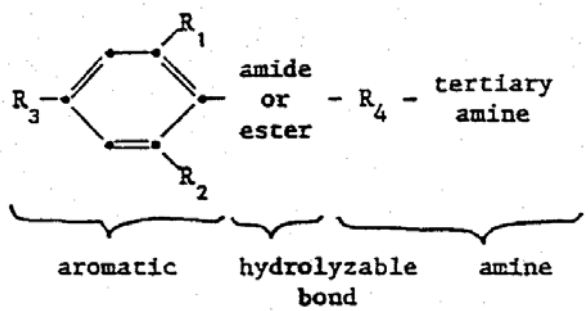
LOCAL ANESTHETICS

1. Objective: The aim of this lecture is to describe the mechanisms of local anesthesia as well as some relevant clinical pharmacology of local anesthetics.

II. Definition: Local anesthesia is the selective numbing of a particular, circumscribed region of the body by a controlled, reversible procedure. Drugs called local anesthetics (LA) are usually employed for these procedures, although directly applied pressure, cooling, or even heating will also produce numbness. The general strategy is to inhibit the propagation or generation of impulses in nerves from a defined anatomical region.

III. Chemistry: Knowledge of the structure of local anesthetic drugs is essential for an understanding of their mechanism of action, potencies and pharmacokinetics. The general structure of a local anesthetic is:



Structures and properties of drugs used clinically are listed in Table 1, along with one experimental derivative, QX-314.

The aromatic group sometimes contains a para-amino group (-NH_2) at R3 (procaine) and additional alkyl groups attached to this amino (tetracaine), or at R_1, R_2 (lidocaine, and other amides).

Amide or ester bonds connect the aromatic moiety to a tertiary (3^o-) amine which can have alkyl groups of lengths from -CH_3 to -C_4H_9 attached to it. The absolute potency of LA increases with increasing alkyl length substituents on both aromatic and 3^o-amine groups. Physico-chemical analysis reveals a monotonic increase of absolute potency with increasing hydrophobicity for all compounds. Since the mechanisms of action are complex (see below), the exact relationships between structure, pKa, and membrane distribution are still not known.

IV. Mechanism of Action: LAs block nerve impulses by interfering with the sodium permeability increase (PNa) which subserves the depolarizing phase of action potentials. The mechanistic details depend on the LA molecule being used.

A. Active species: (3o)-amine local anesthetics (pKa = 7.8-10) exist as equilibrium mixtures of protonated cation and neutral base at physiological pH.

The ionization reactions at neutral pH are quite rapid (-10^{-3} sec).

1. Which form of the LA module blocks P_{Na}?
2. Where does it act: inside or outside the cell or on the membrane?

Evidence to answer these questions comes from:

1. Quaternary (4^o)-amine derivatives (permanent cations, e.g., QX-314 which do not permeate the membrane, block sodium channels (P_{Na}), but only when applied in the cytoplasm.

2. The observed impulse-blocking potency of benzocaine and of lidocaine derivatives where -OH replaces -NR_2 (both permanently neutral molecules). These drugs act identically whether applied externally or cytoplasmically.

Conclusion: Both neutral and protonated species of LA can inhibit Na channels and block impulses. In general, however, the protonated form appears to be more potent.

B. Molecular Mechanisms:

1. The block of sodium current (I_{Na}) or of impulses by 4^o-amine LAs increases in extent with repetitive opening of sodium channels ("use-dependent" block) (Figure 2). Use-dependent block is reversed when stimulation stops.

2. With benzocaine (and some alcohols) and with 3^o-amine anesthetics at alkaline pH, resting nerve block reveals more "inactivated" sodium channels (Fig. 3) but use-dependent block is very weak. 3o-amine LAs show much more use-dependent block at neutral or slightly acid pH than at alkaline pH (external). Internal pH has surprisingly little effect.

3. Inhibition of ionic Na+ current by benzocaine is paralleled by a proportional reduction of "gating current", the movement of charge which results directly from conformational changes of Na channels during activation (Figure 4).

The sodium channel itself appears to be a receptor for local anesthetics. Intentional mutation of part of the channel's inner pore region changes resting and use-dependent pharmacology of various local anesthetic molecules. In addition, in normal channels the membrane potential changes the channel conformations, which in turn have different anesthetic affinities. This is collectively referred to as the "modulated receptor hypothesis" (Figure 5). In addition, there is a non-receptor mediated action of local anesthetic agents, which may occur through a disruption of normal membrane structure.

4. Calcium ions may antagonize the blocking action of some local anesthetics, but this probably is mediated through changes in channel structure and

is not necessarily evidence for direct steric competition between Ca^{2+} and LA binding.

5. LAs also have been shown to inhibit K+ channels, Ca^{2+} channels, and the nicotinic acetylcholine-activated conductance, the substance P receptor and even the G-protein modulation of certain channels. These alternative actions may contribute to spinal (intrathecal) anesthesia and to some aspects of toxicity.

V. Modes of Administration and Pharmacokinetics

A. Injection--minor, to block small regions via peripheral nerve; major (includes iv), to block whole limbs via peripheral nerve.

Clinically, local anesthetics are usually injected as 0.25-1 % (w:v) solutions, equivalent to 10-40 mM, where 1/40-1/100 of those concentrations provide a 50% absolute block of impulses in an isolated, desheathed nerve. Interestingly, less than 10% of the dose of injected drug actually reaches the nerve to provide complete functional block.

B. Infiltration--usually at skin or other superficial surfaces, e.g. scalp, oral mucosa.

C. Topical--superficial application, on skin, tracheal (pre-intubation) to reduce irritation and gag reflex.

D. Central injections--at spinal cord:

1. epidural--blocks roots, but LA also enters cord, CSF.

2. intrathecal--"spinal":
   a. potent block of many dermatomes
   b. drug is often dissolved in a hypo- or hyperbaric solution to control spread.
   c. positioning of patient may also be adjusted to control anatomical distribution of block.

E. Removal--LAs are removed from site of injection by local tissue uptake and local circulation.

1. removal by circulation is often reduced by co-injection of epinephrine, but this in not true for all LAs at all locations.

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2. complications arising:
    a. epinephrine itself may have subliminal blocking action.
    b. epinephrine is usually packaged with anti-oxidant and at acid pH. Antioxidant can be neurotoxic, and low pH renders LA less penetrating, therefore less effective.

F. Metabolism--little intact LA is eliminated from the body.

1. esters--hydrolyzed by tissue and serum cholinesterases (non-specific).

2. amides--oxidized by mixed-function oxidase system, of hepatic ER.

VI. Differential Fiber Blockade: Early papers and most pharmacology texts report that smaller nerve fibers are blocked "before" larger diameter fibers by LA drugs. "Before" almost certainly means earlier during the development of the block, but when a steady-state (absolute) block has been achieved, single impulses in the larger fibers are often more inhibited than those in the smaller ones (Figure 6).

It is unlikely that an absolute differential block, short of a total one, is ever reached under these "clinical" conditions. `During onset of block of a nerve containing many fiber types, we observe functional activities being lost in a consistent sequence: pain, temperature, touch, proprioception, and skeletal muscle tone and voluntary tension. Since both sensory and motor functions are dependent on frequencies of trains of impulses, the modulation of AP frequency rather than the absolute loss of impulses may correspond to the functional deficits observed clinically.

Sensations from more proximal regions are blocked earlier and recover later than those from more distal segments. This reflects the diffusion of anesthetic through the somatotopically organized peripheral nerve.

Reading List

1. Ritchie JM and Greene NM. Chapter 15. Local Anesthetics. In: The Pharmacological Basis of Therapeutics 8th ed. Macmillan, N.Y., pp. 311-331.

A concise yet thorough summary by one of the pioneers (JMR) on mechanisms of LA.

2. Bromage P. (1978) Epidural Anesthesia, Saunders, Philadelphia, PA.

A scholarly treatise ranging from basic neurophysiology and anatomy to clinical complications. Chapters 2-4 are particularly pertinent to these lectures.

3. Dripps, RD, Eckenhoff JE, and Vandam LD (1983) Introduction to Anesthesia. The Principles of Safe Practice. Saunders, Philadelphia, PA.

The best introductory text for anesthesiology, this book places basic science firmly in the context of clinical practice. Emphasize chapter 17; read chapters 18-20 for more clinical information.

4. Butterworth, JF and Strichartz G. (1990) Molecular mechanisms of local anesthesia: A Review. Anesthesiology 72:711-734.

The state of knowledge as of 1989, in excessive detail.