

3. AGONIS DAN ANTAGONIS MUSKARINIK

Zunilda D.S.

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Cholinoceptor-Activating & Cholinesterase-Inhibiting Drugs

Obat Kolinergik / Parasimpatomimetik

Figure 2-1 Overview of the functions of of symphatetic and para symphatetic divisions of the autonomic nervous system (Drawing by Ted Johnson)
 [PDQ, hal 22]

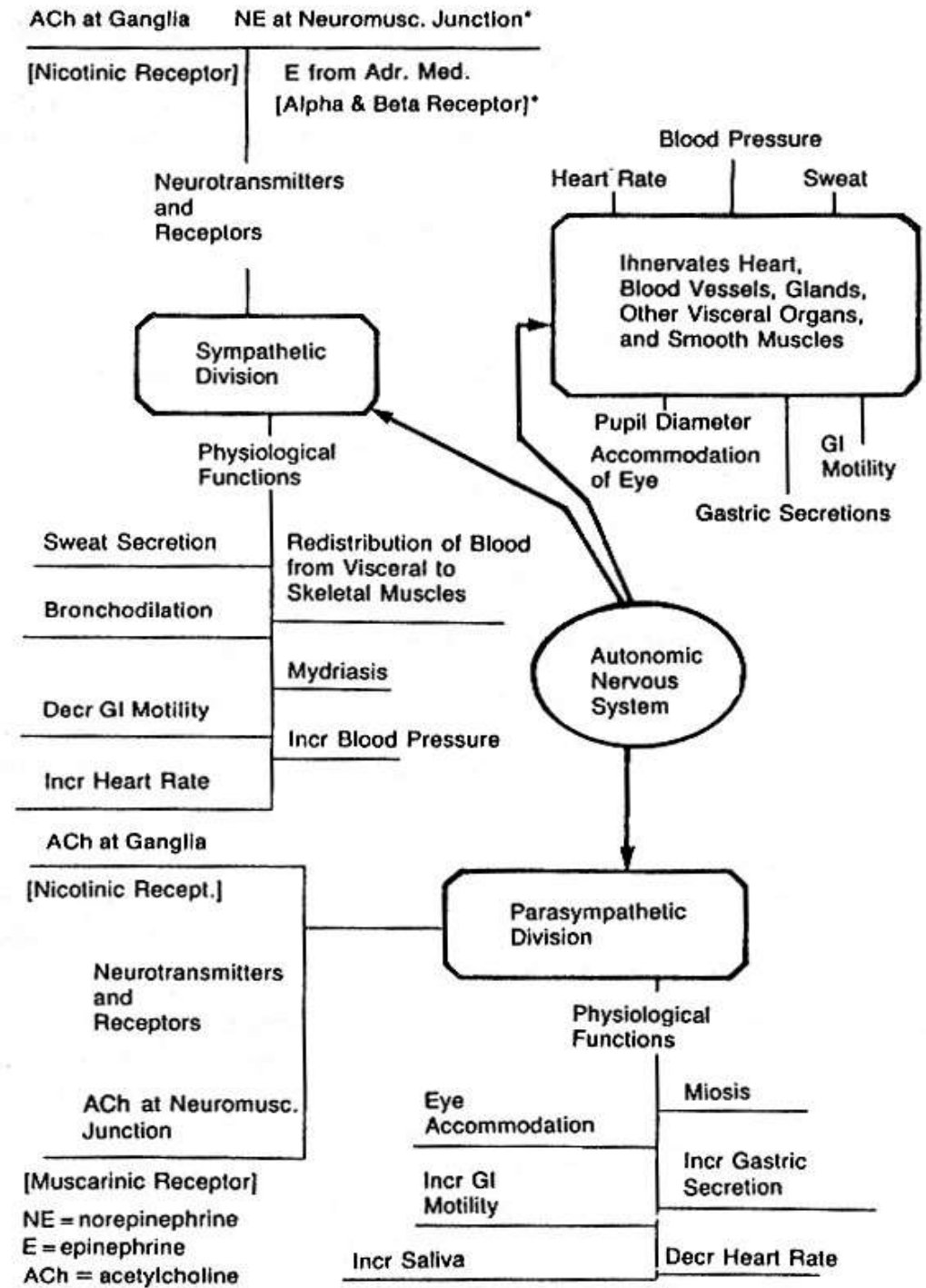
* A few symphatetic nerves, notably those innervating sweat glands, release Ach. In this case the receptors stimulated are muscarinic.

PDQ PHARMACOLOGY

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Manlygraphic Asian Edition, 1989
 Published by
Manlygraphic Publishers Pte Ltd
 by special arrangement with
 B.C. Decker Inc, Toronto, Philadelphia

PDQ (Pretty, Darn Quick)



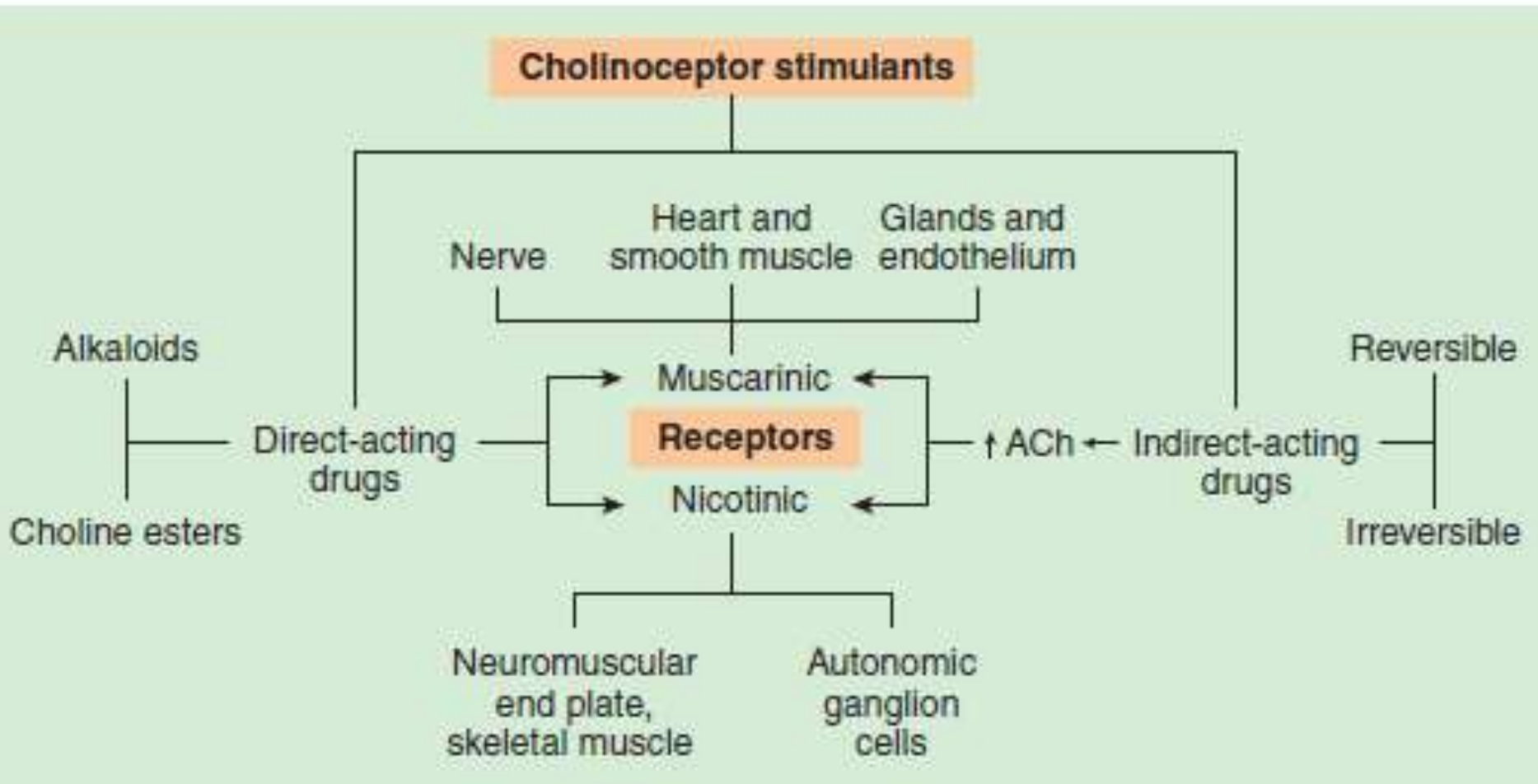
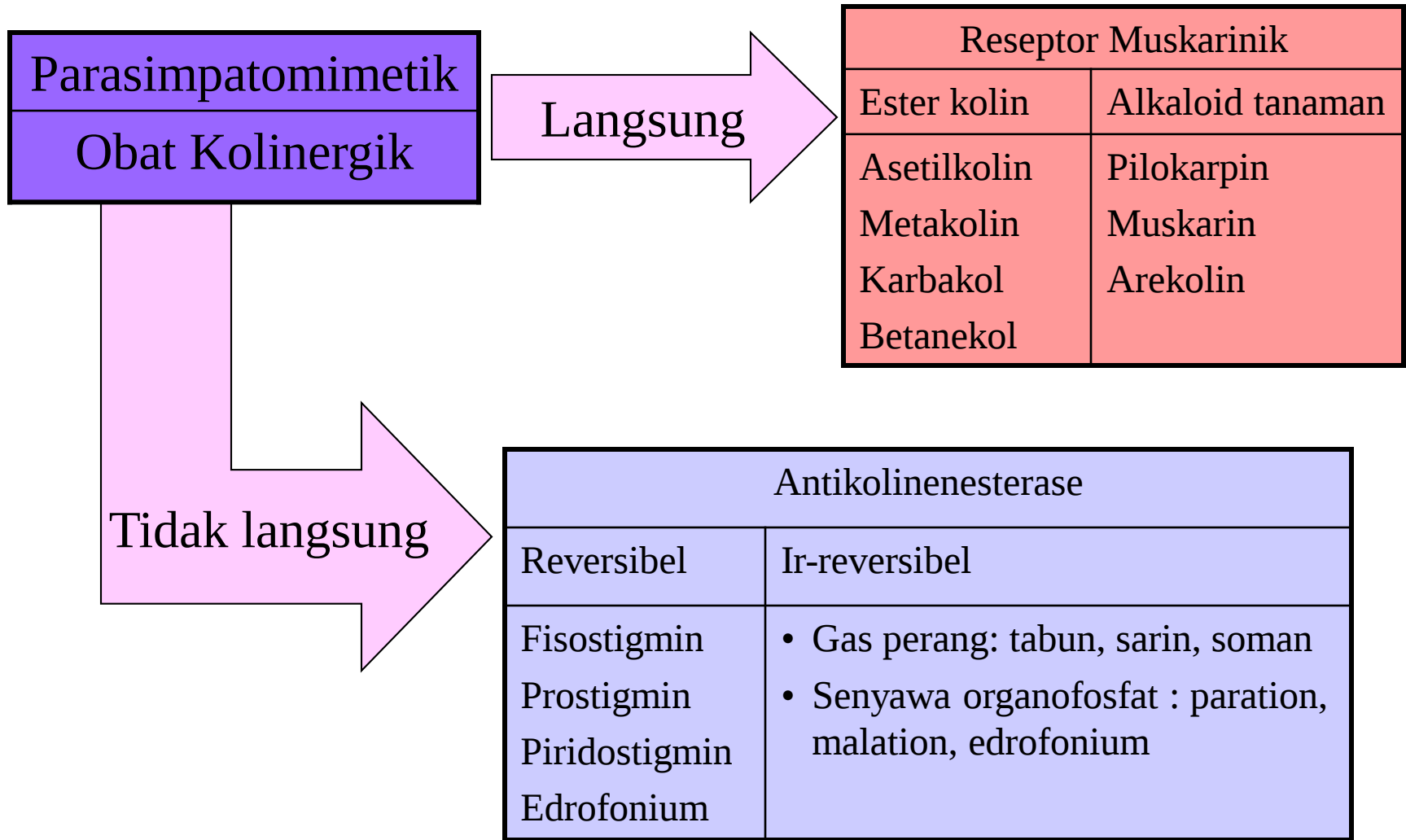
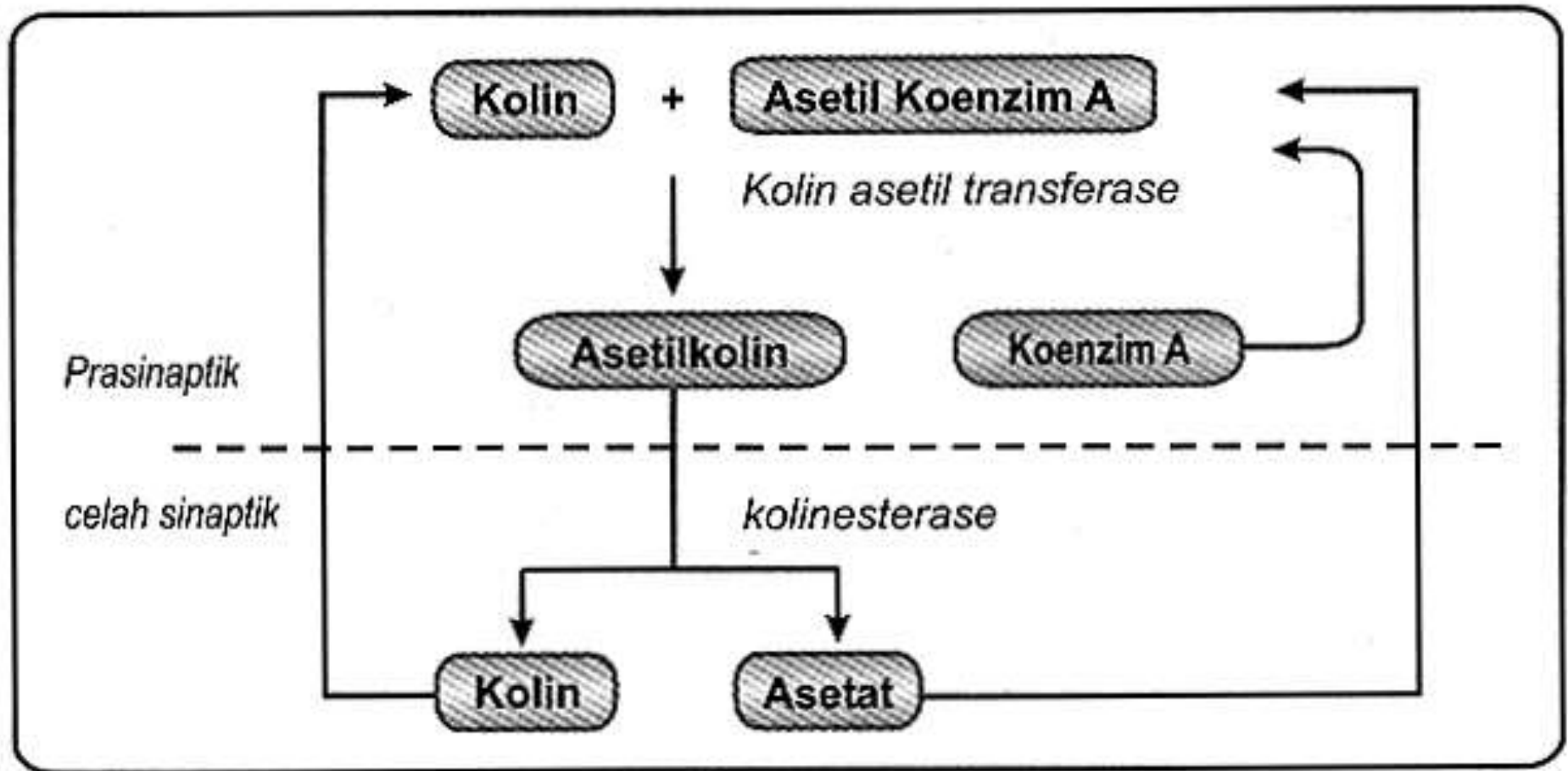
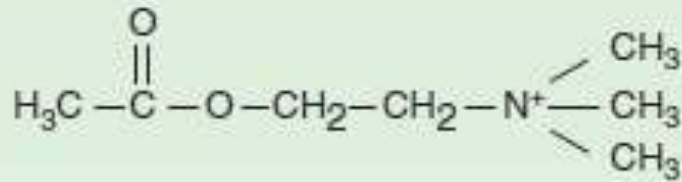


FIGURE 7-1 The major groups of cholinoceptor-activating drugs, receptors, and target tissues. ACh, acetylcholine.

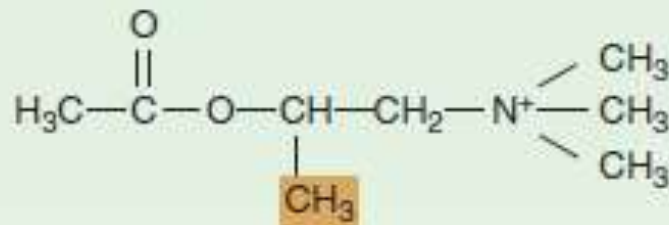




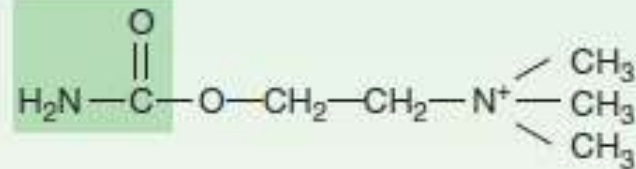
Gb. 2-2 Jalur biosintesis asetilkolin. Setelah disintesis, asetilkolin dimetabolisme lebih lanjut menjadi kolin dan asetat oleh enzim kolinesterase. (diadaptasi dari Nestler, et a., 2000)



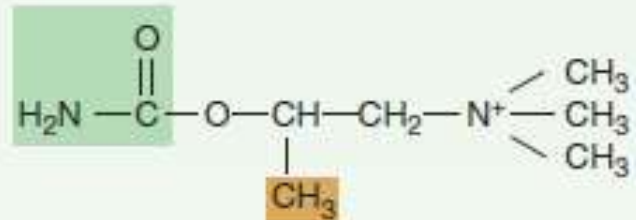
Acetylcholine



Methacholine
(acetyl- β -methylcholine)



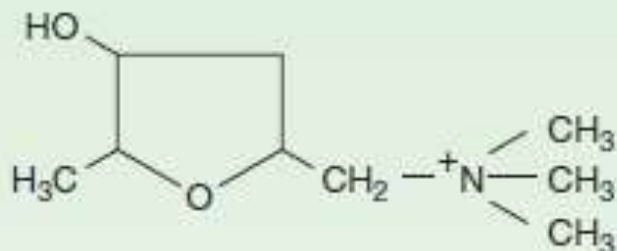
Carbachol
(carbamoylcholine)



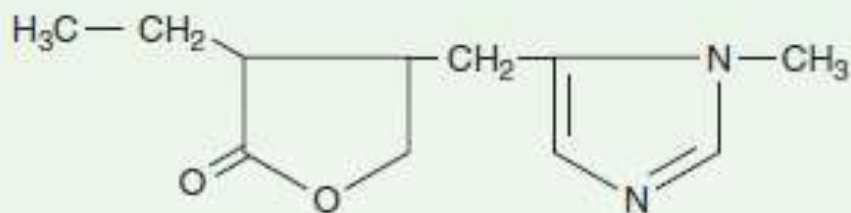
Bethanechol
(carbamoyl- β -methylcholine)

FIGURE 7-2 Molecular structures of four choline esters. Acetylcholine and methacholine are acetic acid esters of choline and β -methylcholine, respectively. Carbachol and bethanechol are carbamic acid esters of the same alcohols.

Action chiefly muscarinic

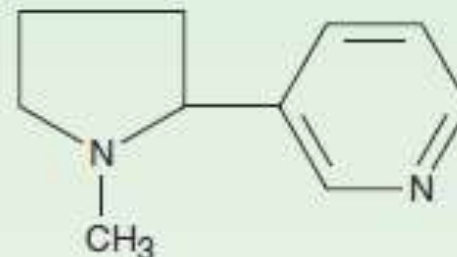


Muscarine

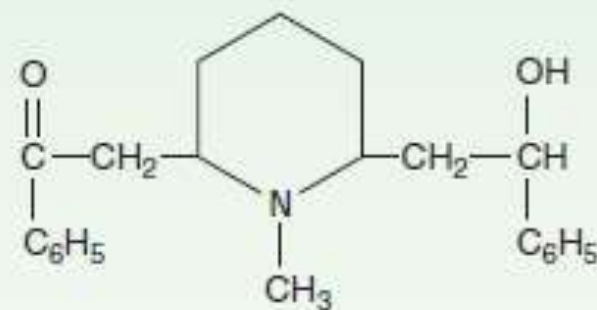


Pilocarpine

Action chiefly nicotinic



Nicotine



Lobelline

FIGURE 7-3 Structures of some cholinomimetic alkaloids.

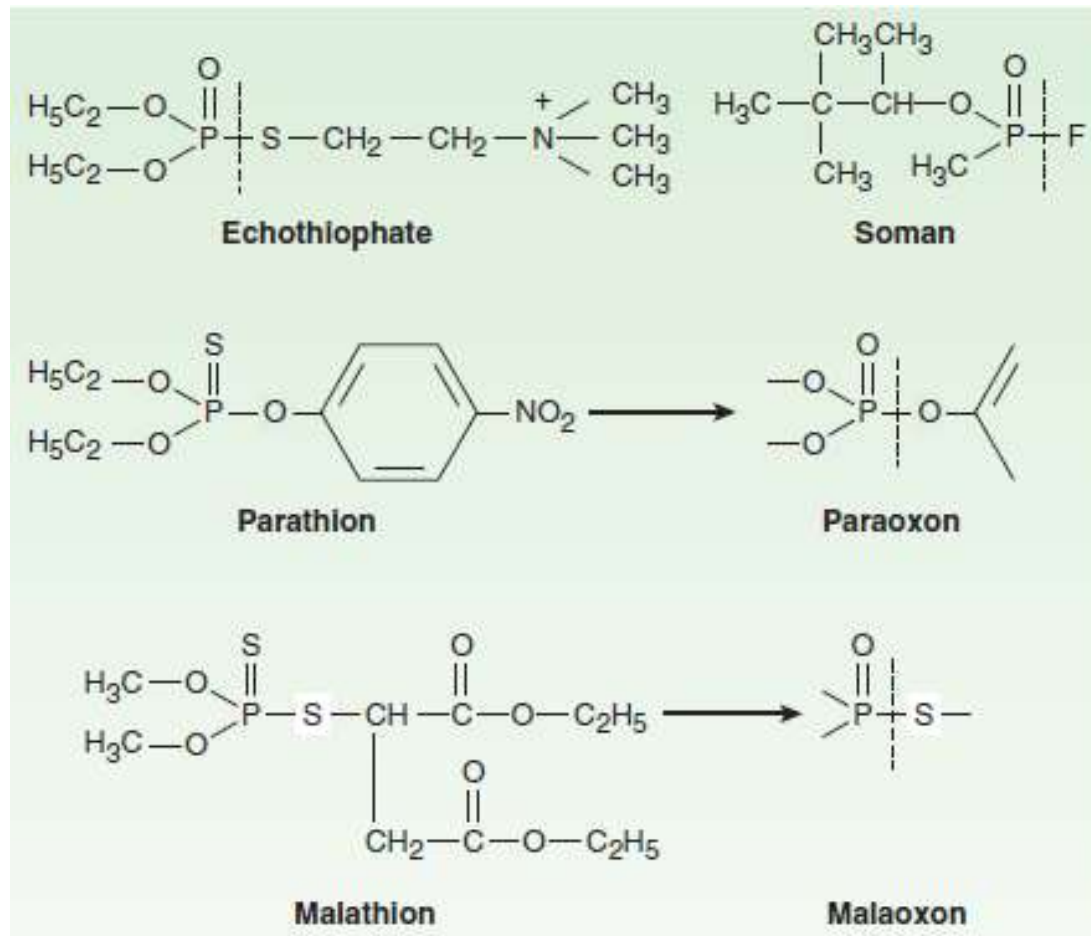


FIGURE 7-7 Structures of some organophosphate cholinesterase inhibitors. The dashed lines indicate the bond that is hydrolyzed in binding to the enzyme. The shaded ester bonds in malathion represent the points of detoxification of the molecule in mammals and birds.

Ester kolin	• Prototipe : asetilkolin • Hanya untuk penelitian, jarang digunakan • Tidak dapat diberikan oral, karena mudah terhidrolisis
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Farmakodinamik

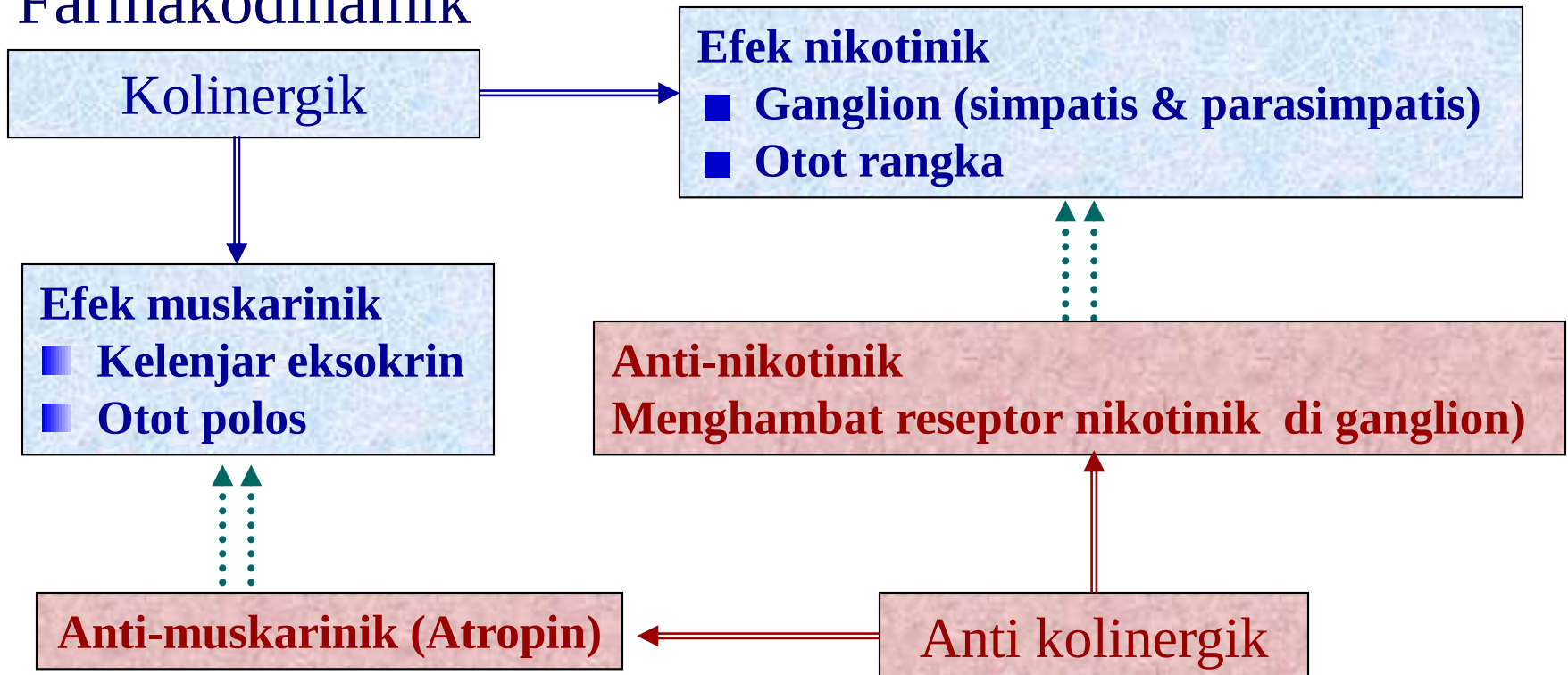


TABLE 7-2 Properties of choline esters.

Choline Ester	Susceptibility to Cholinesterase	Muscarinic Action	Nicotinic Action
Acetylcholine chloride	++++	+++	+++
Methacholine chloride	+	++++	None
Carbachol chloride	Negligible	++	+++
Bethanechol chloride	Negligible	++	None

SUMMARY Drugs Used for Cholinomimetic Effects

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
DIRECT-ACTING CHOLINE ESTERS				
• Bethanechol	Muscarinic agonist • negligible effect at nicotinic receptors	Activates M_1 through M_3 receptors in all peripheral tissues • causes increased secretion, smooth muscle contraction (except vascular smooth muscle relaxes), and changes in heart rate	Postoperative and neurogenic ileus and urinary retention	Oral and parenteral, duration ~ 30 min • does not enter central nervous system (CNS) • <i>Toxicity:</i> Excessive parasympathomimetic effects, especially bronchospasm in asthmatics • <i>Interactions:</i> Additive with other parasympathomimetics
• <i>Carbachol: Nonselective muscarinic and nicotinic agonist; otherwise similar to bethanechol; used topically almost exclusively for glaucoma</i>				
DIRECT-ACTING MUSCARINIC ALKALOIDS OR SYNTHETICS				
• Pilocarpine	Like bethanechol, partial agonist	Like bethanechol	Glaucoma; Sjögren's syndrome	Oral lozenge and topical • <i>Toxicity & interactions:</i> Like bethanechol
• <i>Cevimeline: Synthetic M_3-selective; similar to pilocarpine</i>				
DIRECT-ACTING NICOTINIC AGONISTS				
• Nicotine	Agonist at both N_N and N_M receptors	Activates autonomic post-ganglionic neurons (both sympathetic and parasympathetic) and skeletal muscle neuromuscular end plates • enters CNS and activates N_N receptors	Medical use in smoking cessation • nonmedical use in smoking and in insecticides	Oral gum, patch for smoking cessation • <i>Toxicity:</i> Increased gastrointestinal (GI) activity, nausea, vomiting, diarrhea acutely • increased blood pressure • high doses cause seizures • long-term GI and cardiovascular risk factor • <i>Interactions:</i> Additive with CNS stimulants
• <i>Varenicline: Selective partial agonist at $\alpha 4\beta 2$ nicotinic receptors; used exclusively for smoking cessation</i>				

SUMMARY Drugs Used for Cholinomimetic Effects

Lanjutan

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
SHORT-ACTING CHOLINESTERASE INHIBITOR (ALCOHOL)				
• Edrophonium	Alcohol, binds briefly to active site of acetylcholinesterase (AChE) and prevents access of acetylcholine (ACh)	Amplifies all actions of ACh • increases parasympathetic activity and somatic neuromuscular transmission	Diagnosis and acute treatment of myasthenia gravis	Parenteral • quaternary amine • does not enter CNS • <i>Toxicity:</i> Parasympathomimetic excess • <i>Interactions:</i> Additive with parasympathomimetics
INTERMEDIATE-ACTING CHOLINESTERASE INHIBITORS (CARBAMATES)				
• Neostigmine	Forms covalent bond with AChE, but hydrolyzed and released	Like edrophonium, but longer-acting	Myasthenia gravis • postoperative and neurogenic ileus and urinary retention	Oral and parenteral; quaternary amine, does not enter CNS. Duration 2–4 h • <i>Toxicity & interactions:</i> Like edrophonium
• <i>Pyridostigmine:</i> Like neostigmine, but longer-acting (4–6 h); used in myasthenia • <i>Physostigmine:</i> Like neostigmine, but natural alkaloid tertiary amine; enters CNS				
LONG-ACTING CHOLINESTERASE INHIBITORS (ORGANOPHOSPHATES)				
• Echothiophate	Like neostigmine, but released more slowly	Like neostigmine, but longer-acting	Obsolete • was used in glaucoma	Topical only • <i>Toxicity:</i> Brow ache, uveitis, blurred vision
• <i>Malathion:</i> Insecticide, relatively safe for mammals and birds because metabolized by other enzymes to inactive products; some medical use as ectoparasiticide • <i>Parathion, others:</i> Insecticide, dangerous for all animals; toxicity important because of agricultural use and exposure of farm workers (see text) • <i>Sarin, others:</i> "Nerve gas," used exclusively in warfare and terrorism				

Antikolinesterase

- Reversibel : fisostigmin, prostigmin, piridostigmin, edrofonium
- Ir-reversibel : gas perang (sarin, soman, tabun)
- Takrin : antikolinergik sentral (penderita Alzeheimer)

Farmakodinamik ;

- Mata dan usus ; efek lihat di atas
- Sambungan saraf-otot : menyebabkan otot rangka dalam keadaan terangsang terus menerus , akibatnya terjadi tremor, fibrilasi (pengkerutan otot) dan kejang-kejang.

Farmakokinetik

- ▶ absorpsi setelah pemberian oral dan im → bagus
- ▶ insektisida organofosfat diserap baik melalui kulit
- ▶ metabolit → dalam bentuk hidrolisis

Intoksikasi Senyawa Antikolinesterase

- Reversibel : ekskresi 2-8 jam
- Ir-reversibel : ekskresi beberapa minggu

Gejala keracunan insektisida organofosfat :

- mata miosis kuat
- bronkokonstriksi dan laringospasme
- sekresi saliva dan selaput lendir berlebihan
- muntah dan diare
- keringat berlebihan
- otot rangka : fibrilasi otot, tremor dan kejang-kejang.
- ataksia (gangguan koordinasi gerakan), refleks hilang, bingung, sukar bicara,
- konvulsi, koma, kelumpuhan napas

Intoksikasi (2)

Diagnosis

- ▶ Periksa kadar Asetilkolinesterase dan butirilkolinesterase dalam eritrosit.
- ▶ Jika kadar $< 35 \%$ $\rightarrow$ positif keracunan (Normal = 75 –100 %)

Tindakan :

- ▶ Beri atropin iv/im , tiap 10 menit sampai ada perbaikan seperti :
 - Muka merah
 - Sekresi saliva dan keringat $<<<$
 - Midriasis, takikardia (frekuensi denyut jantung $\rightarrow$ 100 dpm)
- ▶ Beri pralidoksim (PAM) ; suatu kolinesterase reactivator

Indikasi obat kolinergik

- Atoni otot polos saluran cerna dan kemih pada pasca bedah dan keadaan toksik, menghilangkan bayangan gas dalam usus pada waktu foto abdomen → progestigmin
- Glaukoma → fisostigmin
- Miastenia gravis (kelumpuhan otot) → neostigmin
- Menangani demensia pada penyakit Alzheimer → inhibitor kolinesterase kerja lama (Takrin)
- Keracunan atropin : fisostigmin

Antagonis muskarinik Antikoliergik

Anti-kolinergik = parasimpatolitik = Anti-muskarinik

Prototipe → atropin (*Atropa belladonna*) ; skopolamin (*Hyoscyamus niger*)

Farmakodinamik

- Susunan saraf pusat (SSP) :
 - frekuensi jantung <;
 - perangsangan respirasi → dilatasi bronkus
 - depresi napas, eksitasi, disorientasi, delirium dan halusinasi (dosis >>>)
- Mata : midriasis & sikloplegia
- Saluran napas
 - menghambat sekresi hidung, mulut , faring dan bronkus → medikasi pre-anestetik (mengurangi sekresi bronkus)
- Kardiovaskular
 - Dosis < : bradikardia
 - Dosis > : takikardia
 - Wajah : memerah (*facial flush area*) akibat vasodilatasi.
- Saluran cerna
 - Antispasmodik (menghambat peristaltik usus)
 - Menghambat sekresi liur dan lambung
 - Pirenzepin : selektif menghambat sekresi lambung dan pepsin

Tabel 7.2 Efek Atropin dalam hubungannya dengan Dosis
[Goodman & Gilman (Indonesia), hal. 157]

Dosis	Efek
0,5 mg	Sedikit perlambatan jantung, sedikit kekeringan mulut, hambatan pengeluaran keringat
1 mg	Kekeringan mulut teramati; haus, percepatan denyut jantung, kadang-kadang diawali oleh perlambatan, dilatasi pupil yang ringan
2 mg	Frekuensi jantung yang cepat; palpitasi, kekeringan mulut yang nyata ; pupil berdilatasi sedikit kabur penglihatan jarak dekat
5 mg	Semua gejala di atas jelas; kesulitan berbicara dan menelan; gelisah dan kelelahan; sakit kepala; kulit kering, panas; kesulitan berkemih; peristaltis usus berkurang
10 mg atau lebih	Gejala gejala di atas lebih jelas; pulsa cepat dan lemah; iris hampir rusak; penglihatan sangat kabur; kulit merah, panas dan kering; ataksia, gelisah, dan peka rangsangan; halusinasi dan delirium; koma.

Antikolinergik (2)

Farmakodinamik

- ▶ Otot polos lain :

Relaksasi ureter dan saluran urin

Konstriksi sfingter urinaria

- ▶ Kelenjar eksokrin :

menghambat sekresi saliva dan bronkus, kulit muka dan leher → kering ,panas dan merah (temperatur tubuh meningkat) → anhidrosis

Antikolinergik (3)

Farmakokinetik

- ✚ Absorpsi baik, kecuali melalui kulit
- ✚ Pada pasien gagal ginjal, kadar obat akan naik
- ✚ Menimbulkan toleransi glukosa pada pemakaian dosis tinggi

Anti-kolinergik = parasimpatolitik = Anti-muskarinik (3)

Efek samping

- Mulut kerung
- Meteorisme
- Gangguan miksi
- Vasodilatasi pembuluh darah di wajah
- Tidak dapat diberikan pada anak umur < 4 tahun
- Dosis 10 mg pada anak menimbulkan kematian
- Dosis 50 – 100 mg pada dewasa belum fatal (idiosinkrasi)

Gejala keracunan alkaloid belladonna (kecubung)

- ✚ Gejala sentral : idiosinkrasi, eksitasi, bingung, gerakan otot tidak teratur, gangguan bicara (mengigau) dan halusinasi
- ✚ Midriasis
- ✚ Kulit merah, kulit kering dan suhu tubuh meningkat
- ✚ Takikardia
- ✚ Diagnosa : teteskan urin pada mata kucing → midriasis

Pengobatan keracunan alkalod beladona (kecubung)

- Fisostigmin sk
- Bilas lambung
- Beri barbiturat (diazepam)
- Beri napas buatan
- Istirahat di kamar gelap
- Katerisasi
- Bising usus → hilang

Obat sintetik mirip atropin

- Homatropin 2 – 5 % (tetes mata) : midriasis
- Homatropin HBr (2,5 – 5 mg) : antispamosdik
- Skopolamin metilbromid (2,5 mg)
- Mentalin Bromida (50 – 100 mg) ulkus peptikum
- Oksifenium (5 mg) : ulkus
- Karamifen dan triheksifenidil : anti-parkinson
- Ipatronium Br : asma bronkial
- Pirenzepim (50 mg) : tukak peptik
(lebih efektif dikombinasi dengan AH2; simetidin/ranitidin)

Indikasi Antikolinergik

- SSP : parkinsonisme, mabuk kendaraan
- Oftalmologi : midriasis
- Saluran cerna : ulkus peptikum
- Saluran napas : asma, rinitis akut, bronkitis, emfisema
- Medikasi preanastetik : mengurangi ekskresi saluran lendir pada anastesi dengan gas yang merangsang
- Aneresis
- Terapi keracunan Ach-ase inhibitor (insektida, muskarin jamur)