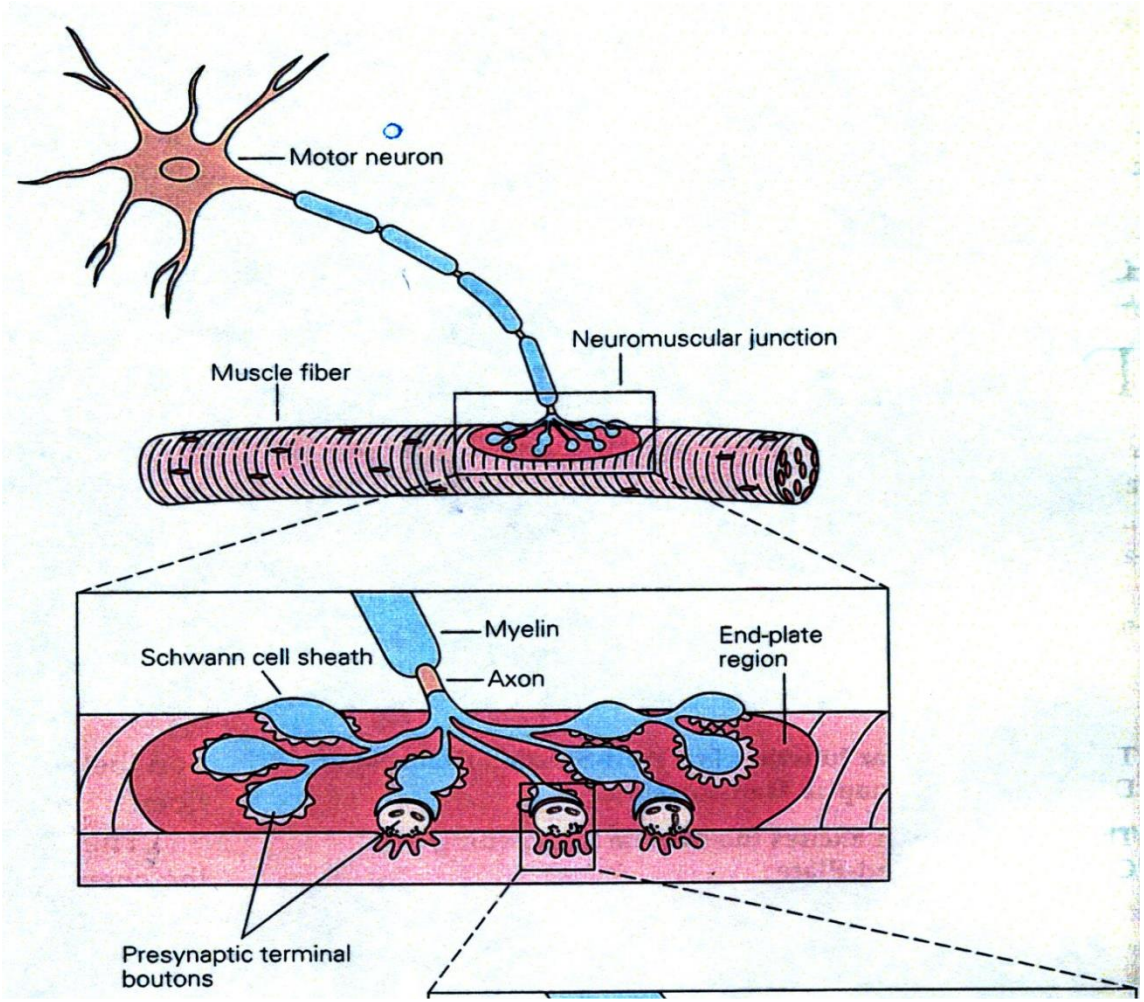
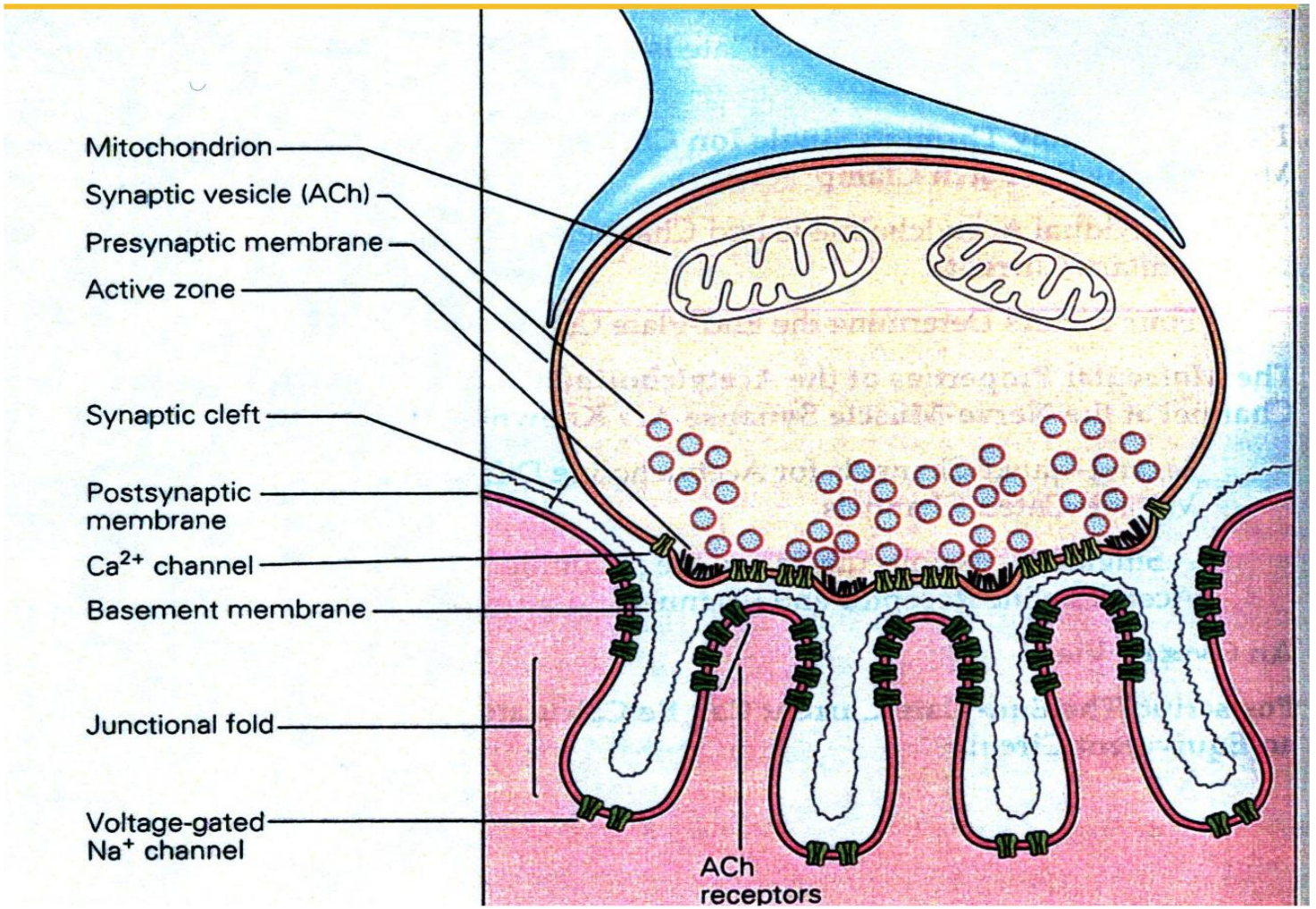
Farmacologia da Junção Neuromuscular

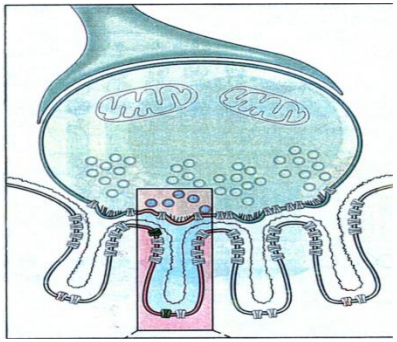
Junção Neuromuscular

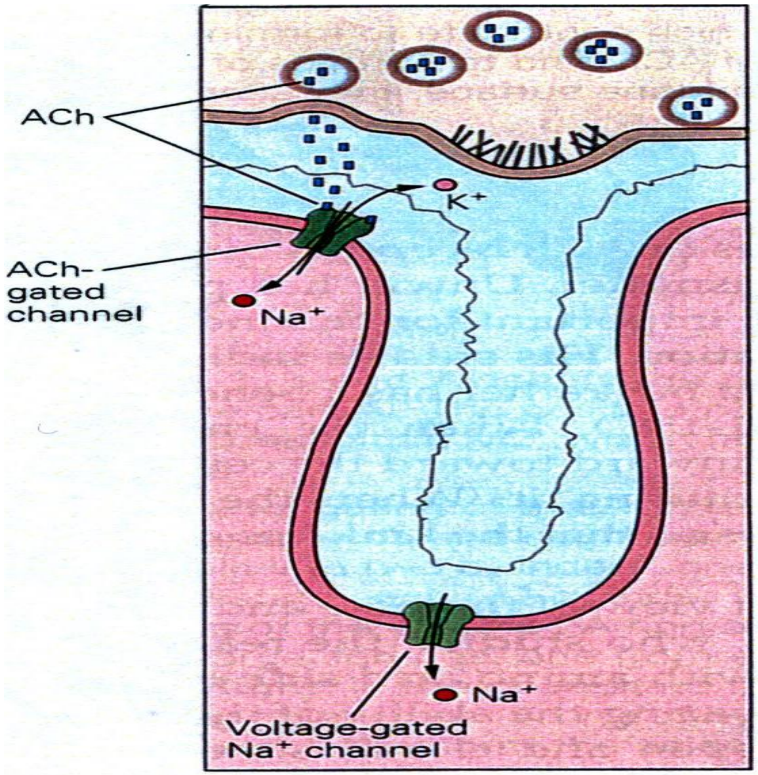


Junção Neuromuscular



Potencial de placa terminal e potencial de ação





ACh binding at transmitter-gated channels

↓

Channel opening

↓

Na^+ inflow
K^+ outflow

↓

Depolarization (end-plate potential)

↓

Opening of voltage-gated Na^+ channels

↓

Na^+ inflow

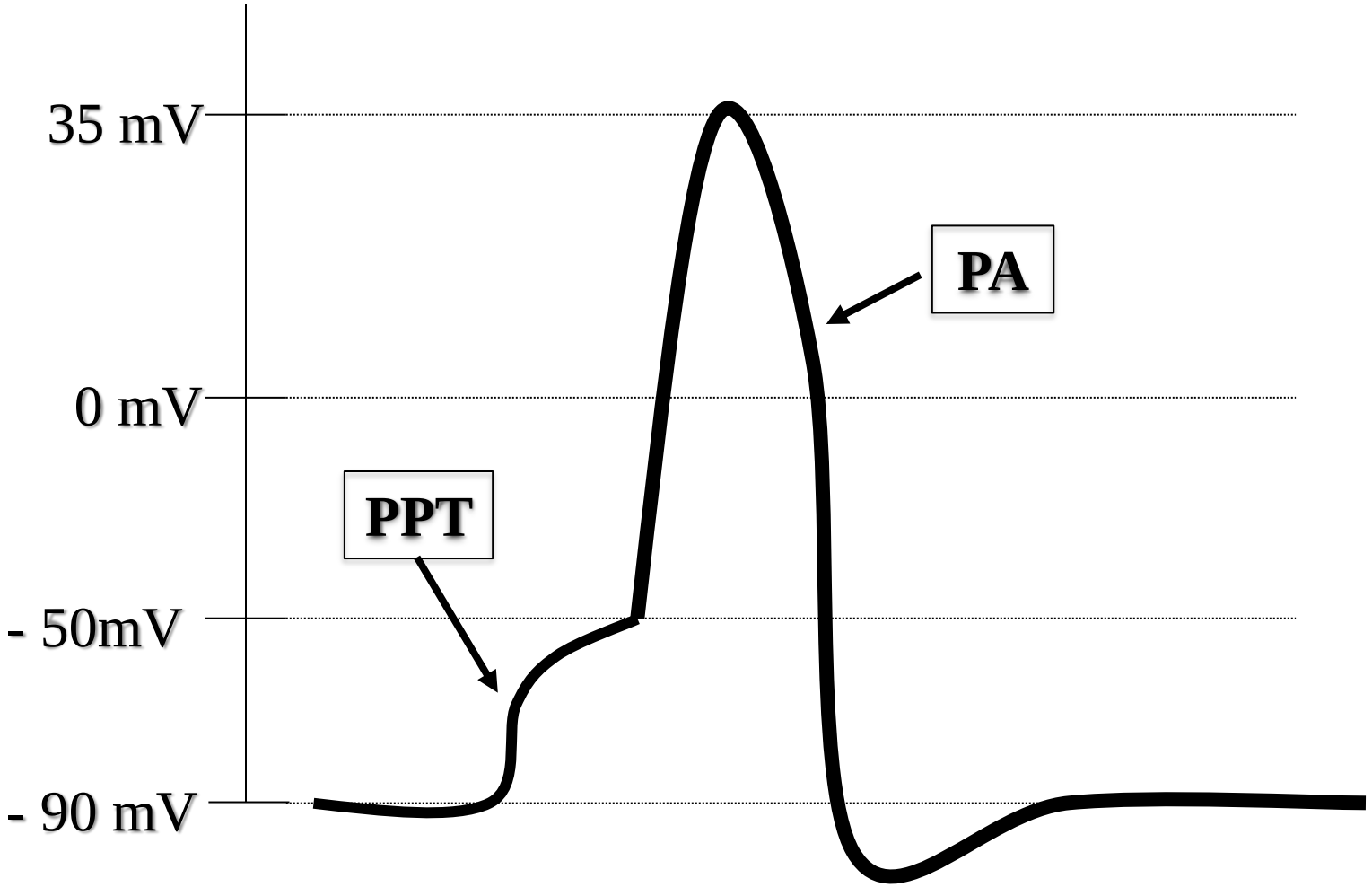
↓

Depolarization

↓

Action potential

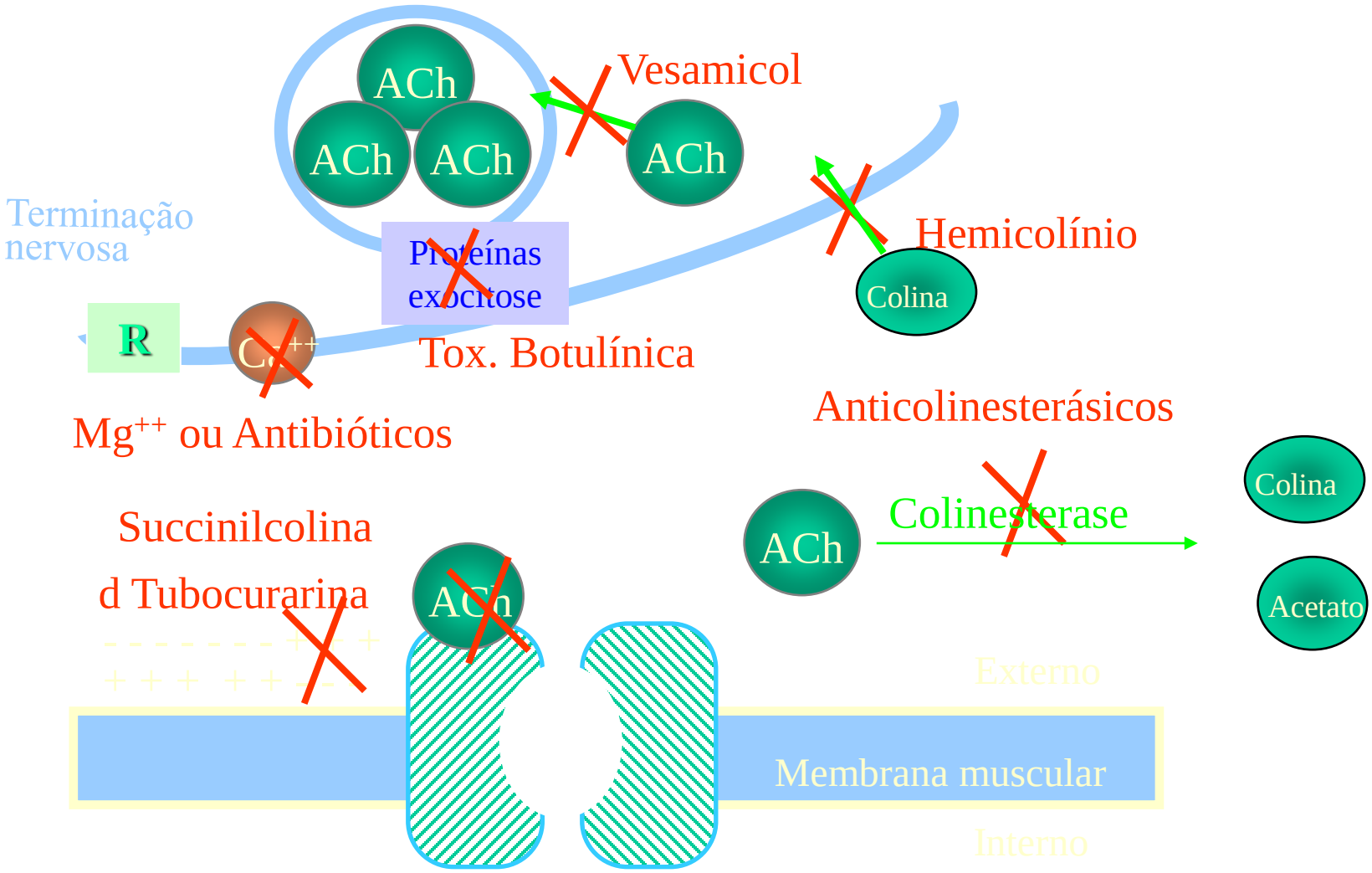
Potencial de placa terminal e Potencial de ação



Farmacologia da Junção Neuromuscular

Inibidores da transmissão neuromuscular – pré-sináptico	• Síntese, armazenamento, liberação
Inibidores da transmissão neuromuscular – pós-sináptico	• Bloqueadores competitivos (não-despolarizantes) • Bloqueadores despolarizantes
Facilitadores da JNM	• Anticolinesterásicos

Fármacos que alteram a JNM



Toxina botulínica–Usos clínicos (sempre aplicação localizada):

1)Neurologia: Síndromes espásticas musculares (blefaroespasmo)

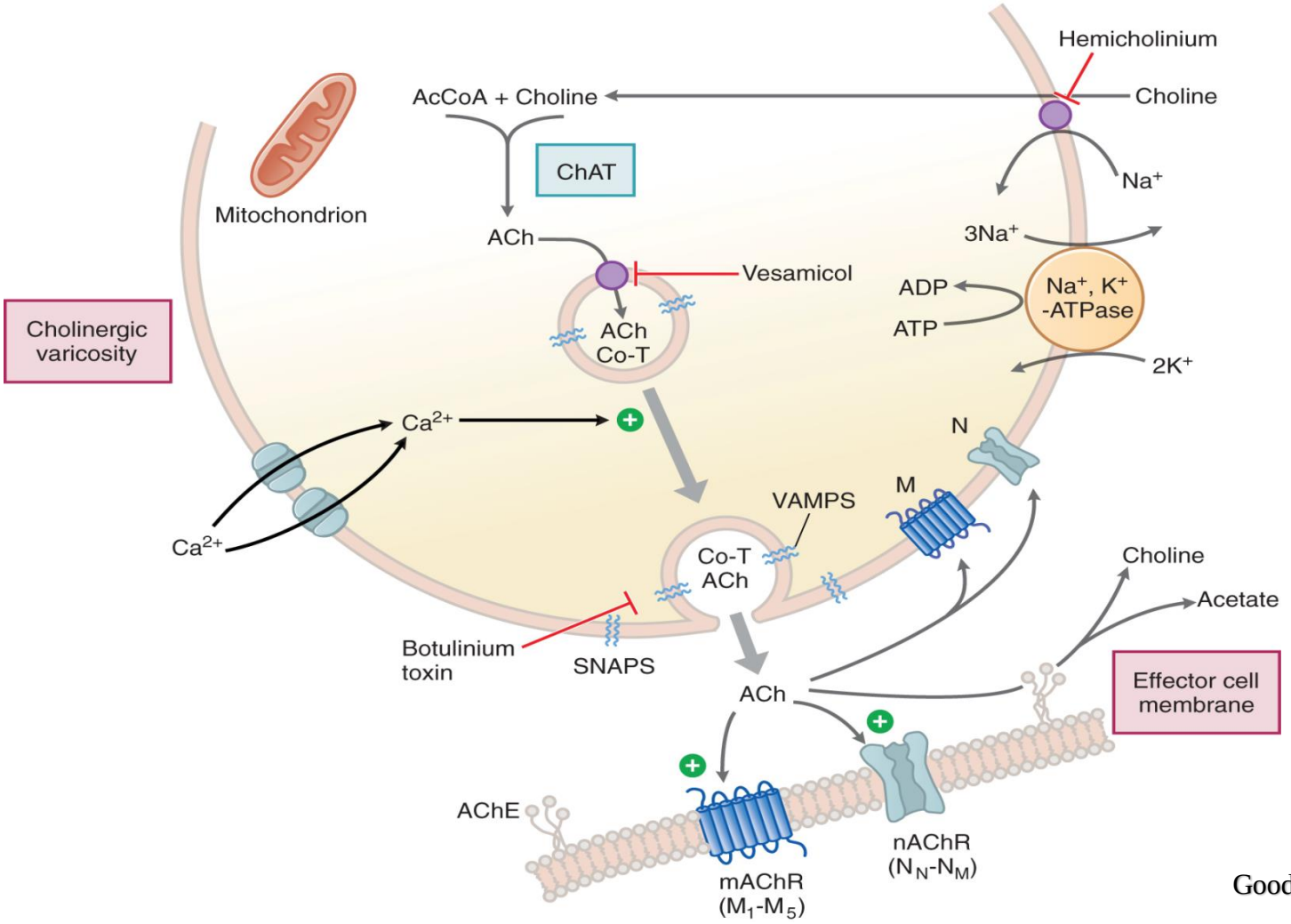
2)Oftalmologia: Estrabismo

3)Cosmético

4)Bexiga hiperativa

Bloqueadores da junção neuromuscular

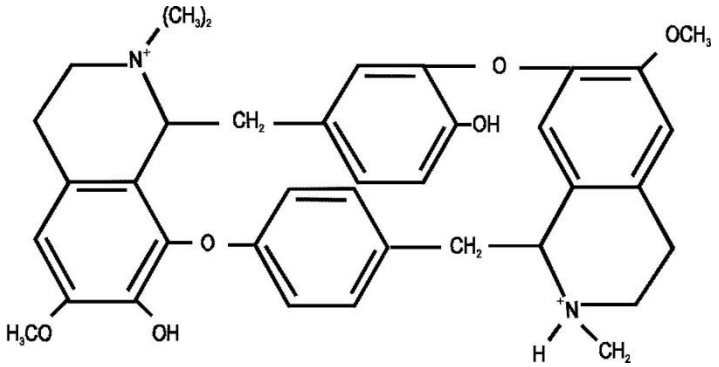
Transmissão colinérgica



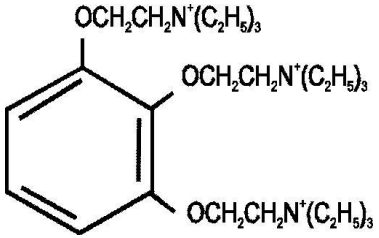
Goodman e Gilman

Bloqueadores Neuromusculares

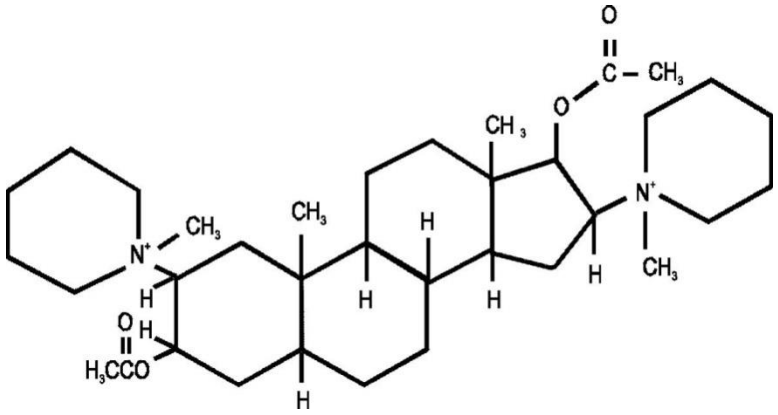
Competitivos ou Não Despolarizantes



d.Tubocurarina

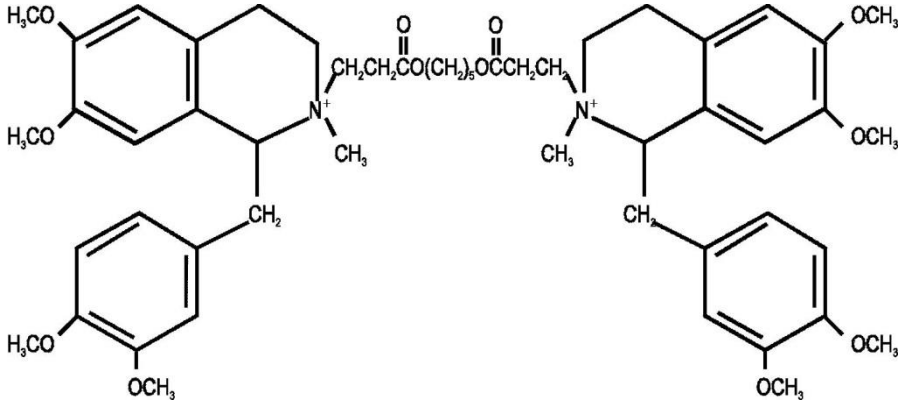


Galamina



Aminoesteróides

Pancurônio



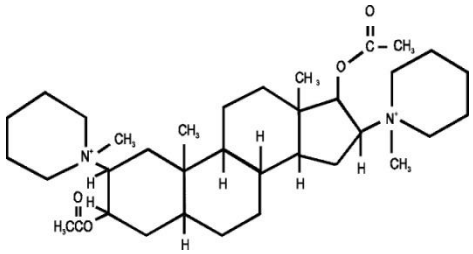
Benzilisoquinolínicos

Atracúrio

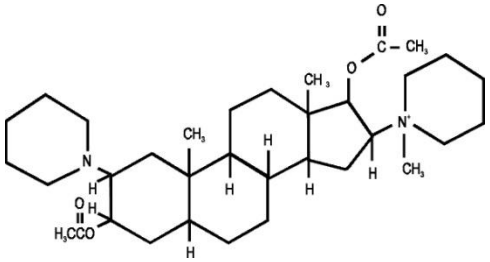
Goodman e Gilman

Bloqueadores neuromusculares competitivos

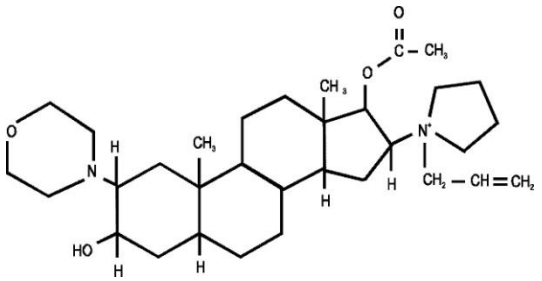
Aminoesteróides



Pancurônio



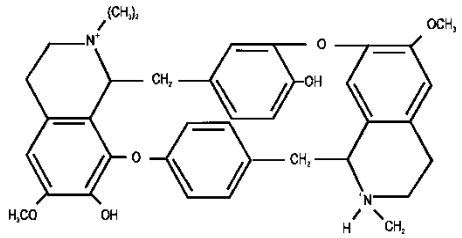
Vecurônio



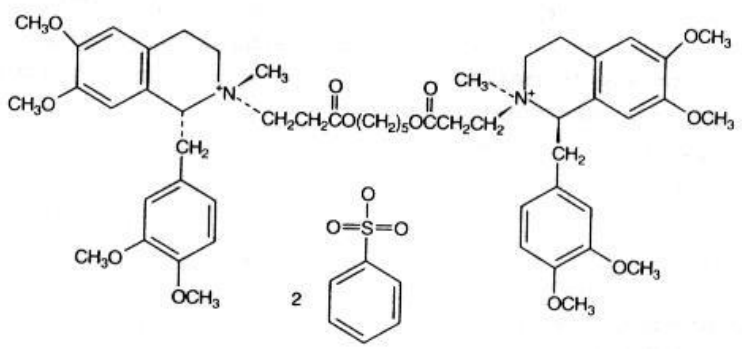
Rocurônio

Goodman e Gilman

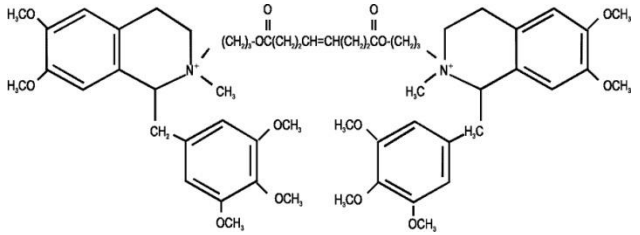
Benzilisoquinolínicos



d-tubocurarina



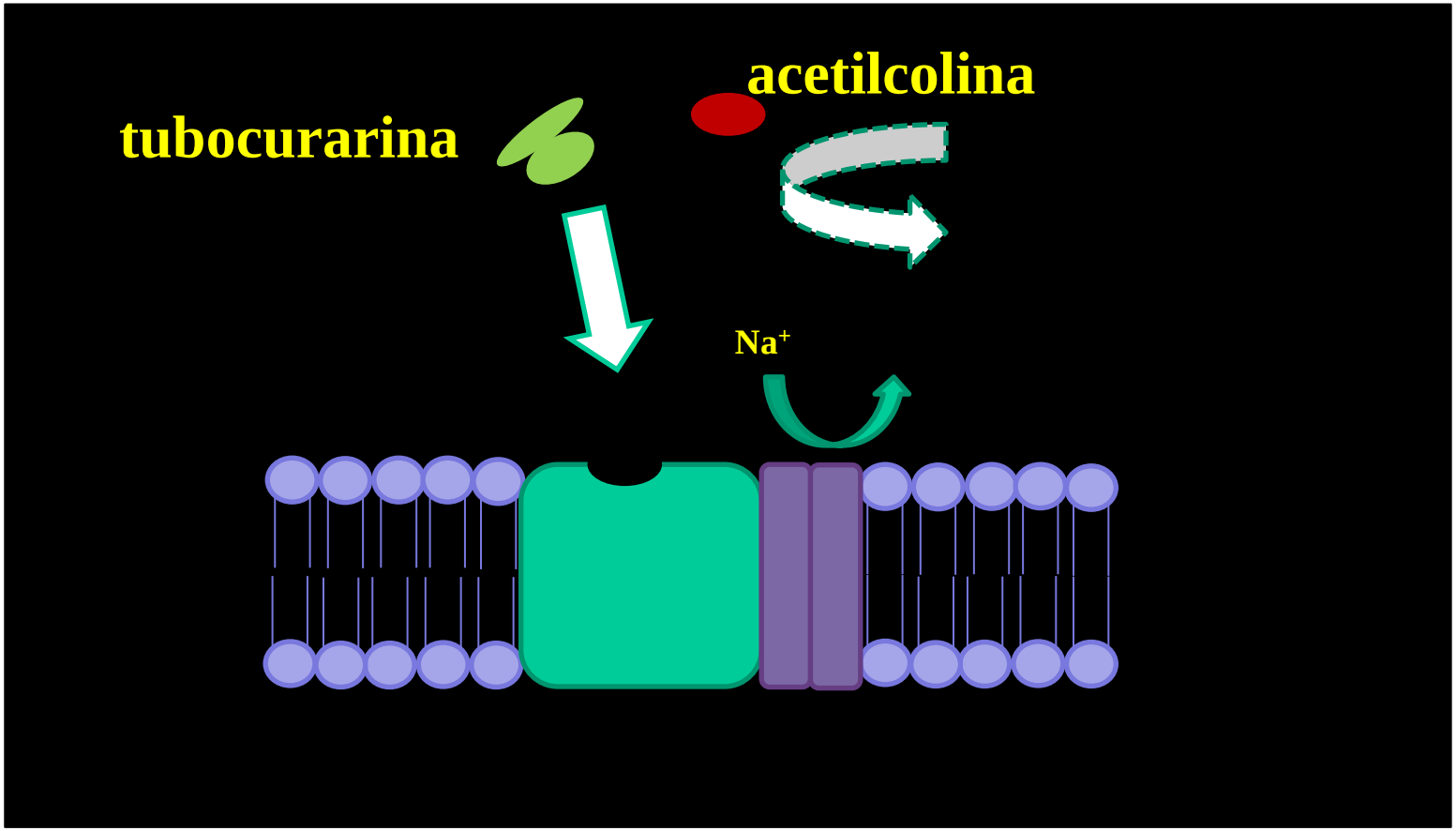
Atracúrio/cisatracúrio



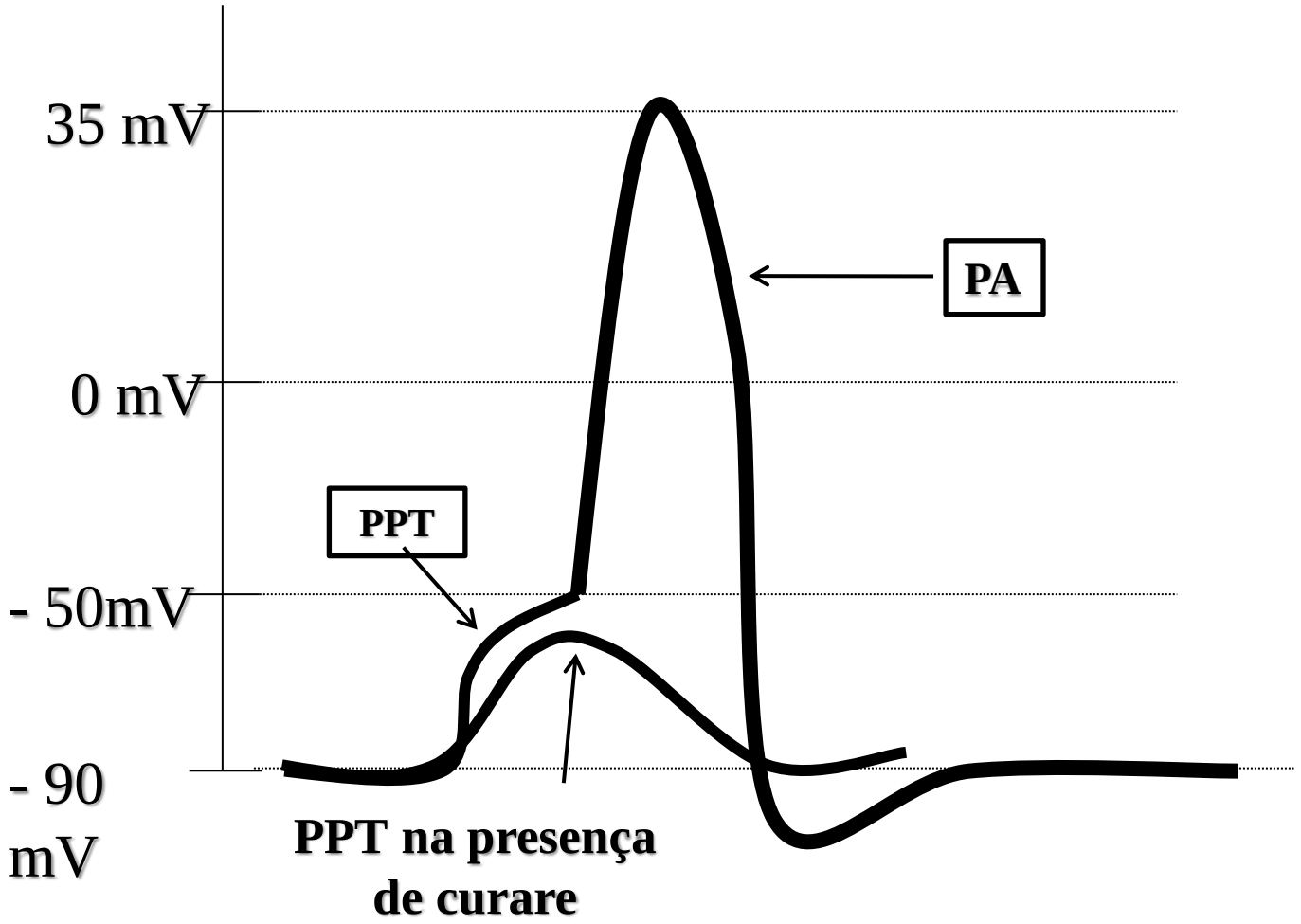
Mivacúrio

Goodman e Gilman

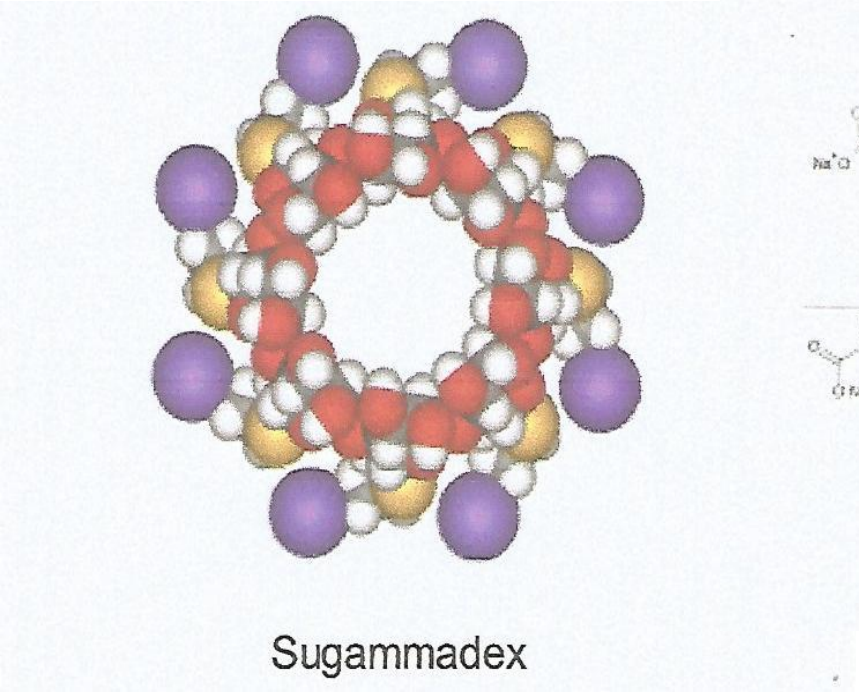
Mecanismo de ação dos bloqueadores neuromusculares competitivos



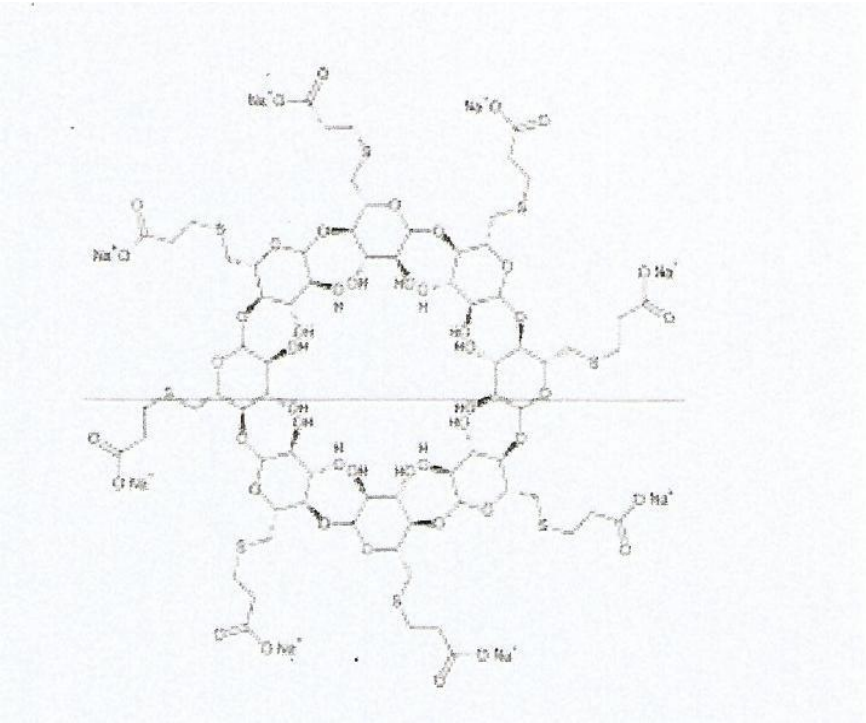
Mecanismo de ação dos bloqueadores neuromusculares competitivos



O bloqueio neuromuscular induzido pelo rocurônio é revertido por sugamadex, fármaco quelante deste bloqueador

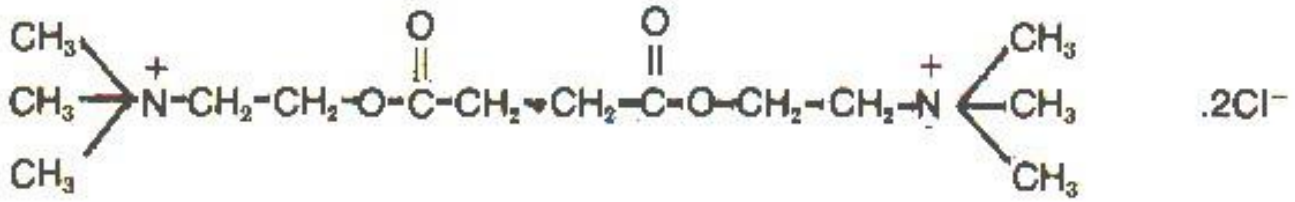


Sugammadex

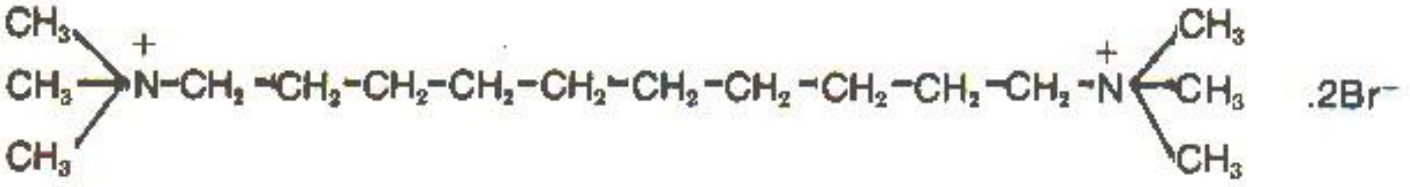


Bloqueadores Neuromusculares

Não Competitivos ou Despolarizantes



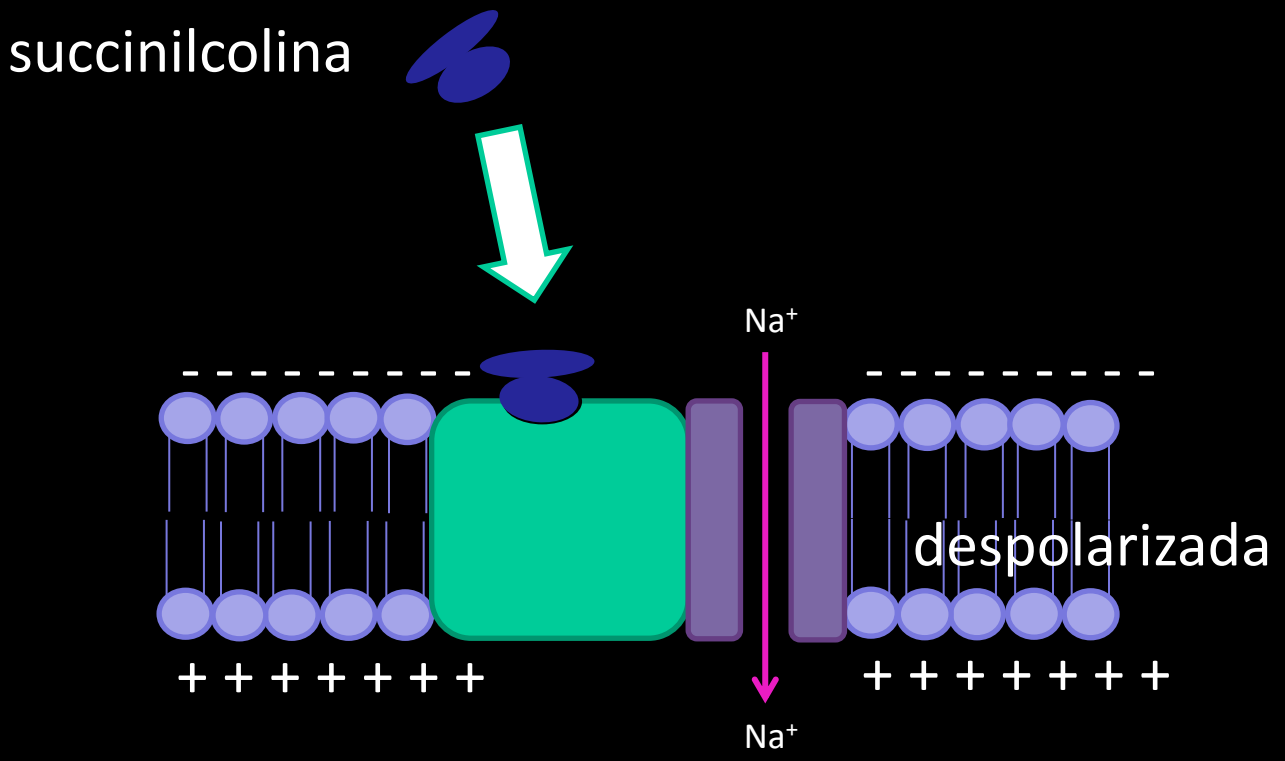
Succinilcolina



Decametônio

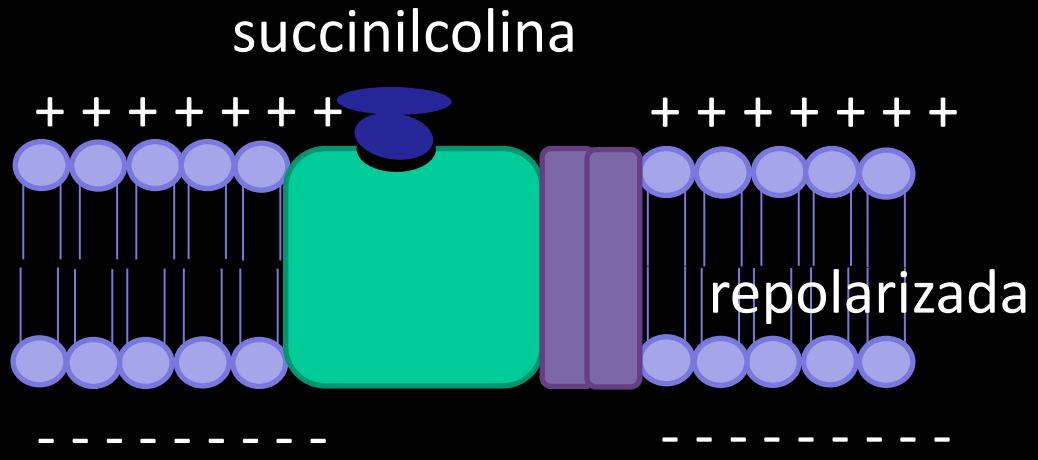
Goodman e Gilman

Bloqueio por Desporalização Fase 1



A membrana despolariza, resulta em uma descarga inicial que produz fasciculações transientes seguidas de paralisia flácida

Bloqueio por Desporalização Fase 2



A membrana repolariza mas o receptor está dessensibilizado ao efeito da Ach

Bloqueadores da JNM

Usos:
1)Relaxamento muscular esquelético para facilitar cirurgias
2) Facilitação da intubação endotraqueal

Efeitos adversos: succinilcolina

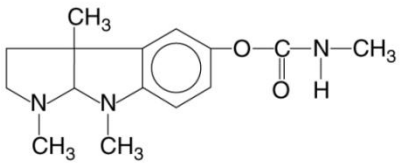
Dores musculares

Hipertermia maligna

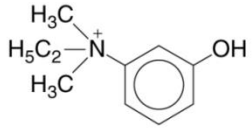
Hiperpotassemia

Facilitadores da transmissão neuromuscular: anticolinesterásicos

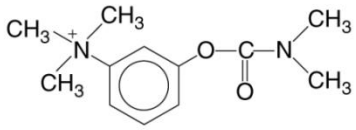
Colinérgicos de ação indireta: anticolinesterásicos



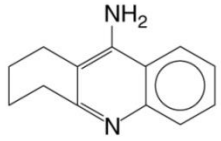
PHYSOSTIGMINE



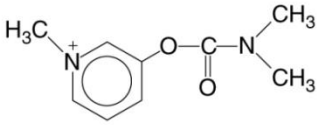
EDROPHONIUM



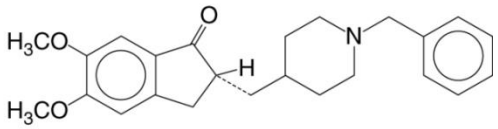
NEOSTIGMINE



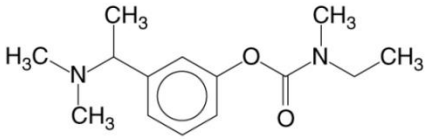
TACRINE



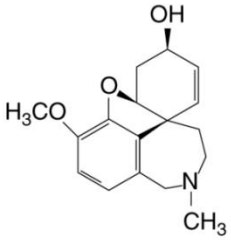
PYRIDOSTIGMINE



DONEPEZIL



RIVASTIGMINE



GALANTAMINE

Goodman e Gilman

Usos clínicos

Neostigmina: reversão da ação de bloqueadores competitivos no fim da cirurgia. Atropina para limitar efeitos parassimpatomiméticos

Neostigmina: não reverte o bloqueio despolarizante. Pode até reforçar o bloqueio.

Neostigmina: tratamento da Miastenia gravis

Edrofônio: teste para Miastenia gravis para distinguir fraqueza causada por overdose de anticolinesterásico (“crise colinérgica”) da fraqueza da própria **miastenia (“crise miastênica”)**

Miastenia Grave

Doença autoimune contra receptores nicotínicos da JNM

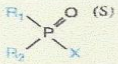
Fraqueza muscular: em decorrência da falha da transmissão neuromuscular.

Paralisia na crise miastênica

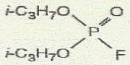
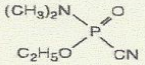
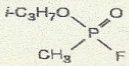
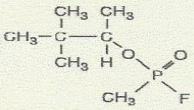
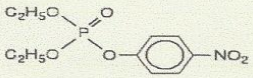
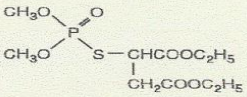
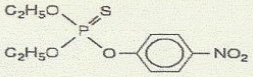
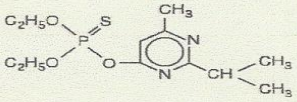
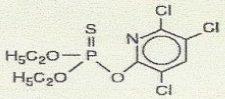
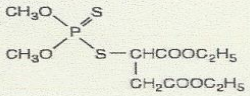
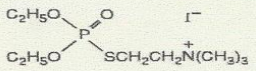
Paciente miastênico: mais sensível ao bloqueador competitivo e mais resistente aos despolarizantes

Table 10–1

Chemical Classification of Representative Organophosphorus Compounds of Particular Pharmacological or Toxicological Interest

General formula  (S)

Group **A**, X = halogen, cyanide, or thiocyanate leaving group; group **B**, X = alkylthio, arylthio, alkoxy, or aryloxy leaving group; group **C**, thionophosphorus or thio-thionophosphorus compounds; group **D**, quaternary ammonium leaving group. R_1 can be an alkyl (phosphonates), alkoxy (phosphorates) or an alkylamino (phosphoramidates) group.

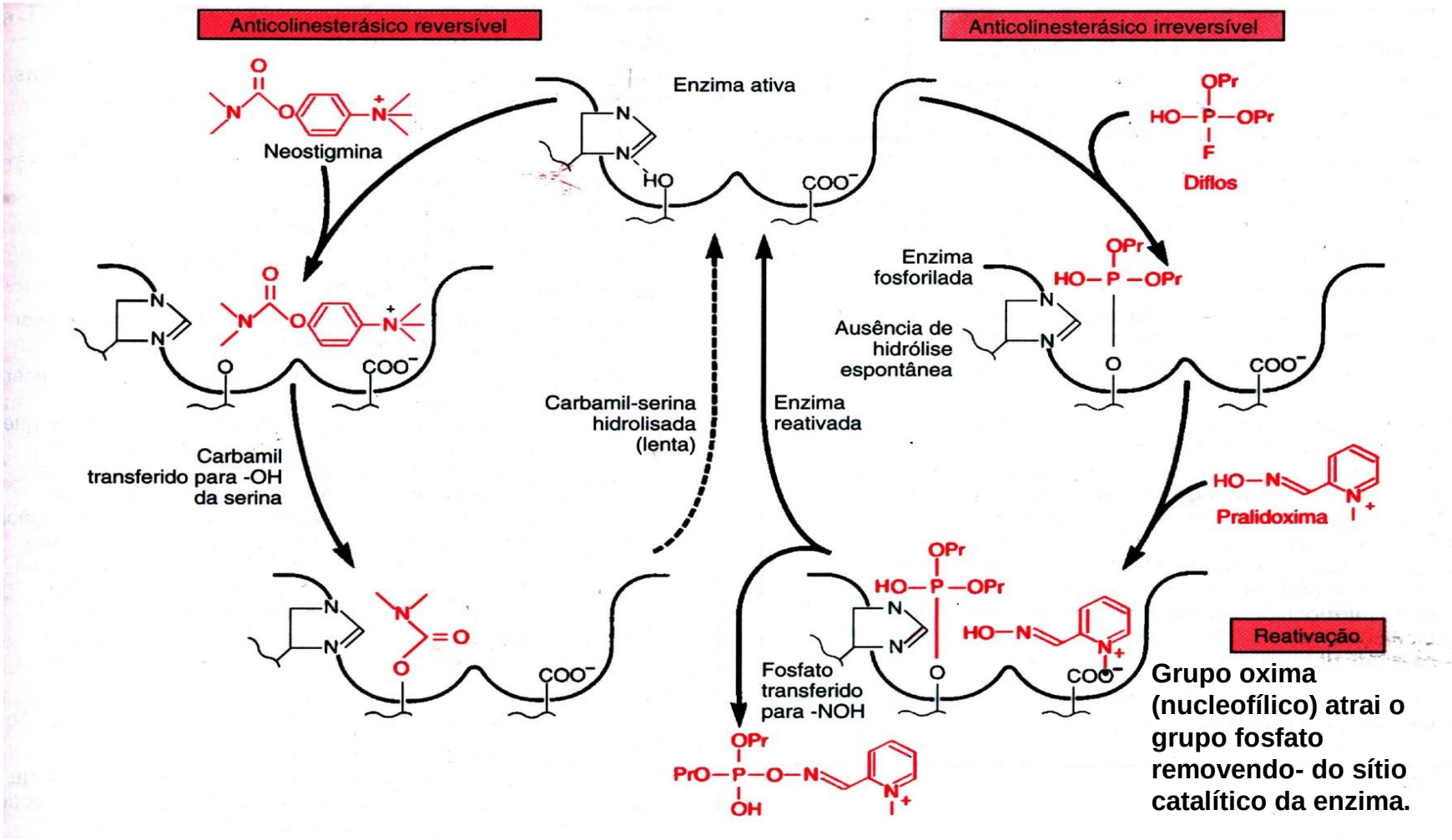
GROUP	STRUCTURAL FORMULA	COMMON, CHEMICAL, AND OTHER NAMES	COMMENTS
A		DFP; Isoflurophate; diisopropyl fluorophosphate	Potent, irreversible inactivator
		Tabun Ethyl N-dimethylphosphoramidocyanidate	Extremely toxic "nerve gas"
		Sarin (GB) Isopropyl methylphosphonofluoridate	Extremely toxic "nerve gas"
		Soman (GD) Pinacolyl methylphosphonofluoridate	Extremely toxic "nerve gas"; greatest potential for irreversible action/ rapid aging
B		Paraoxon (MINTACOL), E 600 *O,O*-Diethyl *O*-(4-nitrophenyl)-phosphate	Active metabolite of parathion
		Malaoxon *O,O*-Dimethyl S-(1,2-dicarboxyethyl)-phosphorothioate	Active metabolite of malathion
C		Parathion *O,O*-Diethyl *O*-(4-nitrophenyl)-phosphorothioate	Agricultural insecticide, resulting in numerous cases of accidental poisoning; phased out in 2003.
		Diazinon, Dimpylate *O,O*-Diethyl *O*-(2-isopropyl-6-methyl-4-pyrimidinyl) phosphorothioate	Insecticide; use limited to non-residential agricultural settings
C		Chlorpyrifos *O,O*-Diethyl *O*-(3,5,6-trichloro-2-pyridyl) phosphorothioate	Insecticide; use limited to non-residential agricultural settings
		Malathion *O,O*-Dimethyl S-(1,2-dicarbethoxyethyl) phosphorodithioate	Widely employed insecticide of greater safety than parathion or other agents because of rapid detoxification by higher organisms
D		Echothiophate (PHOSPHOLINE IODIDE), MI-217 Diethoxyphosphinylthiocholine iodide	Extremely potent choline derivative; administered locally in treatment of glaucoma; relatively stable in aqueous solution

Goodman e Gilman

Intoxicação por anticolinesterásicos organofosforados:
Bloqueio despolarizante da junção neuromuscular (reforço da ação nicotínica) + reforço da ação muscarínica

Reativação da colinesterase

Pralidoxima



Grupo oxima (nucleofílico) atrai o grupo fosfato removendo- do sítio catalítico da enzima.

Referências bibliográficas

Rang, H.P., Ritter, J.M., Flower, R.J. & Henderson, G. *Transmissão colinérgica.* In: Farmacologia, 8ª ed. 2016.

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