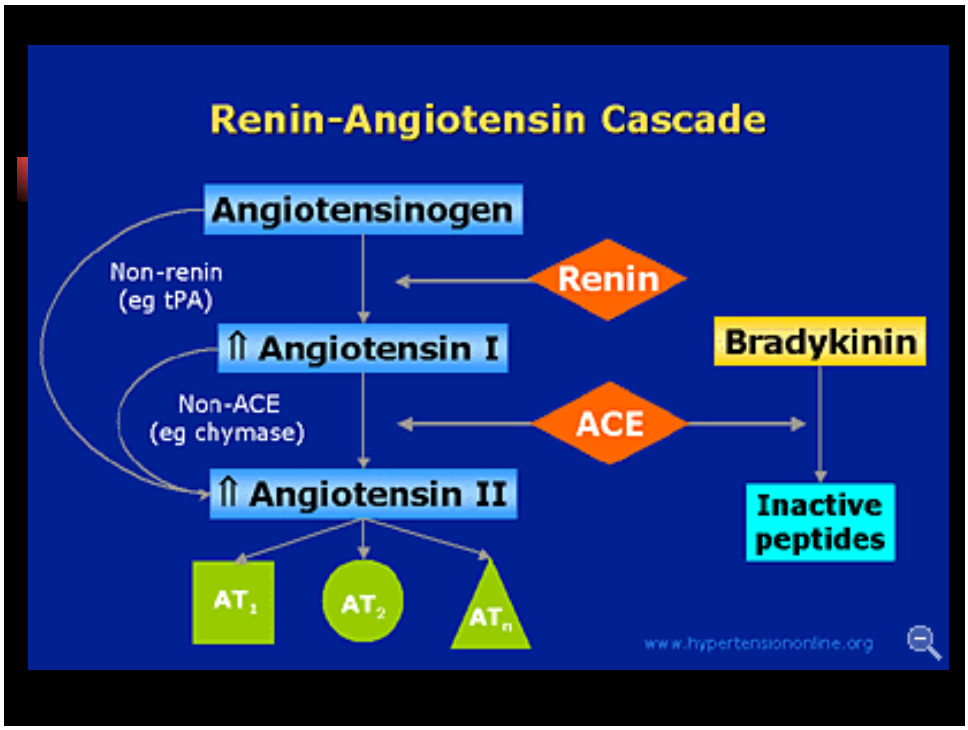
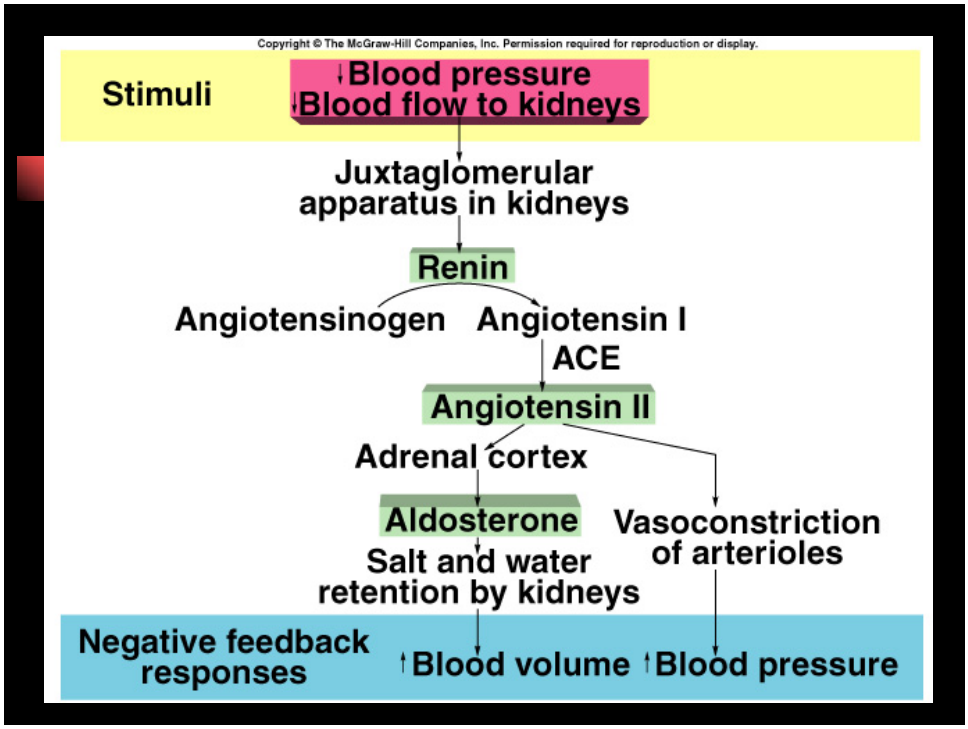
Reseptor Angiotensin

Angiotensin

- Angiotensin: hormon peptida berasal dari angiotensinogen
- Perubahan angiotensin I menjadi angiotensin II dikatalisis oleh ACE
- Angiotensin II : memicu berbagai proses seperti vasokonstriksi dan sekresi aldosteron (hormon yang menyebabkan retensi Na)
- Angiotensin II bekerja pada reseptor angiotensin AT1 yang tergandeng dengan protein Gq


Renin-Angiotensin Cascade
Angiotensinogen
Non-renin
(eg tPA)
Renin
⇑ Angiotensin I
Bradykinin
Non-ACE
(eg chymase)
ACE
⇑ Angiotensin II
Inactive peptides
AT1
AT2
ATn
www.hypertensiononline.org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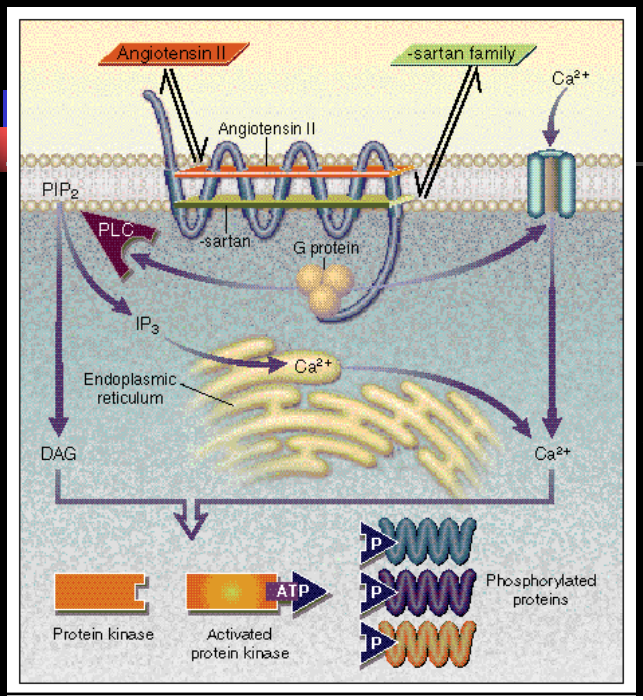
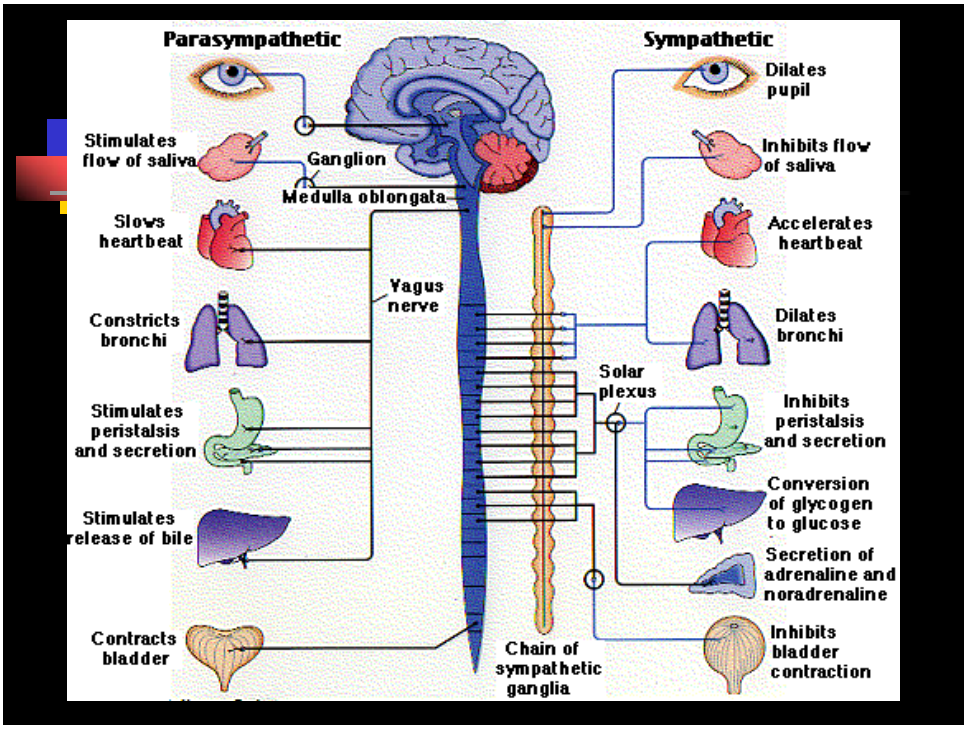
Stimuli
↓Blood pressure
↓Blood flow to kidneys
Juxtaglomerular apparatus in kidneys
Renin
Angiotensinogen
Angiotensin I
ACE
Angiotensin II
Adrenal cortex
Aldosterone
Vasoconstriction of arterioles
Salt and water retention by kidneys
Negative feedback responses
↑Blood volume
↑Blood pressure

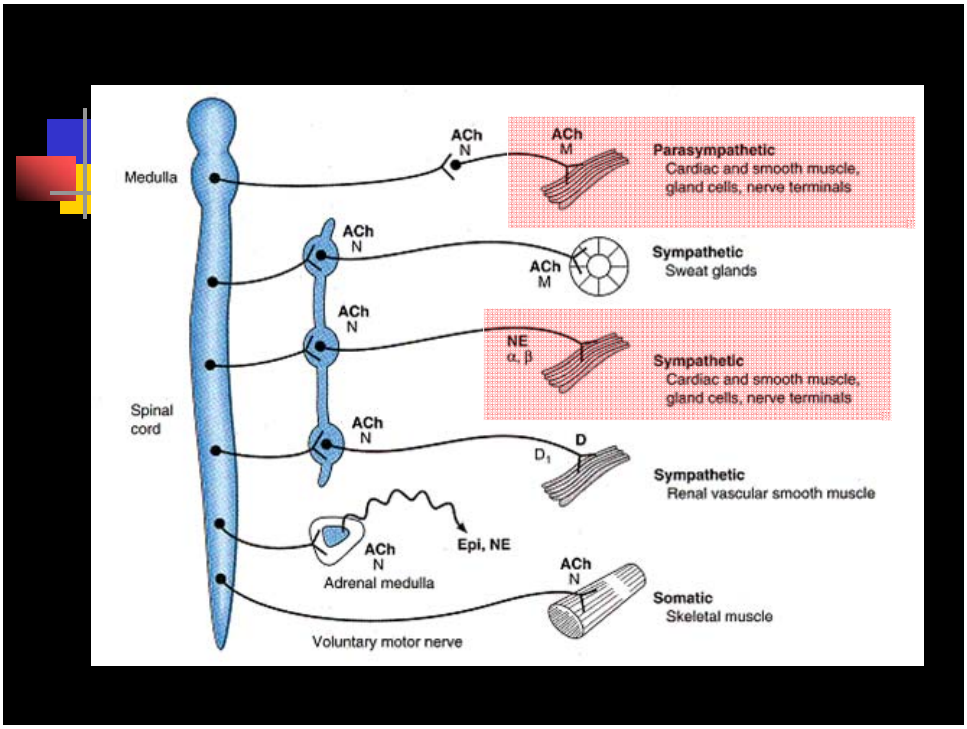


Obat-obat pada AT reseptor:
Famili sartan:
-Candesartan
-Losartan
-Valsartan

Antagonis AT_1 reseptor

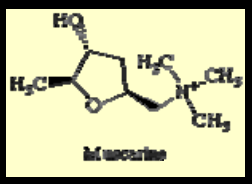
Reseptor asetilkolin muskarinik


Parasympathetic
Sympathetic
Stimulates flow of saliva
Ganglion
Medulla oblongata
Slows heartbeat
Vagus nerve
Constricts bronchi
Stimulates peristalsis and secretion
Stimulates release of bile
Contracts bladder
Dilates pupil
Inhibits flow of saliva
Accelerates heartbeat
Dilates bronchi
Solar plexus
Inhibits peristalsis and secretion
Conversion of glycogen to glucose
Secretion of adrenaline and noradrenaline
Inhibits bladder contraction
Chain of sympathetic ganglia


Medulla
Spinal cord
ACh N
ACh M
Parasympathetic
Cardiac and smooth muscle, gland cells, nerve terminals
Sympathetic
Sweat glands
NE α, β
Sympathetic
Cardiac and smooth muscle, gland cells, nerve terminals
D
D1
Sympathetic
Renal vascular smooth muscle
Epi, NE
Adrenal medulla
Somatic
Skeletal muscle
Voluntary motor nerve

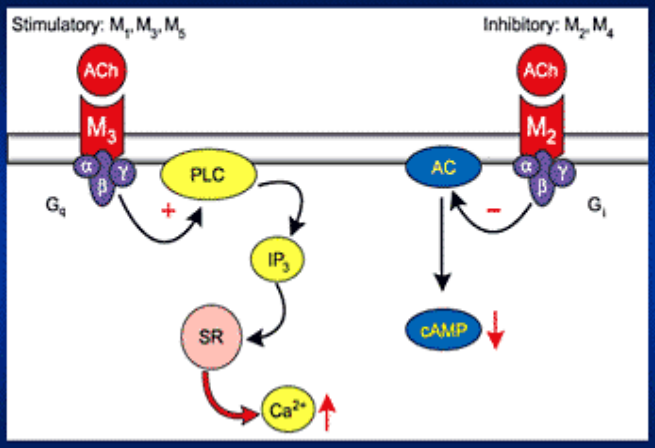
Reseptor asetilkolin muskarinik (mAcHR)

- Reseptor ini pertamakali dikenal karena kemampuannya mengikat muskarin
- Terdapat 5 subtipe, semuanya metabotropik → M_1, M_2, M_3, M_4, M_5
- Reseptor M_1, M_3, dan M_5 terhubung dg protein Gq, sedangkan M_2 dan M_4 terhubung dg protein Gi dan kanal ion K
- Pada reseptor M_1, M_3 dan M_5 : jika teraktivasi → mengaktifkan system fosfatidil inositol (fosfolipase)
- Pada reseptor M_2 dan M_4 : jika teraktivasi → menghambat adenilat siklase dan mengaktifkan kanal ion K

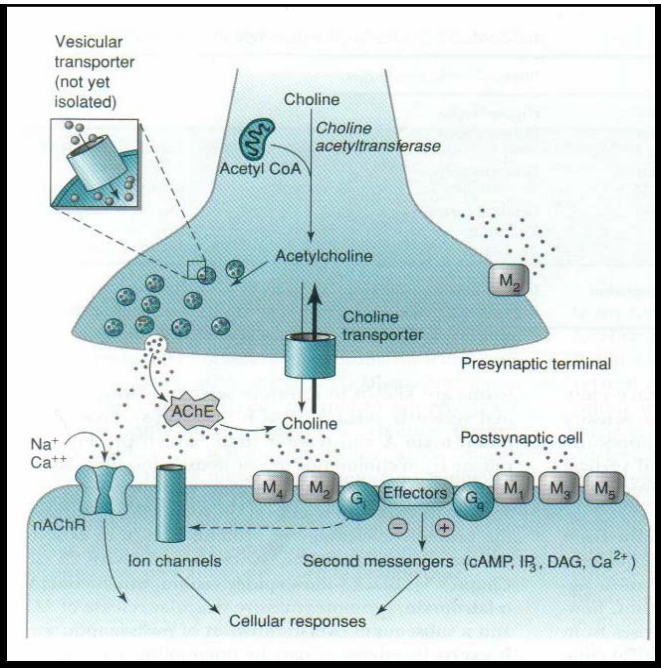


Amanitamuscaria

Muscarinic Receptor Subtypes (M_1- M_5): Signal Transduction



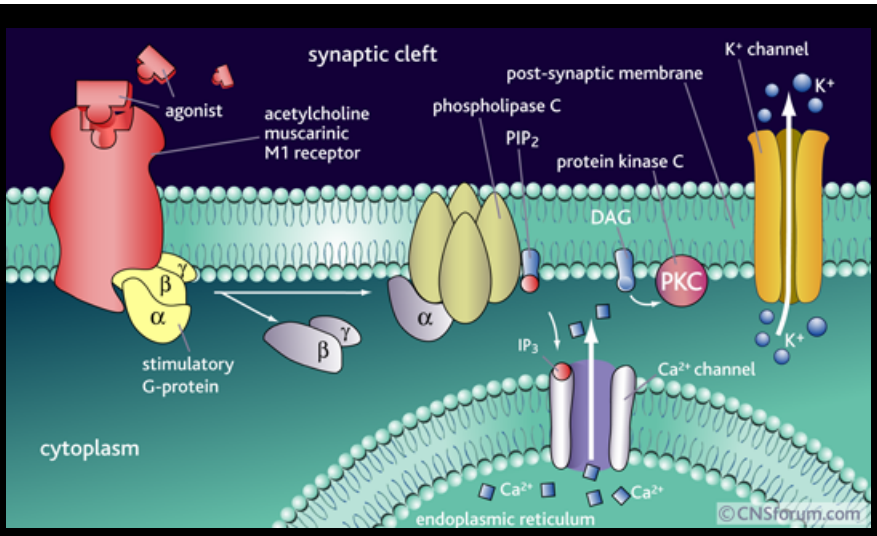
PLC = phospholipase C; AC = adenylyl cyclase; SR = sarcoplasmic reticulum.



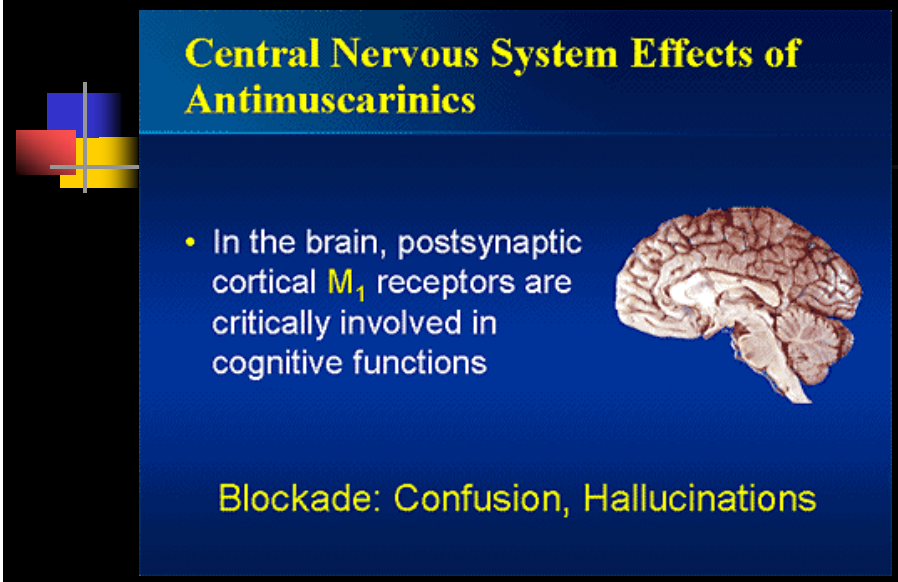
Nestler, 2001, Molecular Neuropharmacology

Reseptor Asetilkolin Muskarinik

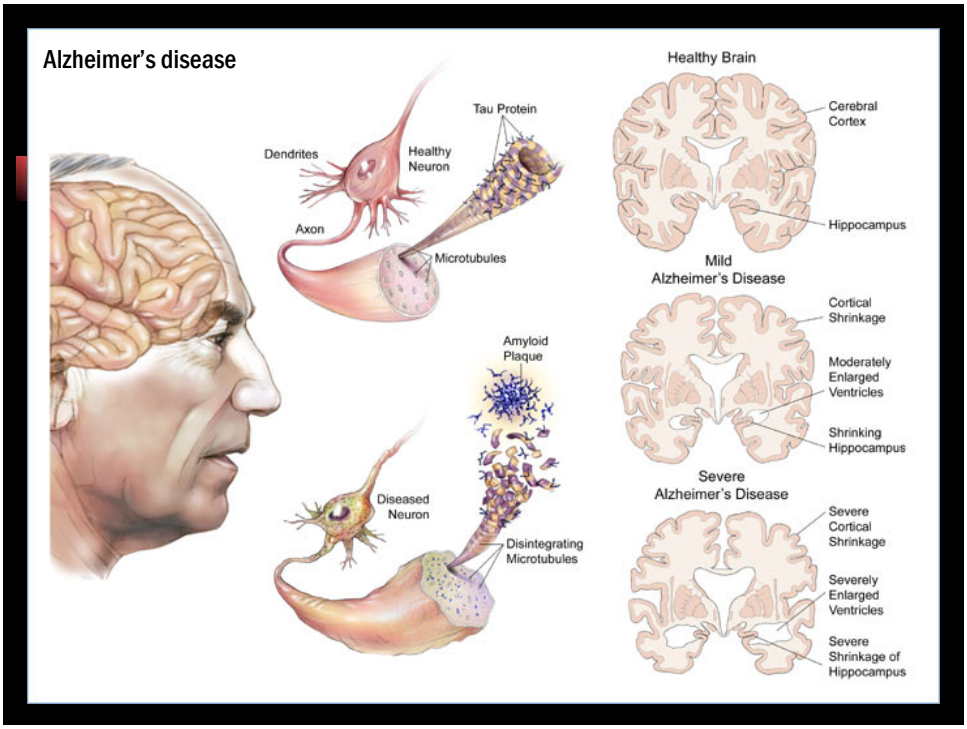
	M1	M2	M3	M4	M5
Distribusi	Cortex, hippocampus, ganglia simpatik, kelenjar saliva	Jantung, CNS, otot polos	Kelenjar eksokrin, saluran cerna, otot polos, otak, mata	Neostriatum (otak)	Substantia nigra (otak), mata
G Protein terkait	Gq	Gi	Gq	Gi	Gq
Respon intraseluler	Aktivasi PLC	Inhibisi adenilat siklase	Aktivasi PLC	Inhibisi adenilat siklase	Aktivasi PLC
Contoh peranan dlm sistem biologis	Berperan dlm fungsi kognitif dan memori, stimulasi sekresi asam lambung	mengatur denyut jantung, suhu tubuh, kontrol gerakan, analgesia	Mengatur motilitas GI, sekresi kelenjar (salivation, lacrimation), konstriksi otot polos bronkus	mengatur analgesia, mgk mengatur pelepasan dopamin	Mengatur pelepasan dopamin; regulasi dilatasi pembuluh darah otak.



The acetylcholine muscarinic M1 receptor is the most abundant sub-type of the acetylcholine receptor in the brain. When an agonist, such as acetylcholine, binds to this receptor a series of down-stream signaling mechanisms or secondary messengers are initiated. This results in the opening of potassium channels and the propagation of a nerve impulse.



Alzheimer : kurang aktivitas kolinergik → obat : xanomelin dan taksaklidin → agonis M1



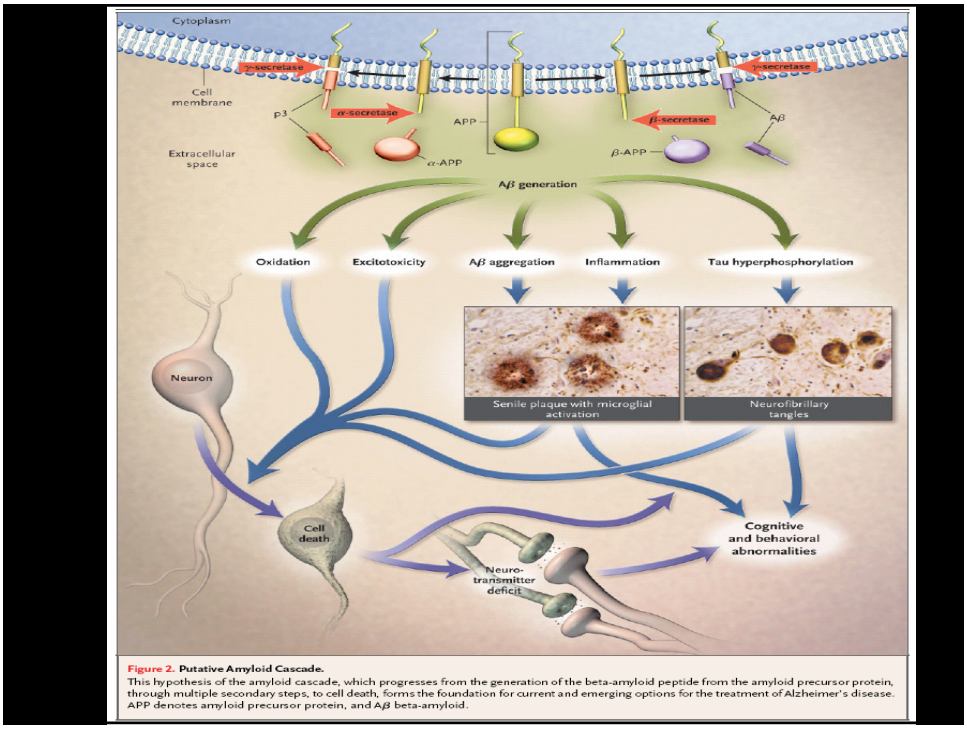


Figure 2. Putative Amyloid Cascade.
This hypothesis of the amyloid cascade, which progresses from the generation of the beta-amyloid peptide from the amyloid precursor protein, through multiple secondary steps, to cell death, forms the foundation for current and emerging options for the treatment of Alzheimer's disease. APP denotes amyloid precursor protein, and Aβ beta-amyloid.

M1 Muscarinic Agonists Target Major Hallmarks of Alzheimer's Disease -an Update

Fisher, Abraham (Current Alzheimer Research, 4 (5), 2007 , pp. 577-580(4)

Abstract:

The M1 muscarinic receptor (M1 mAChR), preserved in Alzheimer's disease (AD), is a pivotal target that links major hallmarks of AD, e.g. cholinergic deficiency, cognitive dysfunctions, β-amyloid (Aβ) and tau pathologies. Some muscarinic agonists, while effective in AD, had limited clinical value due to adverse effects and lack of M1 selectivity. The M1 selective muscarinic agonists AF102B [Cevimeline], AF150(S) and AF267B - :

i) elevated αAPPs, decreased Aβ levels and tau hyperphosphorylation, and blocked Aβ-induced neurotoxicity, in vitro, via M1 mAChR-modulation of kinases (e.g. PKC, MAPK and GSK3β);
ii) restored cognitive deficits, cholinergic markers, and decreased tau hyperphosphorylation in relevant models with a wide safety margin.

..... truncated

Am J Psychiatry 2008; 165:1033-1039 (published online July 1, 2008);

Selective Muscarinic Receptor Agonist Xanomeline as a Novel Treatment Approach for Schizophrenia

Anantha Shekhar, M.D., Ph.D., et al.

OBJECTIVE: There are significant unmet needs in the treatment of schizophrenia, especially for the treatment of cognitive impairment, negative syndrome, and cognitive function. Preclinical data suggest that agonists with selective affinity for acetylcholine muscarinic receptors provide a potentially new mechanism to treat schizophrenia. The authors studied xanomeline, a relatively selective muscarinic type 1 and type 4 (M1 and M4) receptor agonist, to determine if this agent is effective in the treatment of schizophrenia.

METHOD: In this pilot study, the authors examined the efficacy of xanomeline on clinical outcomes in subjects with schizophrenia (N=20) utilizing a double-blind, placebo-controlled, 4-week treatment design. Outcome measures included the Positive and Negative Syndrome Scale (PANSS) for schizophrenia, the Brief Psychiatric Rating Scale (BPRS), the Clinical Global Impression (CGI) scale, and a test battery designed to measure cognitive function in patients with schizophrenia.

- **RESULTS:**

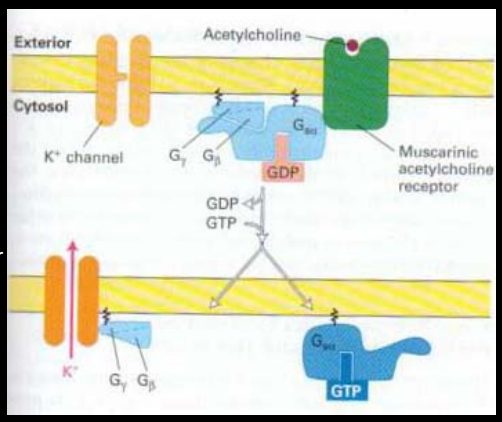
  Subjects treated with xanomeline did significantly better than subjects in the placebo group on total BPRS scores and total PANSS scores. In the cognitive test battery, subjects in the xanomeline group showed improvements most robustly in measures of verbal learning and short-term memory function.
- **CONCLUSIONS:**

  These results support further investigation of xanomeline as a novel approach to treating schizophrenia.

Aktivasi M2 di otot jantung

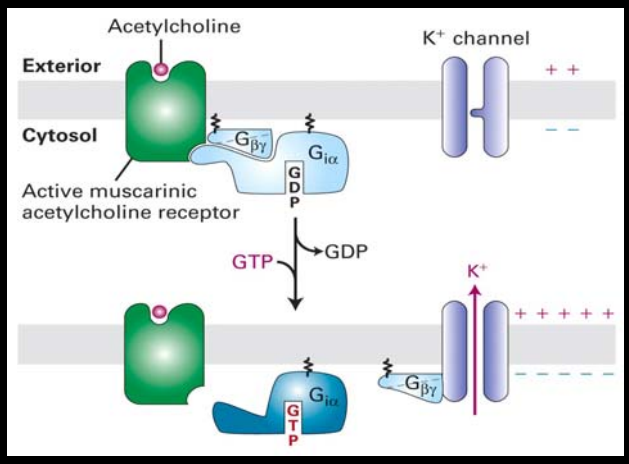
eksterior

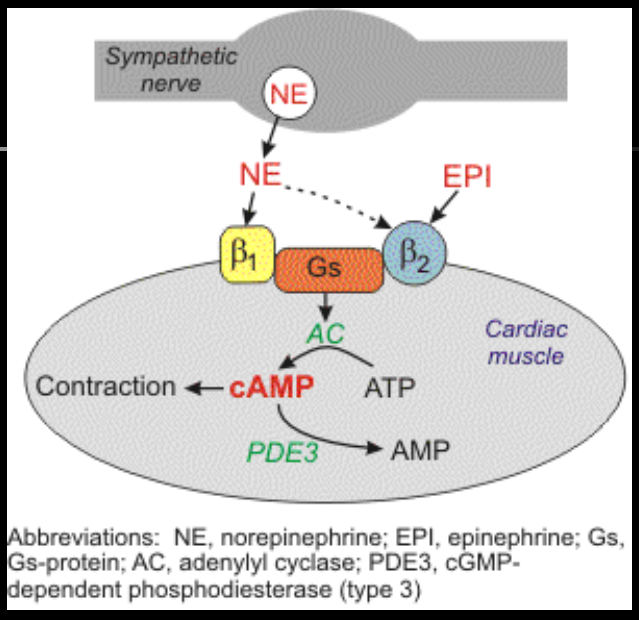
sitosol



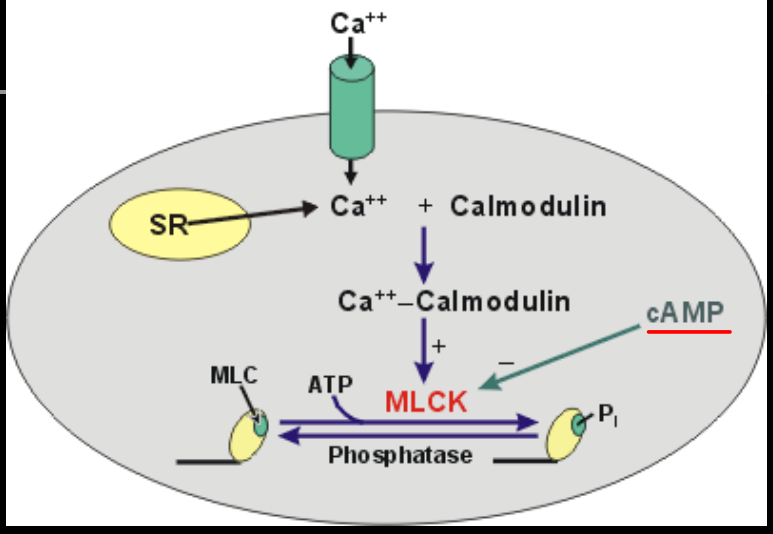
- Jika teraktivasi → subunit Giα menghambat adenilat siklase → cAMP turun → kontraksi otot jantung berkurang (efek inotropik negatif)
- sementara itu, kompleks subunit βγ beraksi langsung membuka kanal ion K^+ pada membran sel otot → hiperpolarisasi membran → frekuensi kontraksi otot jantung berkurang (efek kronotropik negatif)

The $G_{\beta\gamma}$ May also Function as a Activator





Abbreviations: NE, norepinephrine; EPI, epinephrine; Gs, Gs-protein; AC, adenylyl cyclase; PDE3, cGMP-dependent phosphodiesterase (type 3)

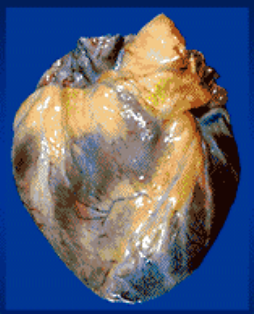


Pada otot polos

Cardiac Effects of Antimuscarinics

- Main effect of ACh in the heart is M_2 receptor-driven slowing of heart rate

Blockade: Tachycardia
Palpitations

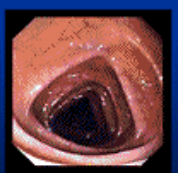


GI Effects of Antimuscarinics

M_3 receptors contribute 75% of the muscarinic effect on gut motility; M_2 receptors may play permissive role

Blockade: Slowing of Transit Time
Constipation

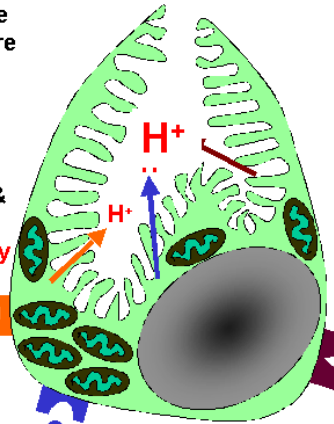
G-E junction



Colon

When all three stimulators are present, acid secretion is maximally stimulated

Ach, gastrin & histamine act synergistically



Histamine H_2 receptor

gastrin receptor

Ach m3 receptor

Histamine

ECL cell

Gastrin

ACh

Distribution of Muscarinic Receptor Subtypes in the Human Eye

Human Iris Sphincter (%)

M_1	M_2	M_3	M_4	M_5
7	8	59	11	5

M_3 receptors predominate; other subtypes may contribute to function

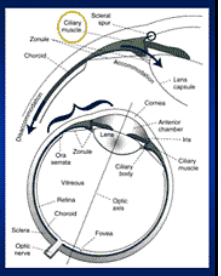
Gil DW et al. *Invest Ophthalmol Vis Sci.* 1997;38:1434-1442.

Distribution of Muscarinic Receptor Subtypes in the Human Eye

Human Ciliary Muscle (%)

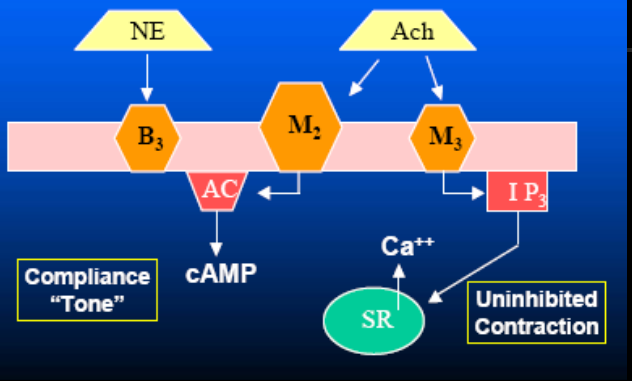
M_1	M_2	M_3	M_4	M_5
1	5	74	5	2

M_3 receptors predominate; other subtypes may contribute to function

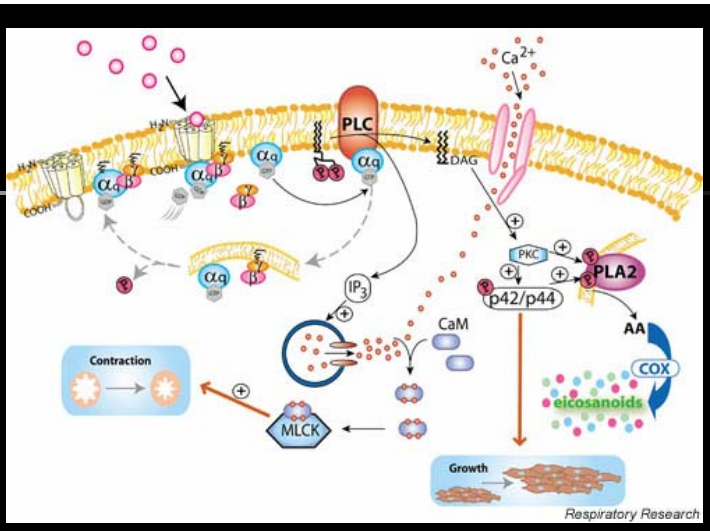


Gil DW et al. *Invest Ophthalmol Vis Sci.* 1997;38:1434-1442.

Bladder Receptors

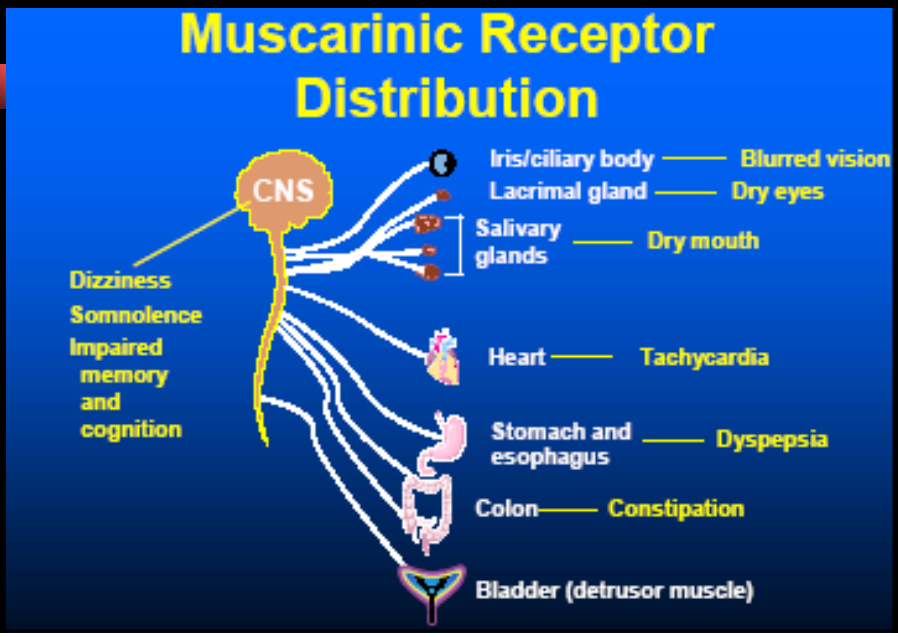


How do antimuscarinics work? The most common muscarinic receptors within the bladder wall are the M2 and M3 muscarinic receptors. While the M2 receptors are the most numerous, the M3 muscarinic receptors are thought to be the functional receptor that induces smooth muscle contraction. In this regard antimuscarinic agents are thought to competitively antagonize these receptors and prevent unwanted, involuntary bladder contractions from occurring.



Gq-coupled receptor signaling in airway smooth muscle. Airway smooth muscle (ASM) is innervated by postganglionic parasympathetic nerves that release acetylcholine (acting on m3 mAChRs) to control resting ASM tone.

Efek blokade reseptor muskarinik



Contoh pemakaian klinis obat anti muskarinik

Organ	Subtipe Reseptor	Obat	Pemakaian
CNS	M2 dan M4	Benztropin Skopolamin	Mengatasi gejala Parkinson Mencegah atau mengurangi motion sickness
Mata	M3	Atropin	Menghasilkan efek midriasis dan sikloplegia (kelumpuhan otot mata)
Bronkus	M3	Ipratropium, tiotropium	Bronkodilatasi
GI tract	M1 dan M3	Methscopolamin	Mengurangi motilitas lambung – dikombinasi dengan obat anti ulcer
Saluran Kemih	M2 dan M3	Oxybutinin, darifenacin	Mengatasi radang dan kejang kandung kemih post operasi, overactive bladder

Agonis muskarinik?

- pilokarpin → agonis M3 → indikasi: xerostomia* following irradiation for head and neck cancer, dry mouth and dry eyes in Sjögren's syndrome*
- arekolin, karbakol → tidak digunakan secara klinis. Efeknya menyebabkan salivasi berlebihan dan berkeringat
- xanomelin dan talsaklidin → M1 agonis → pengobatan Alzheimer, gangguan kognitif pada Skizoprenia

*Xerostomia = mulut kering akibat produksi kelenjar saliva berkurang karena berbagai sebab
*Sjögren's syndrome = penyakit autoimune yang menyerang kelenjar-kelenjar eksokrin yang memproduksi saliva dan air mata