PHARMACOLOGY OF LOCAL ANESTHETICS

1860 Albert Niemann isolated crystals from the coca shrub – and called it "cocaine" – he found that it reversibly numbed his tongue! Sigmund Freud became aware of the mood altering properties of cocaine, and thought it might be useful in curing morphine addiction. Freud obtained a supply of cocaine (from Merck) and shared it with his friend Carl Koller, a junior intern in ophthalmology at the University of Vienna

1884 Following preliminary experiments using conjunctival sacs of various animals species, Koller did first eye surgery in humans using cocaine as local anesthetic

1905 German chemist Alfred Einhorn produced the first synthetic estertype local anesthetic - novocaine (procaine) - retained the nerve blocking properties, but lacked the powerful CNS actions of cocaine

1943 Swedish chemist Nils Löfgren synthesized the first amide-type local anesthetic - marketed under the name of xylocaine (lidocaine)

Mechanism of Action

 conduction of nerve impulses is mediated by action potential (AP) generation along axon

 Cationic form of anesthetic binds at inner surface of Na+ channel – preventing Na+ influx (rising phase of membrane potential) which initiates AP → blockade of nerve impulses (e.g., those mediating pain).

Mechanism of Action

depolarization Na+ channel (resting) Na+ channel (open) action potential

rapid

Na+ channel (inactivated)

Na+ channel (resting) Na+ channel (open) II no depolarization

local anesthetic

slow

Na+ channel - local anesthetic complex (inactive)

local anesthetic

Pharmacological effects and toxicities

Functional consequences of Na+ channel blockade by local anesthetics:

 nerves: decrease or abolition of conduction vascular smooth muscle: vasodilatation heart: decreased excitability (reduced pacemaker activity, prolongation of effective refractory period) central nervous system: increased excitability, followed by generalized depression

Na+ channels are present in all nerves and local anesthetics, at sufficient concentrations, can completely block action potential generation and conduction

 "differential nerve blockade" – nerve fibres differ markedly in their susceptiblity to conduction blockage by local anesthetics (this is the basis of their clinical use) e.g., small, non-myelinated neurons mediating pain are much more susceptible that large, myelinated fibres mediating motor functions

Effects of local anesthetics on vascular smooth muscle

Blockade of Na+ channels in vascular smooth muscle by local anesthetics vasodilatation consequences of vasodilatation: enhanced rate of removal of anesthetic from site of administration (decreased duration of anesthetic action and increased risk of toxicity) hypotension (may be intensified by anestheticinduced cardiodepression)

Effects of local anesthetics on heart

 Local anesthetics can reduce myocardial excitability and pacemaker activity and also prolong the refractory period of myocardial tissue – this is the basis of the antiarrhythmic effects of local anesthetics

 Local anesthetic-induced myocardial depression (compounded by anesthetic-induced hypotension) can also be a manifestation of toxicity and can lead to cardiovascular collapse and even death!

Effects of local anesthetics on CNS

 As is the case with CNS depressants generally (e.g., alcohol) local anesthetics (at toxic doses) produce a biphasic pattern of excitation followed by depression

 The excitatory phase likely reflects the preferential blockade of inhibitory neurons and effects can range from mild hyperactivity to convulsions)

 The subsequent depressive phase can progress to cardiovascular collapse and even death if unmanaged

Applications of local anesthesia:

 nerve block: injected locally to produce regional anesthesia (e.g., dental and other minor surgical procedures) topical application: to skin for analgesia (e.g., benzocaine) or mucous membranes (for diagnostic procedures)

 spinal anesthesia: injection into CSF to produce anesthesia for major surgery (e.g., abdomen) or childbirth local injection: at end of surgery to produce long-lasting post-surgical analgesia (reduces

need for narcotics) i.v. infusion: for control of cardiac arrhythmias (e.g., lidocaine for ventricular arrhythmias)