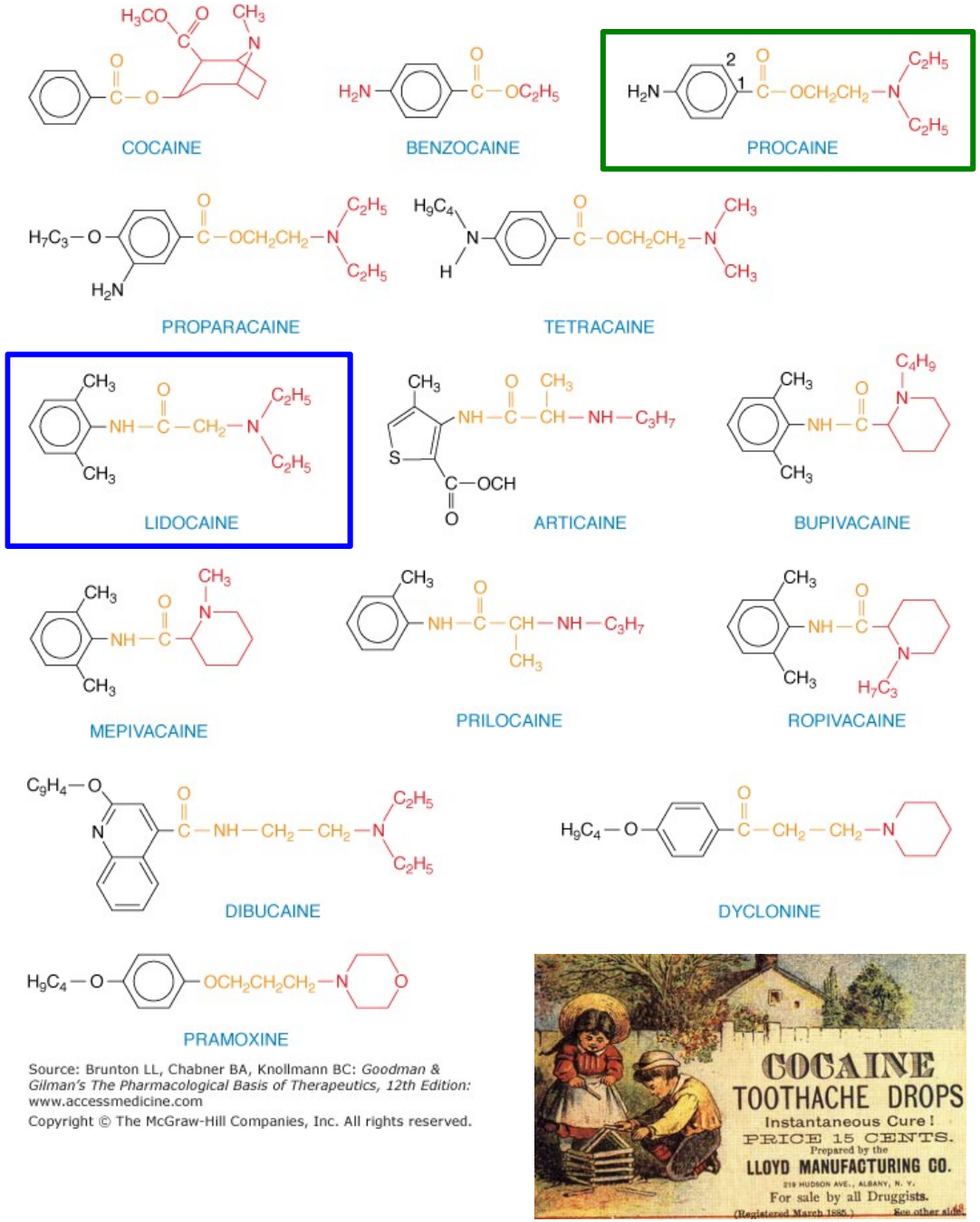
Caravaggio, *Il cavadenti*, 1608

ANESTETICI LOCALI



CHIMICA

Structural formulas of selected local anesthetics. Most local anesthetics consist of a hydrophobic (aromatic) moiety (**black**), a linker region (**orange**), and a substituted amine (hydrophilic region, in **red**).

Procaine is a prototypic **ester-type** local anesthetic; esters generally are ***well hydrolyzed by plasma esterases***, contributing to the relatively short duration of action of drugs in this group.
Lidocaine is a prototypic **amide-type** local anesthetic; these structures generally are ***more resistant to clearance*** and have ***longer durations of action***.

There are exceptions, including benzocaine (poorly water soluble; used only topically) and the structures with a ketone, an amidine, and an ether linkage. Chloroprocaine has a chlorine atom on C2 of the aromatic ring of procaine.

FARMACOCINETICA

INTERESSE

•velocità di estinzione dell'effetto

•tossicità

ASSORBIMENTO

•varia in funzione di dose, sede, legame alle proteine tissutali, uso di vasocostrittori (catecolamine)

DISTRIBUZIONE

•ampia (tessuto adiposo)

•legame degli amidici con l'α_1-glicoproteina acida

METABOLISMO

•esteri: velocissimo (T/2 < 1 min!)

•amidi: epatico (attenzione agli epatopatici!)

es. lidocaina (soggetto normale: T/2<2 ore – epatopatico: T/2>6 ore)

ELIMINAZIONE

•urinaria (> in urine acide)

FARMACODINAMICA

MECCANISMO ELEMENTARE D'AZIONE

•Inibizione dei flussi del **Na^+** (>>>> K^+!)

EFFETTI (in funzione della dose)

↑ Soglia eccitazione

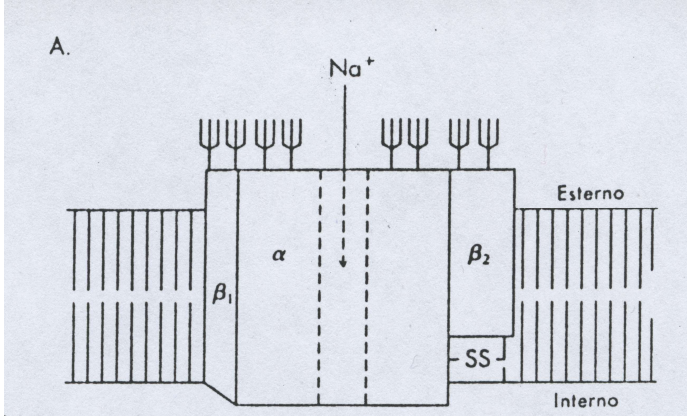
→ ↓ velocità conduzione

→ ↓ velocità ascesa e ampiezza potenziale d'azione

→ estinzione potenziali d'azione

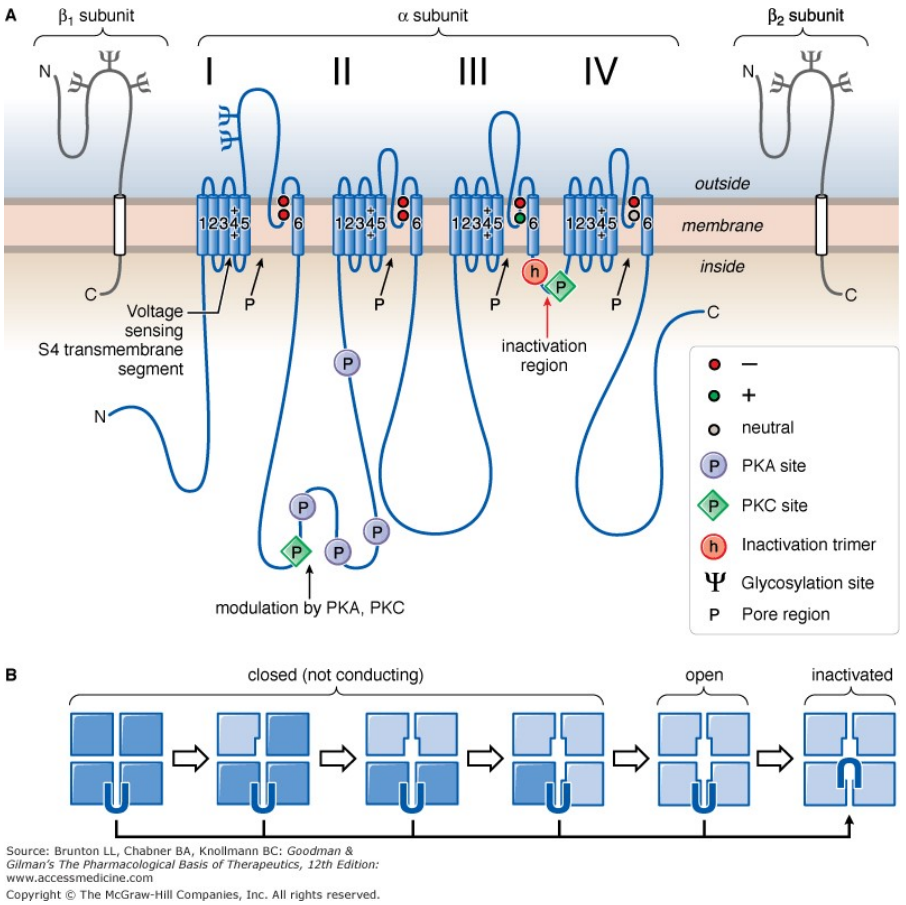
N.B. nessun effetto sul potenziale di riposo

MECCANISMO D'AZIONE
Il canale del sodio



Il canale del sodio è un eterotrimero costituito da due sub-unità β (β_1 e β_2) e una sub-unità α contenente 4 domini omologhi che circoscrivono il "poro".

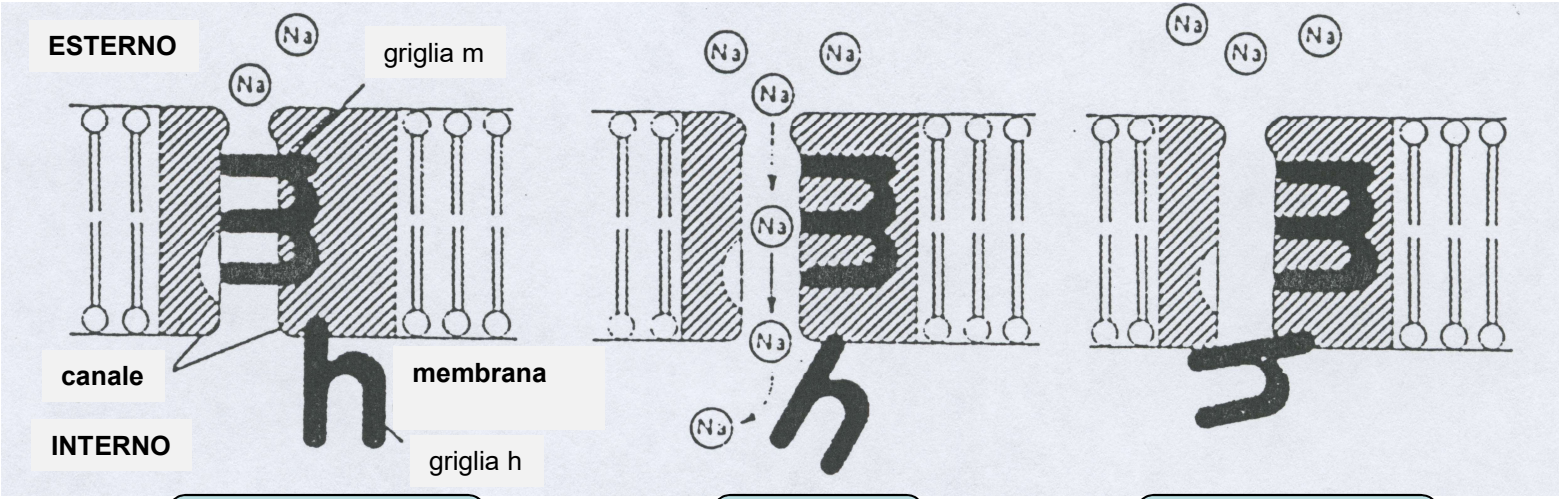
Structure and function of voltage-gated Na+ channels



Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

A. A two-dimensional representation of the α (center), β1 (left), and β2 (right) subunits of the voltage-gated Na+ channel. The polypeptide chains are represented by continuous lines. Cylinders represent regions of trans-membrane helices. Ψ indicates sites of demonstrated glycosylation. Note the repeated structure of the four homologous domains (I-IV) of the subunit. **Voltage Sensing**. The S4 trans-membrane segments in each homologous domain of the α subunit serve as voltage sensors. (+) represents the positively charged amino acid residues at every third position within these segments. Electrical field (negative inside) exerts a force on these charged amino acid residues, pulling them toward the intracellular side of the membrane; depolarization allows them to move outward. **Pore**. The S5 and S6 trans-membrane segments and the short membrane-associated loop between them (*P* loop) form the walls of the pore in the center of an approximately symmetrical square array of the four homologous domains (see panel ***B***). The amino acid residues indicated by circles in the *P* loop are critical for determining the conductance and ion selectivity of the Na+ channel. **Inactivation**. The short intracellular loop connecting homologous domains III and IV serves as the inactivation. It is thought to fold into the intracellular mouth of the pore and occlude it within a few milliseconds after the channel opens. Three hydrophobic residues (isoleucine–phenylalanine–methionine; IFM) at the position marked **h** appear to serve as an inactivation particle. **Modulation**. The gating of the Na+ channel can be modulated by protein phosphorylation. Phosphorylation of the inactivation gate between homologous domains III and IV by PKC slows inactivation. Phosphorylation of sites in the intracellular loop between homologous domains I and II by either PKC or PKA reduces Na+ channel activation.

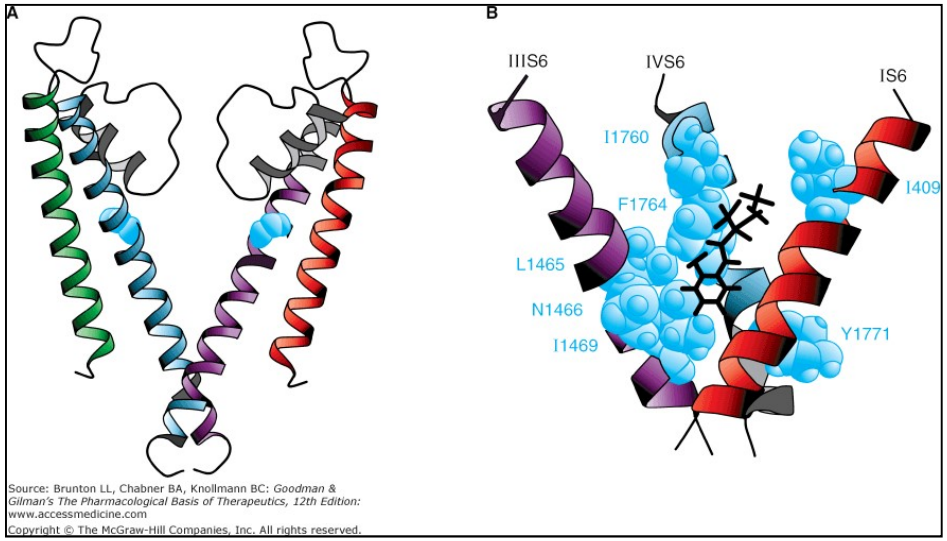
B. The four homologous domains of the Na+ channel subunit are illustrated as a square array, as viewed looking down on the membrane. Upon depolarization, each of the four homologous domains sequentially undergoes a conformational change to an activated state. After all four domains have activated, the Na+ channel can open. Within a few milliseconds after opening, the inactivation gate between domains III and IV closes over the intracellular mouth of the channel and occludes it, preventing further ion conductance.



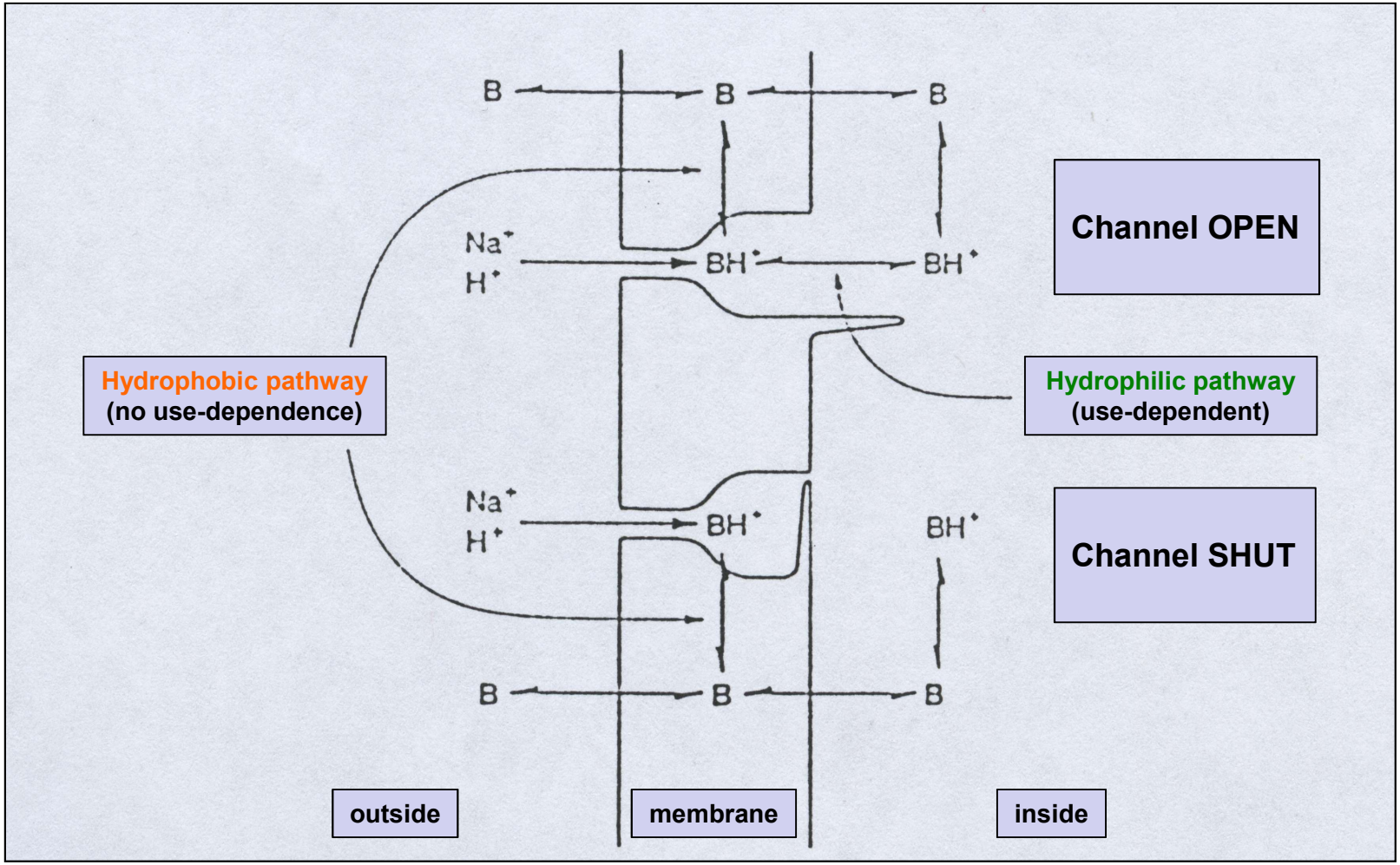
Stato inattivato, chiuso
disponibile per riattivazione

Attivato, aperto
conducente

Stato inattivato, bloccato,
e non disponibile

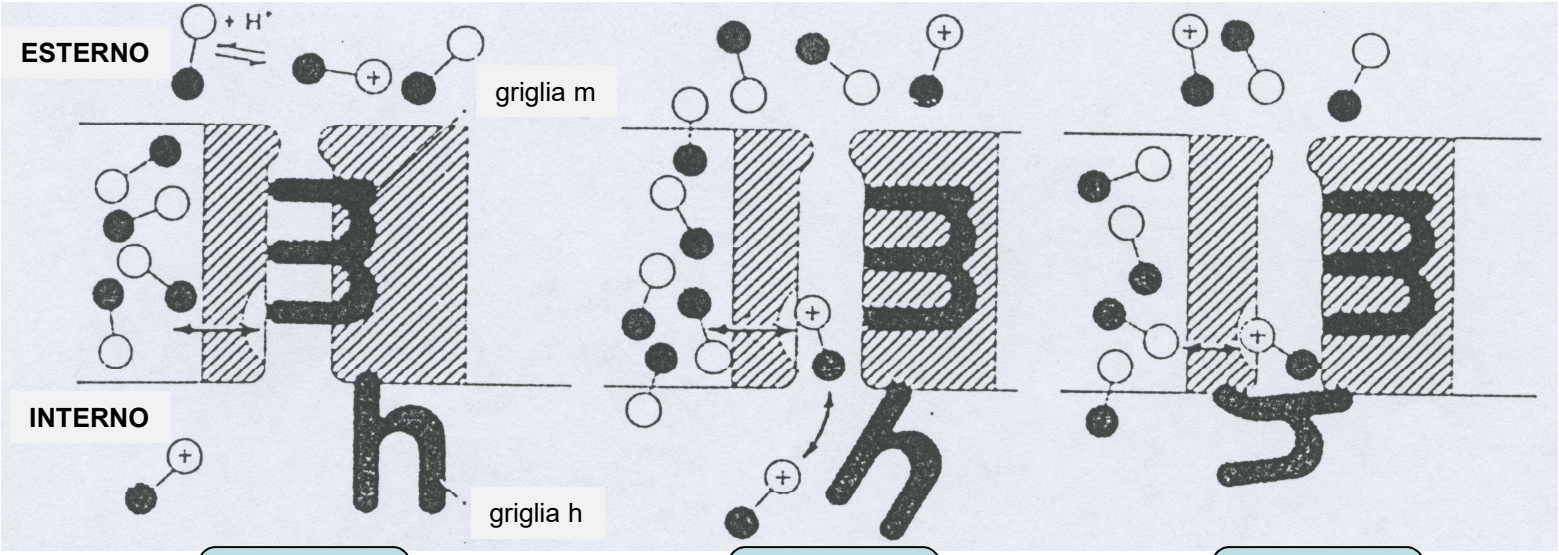


Basta una molecola di anestetico legata
al segmento 6 del I, III e IV dominio per bloccare il canale



Interaction of local anesthetics with Na^+ channels

The **blocking site within the channel** can be reached **via the open channel gate** on the inner surface of the membrane by the charged species, BH^+ (**hydrophilic pathway**), or directly **from the membrane** by the uncharged species, B (**hydrophobic pathway**).


ESTERNO
+ H+
griglia m
INTERNO
griglia h
Stato di riposo
Stato attivato bloccato
Stato inattivato, bloccato

Caratteristiche del blocco

- Voltaggio e tempo-dipendenza
- Reversibilità
- Sensibilità diverse delle diverse fibre (piccolo calibro → elevata frequenza)

NB - debole blocco giunzione neuro-muscolare
- effetto antiaritmico

Sensibilità al blocco anestetico delle nervose in funzione del calibro

Tipo di fibra	Funzione	Diametro (μm)	Mielinizzazione	Velocità di conduzione (m/sec)	Sensibilità al blocco
Aα	Propriocettiva, motrice	6-22	Notevole	10-85	+
Aβ	Tattile, pressoria	6-22	Notevole	10-85	++
Aγ	Fusi muscolari	3-6	Notevole	15-35	++
Aδ	Dolorifica, termica	1-4	Notevole	5-25	+++
B	Autonoma pregangliare	<3	Scarsa	3-15	++++
C Radice dorsale	Dolorifica, termica	0.4-1.2	Assente	0.1-2	++++
C Simpatica	Postgangliare	0.3-1.3	Assente	0.7-1.3	++++

N.B. **Le fibre C hanno frequenza di scarica elevata e lunga durata del potenziale d'azione** (>3 msec).
Le fibre Aα sono prevalentemente all'esterno del tronco nervoso.
Quindi l'ordine di priorità è:
dolore → freddo → caldo → tatto → propriocezioni → funzione motrice

TOSSICITÀ

SNC
•(euforia da cocaina)
•insonnia, vuoto mentale, disturbi visivi e uditivi, irrequietezza
→ nistagmo, tremore
→ convulsioni, morte
N.B.: neurotossicità periferica

CARDIOVASCOLARE
•antiaritmici
→ collasso, morte (bupivacaina!)

SANGUE
•psilocaina → MetaHb

ALLERGIA
•esteri frequente
•amidi rara