocked first, later the perception of pain stimuli, and then also the touch

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LA - mechanism of action

- penetration into sensitive nerve fibers
- blockade of voltage-gated sodium channels responsible for fast depolarization along nerves
- binding on the inner side of the nerve membrane, and preventing Na^+ ions flow

other effects:

- vasodilation (sympathetic nerve fibers blockade)
- antiarrhythmic/proarrhythmic effects (influence on Na^+ channels in myocardium)

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LA - chemical structure

- amphiphilic substances:
  - aromatic group is lipophilic
  - nitrogen group is hydrophilic (ionisable)

connected via **ester** or **amide** bond (ester-type and amide-type)

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LA - chemical structure

- LA are weak bases

  pKa = 8-9, efficacy of LA depends on tissue pH
  – ratio of ionized/non-ionized form

- higher pH = increased efficacy– more molecules are non-ionized = increased penetration to nerve fibers

- low pH = less effective, ionized molecules of LA do not penetrate to neurons, e.g. in tissues with inflammation

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LA - pharmacokinetics

- **absorption** depends on drug concentration on the site of administration, dose, blood perfusion, physical-chemical properties of drug and on the presence of vasoconstrictor agents

- **distribution**

- in the whole body, amides: strong binding to plasma proteins

- **metabolisation**

- plasmatic esterases are involved - fast (ester LA)
- hepatic metabolism via CYP- slower (amide LA)

- **excretion** of metabolites - kidneys

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Vasoconstrictor agents

- additives for lowering systemic toxicity
- compensation of vasodilation induced by LA
- decrease in LA consumption
- increased duration of analgesia (delayed diffusion of LA)

in acral parts with caution – risk of ischemic necrosis

adrenaline, ev. **noradrenaline**

alfa1-agonists (nafazolin)

derivatives of vasopressin

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LA – routes of administration

- **topical (surface)** anesthesia - transdermal penetration of LA in the form of solution, spray, gel, ointment

mucosa, cornea, esophagus, respiratory tract, decubitus

- frequently used in urology (catheterization) and before other painful instrumental procedures, inhalation of trimecaine before bronchoscopy

EMLA (eutectic mixture of local anesthetics) – mixture of lidocaine and prilocaine for topical use on intact skin.

EMLA is frequently used in pediatrics approximately 15-60 minutes before invasive procedure (blood collection, cannulation).

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LA – routes of administration

- **infiltration anesthesia**

  subcutaneous, submucosal, intramuscular, intraarticular

blocks nerve conduction near their site of administration

- low concentrations of both LA and vasoconstrictor agents

- often used for minor surgical and dental procedures

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LA – routes of administration

conduction anesthesia

- **peripheral** – block of both nerve trunks and individual nerves

- **central** – always without vasoconstrictor agents!

epidural anesthesia – perioperative and obstetric analgesia – it is necessary to stop in advance use of warfarin (+ anticoagulant agents), ASA (+ antiplatelet agents), LMWH, usual amount of LA 16 mL

subarachnoideal anesthesia (spinal, lumbal) – intrathecal administration of LA into intervertebral space, usual amount of LA 4 mL

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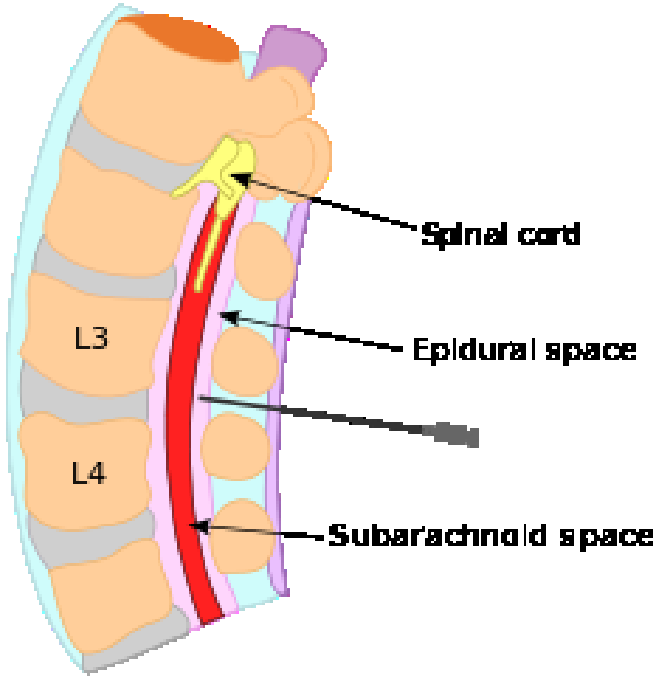

https://upload.wikimedia.org/wikipedia/commons/thumb/b/ba/Epidural_blood_patch.svg/250px-Epidural_blood_patch.svg.png

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LA – routes of administration

- **intravenous regional anesthesia (Bier block)**

- trimecaine 1%, lidocaine 0,5 %

- toxic LA should not be used (bupivacaine)

- quick onset and inhibition of motor functions

- exsanguination of the limb (elevation + tourniquets), procedures max. up to 2 hrs (risk of ischemia)

- no postoperative analgesia

- bleeding must be stopped carefully

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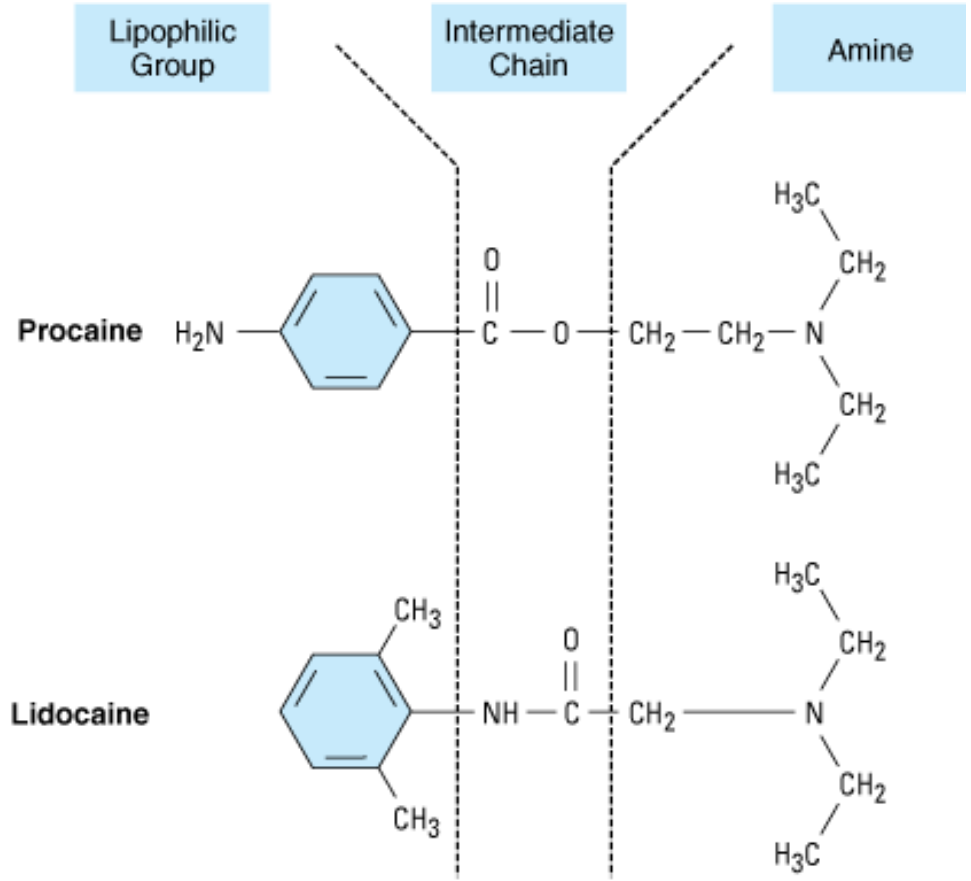

https://dentistryandmedicine.blogspot.cz/2012/05/regional-anesthesia-manualupper.html

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Ester type of LA

cocaine

- the first known LA (in use since 1884)
- natural compound, isolated from leaves of Erythroxylon coca
- central psychostimulant with high risk of addiction
- for surface anesthesia

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Ester type of LA

procaine

- the oldest synthetic LA (1905)
- slow onset, short duration
- for infiltration and conduction anesthesia (it penetrates poorly the skin)

tetracaine

- fast onset
- high systemic toxicity – only for surface anesthesia of oral cavity and throat (combined with chlorhexidine)

benzocaine

- only for topical anesthesia of oral cavity, ear and throat (available in combination with antiseptics)

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Ester type of LA

LA of ester type are structurally similar to para-aminobenzoic acid

→ high allergenic potential

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Amide type of LA

trimecaine

- universal, for all types of local anesthesia
- used also as the class I antiarrhythmic drug

lidocaine (syn. xylocaine and lignocaine)

- universal LA for surface, infiltration and conduction anesthesia
- class I antiarrhythmic drug

in patents treated with betalytics, $Ca2^{+}$ channel blockers and in patients with epilepsy doses of trimecaine and lidocaine must be halved

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Amide type of LA

mepivacaine

- in dentistry, in patients with KI of catecholamines

articaine

- used in dentistry
- fast onset, long effect

bupivacaine

- all type of local anesthesia
- treatment of acute pain - continually to epidural space
- cardiotoxic

levobupivacaine

- lower cardiovascular toxicity and neurotoxicity

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Amide type of LA

ropivacaine

- for all types of anesthesia except from subarachnoidal

prilocaine

- surface anesthesia EMLA
- spinal anesthesia for short surgical procedures

cinchocaine (dibucaine)

- surface (topical) anesthesia
- highly toxic

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Amide type of LA

Allergic reactions are less frequent

→ LA of amide type are used more frequently than LA of ester type

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LA - according to their efficacy

- weak
  procaine (effect lasts approximately 45 minutes), benzocaine

- intermediate
  trimecaine, lidocaine (effect lasts approximately 90 minutes)

- strong
  tetracaine, articaine, bupivacaine (effect lasts approximately 120 minutes-12 hours), levobupivacaine, ropivacaine, mepivacaine

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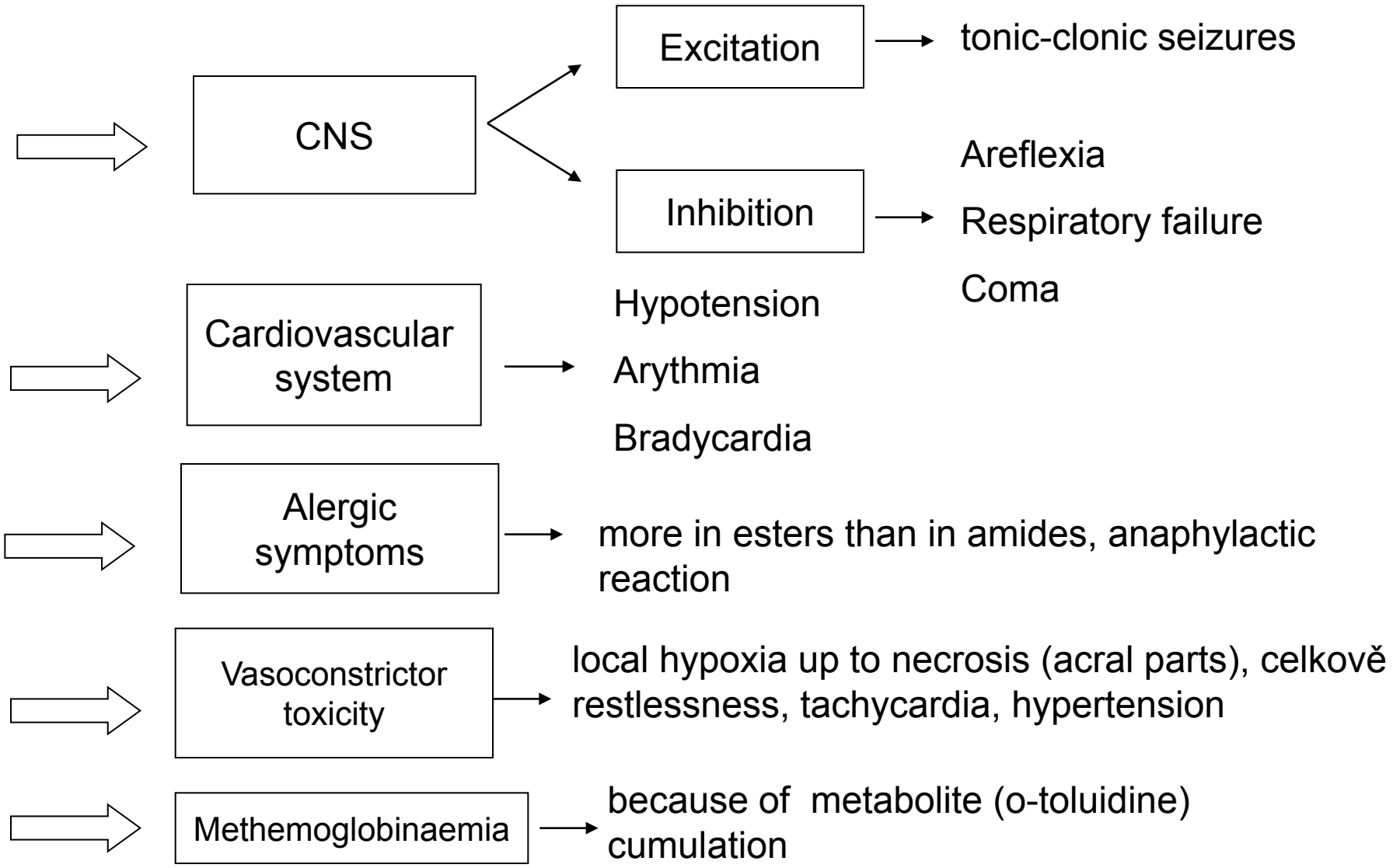
Toxic effects of LA



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Alergic and anaphylactic reaction to LA

symptoms:

- pruritus
- urticaria
- swellings
- anaphylactic shock- restlessness, anxiety, breathlessness, vomiting
- Quincke‘s oedema – without inflammation, fast onset in face, affecting lips, face and throat (suffocation!!)

therapy:

- oxygen and infusion of 5% substituive solution with noradrenaline
- hydrocortisone i.v.
- antihistamines
- in case of respiratory failure, keep free airways, artificial respiratory ventilation

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Systemic toxic reaction to LA

symptoms: (most often till 15 min from LA administration):
- restlessness, hand tingling, hot or cold, nausea, vertigo, cold sweat
- tachypnea
- tremor, fasciculations, seizures
- tachycardia, increased blood pressure in the beginning with the subsequent decrease, unconsciousness, bradycardia
- in the final phase respiratory and cardivascular failure

therapy:
- lay down patient, oxygen in respiratory insufficiency
- diazepam i.v. in seizures
- slow adrenaline continually i.v. if there is critical decrease of BP
- resuscitation in respiratory and cardiac failure

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Some of the LA can be also used as antiarrhythmic agents (class 1b).

lidocaine

trimecaine

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