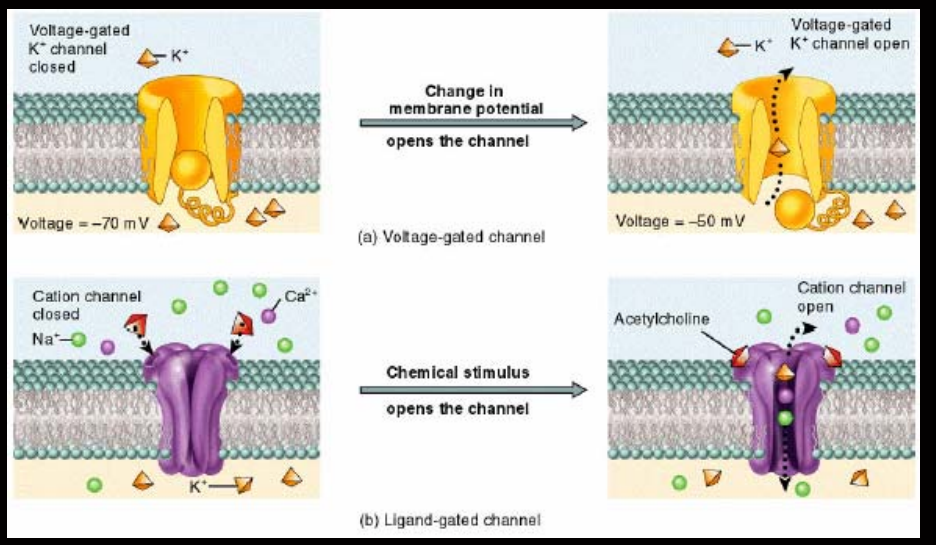
BERDASARKAN SIGNAL TRANSDUKSINYA, Reseptor diklasifikasikan sbb :

- reseptor terkait dg kanal ion – ionotropic receptor
- reseptor terhubung dg protein G – G Protein-coupled receptors (GPCRs)
- reseptor terkait dg tyrosine kinase – tyrosine kinase- linked receptor
- reseptor inti - nuclear receptor

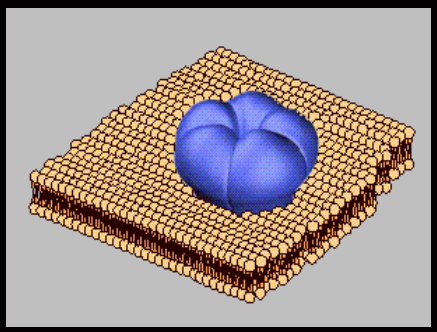
Reseptor kanal ion (ionotropik)

Perbedaan ?



Reseptor kanal ion (ionotropik)

- Teraktivasi sebagai respon terhadap ligan spesifik
- Selektif terhadap ion tertentu
- Terlibat dalam signaling sinaptik yang relatif cepat (dibandingkan dengan melalui reseptor protein G)
- Contoh :
  - reseptor asetilkolin nikotinik
  - reseptor GABAa
  - reseptor glutamat (NMDA)
  - reseptor serotonin (5-HT3)

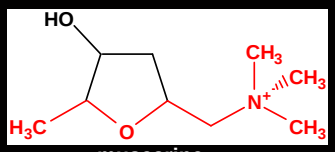


Reseptor Asetilkolin Nikotinik (nAchR)

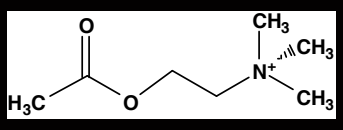
Asetilkolin:

- molekul pertama yang diidentifikasi sebagai neurotransmitter
- aksinya pada sistem syaraf otonom di perifer maupun CNS
- memiliki 2 macam reseptor yaitu nikotinik dan muskarinik
- berperan antara lain dalam regulasi belajar (learning), memori, kontrol gerakan, dan mood (perasaan) → contoh: penyakit Alzheimer (pikun) disebabkan karena degenerasi sistim kolinergik, myasthenia gravis

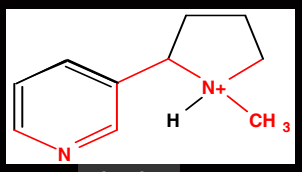
Nicotinic and muscarinic receptors



muscarine



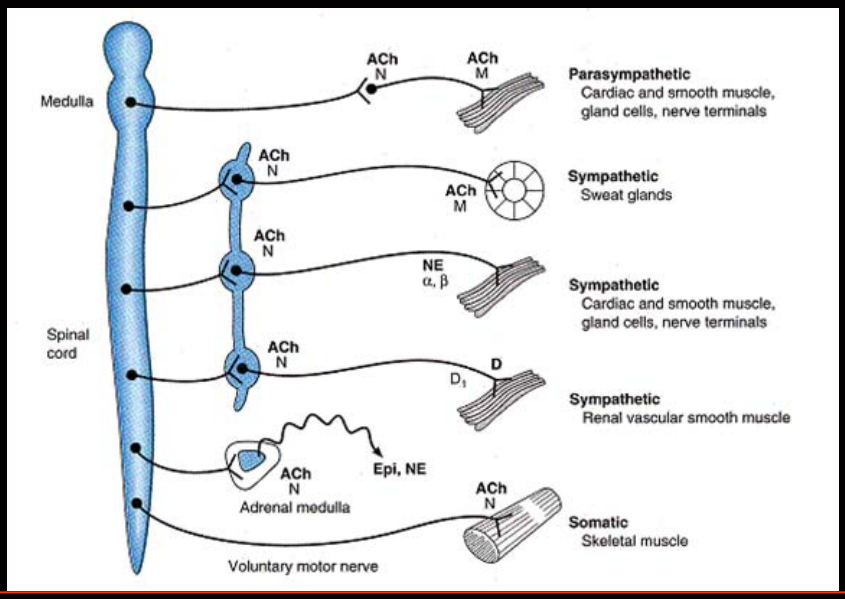
ACh



nicotine

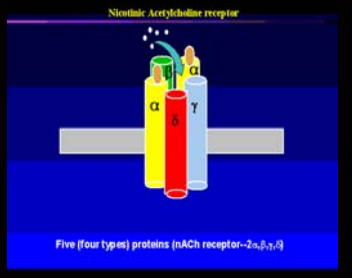
Muscarine m1-m5 receptors
GPCRs

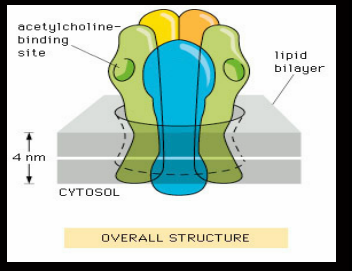
Nicotine receptors
ionchannels



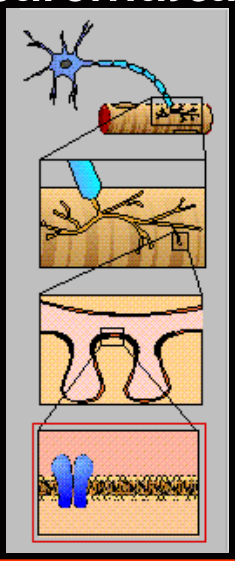
Reseptor asetilkolin nikotinik :

- Suatu protein pentamer yang terdiri dari 5 subunit yaitu $\alpha 2\beta\gamma\delta$
- Terkait dengan kanal Na^+
- berlokasi di neuromuscular junction, ganglia otonom, medula adrenal, dan CNS
- pertama kali dikarakterisasi dengan kemampuannya mengikat nikotin
- agonis asetilkolin akan mengaktivasi reseptor ini menyebabkan terjadinya influks Na^+ dan selanjutnya terjadi depolarisasi seluler → efek fisiologis
- Reseptor asetilkolin nikotinik yang paling banyak dipelajari : pada neuromuscular junction → pertemuan antara sel saraf dengan sel otot

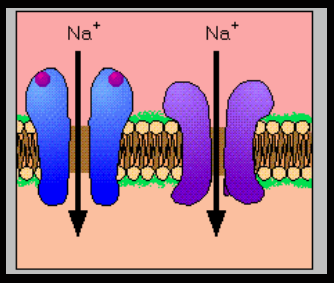




Neuromuscular junction

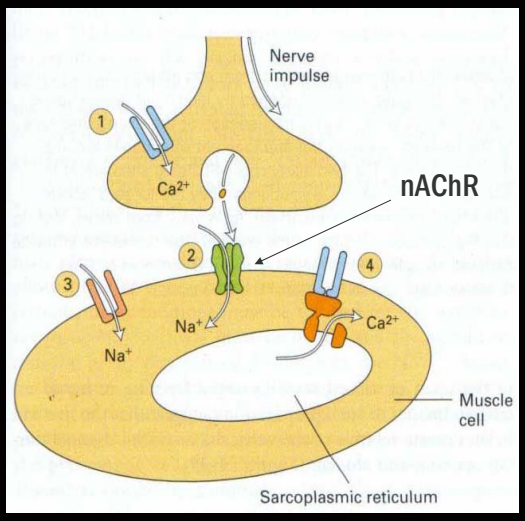


nicotine ACh receptor



Na^+ - excitatory
muscle contraction

nAChR di neuromuscular junction



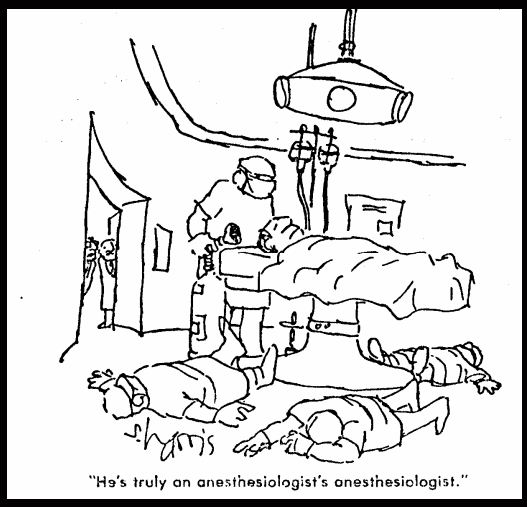
Datang impuls saraf
→ membuka kanal Ca
→ Memicu pelepasan ACh
→ ACh mengikat nAChR yang terhubung dgn kanal Na
→ Kanal Na membuka
→ Na masuk → depolarisasi parsial → mengaktivasi kanal Na lain *(voltage-gated)*
→ depolarisasi lebih besar
→membuka kanal Ca *(voltage-gated)* di SR →
→Ca intrasel naik →
kontraksi otot

Neuromuscular blocking agent (obat pelemas otot)

Secara klinis:

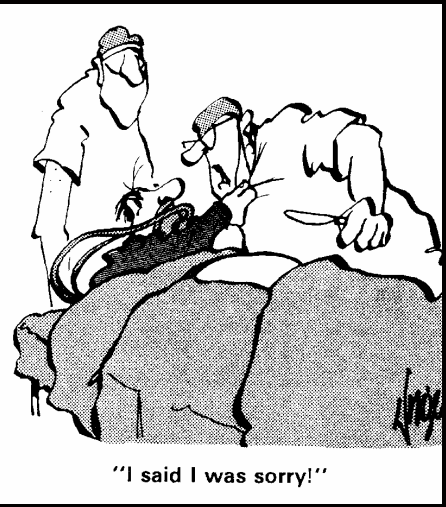
- Digunakan sebagai obat tambahan pada pembiusan di mana digunakan alat bantu pernafasan
- Tidak digunakan untuk suatu intervensi/terapi

Hazards of Deep Anesthesia

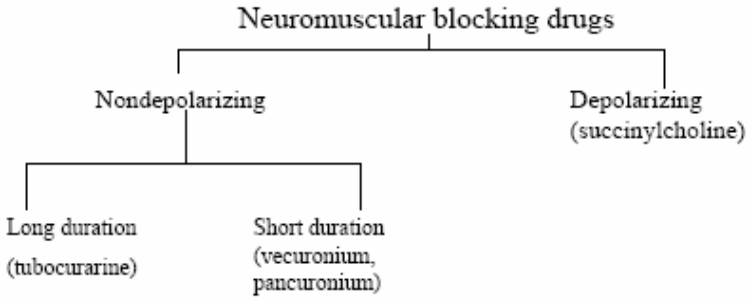


Untuk mendapatkan relaksasi otot dan mengurangi gerak refleks pada operasi besar, dibutuhkan anestesia dalam dosis besar. Hal ini seringkali menyebabkan kematian di meja operasi...

Hazards of Light Anesthesia



Namun sebaliknya, anestesia yang terlalu ringan juga berbahaya..... Terutama untuk dokter bedahnya ..



Neuromuscular blocking drugs are used to induce complete skeletal muscle relaxation in surgery

Non-depolarizing blocking agents:

Curare

- Awalnya berasal dari Amerika selatan, digunakan untuk racun pada panah → untuk membunuh/berburu binatang
- mengikat reseptor nACh, memblok aksi asetilkolin sehingga menyebabkan kelumpuhan otot

Contoh :

Tubocurarine:

- Onset of action is 4 – 6 minutes
- Duration of activity is 8 – 120 minutes

Pancuronium:

- Onset of action is 4 – 6 minutes
- Duration of activity is 120 – 180 minutes

Vecuronium:

- Onset of activity is 2 – 4 minutes
- Duration of activity is 30 – 40 minutes

Tubocurarine

Meskipun pertama kali diperkenalkan pada tahun 1912 oleh Läwen di Germany, ekstrak murni curare pertama dipakai untuk anesthesia pada 1941 oleh H.R Griffith of McGill untuk mengurangi nyeri dan memblok gerakan refleks otot.
Awalnya curare digunakan untuk racun panah oleh penduduk asli South America utk melumpuhkan buruannya → dari tanaman *Strychnos toxifera, S. castelnaei, S. crevauxii,* dan *Chondodendron tomentosum* .

Senyawa aktif utamanya adalah tubocurarine – merupakan prototype neuromuscular blocking drug.

Non-depolarizing agents (lanjutan):

Mechanism of action:

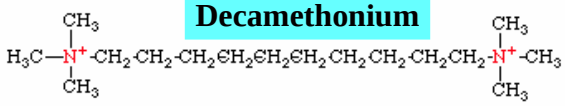
- Menduduki reseptor tanpa menyebabkan aktivasi dari kanal ion → mencegah depolarisasi

Effects:

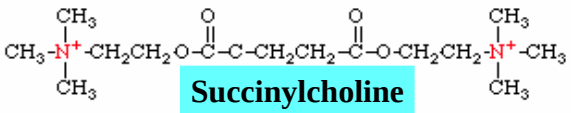
- Terutama menyebabkan paralisis (kelumpuhan) → skeletal muscle relaxation
- Selain itu, juga menyebabkan efek samping otonom :
  - hypotension and tachycardia
  - bronchospasm (histamine release)

Depolarizing Blockers

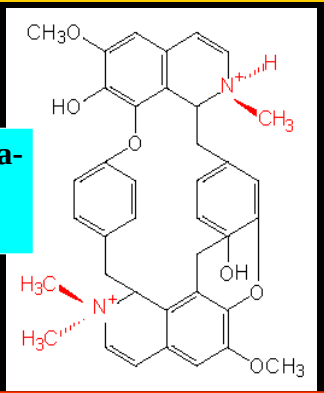
Decamethonium



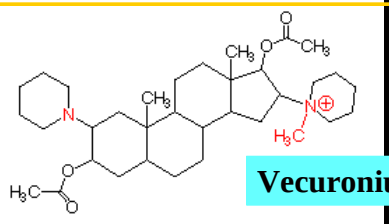
Succinylcholine



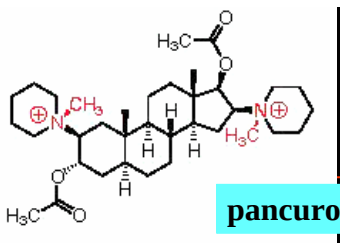
Non depola-rizing Blockers



D-tubocurarine



Vecuronium

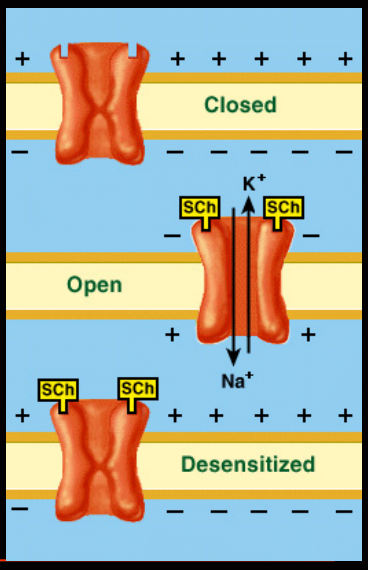


pancuronium

Depolarizing blocking agent

Chemical agents that bind to the ACh receptor and, like ACh, cause channel opening (i.e, agonists of ACh) can also inhibit neuromuscular transmission. To do so, they must be less readily destroyed by the AChE. Such agents are called "depolarizing" blockers, an example of which is succinylcholine.

Like ACh, these agents cause depolarization of the end-plate region (**figure**). Unlike ACh, however, they are poorly destroyed by the AChE. Thus, they cause a persistant depolarization of the end-plate. Initially, this leads to a series of action potentials across the muscle membrane and an associated series of involuntary muscle contractions.

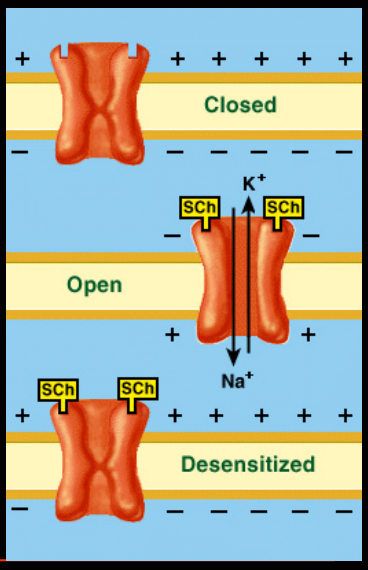


Depolarizing blocking agent

With time, however, the persistence of the agonist causes the receptor to become inactive or desensitized. That is, the channel closes in spite of the agonist bound to it.

When enough receptors become desensitized, neuromuscular transmission is blocked and the muscle is paralyzed. The molecular mechanism for desensitization is not yet clear.

Both competitive and depolarizing neuromuscular blockers are used clinically to relax muscles for surgery or tracheal intubation.



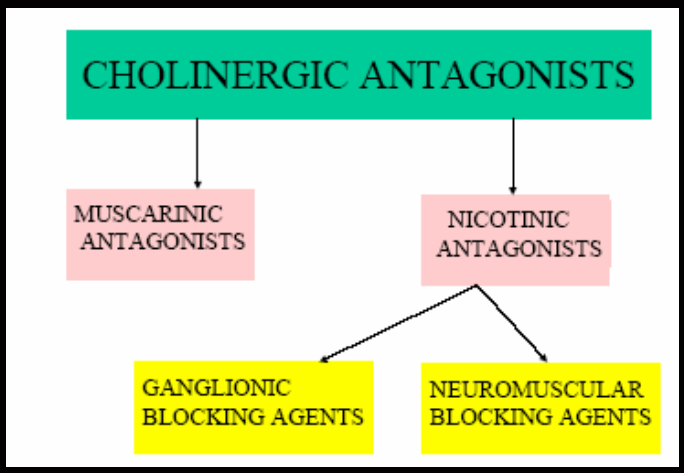
Depolarizing blocking agents:

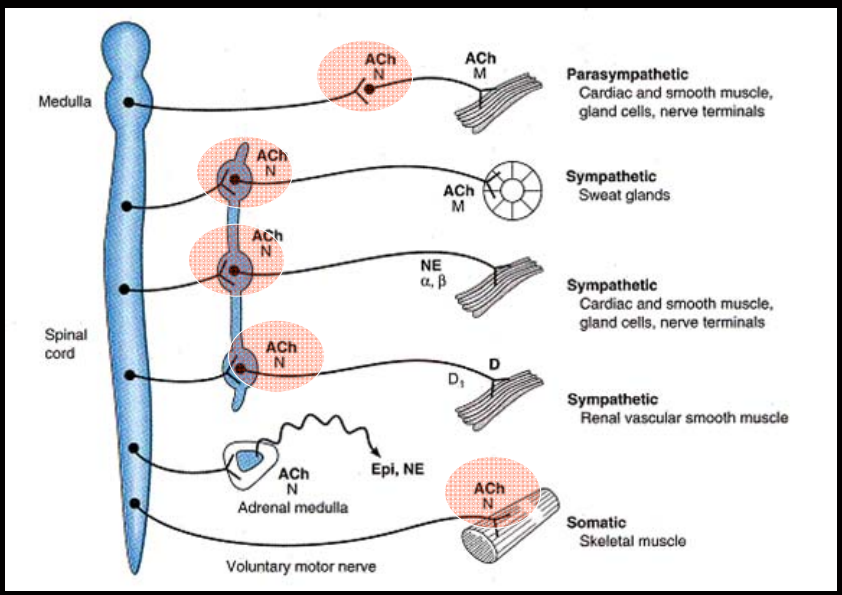
- Depolarizing blocking agents work by depolarizing the plasma membrane of the muscle fiber, similar to acetylcholine. However, these agents are resistant to degradation by acetylcholinesterase, and can persistently depolarize the muscle fibers as opposed to the transient depolarization by ACh which is rapidly degraded.
- Initially, they cause muscular fasciculations (muscle twitches) while they are depolarizing the muscle fibers. Eventually, after sufficient depolarization has occurred, the muscle is no longer responsive to ACh released by the motoneurons.
- Hence, full neuromuscular block has been achieved.

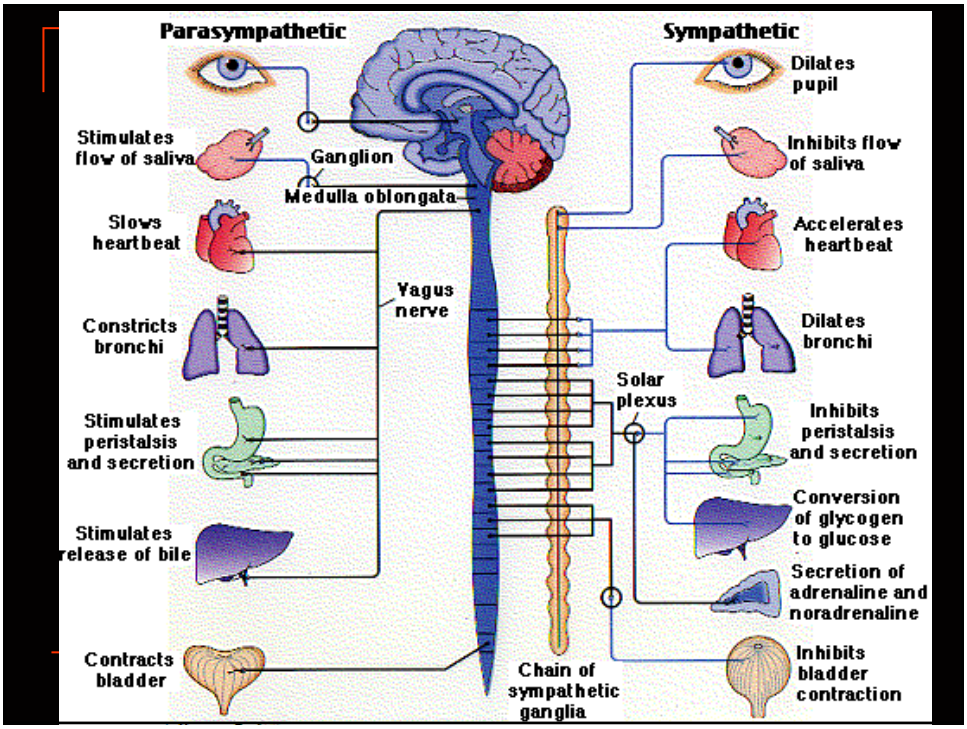
penjelasan

- Untuk otot yang hanya diinervasi oleh satu saraf → harus ada *action potential* sebelum terjadinya kontraksi
- Untuk menghasilkan suatu *action potential*, kanal Na teraktivasi voltage harus diaktivasi (setelah itu akan mengalami inaktivasi)
- Untuk dapat diaktivasi lagi agar ada potensial aksi lebih lanjut, kanal yang terinaktivasi sebelumnya harus direpolarisasi dulu untuk kembali ke kondisi *resting state* nya
- Obat-obat *depolarizing bloking agent* ini memperlama depolarisasi → mencegah kembalinya ke *resting state*.
- Karena itu : pelepasan asetilkolin lebih lanjut tidak bisa memicu potensial aksi → No more action potentials: muscle is then paralyzed even though receptors are activated.

Obat-obat/senyawa yang beraksi langsung pada nAChR







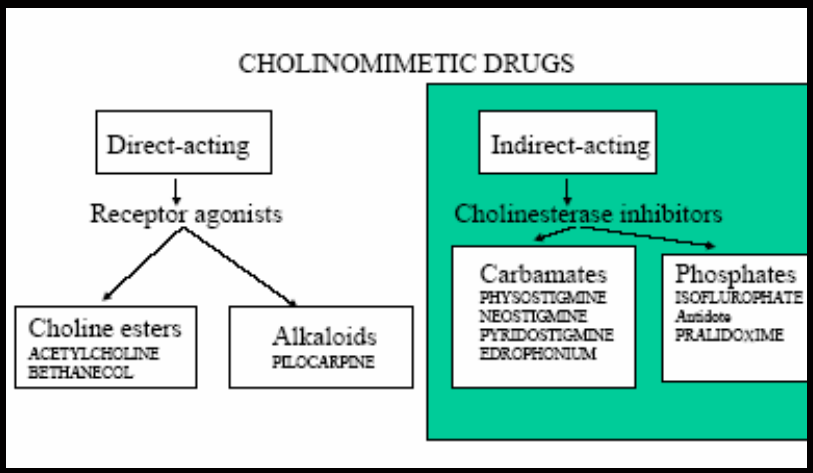
Ganglionik blocking drug

- Bekerja pada nAChR di ganglion
- Memblok kerja saraf simpatik dan parasimpatik
- Memiliki efek kuat pada sistim kardiovaskuler → vasodilatasi karena penghambatan pada sistem saraf simpatik, berkurangnya kekuatan kontraksi jantung, dan meningkatkan denyut jantung (takikardi)
- Efek pada gastrointestinal (karena diatur oleh sistem parasimpatik) → berkurangnya motilitas GI, konstipasi
- Penggunaan secara klinis terbatas
- misal: Trimethaphan →produce controlled hypotension during certain anesthetic procedures
- Hexamethonium → no longer used

Effects of Ganglionic Blockade

Site	Predominant Tone	Effect
Arteries	Sympathetic	Dilate - ↓ BP
Veins	Sympathetic	Dilate - ↓ venous return
Heart	Parasympathetic	Tachycardia - ↑ HR
Iris	Parasympathetic	Mydriasis (pupil membesar)
Ciliary Muscle	Parasympathetic	Cycloplegia (kelumpuhan otot)
GIT	Parasympathetic	↓ motility and tone
Bladder	Parasympathetic	Urinary retention
Salivary Glands	Parasympathetic	Dry mouth
Sweat Glands	Sympathetic (cholinergic)	↓ sweating

Obat-obat/senyawa yang beraksi langsung pada nAChR



Chantix (varenicline)

- Company: Pfizer
  Approval Status: Approved May 2006
  Treatment for: Smoking Cessation

General Information

- Chantix (varenicline) is a partial nicotinic acetylcholine receptor agonist, designed to partially activate this system while displacing nicotine at its sites of action in the brain.
- Chantix is specifically indicated for use as an aid in smoking cessation

Mechanism of Action

- Chantix is an alpha-4 beta-2 neuronal nicotinic acetylcholine receptor agonist
- The drug shows high selectiviyty for this receptor subclass, relative to other nicotinic receptors (>500-fold alpha-3 beta-4, >3500-fold alpha-7, >20,000-fold alpha-1 beta gamma delta) or non-nicotinic receptors and transporters (>2000-fold).
- The drug competitively inhibits the ability of nicotine to bind to and activate the alpha-4 beta-2 receptor.
- The drug exerts mild agonistic activity at this site, though at a level much lower than nicotine; it is presumed that this activation eases withdrawal symptoms.

Reseptor GABA

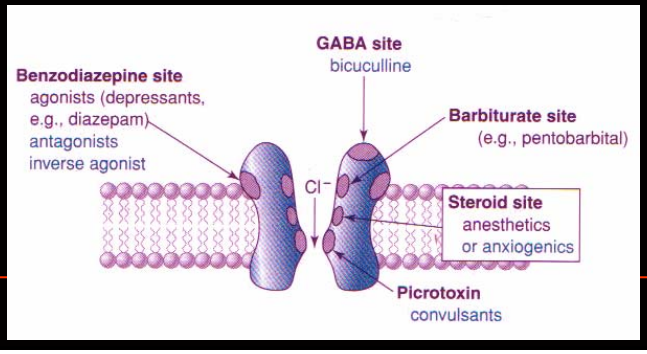
Reseptor GABA

GABA *(gamma-aminobutyric acid)*:

- merupakan neurotransmiter inhibitor utama di otak → didukung fakta bahwa banyak penyakit saraf disebabkan karena adanya degenerasi saraf GABAergik → contoh: epilepsi
- Disintesis dari glutamat dg bantuan enzim glutamic acid decarboxylase (GAD), didegradasi oleh GABA-transaminase
- Sekali dilepaskan, GABA berdifusi menyeberangi celah untuk berinteraksi dengan reseptornya → menimbulkan aksi penghambatan fungsi CNS
- GABA yang sudah terdisosiasi dari reseptornya diambil kembali (re-uptake) ke dalam ujung presinaptik atau ke dalam sel glial dengan bantuan transporter GABA.

Reseptor GABA:

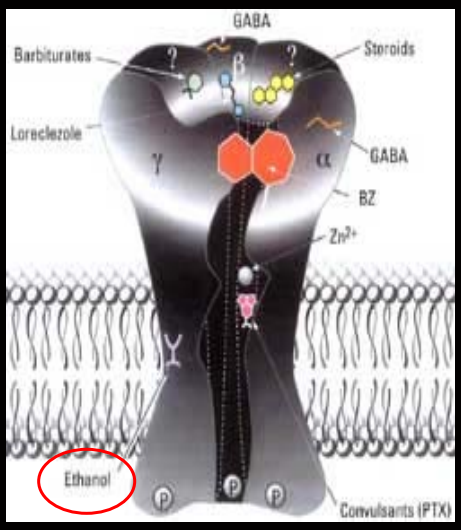
- Terdiri dari 2 jenis: ionotropik (GABA-a) dan metabotropik (GABA-b)
- Reseptor GABA-a terletak di postsinaptik→ cukup penting karena dia merupakan tempat aksi obat-obat benzodiazepin dan golongan barbiturat
- Reseptor ini memiliki beberapa tempat aksi obat : benzodiazepin site, GABA site, barbiturat site, neurosteroid site
- Reseptor GABA-a terhubung dengan kanal Cl-



GABA reseptor is one of the places where alcohol (ethanol) acts.

Thus, one key action of alcohol is to reduce the activity of brain cells, by making GABA-mediated inhibition more effective.

Alcohol acts on a number of different transmitter receptors in the brain. The balance between these various actions is the key to intoxication and, ultimately, the deleterious effects of long-term chronic alcohol abuse.

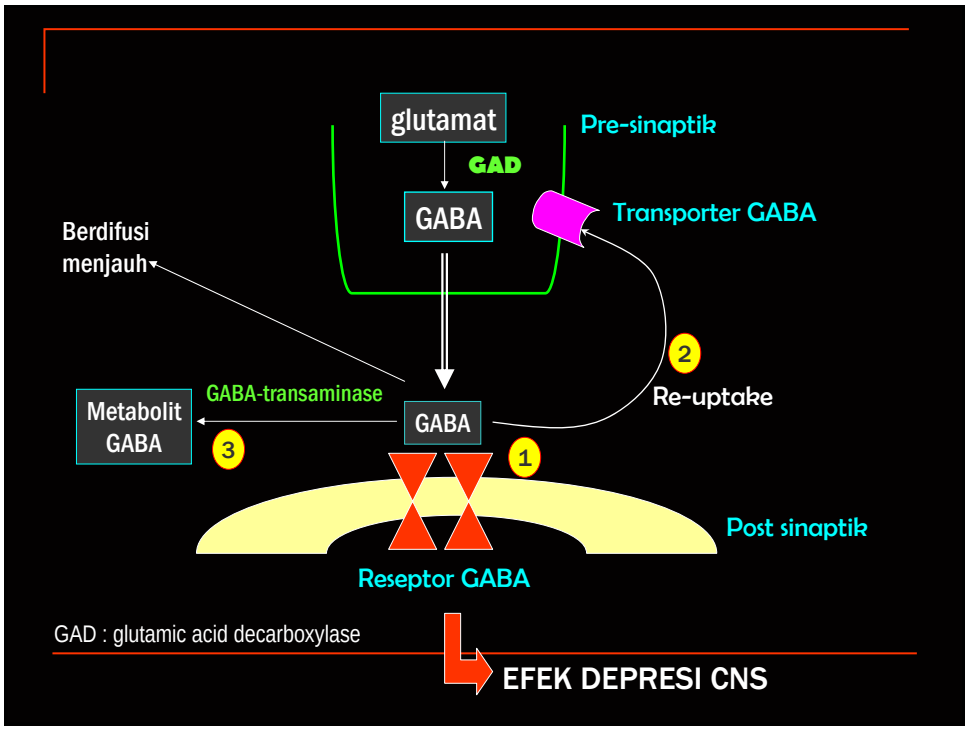


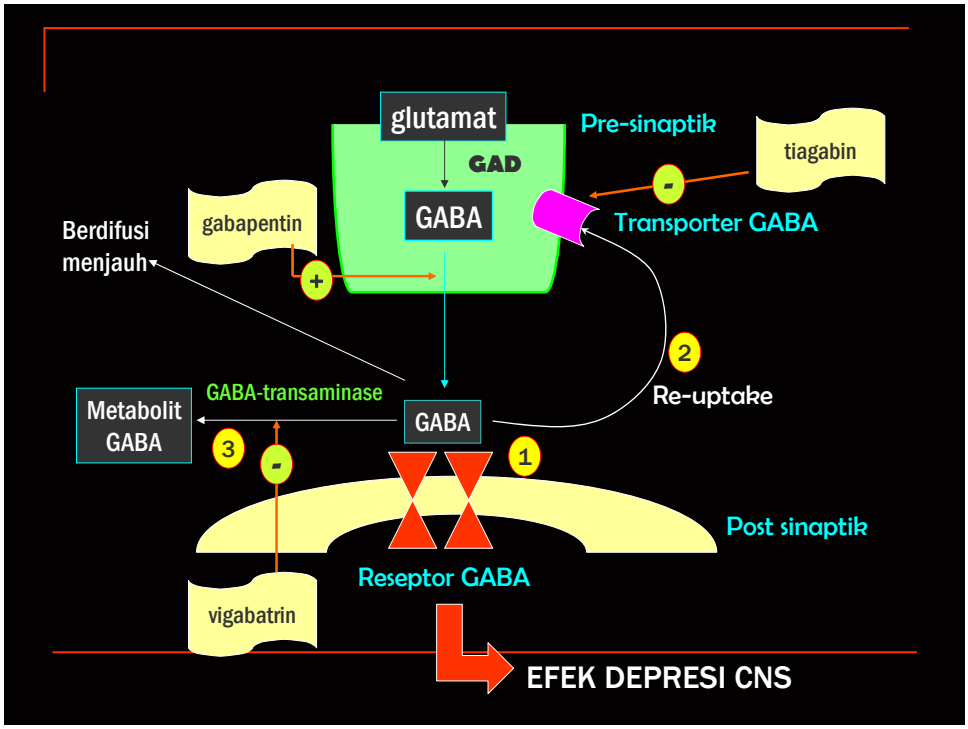
Rangkaian peristiwa pada aktivasi reseptor GABA :

GABA lepas dari ujung saraf gabaergik → berikatan dengan reseptornya → membuka kanal Cl → ion Cl masuk → hiperpolarisasi membran sel saraf → efek penghambatan transmisi saraf → depresi CNS

Bagaimana aksi obat-obat yang bekerja pada reseptor GABA ?

- Obat-obat benzodiazepin (diazepam, klordiazepoksid, lorazepam) → meningkatkan afinitas reseptor terhadap GABA pada GABA site → mengaktivasi reseptor GABA → meningkatkan frekuensi pembukaan kanal Cl→ hiperpolarisasi → depresi CNS
- Obat-obat barbiturat (fenobarbital, pentobarbital) → memperlama pembukaan kanal Cl → hiperpolarisasi → depresi CNS
- Pikrotoksin (konvulsan) → mengeblok kanal Cl → mengeblok efek penghambatan post-sinaptik GABA → efek eksitatori > → konvulsi


glutamat
Pre-sinaptik
GAD
GABA
Transporter GABA
Berdifusi menjauh
2
Re-uptake
Metabolit GABA
GABA-transaminase
GABA
3
1
Post sinaptik
Reseptor GABA
GAD : glutamic acid decarboxylase
EFEK DEPRESI CNS


glutamat
Pre-sinaptik
tiagabin
GAD
GABA
Transporter GABA
gabapentin
Berdifusi menjauh
+
2
Re-uptake
Metabolit GABA
GABA-transaminase
GABA
3
1
Post sinaptik
Reseptor GABA
vigabatrin
EFEK DEPRESI CNS

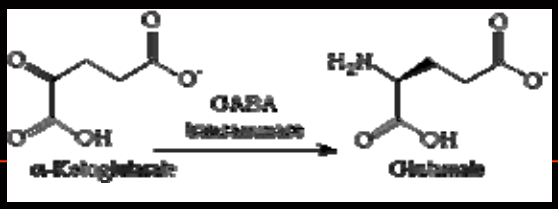
Reseptor NMDA dan 5-HT3

N Methyl D aspartat

5-hydroxy tryptamine

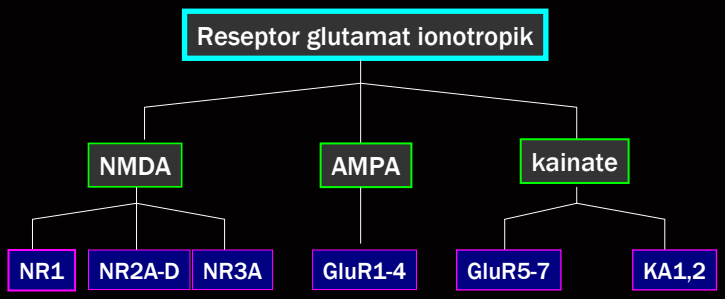
Glutamat ?

- Merupakan asam amino yang termasuk neurotransmiter eksitatori → berperan penting dalam fungsi sistem saraf pusat
- Memenuhi kriteria sebagai neurotransmiter karena :
  - Terlokalisasi pada ujung saraf presinaptik (yaitu di cerebellum dan hippocampus)
  - Dilepaskan dengan mekanisme Ca^{++}-dependent
  - Memiliki mekanisme inaktivasi, (yaitu melalui Na^{+}-dependent reuptake)
  - Memiliki reseptor yang teridentifikasi secara farmakologi



Reseptor glutamat

- Reseptor glutamat : ionotropik dan metabotropik

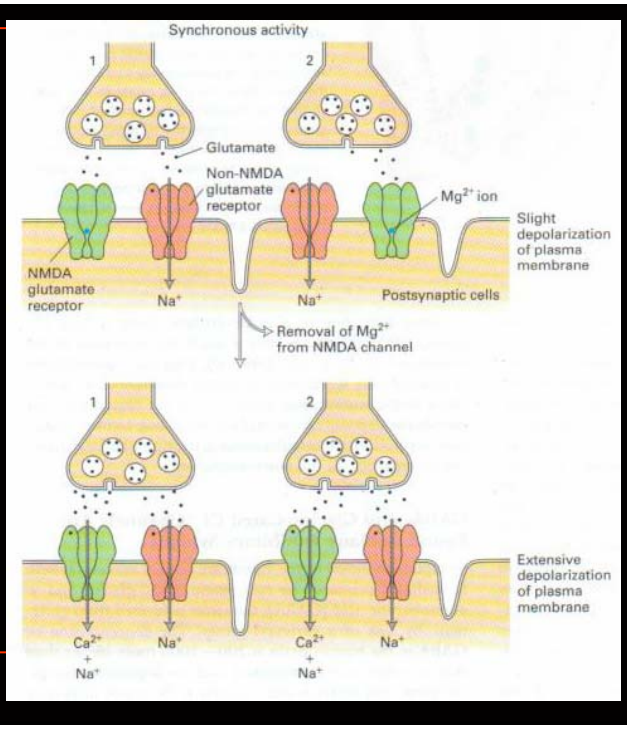


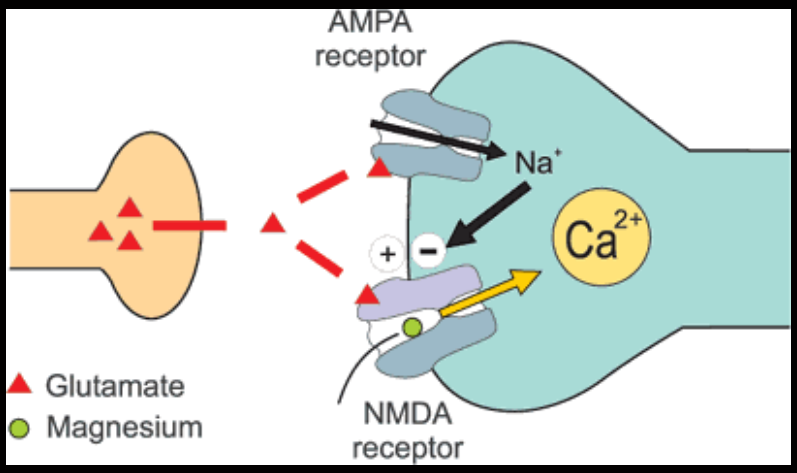
NMDA = N-Methyl D-Aspartate
AMPA = α-Amino-3-hydroxy-5-Methyl 4-isoxazole Propionic Acid

Reseptor NMDA
(N-methyl D-aspartat)

- terdapat pada cortex cerebral dan hippocampus, dan berperan dalam fungsi belajar dan memori
- Reseptor ini terkait dengan kanal ion bagi ion Na dan Ca
- memiliki afinitas terhadap ion Mg^{++} → Akibatnya ion Mg^{++} dapat mengikat reseptor NMDA dan memblokade kanal yang sedianya akan dilewati oleh ion Na^{+} atau Ca^{++}.
- Tetapi jika terjadi depolarisasi, afinitas Mg^{++} dengan reseptor tersebut menjadi berkurang → Mg^{++} akan terlepas dan kanal tidak lagi terblokade → Karena itu, aktivitas reseptor NMDA memerlukan reseptor lain untuk menginisiasi aktivasinya, yaitu reseptor glutamat non-NMDA

Aktivasi reseptor NMDA





Peran reseptor NMDA dan ligannya dalam sistem biologi

- Aktivasi reseptor NMDA → meningkatkan Ca dan Na intrasel
- Akan memicu signaling yang berperan dalam *learning and memory*
- Tetapi : overstimulasi NMDA receptors oleh glutamat → excess intracellular calcium → menyebabkan excitotoxicity → kematian sel saraf karena pengaruh glutamat
- Kematian sel saraf : apoptosis
- Kematian sel saraf → terlibat dalam berbagai penyakit yang ditandai dengan degenerasi sel saraf : Alzheimer, stroke, demensia, dll.
- Juga bisa memicu konvulsi

Perlu dikembangkan obat untuk mencegah apoptosis sel saraf

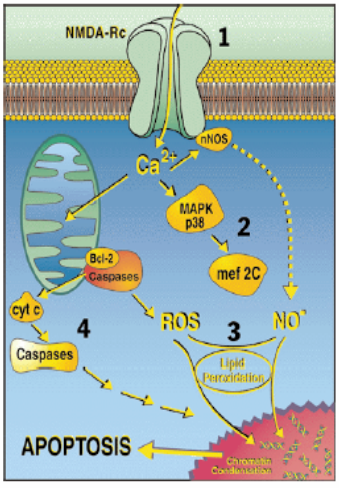
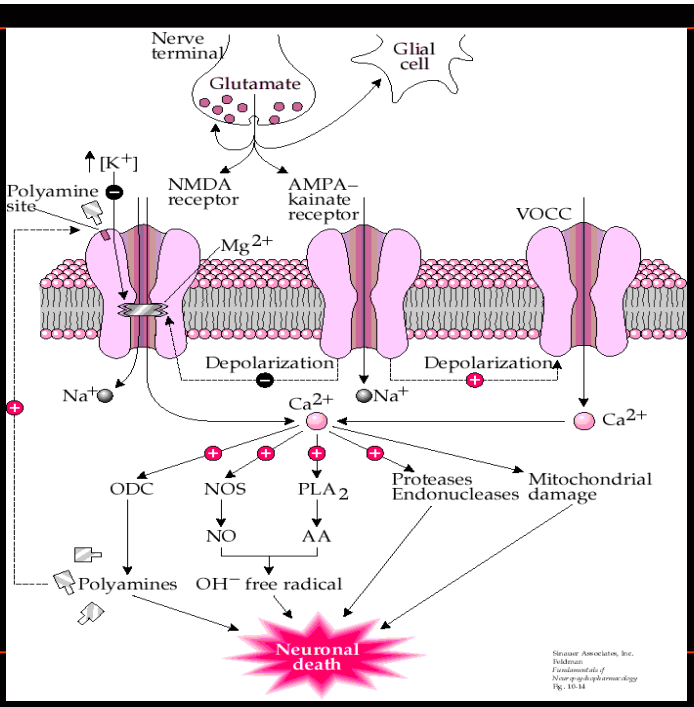


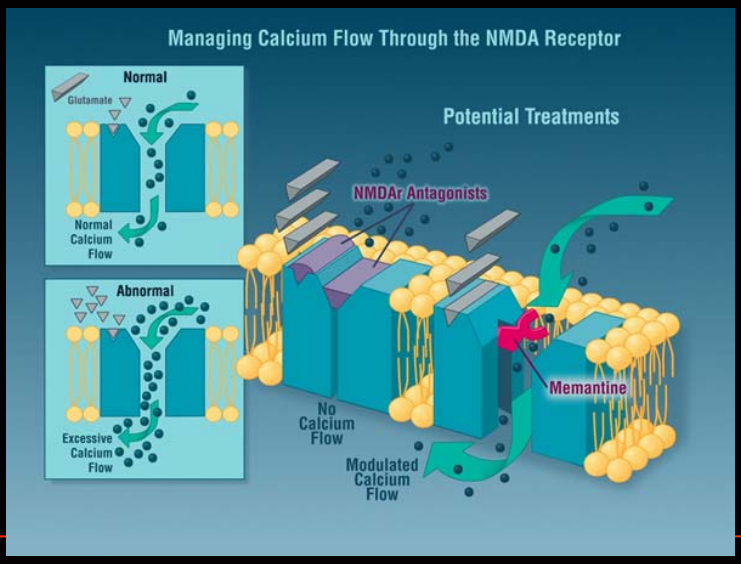
Figure Legend
Schematic illustration of the signaling pathways discovered or characterized in the Neurodegenerative Disease Program that can be targeted to prevent neuronal apoptosis and thus treat various neurologic diseases. Drug or molecular therapies are being developed to (1) antagonize NMDA receptors (NMDA-Rc), (2) modulate activation of the p38 mitogen activated kinase (MAPK) - MEF2C (transcription factor) pathway, (3) prevent toxic reactions of free radicals such as nitric oxide (NO) and reactive oxygen species (ROS), and (4) inhibit apoptosis-inducing enzymes including caspases.



Obat pada reseptor NMDA

- Obat yang dikembangkan: antagonis reseptor NMDA → sebagai neuroprotective agents pada stroke (taxoprodil, ifenprodil) → tetapi banyak yang gagal dlm uji klinik
- Mengapa ?
- Antagonis kuat → memblok aliran Ca → too much is as harmful as too little
- Obat baru yang disetujui FDA th 2002 untuk mencegah demensia : Memantin → regulasi aliran Ca melalui reseptor NMDA

Aksi Memantine pada reseptor NMDA
disetujui digunakan di EU untuk treatment demensia



Perkembangan baru ?

- Sistem glutamat terlibat dalam patofisiologi depresi → elevated levels of NR2C subunit in depressed patients (Karolewics, 2005)
- Ketamin (suatu antagonis reseptor NMDA) → memiliki efek antidepresan dengan onset lebih cepat dibandingkan antidepresan lainnya → new drug for treating depression?
- "After the positive results from the clinical trial of ketamine [from the 2006 study], we decided to use the mouse depression model to study how the NMDA and AMPA interaction figures into ketamine's rapid effect on depression," said Husseini Manji, M.D., director of the Mood and Anxiety Disorders Program at NIMH
- "Ketamine is probably not going to be useful for treatment because of its psychotomimetic side effects. So we are interested in a specific NMDA receptor subunit called NR2B. It can help us narrow the molecular target and develop drugs with similar therapeutic effects as ketamine, but hopefully without the psychotomimetic, dissociative side effects."

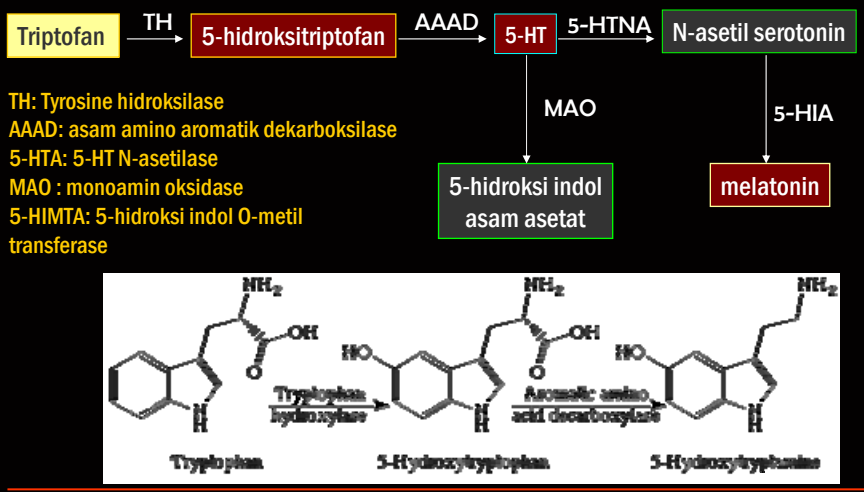
Reseptor serotonin-3 (5HT-3)

Reseptor serotonin (5-HT)

Serotonin:

- neurotransmiter amina yang terlibat dalam berbagai proses di otak, dan perubahan aktivitasnya dapat menyebabkan berbagai kondisi neuropsikiatrik seperti: depression, schizophrenia, anxiety disorder (social phobia, obsessive-compulsive, panic disorders), autisme, migraine, dan gangguan saluran cerna seperti : eating disorders, vomiting and irritable bowel syndrome
- > 90% 5-HT tubuh disintesis oleh enterechromaffin cells di mukosa usus, selain yang ada di sel saraf

Jalur biosintesis dan degradasinya:



Reseptor 5-HT

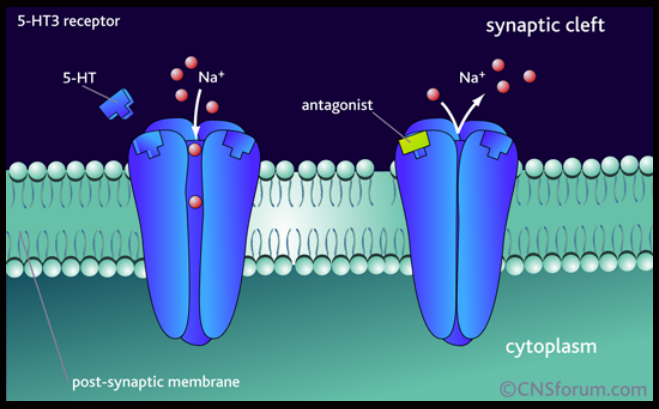
- Memiliki 7 anggota famili reseptor dengan jumlah total reseptor 14 jenis, contoh : 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, dll. → masing-masing memiliki fungsi yang berbeda
- 5-HT dan reseptornya dijumpai baik pada central and peripheral nervous system (CNS/PNS),
- Juga terdapat pada sejumlah jaringan nonneuronal di usus, sistem kardiovaskuler, dan darah

Table 1. Different 5-HT receptor subtypes

	5-HT_1	5-HT_2	5-HT_3	5-HT_4	5-ht_5	5-ht_6	5-HT_7
Subtypes	5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-ht_{1E}, 5-ht_{1F}	5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}	5-HT_{3A}, 5-HT_{3B}		5-ht_{5A}, 5-ht_{5B}		
Major signalling pathway	cAMP↓	IP_3↑	Ion channel	cAMP↑	cAMP?	cAMP↑	cAMP↑

Reseptor 5-HT3

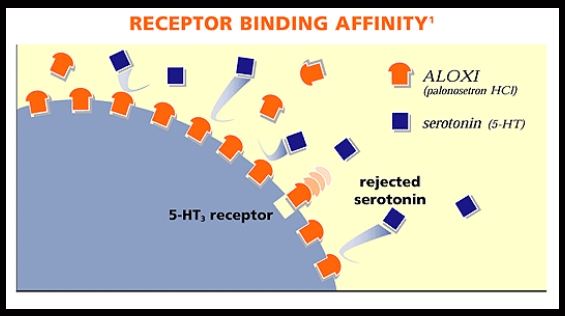
- Reseptor 5-HT3 merupakan satu-satunya subtipe reseptor 5-HT yang ionotropic, lainnya metabotropic
- terdapat di spinal cord, cortex, hippocampus, dan saluran cerna (usus)
- Terkait dengan kanal Na
- jika serotonin terikat pada reseptor → kanal kation membuka → ion Na masuk → terjadi depolarisasi arus yang cepat dan singkat → reseptor teraktivasi → berbagai efek selular
- Misalnya : Reseptor 5-HT3 terlibat dalam mual dan muntah karena kemoterapi dan radiasi

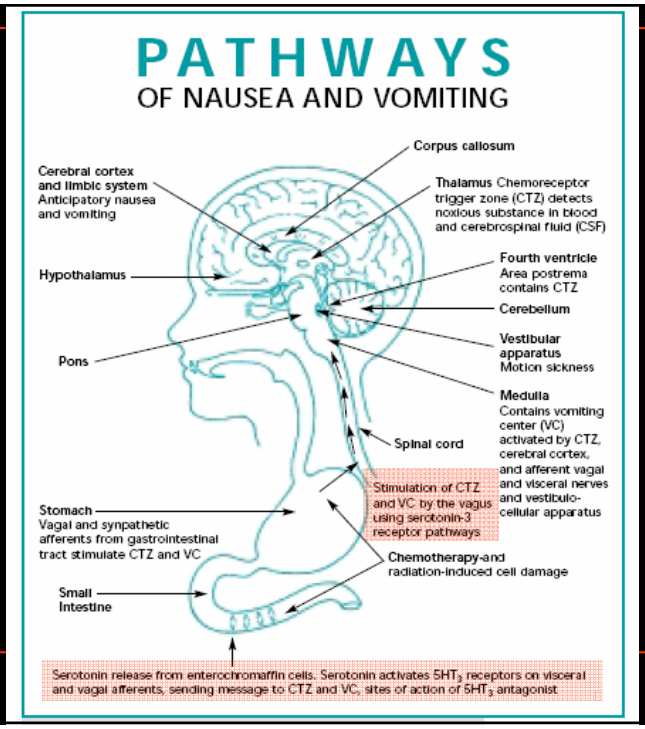


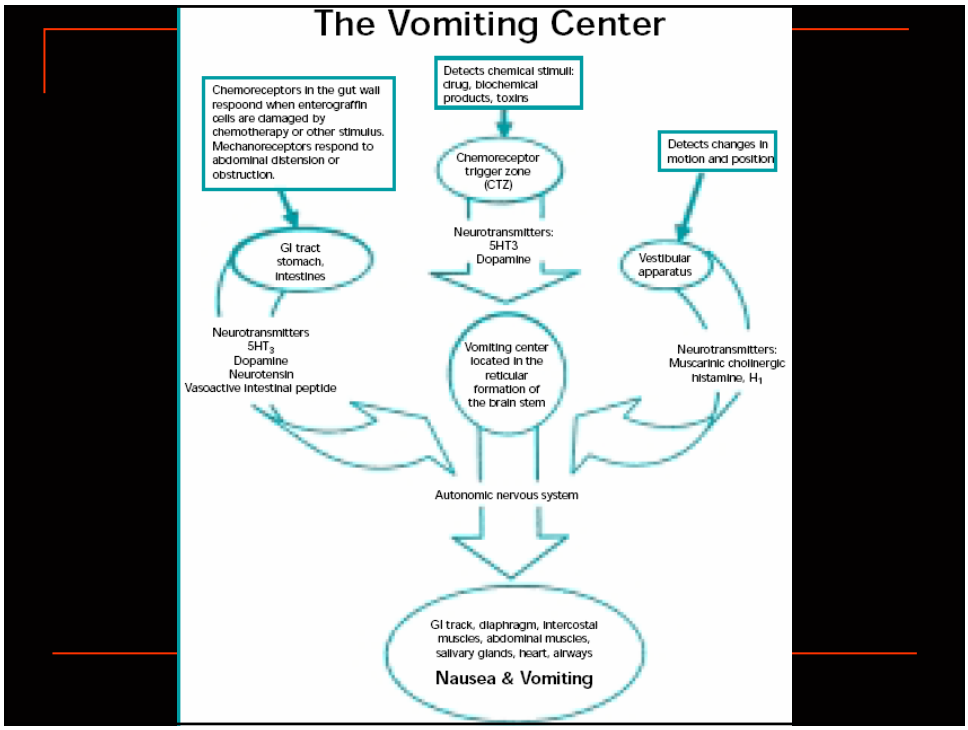
Binding of an agonist at the 5-HT binding site causes a conformational change and activation of the 5-HT3 receptor. As a ligand gated ion channel this permits the movement of positively charged ions from the synaptic cleft into the cytoplasm. Binding of an antagonist at the 5-HT binding site prevents this activation and cell depolarisation is inhibited.

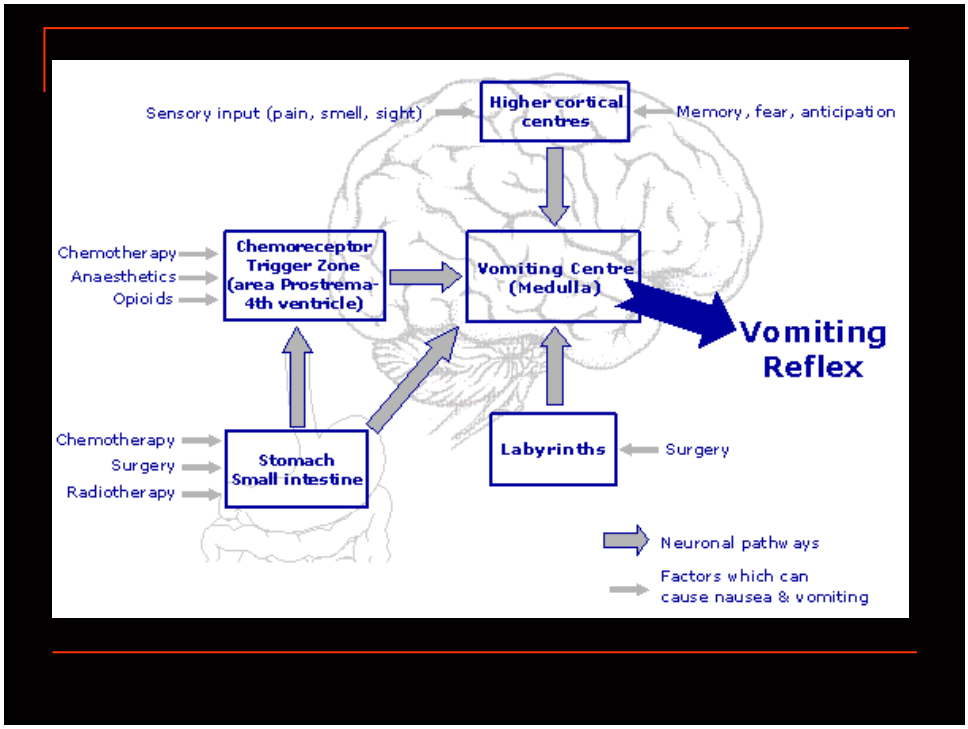
Obat yang beraksi pada reseptor 5-HT3 ?

- Antagonis : ondansetron, tropisetron, granisetron, dolasetron, palonosetron → digunakan scr klinis untuk pengobatan mual dan muntah akibat kemoterapi atau radiasi






The Vomiting Center
Chemoreceptors in the gut wall respoond when enterograffin cells are damaged by chemotherapy or other stimulus. Mechanoreceptors respond to abdominal distension or obstruction.
Detects chemical stimuli: drug, biochemical products, toxins
Detects changes in motion and position
Chemoreceptor trigger zone (CTZ)
GI tract stomach, intestines
Neurotransmitters: 5HT3 Dopamine
Vestibular apparatus
Neurotransmitters $5HT_3$ Dopamine Neurotensin Vasoactive intestinal peptide
Vomiting center located in the reticular formation of the brain stem
Neurotransmitters: Muscarinic cholinergic histamine, H_1
Autonomic nervous system
GI track, diaphragm, intercostal muscles, abdominal muscles, salivary glands, heart, airways
Nausea & Vomiting


Sensory input (pain, smell, sight)
Higher cortical centres
Memory, fear, anticipation
Chemotherapy
Anaesthetics
Opioids
Chemoreceptor Trigger Zone (area Prostrema-4th ventricle)
Vomiting Centre (Medulla)
Vomiting Reflex
Chemotherapy
Surgery
Radiotherapy
Stomach Small intestine
Labyrinths
Surgery
Neuronal pathways
Factors which can cause nausea & vomiting

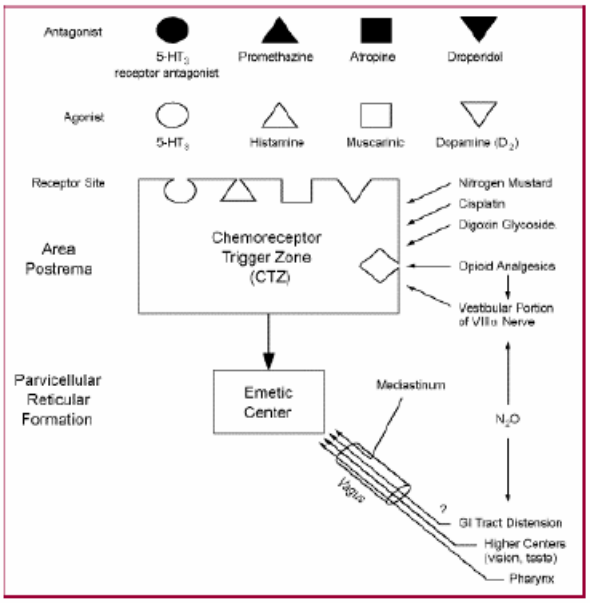
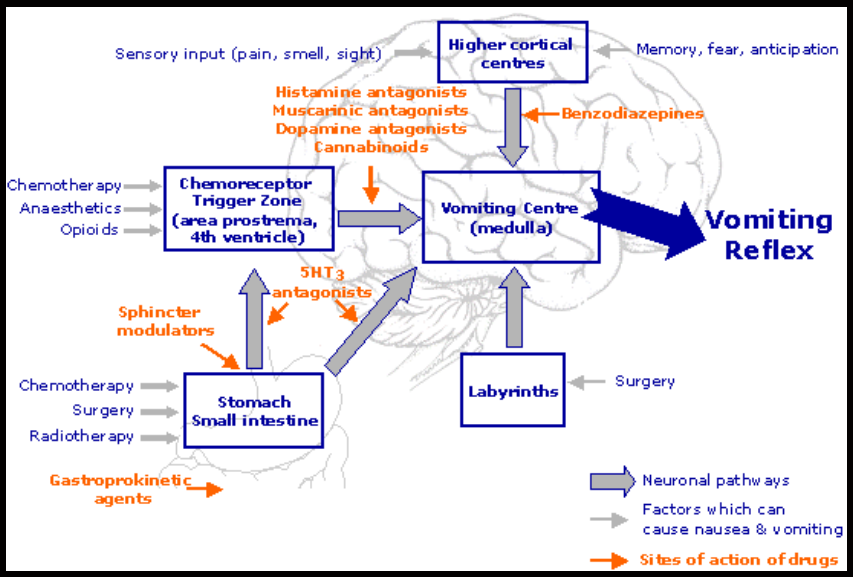


Figure 5. Schematic Diagram of Receptors of the CTZ and Vomiting Center.



Aktivitas farmakologis lainnya ?

- Selain antiemetik, antagonis 5HT3 digunakan pada pengobatan gangguan saluran cerna seperti irritable bowel syndrome (IBS)
- IBS adalah gangguan fungsional GI tract yang disebabkan oleh : gangguan motilitas GI dan persepsi sensorik di viseral, dan hiperalgesia viseral
- Gejala:
  - Abdominal pain or discomfort
  - Abdominal bloating or distension
  - Faecal urgency
  - Constipation, diarrhea, or both

Antagonist reseptor 5HT-3 ?

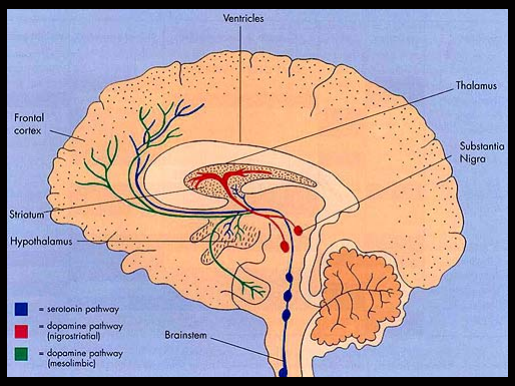
- Merupakan salah satu alternatif terapi, terutama yang predominan diare, karena berefek :
  - Modulation of visceral sensitivity,
  - enhanced compliance (increasing the ability of the gut to adapt to distension),
  - involved in peristalsis, and
  - increase in fluid absorption.

  For all of these reasons, 5-HT3 receptor antagonists may slow transit

Contoh obatnya : alosetron, cilansetron

Reseptor 5-HT3 ..... Lanjutan

- Pada penyakit psikiatrik, receptor 5-HT_3 juga diduga terlibat dalam schizophrenia dan anxiety
- Aktivasi reseptor 5-HT_3 di otak dapat memicu/mengontrol pelepasan dopamin sehingga antagonist reseptor 5-HT_3 dapat menghasilkan efek sentral yang sebanding dengan antipsychotics and anxiolytics



Perkembangan baru ?

Does a Single Intravenous Injection of the 5HT3 Receptor Antagonist Ondansetron Have an Analgesic Effect in Neuropathic Pain? A Double-Blinded, Placebo-Controlled Cross-Over Study

Gary J. McCleane, MD, Rie Suzuki, PhD*, and Anthony H. Dickenson, PhD*

From Rampark Pain Centre, Lurgan, Northern Ireland, and the *Department of Pharmacology, University College, Gower Street, London

Neurokinin–1-expressing neurones in lamina I to III of the spinal cord are intimately involved in the regulation of ascending and spino-bulbal pathways that regulate excitatory transmission. In experimental animals, ablation of these neurones reduces the responses to a variety of nociceptive stimuli. Furthermore, in animals, spinal application of the selective 5HT3 receptor antagonist ondansetron mimics these effects, indicating that 5HT3 receptors play a pronociceptive role and mediate descending excitatory controls that allow spinal neurones to fully code peripheral stimuli. In this study, we examined the potential analgesic effect of a single IV injection of ondansetron in humans with chronic neuropathic pain. Each consenting subject received a single IV injection of 8 mg ondansetron and placebo in varying order at least 1 wk apart with pain scores being recorded for the 48 h preceding and after each injection. Pain scores were significantly reduced 2 h after ondansetron injection (but at no other time point). This suggests that ondansetron can have an analgesic effect in neuropathic pain. Side effects were minor and infrequent.

(Anesth Analg 2003;97:1474–8)

Table 3. Changes in Pain Scores From Baseline to Treatment and From Placebo to Active Treatment

	Change from baseline to active treatment with ondansetron	Difference between placebo and ondansetron treatment
Burning pain	−0.22 (1.10)	−1.0 (1.13)
Shooting/lancinating pain	0.31 (1.25)	0.21 (0.95)
Numbness	−0.29 (0.95)	−0.5 (0.89)
Paresthesia	0.35 (0.98)	−0.37 (0.99)
Allodynia	−0.44 (0.86)	−0.25 (0.81)
Overall pain	−1.17 (0.89)*	−1.09 (0.79)*

Data expressed as mean (95% confidence intervals).
Pain scores were measured on an 11-point Likert scale at t = +2 h after injection of placebo or ondansetron.
* $P < 0.02$.

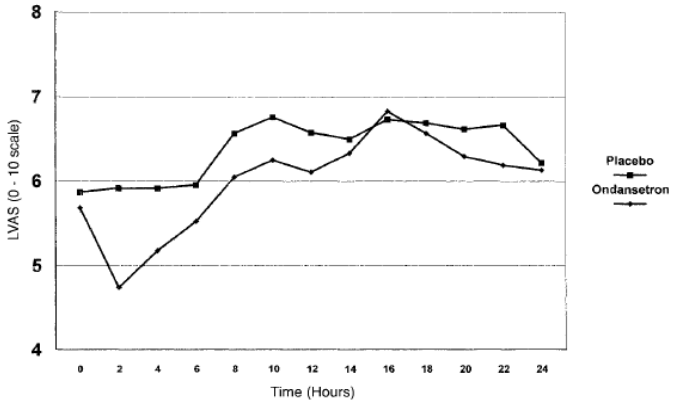


Figure 1. Single intravenous dose of ondansetron 8 mg versus placebo in 26 human subjects with chronic refractory neuropathic pain. Mean pain scores (Likert scale) recorded every 2 h for 24 h after administration of placebo or ondansetron 8 mg.

Effect of ondansetron, a 5-HT_3 receptor antagonist, on fatigue in chronic hepatitis C: a randomised, double blind, placebo controlled study

T Piche, G Vanbiervliet, F Cherikh, Z Antoun, P M Huet, E Gelsi, J-F Demarquay, F-X Caroli-Bosc, S Benzaken, M-C Rigault, C Renou, P Rampal, A Tran

Gut 2005;**54**:1169–1173. doi: 10.1136/gut.2004.055251

See end of article for authors' affiliations

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Background and aims: There are no available effective therapies for fatigue associated with chronic hepatitis C (CHC). The serotonin antagonist ondansetron has been shown to be effective in the chronic fatigue syndrome. In this randomised, placebo controlled, double blind trial, we investigated the effect of orally administered ondansetron on fatigue in CHC.
Methods: Thirty six patients with CHC were included if fatigue was their predominant symptom and they scored more than 4 on a visual analogue scale (0–10). During the study, fatigue and depression were measured on days 0, 15, 30, and 60 using a validated self report questionnaire (fatigue impact scale and Beck depression inventory). Patients were randomised to receive ondansetron tablets 4 mg twice daily or placebo for one month followed by an additional four weeks of observation.
Results: Fatigue score was 85.4 (28.2) and 98.2 (26.9) in the ondansetron and placebo groups, respectively (NS). Ondansetron significantly reduced the fatigue score with more than 30% improvement on day 15 (57.1 (38.9); $p<0.01$), day 30 (54.5 (37.6); $p<0.01$), and day 60 (60.8 (37.3); $p<0.01$) whereas placebo did not. Overall, the reduction in fatigue was significantly higher with ondansetron compared with placebo (ANOVA for repeated measurements) for the whole follow up period ($p=0.03$) or for the treatment period only ($p=0.04$). Ondansetron also significantly reduced depression scores.
Conclusions: The 5-hydroxytryptamine receptor type 3 antagonist ondansetron had a significant positive effect on fatigue in CHC. These observations support the concept that fatigue involves serotoninergic pathways and may encourage further evaluations of the efficacy of ondansetron on fatigue in chronic liver diseases.

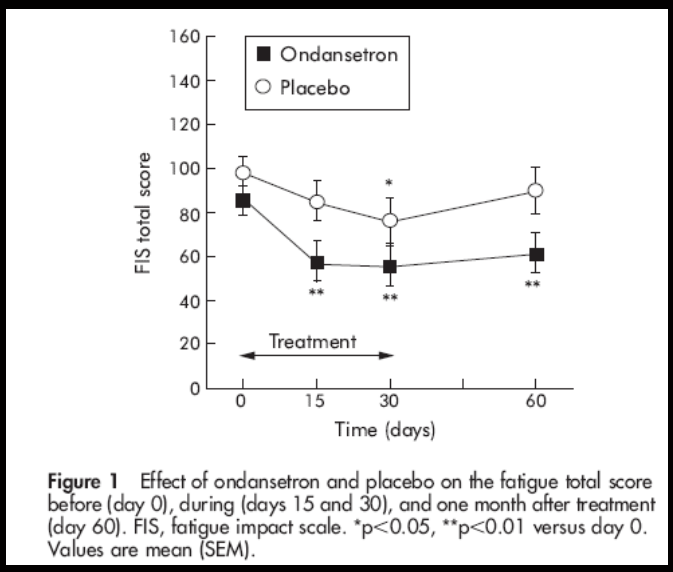
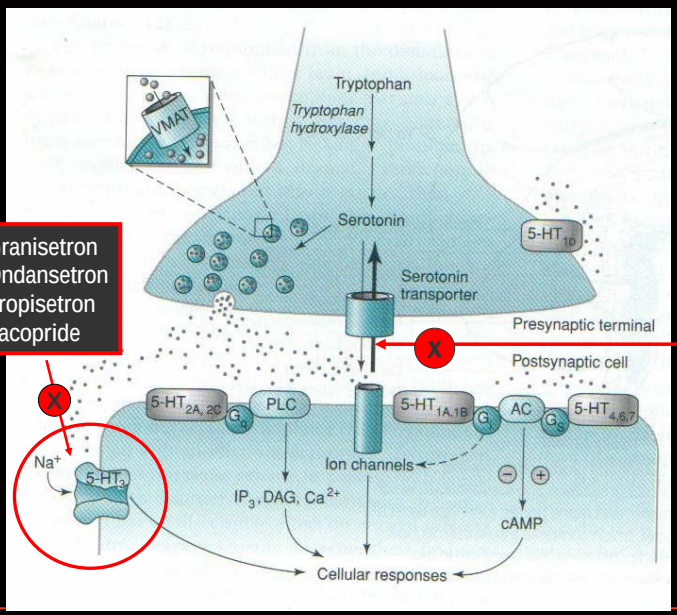


Figure 1 Effect of ondansetron and placebo on the fatigue total score before (day 0), during (days 15 and 30), and one month after treatment (day 60). FIS, fatigue impact scale. *p<0.05, **p<0.01 versus day 0. Values are mean (SEM).



Granisetron
Ondansetron
Tropisetron
Zacopride

Obat lain yang bekerja pada sistem serotonergik : **SSRI**

Obat SSRI

Contoh:
-Fluoksetin
-Fluvoksamin
-Paroksetin
-Sertralin

SSRI : selective serotonin re-uptake inhibitor

Selesai .....

Sumber internet

- http://www.blackwellpublishing.com/matthews/channel.html --> tentang action potential
- http://www.blackwellpublishing.com/matthews/nmj.html --> tentang fusi vesikel sinaptik dan pelepasan neurotransmiter
- http://www.blackwellpublishing.com/matthews/neurotrans.html --> perbandingan aksi neurotransmiter langsung dan tidak langsung
- Sodium-Potassium Pump: http://www.nd.edu/~aseriann/nak.html
- Sodium-Potassium Pump – animations
- http://www.brookscole.com/chemistry_d/templates/student_resources/shared_resources/animations/ion_pump/ionpump.html
- http://arbl.cvmbs.colostate.edu/hbooks/molecules/sodium_pump.html
- http://www.cat.cc.md.us/courses/bio141/lecguide/unit1/eustruct/sppump.html
- http://info.bio.cmu.edu/Courses/BiochemMols/Channels/channelsIntro.htm