Effects of Local Anesthetics on Inflammatory Response

Essay

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Ahmed Abd El Hakiem

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List of Abbreviations

-	Negative
~	Approximately
+	Positive
<	less than
>	more than
Å	Angstrom
ACLS	advanced cardiac life support
ARDS	adult respiratory distress syndrome
ATP	Adenosine tri-phosphate
Ca^{2+}	Calcium
cAMP	cyclic adenosine mono-phosphate
CD	convulsive dose
C_m	conduction minimum
CNS	Central nervous system
CVS	Cardiovascular system
D	Domain
DRG	dorsal root ganglion
EDTA	ethylenediaminetetraacetic acid
EEG	Electroencephalogram
Fe^{2+}	ferrous iron
Fe^{3+}	ferric iron
g	Gram
h	Hour
HSV	herpes simplex virus
IA	intra arterial
IC	Intracellular
IL	Interleukin
IM	Intramuscular
iNOS	inducible nitric oxide synthase
IV	Intravenous
K^+	Potassium
kg	Kilogram
LA	local anesthetics
LD	lethal dose
LDH	lactate dehydrogenase
LT	Leukotriene
M1	muscarinic 1 receptors
MAC	Minimum alveolar concentration

Mg	Magnesium
MH	malignant hyperthermia
MIC	minimum intracellular
min	Minute
ml	Milliliter
mmol	Millimole
mv	Millivolt
Na+	Sodium
NADPH	nicotinamide adenine dinucleotide phosphate
NHE	sodium hydrogen exchanger
NMDA	N-methyl-D-aspartate
NSAID	non-steroidal anti-inflammatory drugs
ºC	degree Celsius
ºF	Fahrenheit
PABA	para-aminobenzoic acid
PaO_2.	Arterial partial pressure of Oxygen
PCO_2	Arterial partial pressure of carbon dioxide
PG	prostaglandin
PLA_2	phospholipase A_2
PMNs	polymorphonuclear granulocytes
PVCs	Premature ventricular contractions
rhG-CSF	Recombinant human granulocyte colony-stimulating factor
S	segment
SOD	superoxide dismutase
TNF	tumour necrosis factor
TTX	Tetrodotoxin
TX	thromboxane
α	alpha
β	beta
γ	gamma
δ	delta
μ	micron

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Introduction

Introduction

Local anesthetics have been shown to attenuate inflammatory responses both in vivo and in vitro. Recent studies demonstrated the ability of local anesthetic infusions to protect against sepsis-induced mortality, as well as renal and hepatic dysfunction **(Gallos et al, 2004).**

Local tissue inflammation caused by injury or inflammatory processes may be reduced by section or local anesthetic block of the nerve supplying the inflamed area **(Pham-Marcou et al, 2005).**

Inflammatory diseases alter the pharmacokinetics and pharmacodynamics of various drugs, resulting in their decreased clinical effects and increased adverse effects **(Aitken et al, 2006).**

Local anesthetics have anti-inflammatory effects in vivo and inhibit neutrophil functions in vitro, but how these agents act on neutrophils remains unclear **(Akio Jinnouchi et al, 2005).**

Surgery-induced stimulation of the inflammatory response plays a major role in the development of several postoperative disorders. Local anesthetics possess anti-inflammatory activity and are thought to positively affect patient's outcome after surgery **(Susanne Herroeder et al, 2007).**

Major abdominal surgery elicits a broad variety of alterations in hemodynamic, endocrine-metabolic, and immune responses. Although inflammation is crucial for structural and functional repair of tissue

damage, excessive stimulation of the inflammatory response has major impact on the development of several inflammatory disorders preoperatively, such as impaired gastrointestinal motility. Anesthetic interventions that modulate inflammatory responses might thus decrease frequency and severity of such complications, thereby minimizing morbidity and mortality **(Susanne Herroeder et al 2007).**

Aim of work

The aim of this work is to gain the basic knowledge about effects of local anesthetics on inflammatory response. It will describe local anesthetic pharmacology, modulation of inflammatory response by local anesthetics and clinical implications of using local anesthetics on alteration of inflammatory response to improve patients' outcome.

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PHARMACOLOGY OF LOCAL ANESTHETICS.

Pharmacology of local anesthetics

Local and regional anesthesia techniques depend on a group of drugs called local anesthetics that produces transient loss of sensory, motor, and autonomic function when the drugs are injected or applied in proximity to neural tissue. (Morgan, et al 2006).

Theories of local anesthetics action:

Like other cells, neurons maintain a resting membrane potential by active transport and passive diffusion of ions. An electrogenic sodium–potassium pump (Na^+-K^+-ATPase) couples the transport of three sodium ions out of the cell for every two potassium ions it moves into the cell. This creates a concentration gradient that favors the extracellular diffusion of potassium and the intracellular diffusion of sodium. The cell membrane is normally much more permeable to potassium than to sodium, however, so a relative excess of negatively charged ions (anions) accumulates intracellularly. This accounts for the negative resting potential difference (–70 mv polarization). (Morgan, et al 2006).

Unlike most other types of tissue, neurons have membrane-bound, voltage-gated sodium and potassium channels that produce membrane depolarization following chemical, mechanical, or electrical stimuli. If the depolarization exceeds a threshold level (about –55 mv), voltage-gated sodium channels are activated, allowing a sudden and spontaneous influx

of sodium ions and generating an action potential that is normally conducted as an impulse along the nerve axon. The increase in sodium permeability causes a relative excess of positively charged ions (cations) intracellularly, resulting in a reversal of membrane potential to +35 mv. However, a subsequent rapid drop in sodium permeability (caused by inactivation of voltage-gated sodium channels) along with a transient increase in potassium conductance through voltage-gated potassium channels (allowing more potassium to exit the cell) return the membrane to its resting potential. Baseline concentration gradients are eventually reestablished by the sodium–potassium pump. (Morgan, et al 2006).

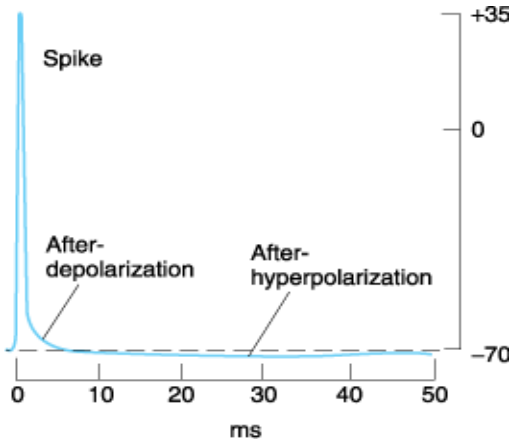

Fig. 1 The complete action potential of a large mammalian myelinated fiber. Drawn without time or voltage distortion to show the proportions of the components. (Morgan, et al 2006).

Structure of Na + channels:

Na+ channel consists of four domains. An intracellular link between DIII and DIV is important for Na+ channels function: it underlies 'fast' inactivation. Another type of inactivation, the slow ' C-type', appears to involve the pore loops. In addition to the pore forming α-subunit, at least nine variants of which have been expressed (10 gene sequence are known), there are three auxiliary subunits (β1- 3). These β-subunits have been shown to influence the activation and inactivation characteristics of expressed α- subunits, and to affect the level of expression of channel proteins. (Baker, et al 2001).

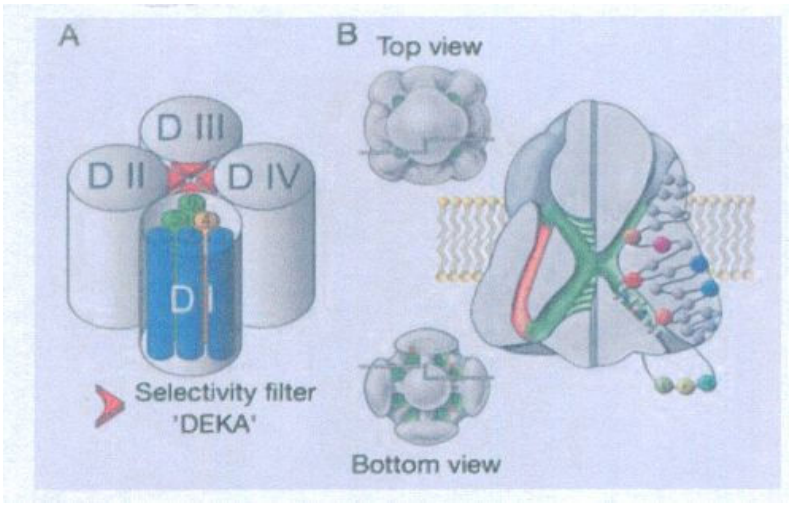

Fig. 2 Structures of a Na+ channel α- subunit. (A) Schematic diagram of the four domains DI-DIV. each domain consists of six segments, which span the membrane. Part of the pore loops, the amino acid links between the S5 and the S6 segments are symbolized as red triangles. These four amino acid links DEKA from the selectivity filter in the outer pore mouth. (B) 3D sketches of a Na+ channel with a top and bottom views and large cross section as derived from data of cryo-electron microscopy and single particle analysis. On the left side of the large cross section the is through S4 segment and on the right side the cross section is through S6 segment over laid with the amino acid sequence of rat brain Na+ channel. (Scholz, 2002.)