FARMAKODINAMIK 2

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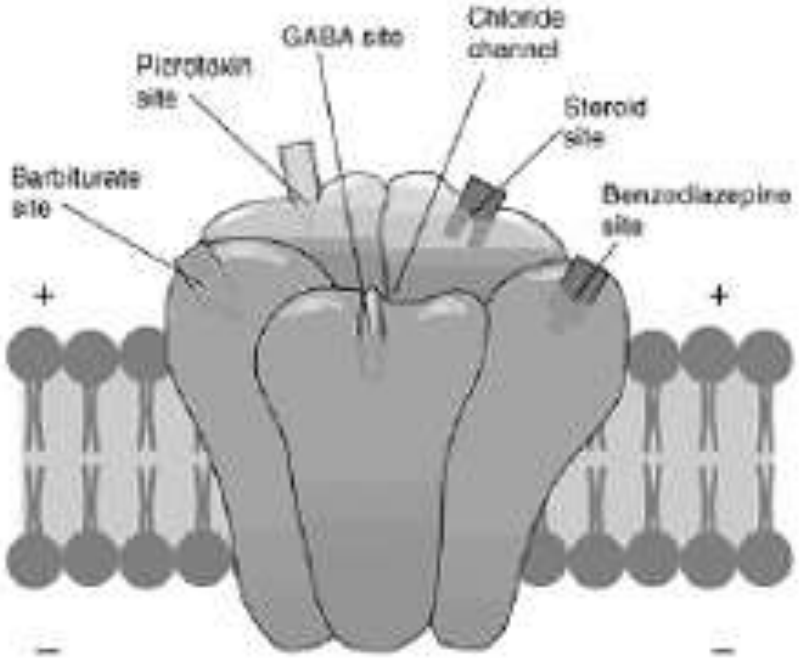
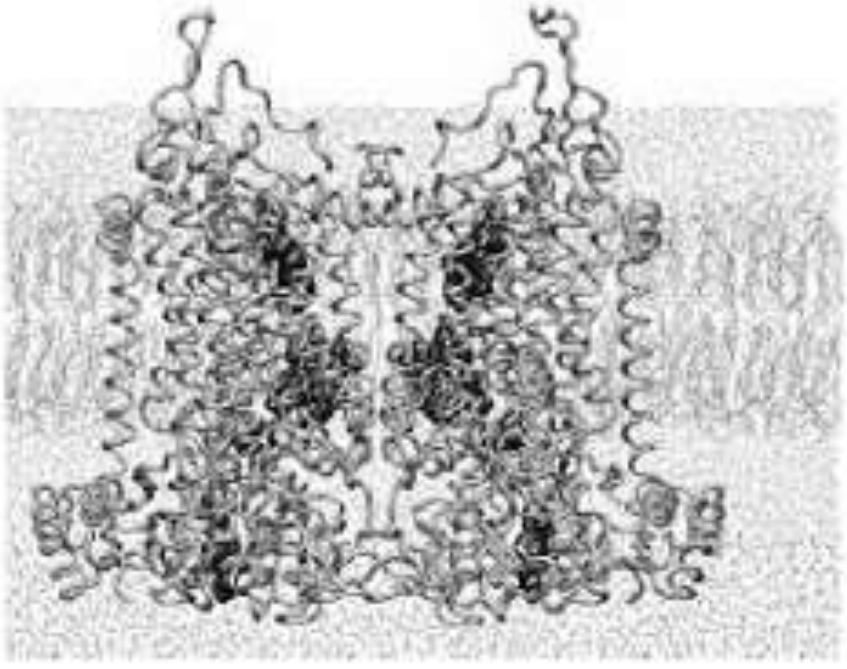
Reseptor ?

- Suatu makromolekul seluler yang secara spesifik dan langsung berikatan dengan ligan (obat, hormon, neurotransmiter) untuk memicu signaling kimia antara dan dalam sel → menimbulkan efek





Fungsi reseptor ?

- mengenal dan mengikat suatu ligan/obat dengan spesifisitas yang tinggi
- meneruskan signal ke dalam sel melalui:
  - perubahan permeabilitas membran
  - pembentukan *second messenger*
  - mempengaruhi transkripsi gen

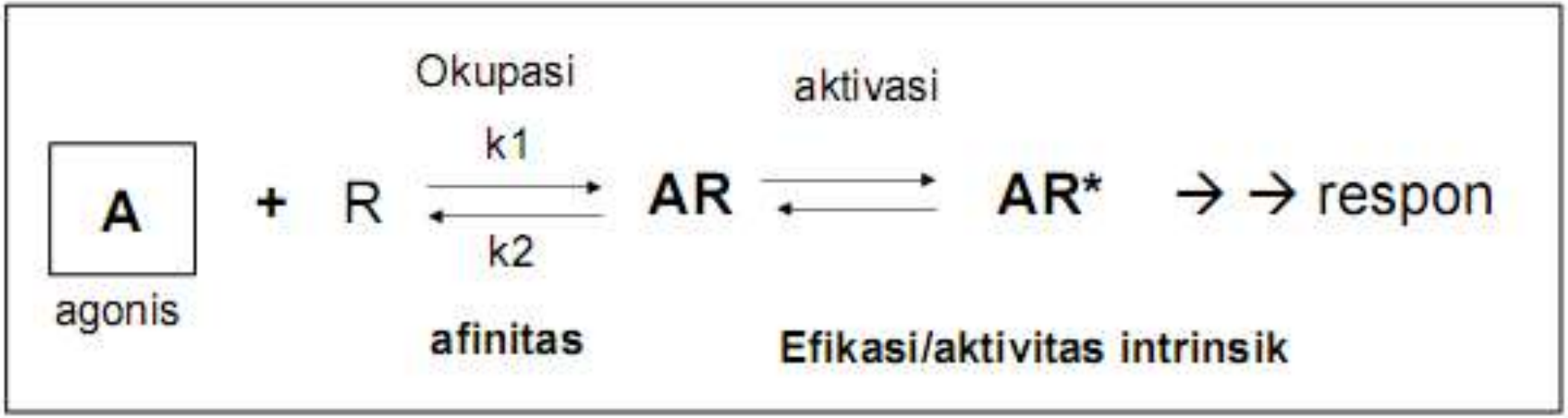
Beberapa istilah penting:

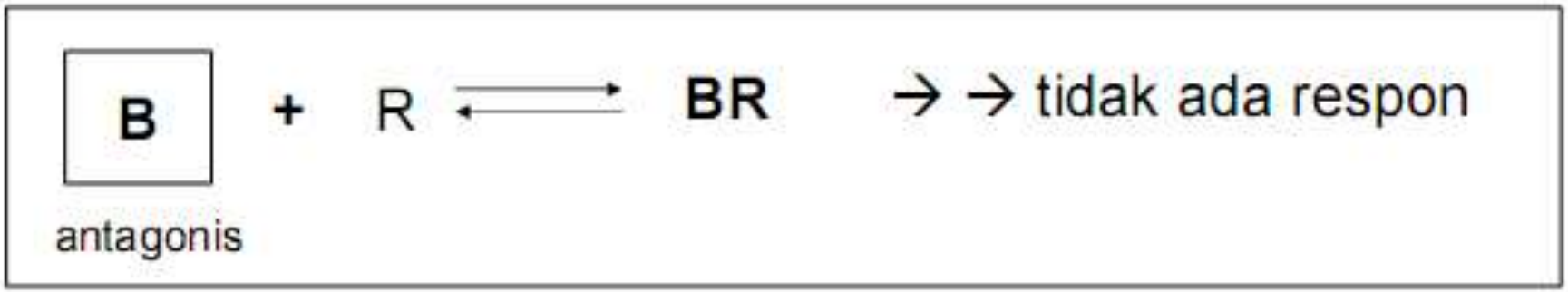
- Ligan : Molekul spesifik (obat) yang dapat mengikat reseptor
- Afinitas: Kemampuan ligan untuk mengikat reseptor → arti ?
  afinitas besar = semakin mudah berikatan dengan reseptor (cocok)
- Efikasi: Perubahan/efek maksimal yang dapat dihasilkan oleh suatu obat

Analogi kunci dan gembok → obat dengan reseptor seperti kunci dan gemboknya → Kenyataan ?

- Suatu reseptor dapat berikatan dengan sekelompok senyawa kimia yang sejenis *(a family of chemicals or hormones)*
- Setiap senyawa tadi akan menunjukkan afinitas yang berbeda terhadap reseptor (ikatan kuat atau lemah)
- Setiap senyawa akan menghasilkan efikasi yang berbeda

Aksi obat spesifik

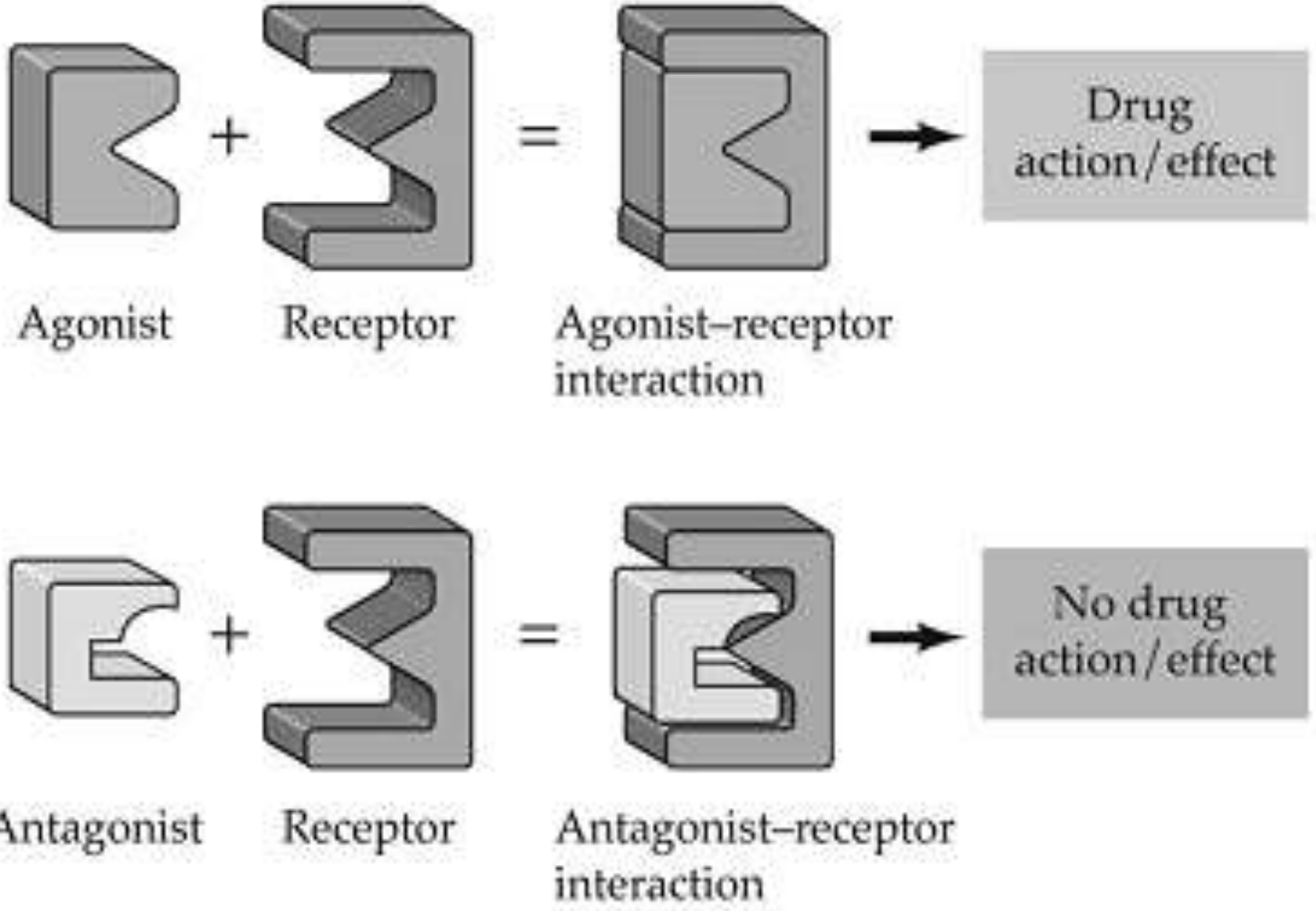


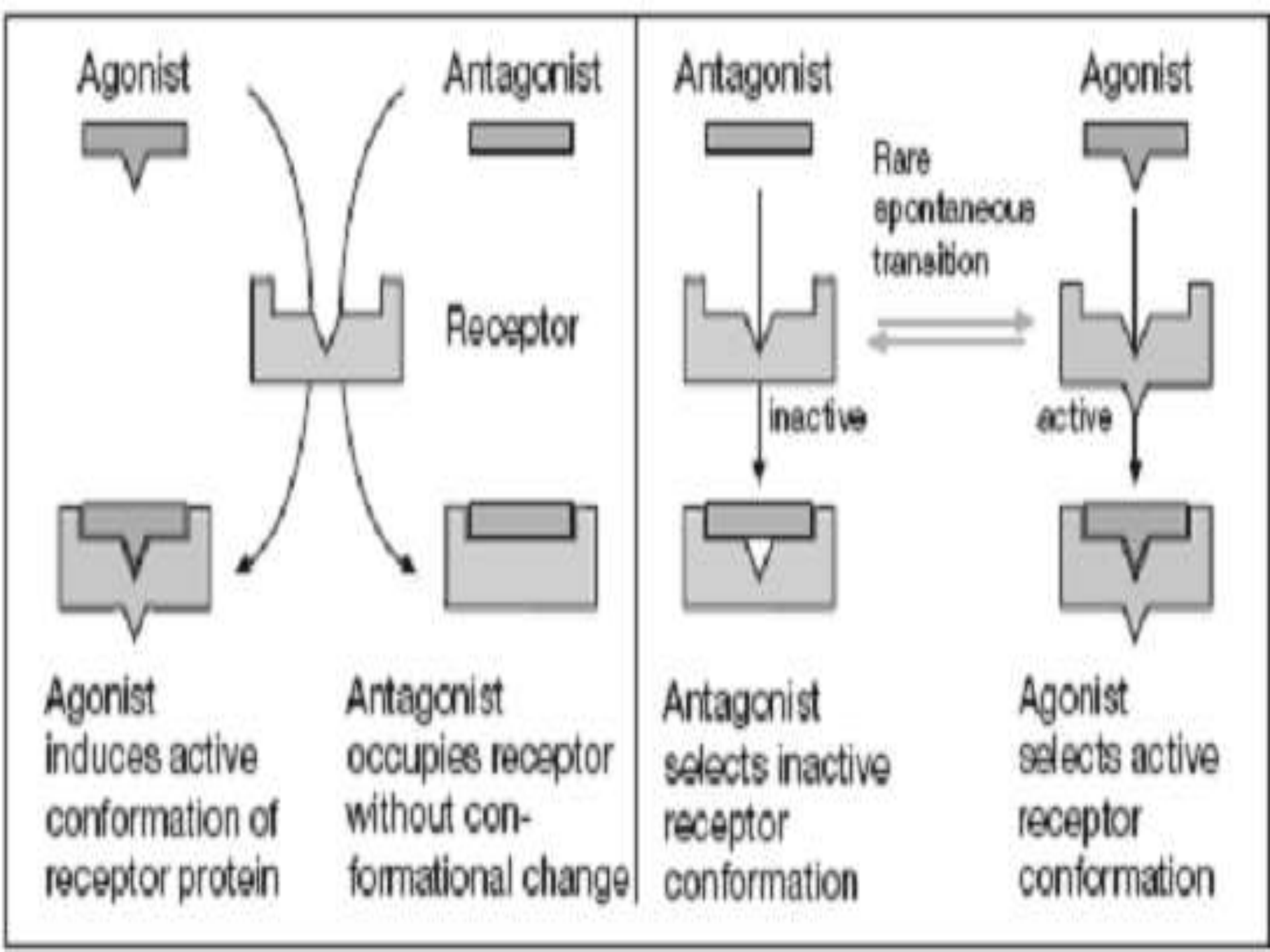


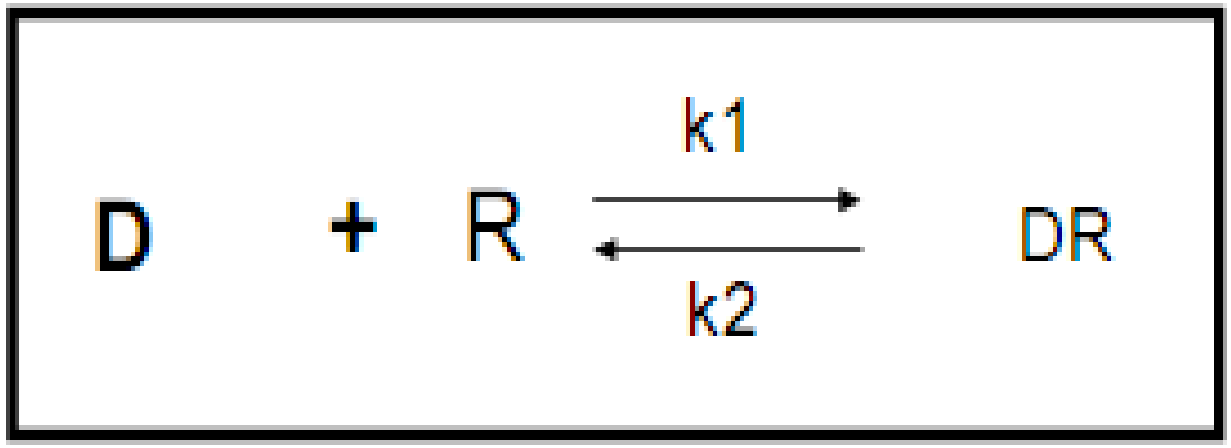
R : Konsentrasi reseptor dalam biofase

k1 : Konstanta/tetapan laju asosiasi (pengabungan) obat dan reseptor

k2 : Konstanta / tetapan laju disosiasi (peruraian) komplek obat – reseptor


Drug action/effect
Agonist
Receptor
Agonist–receptor interaction
No drug action/effect
Antagonist
Receptor
Antagonist–receptor interaction


Agonist
Antagonist
Receptor
Agonist induces active conformation of receptor protein
Antagonist occupies receptor without con-formational change
Antagonist
Agonist
Rare spontaneous transition
inactive
active
Antagonist selects inactive receptor conformation
Agonist selects active receptor conformation



Afinitas = k_1/k_2

Kd = konstanta disosiasi = k_2/k_1

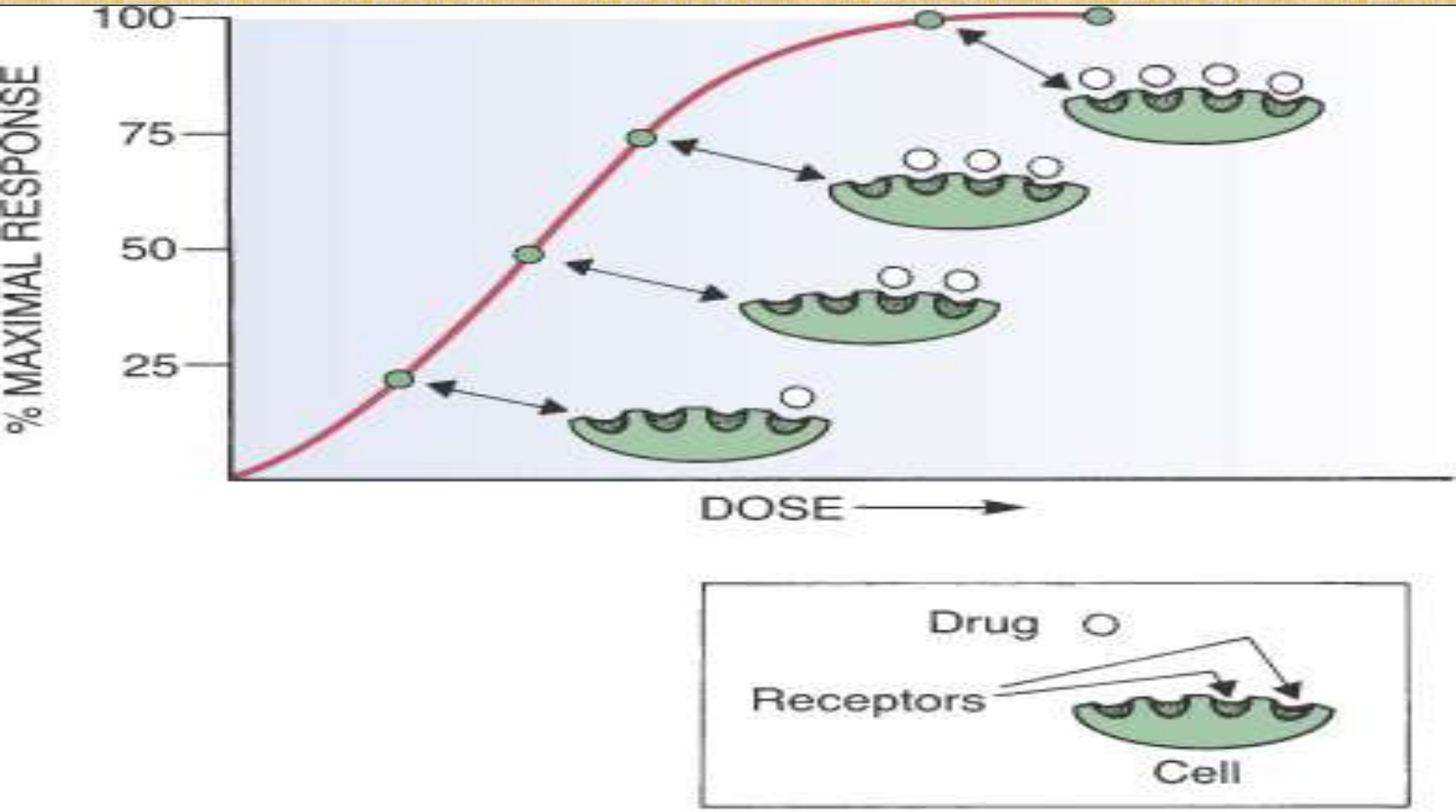
Jika k_2/k_1 besar : bagaimana afinitasnya ?

Aksi obat spesifik (lanjutan)

- Diawali dengan okupasi (pendudukan) obat pada tempat aksinya
- Obat = Ligan
  - Agonis → ligan/obat yang dapat berikatan dengan reseptor dan menghasilkan efek
  - Antagonis → ligan yang dapat berikatan dengan reseptor tapi tidak menghasilkan efek
- Tempat aksi = Reseptor

Efek/respon yang ditimbulkan:
- Sebanding dengan jumlah reseptor yang berinteraksi dengan obat
- Sebanding dengan komplek obat-reseptor yang terbentuk

MODEL OF SIMPLE OCCUPANCY THEORY



SYARAT AGONIS DAPAT MENIMBULKAN RESPON

1. Afinitas

kemampuan obat untuk berinteraksi dengan reseptornya → parameter ??

$$pD_2 = \log(1 / [D]_{maks/2})$$
$$= -\log([D]_{maks/2})$$
$$= \log(I / K_D)$$

ukuran kemampuan agonis untuk berinteraksi membentuk komplek dengan suatu reseptor → Makna ??

nilai pD_2 besar maka afinitas semakin besar dan sensitivitas reseptor terhadap obat juga semakin besar

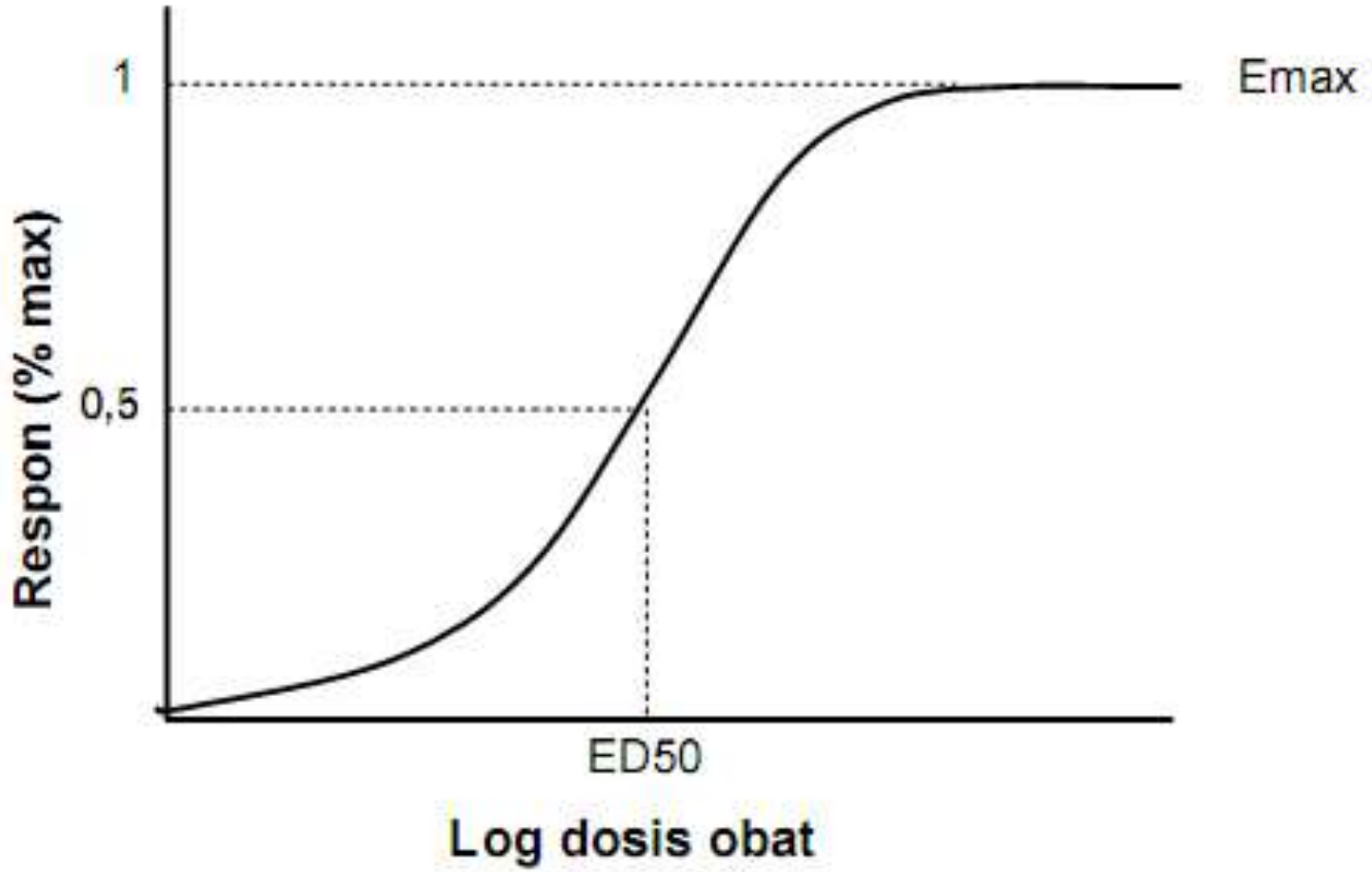
2. Aktivitas intrinsik/efikasi

kemampuan suatu obat untuk menghasilkan efek atau respon jaringan → Fungsi ??

menentukan besarnya efek maksimum yang dicapai oleh suatu senyawa

efek maksimum ??
= efek dalam skala respon maksimum jaringan

Apabila dibuat plot antara dosis obat vs efek/ respon, maka kurva yang dihasilkan :



Macam agonis

- Full agonis
- Partial agonis

Full Agonist

Large stimulus to cellular signaling machinery

↓

LARGE EFFECT

Aktivitas intrinsik = 1

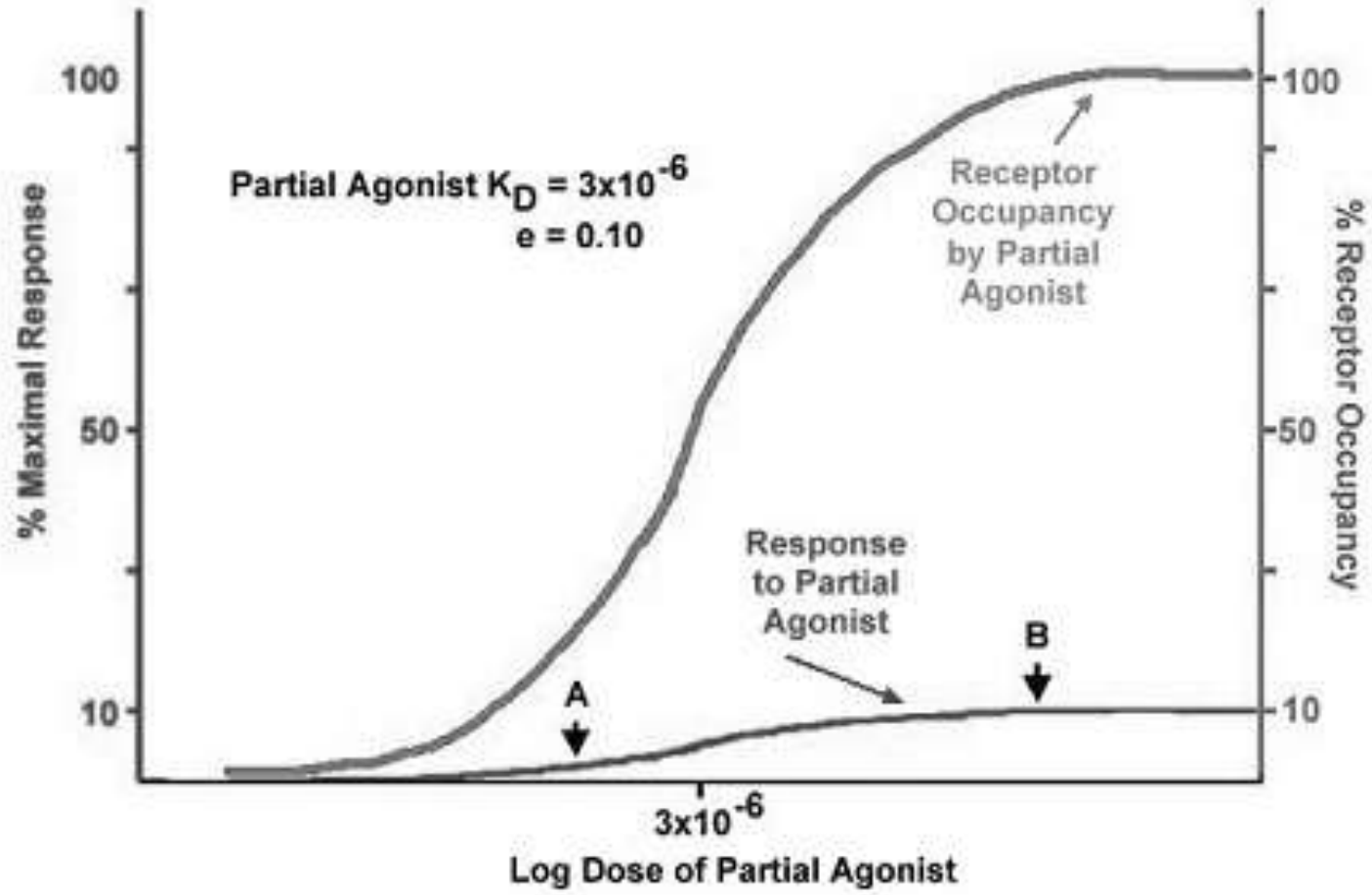
Partial Agonist

Small stimulus to cellular signaling machinery

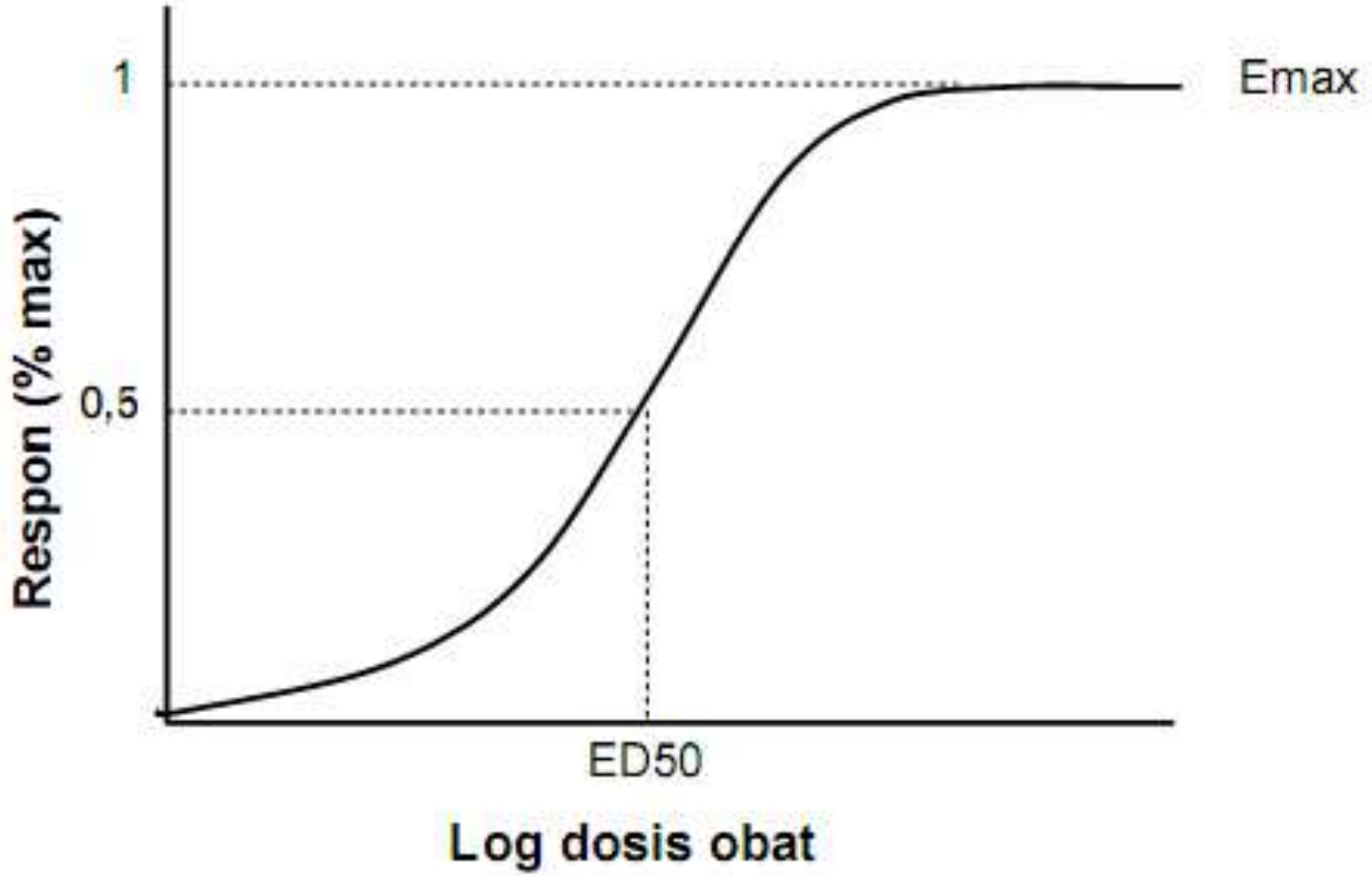
↓

small effect

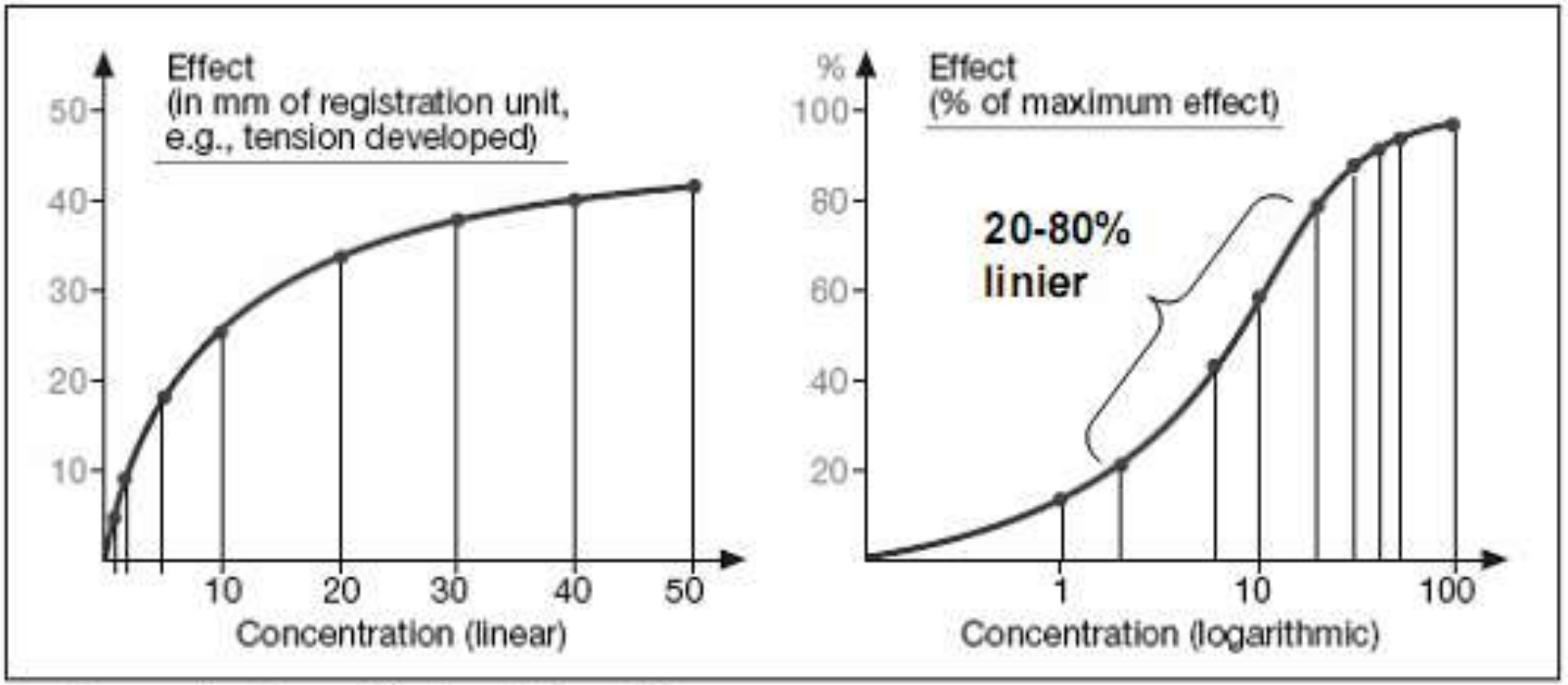
Aktivitas intrinsik < 1


100
50
10
% Maximal Response
Partial Agonist $K_D = 3x10^{-6}$
e = 0.10
Receptor Occupancy by Partial Agonist
Response to Partial Agonist
A
B
100
50
10
% Receptor Occupancy
$3x10^{-6}$
Log Dose of Partial Agonist

Apabila dibuat plot antara dosis obat vs efek/ respon, maka kurva yang dihasilkan :



Macam kurva dose vs response



B. Concentration-effect relationship

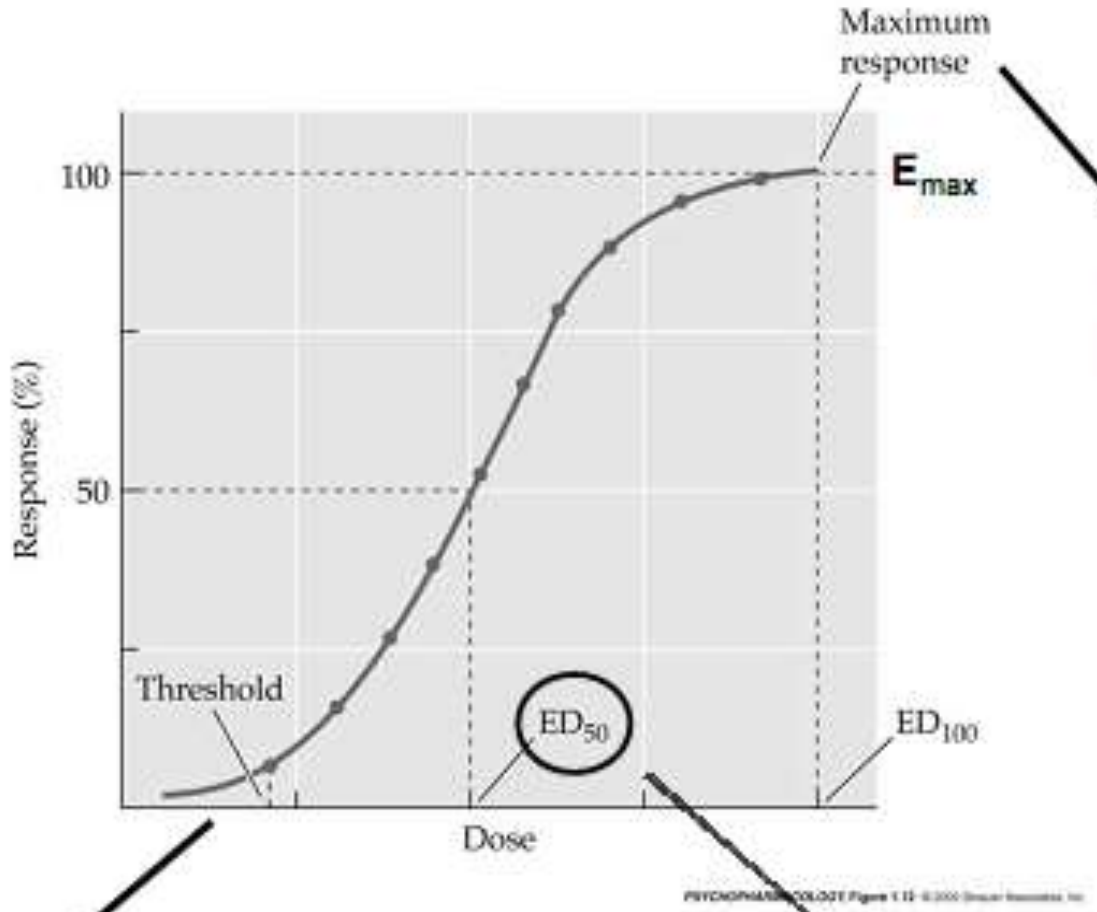
Kurva hiperbolik

Kurva sigmoid

Lebih banyak dipakai → lebih mudah dalam analisa farmakodinamika

- Dose-response curve:

Used to evaluate receptor activity. Describes the amount of response for a given drug dose

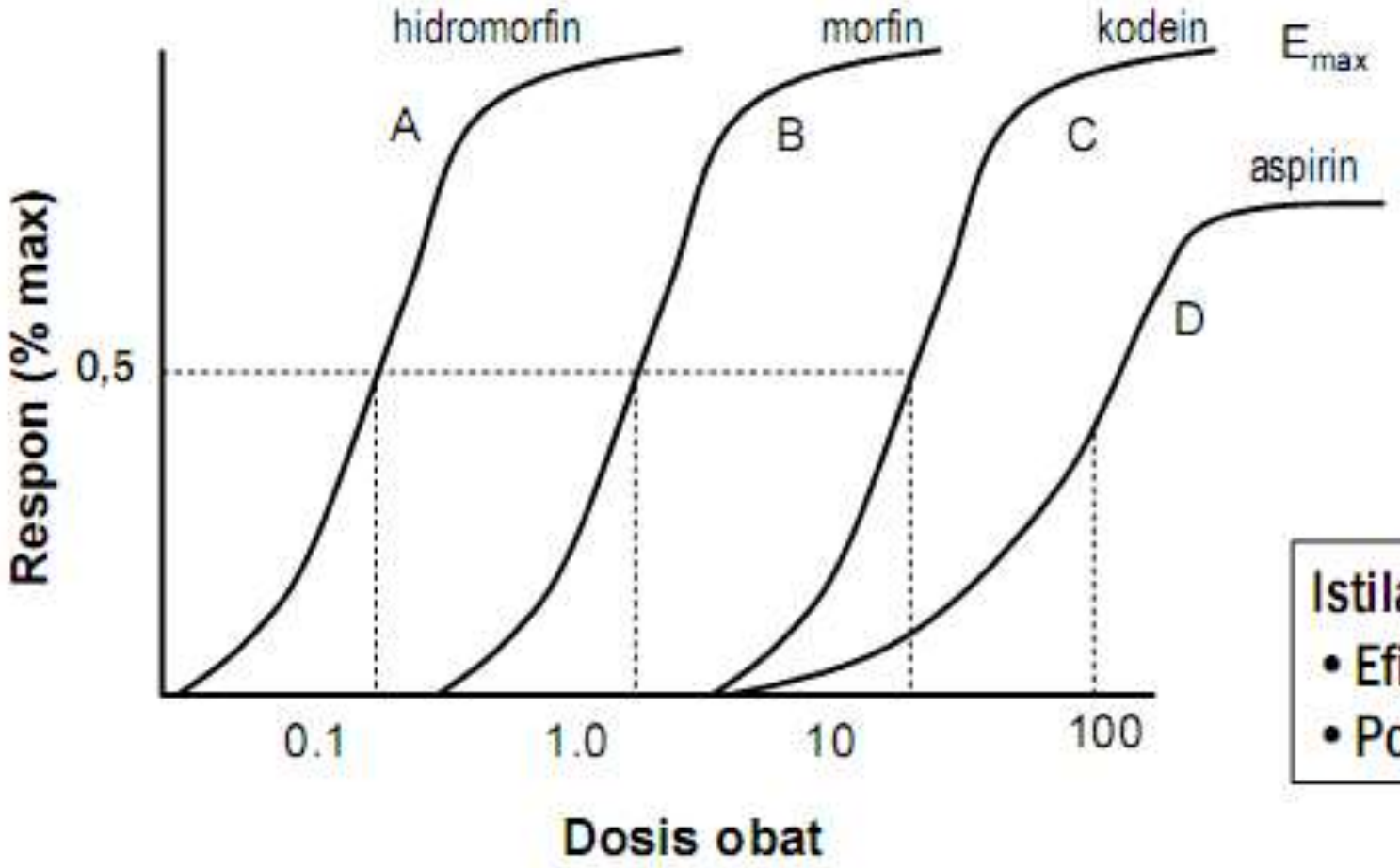


High dose = more receptors occupied.

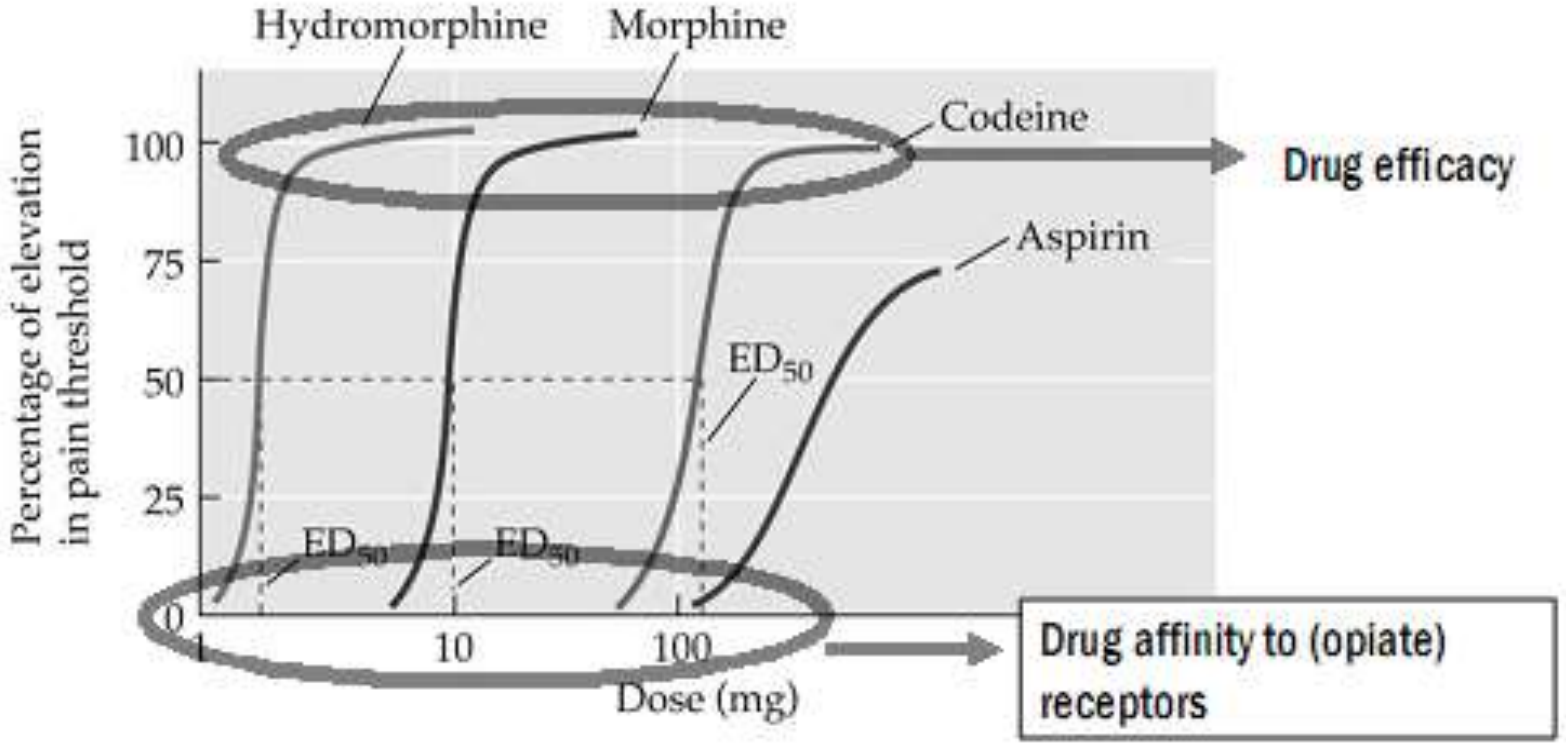
Low doses of drug = few receptors being occupied.

50% effective dose.

Obat A, B, dan C adalah seri agonis, semua dapat mencapai E_{max}.
Obat mana yang paling poten ? Bagaimana dengan obat D ?



Istilah:
- Efikasi ?
- Potensi ?



Increasing concentration produces greater analgesia.

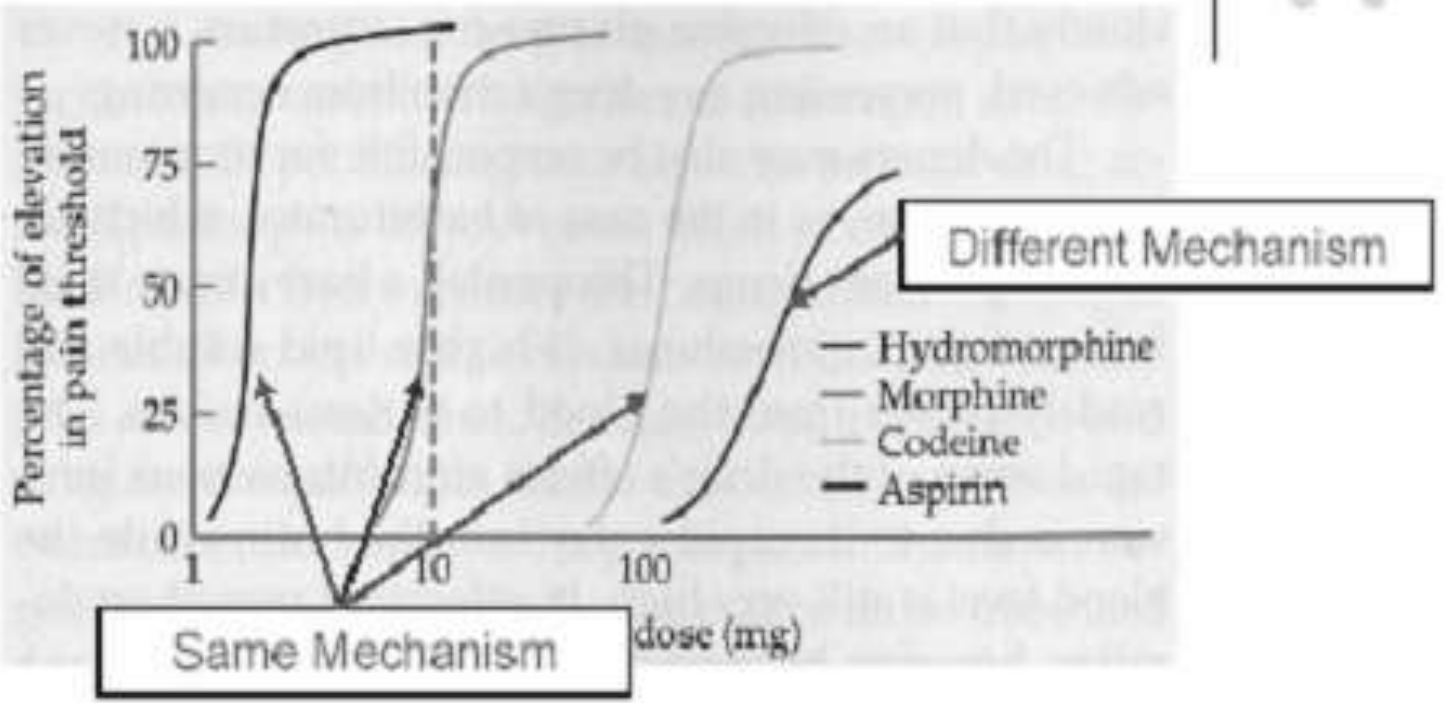
Absolute amount of drug necessary to produce effect = drug potency (ED_{50})

Shape of curves indicates they work through same mechanism

Aspirin = different mechanism (shape of curve is different)

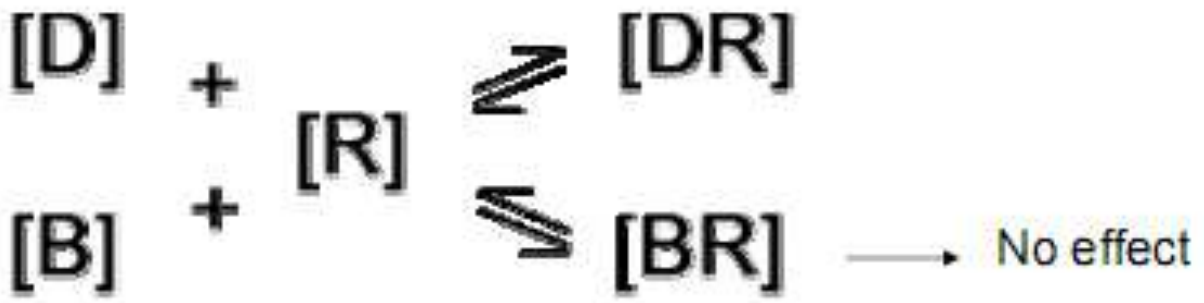
Dose-Response Curves

What can the dose-response curve tell us?



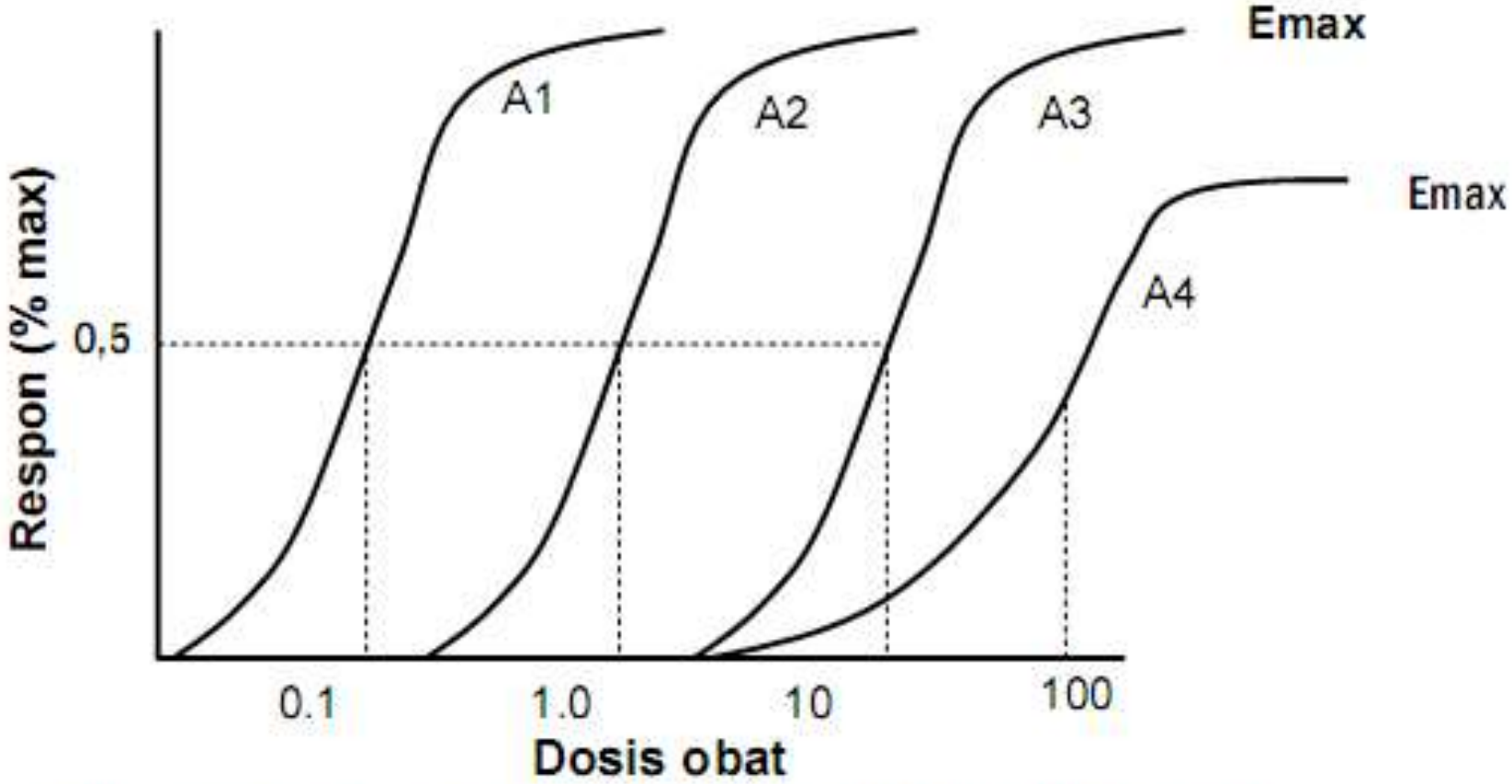
- **Mechanism of Action** (e.g., receptor)
  - Despite great differences in potency among the three opiate drugs, their maximum effectiveness and shapes are the same.
  - This similarities indicate that the three drugs are acting at the same receptors, but with different accessibility, affinity and efficacy.

Antagonis



D = drug/agonis
B = antagonis

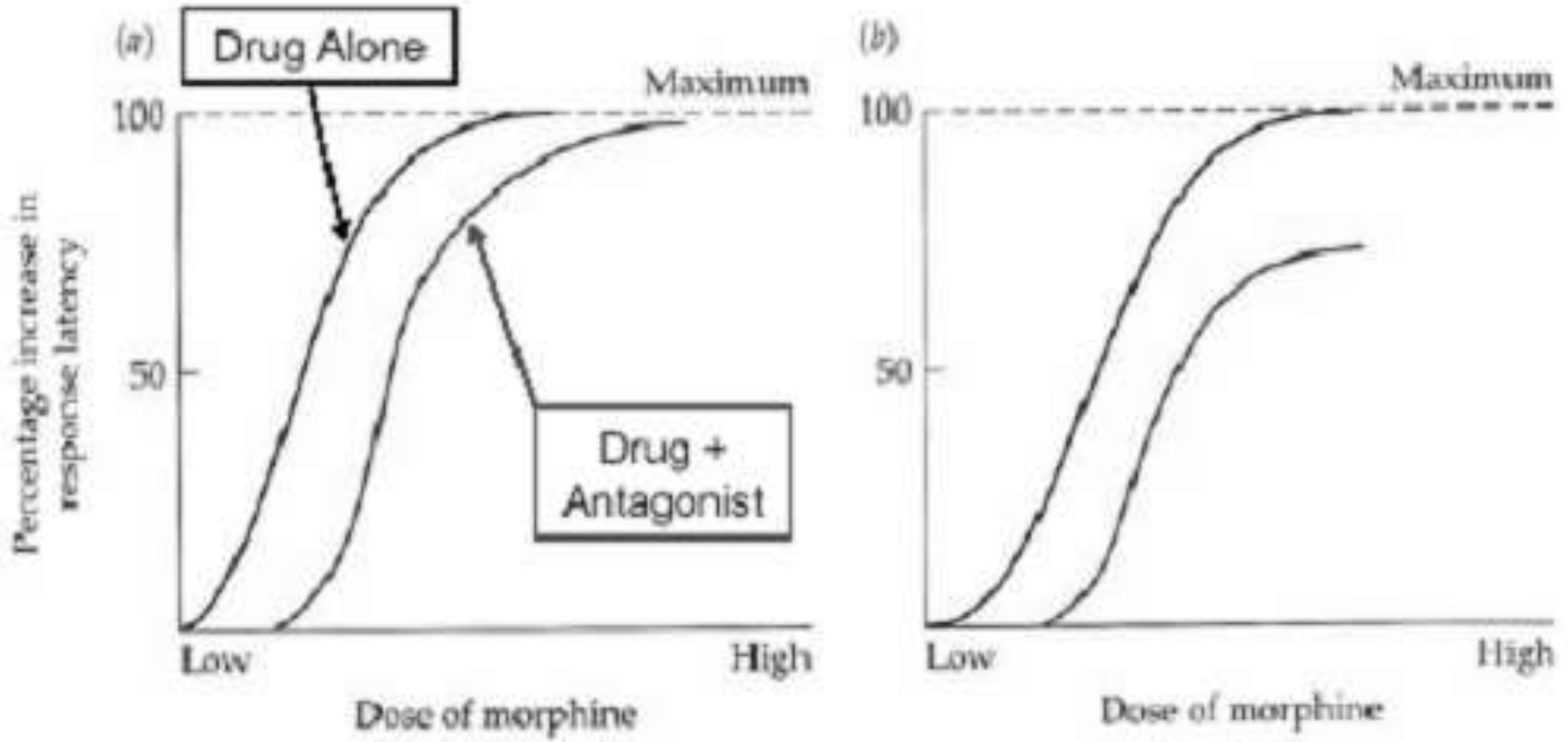
Kurva dosis vs respon suatu obat dengan keberadaan suatu antagonis (bloker)



Kurva akan bergeser ke kanan, jika reseptor telah jenuh, maka peningkatan dosis tidak bisa mencapai efek maksimumnya

Macam Antagonis

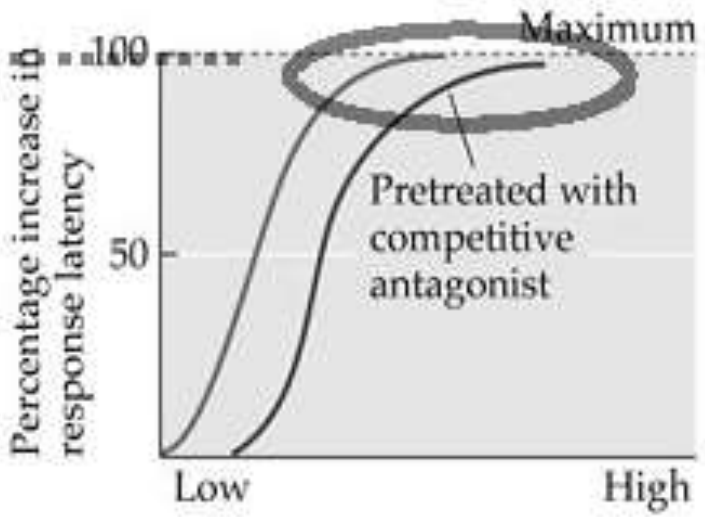
- Antagonis kompetitif
- Suatu obat yang mengikat reseptor secara reversibel pada daerah yang sama dengan tempat ikatan agonis, tetapi tidak menyebabkan efek
- Efek antagonis kompetitif dapat diatasi dengan peningkatan konsentrasi agonis, sehingga meningkatkan proporsi reseptor yang dapat diduduki oleh agonis
- Antagonis irreversibel
- Antagonis yang dapat mengikat reseptor secara kuat dan bersifat irreversibel → tidak bisa diatasi dengan penambahan agonis
- Antagonis non-kompetitif
- Suatu antagonis yang dapat mengurangi efektifitas suatu agonis melalui mekanisme selain berikatan dengan tempat ikatan agonis pada reseptor



- What type of antagonist is present?
  - Graph A? **Antagonis kompetitif**
  - Graph B? **Antagonis nonkompetitif atau irreversibel**

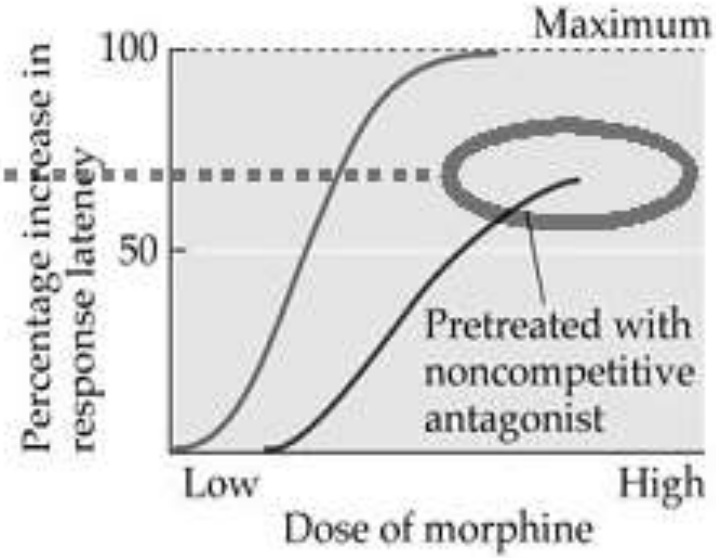
competitive antagonism

- When pre-treating with naloxone, dose-response curve for morphine's effects shifts to the right. Addition of naloxone diminished morphine's potency.



non-competitive antagonism

- Reduce the effects of the agonist in ways other than competing for the receptor.



PSYCHOPHARMACOLOGY, Figure 1.16

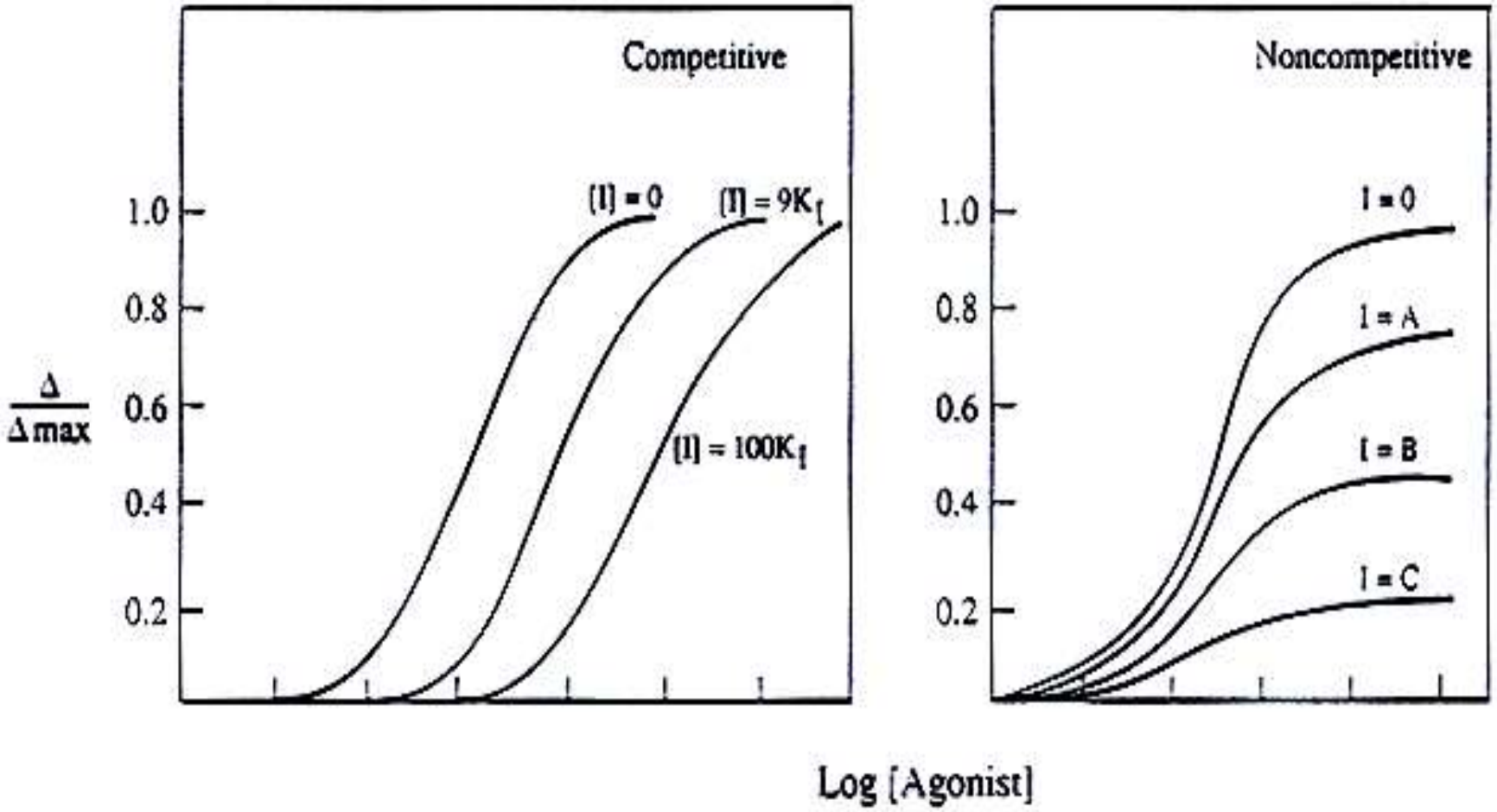


Fig. 1-35. Analysis of antagonism by semilogarithmic plots. The left panel shows the pattern for competitive antagonism of a response to an agonist produced by increasing concentration of competitive inhibitor I. A parallel rightward shift in the response curve without a change in maximal response occurs. The extent of rightward shift is a consequence of the ratio of [I] to K_I, the equilibrium dissociation constant of the inhibitor. The right panel shows the pattern expected for noncompetitive antagonism. in which the maximal response decreases. without a change in the concentration producing half maximal-response. as the inhibitor concentration increases. A < B < C.

Inverse agonist

Obat yang memiliki efek yang berlawanan dengan agonis, jika berikatan dengan reseptor yang sama dengan agonis

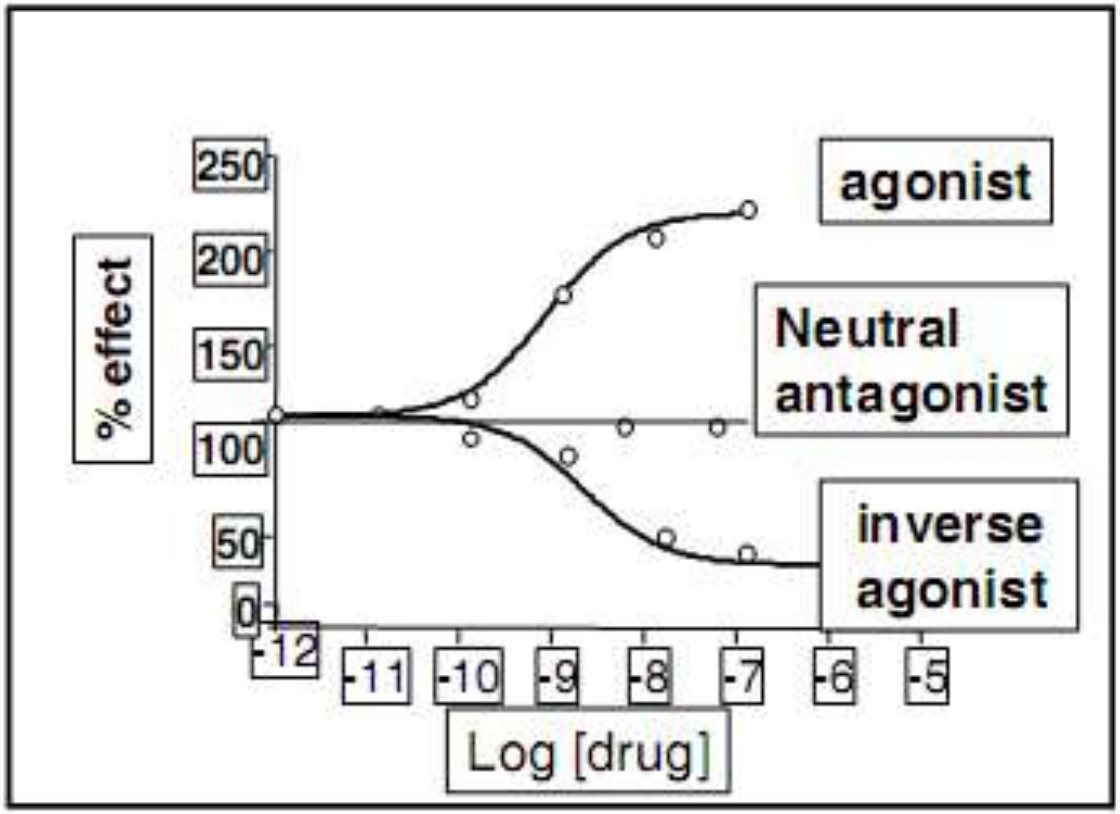
Contoh :

Reseptor GABA yang terhubung dengan kanal ion Cl akan terbuka jika ada agonis yang berikatan dan mengaktifkannya, sedangkan jika reseptor tersebut berikatan dan diaktifkan oleh inverse agonis, kanal ion pada reseptor akan tertutup

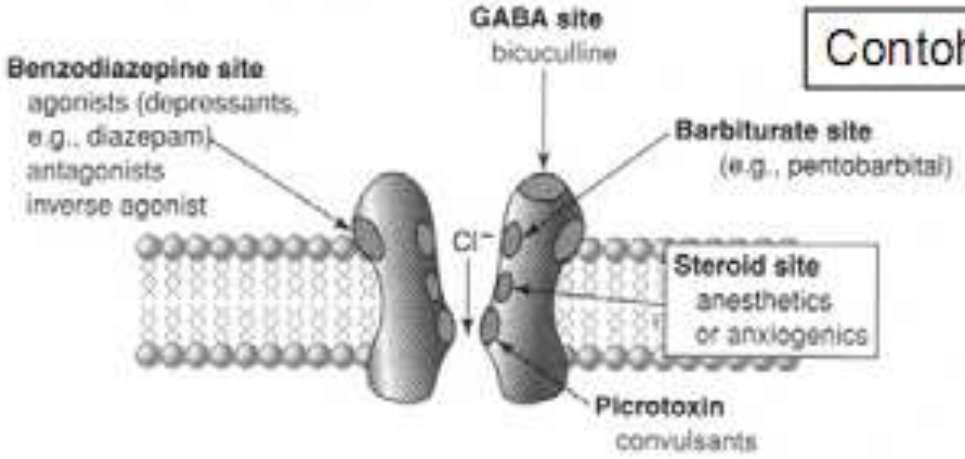
Jadi :

Inverse agonis tetap bisa mengaktifkan reseptor, tetapi efeknya adalah kebalikan dari agonis

Apa bedanya dengan antagonis ?



Agonis : diazepam, fenobarbital
Inverse agonis : β-carbolin

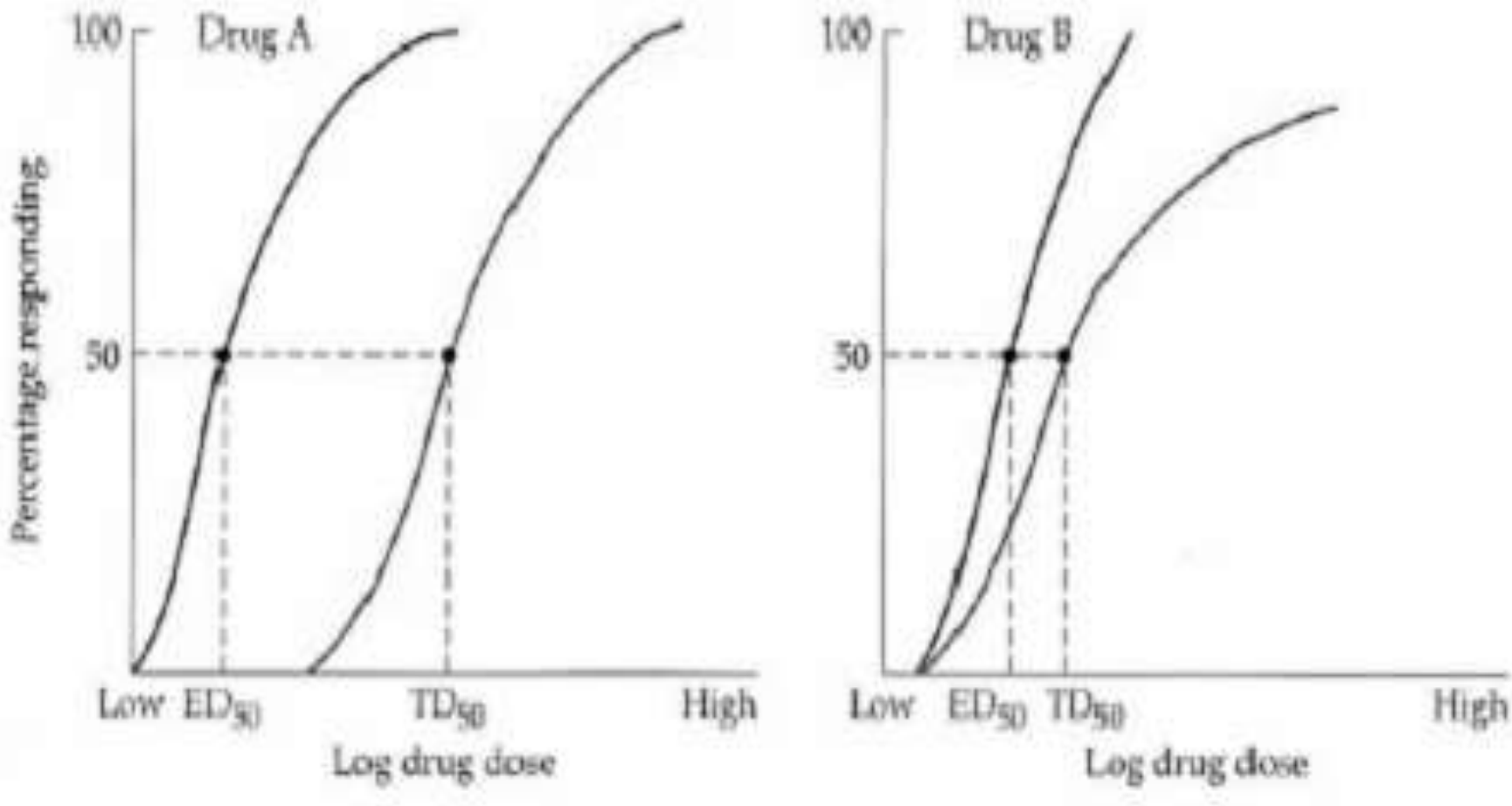


Contoh : reseptor GABA

The Therapeutic Index

- ED50 = dosis yang diperlukan agar menghasilkan efek terapi pada 50% populasi
- LD50 = dosis yang yang menyebabkan kematian pada 50% populasi
- Rasio dosis letal (LD50) dengan dosis efektif (ED50) disebut indeks terapi
- Definisi formal :

$$\text{Index terapi} = LD_{50}/ED_{50}$$



- Which drug has the higher Therapeutic Index?
- Which drug is more safe?

Receptor Regulation

- **Supersensitization or Up-regulation**

  1. Prolonged/continuous use of receptor blocker

  2. Inhibition of synthesis or release of hormone/neurotransmitter - Denervation

- **Desensitization or Down-regulation**

  1. Prolonged/continuous use of agonist

  2. Inhibition of degradation or uptake of agonist

Homologous vs. Heterologous

DYNAMICS OF RESEPTOR

RESEPTOR REGULATION

REGULATION → HOMEOSTASIS

*DESENSITIZATION
*DOWN REGULATION
*SUPERSENSITIZATION
*UP REGULATION

SIFAT REGULASI → HOMOLOG
HETEROLOG → CROSS-TALK

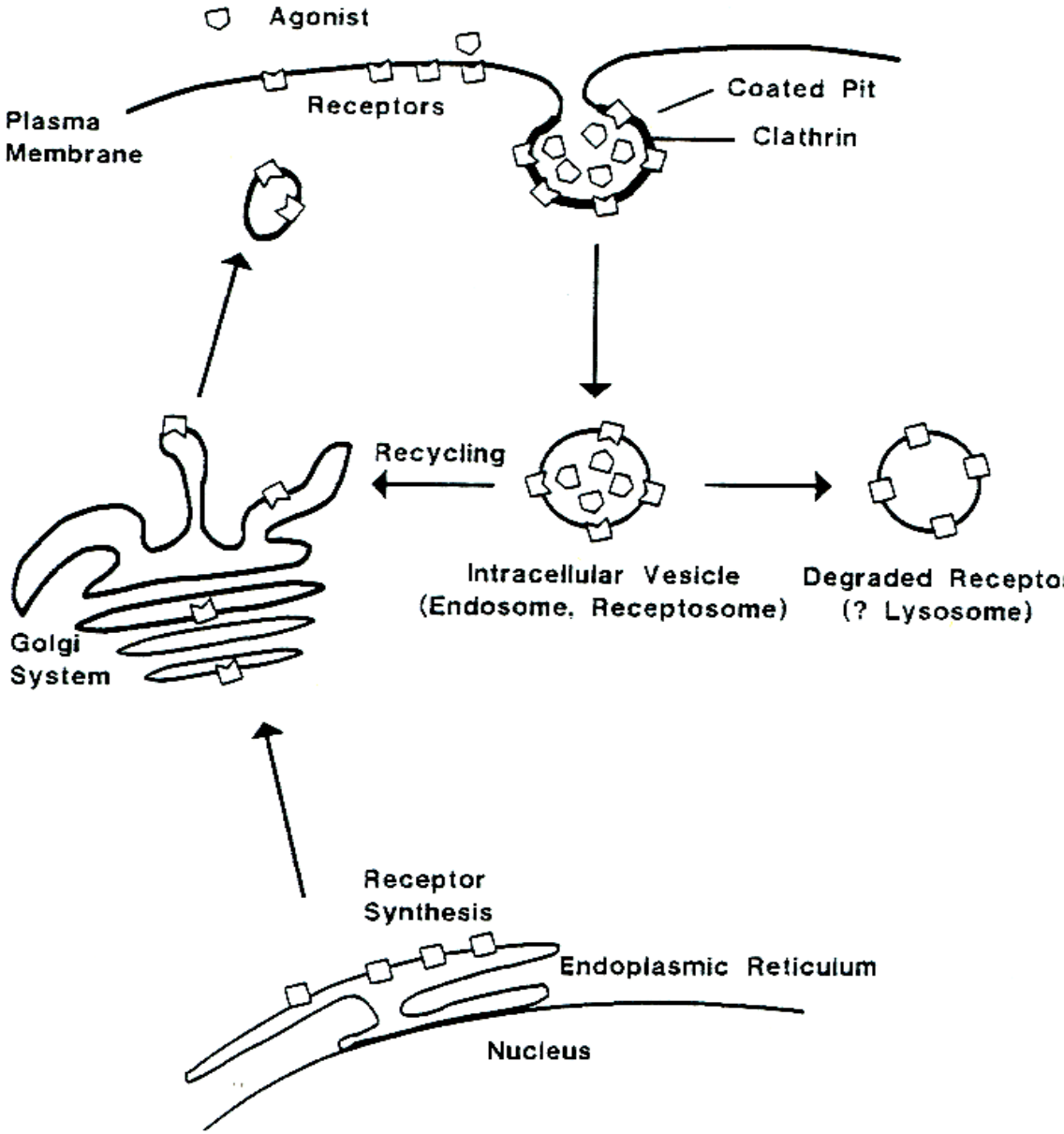


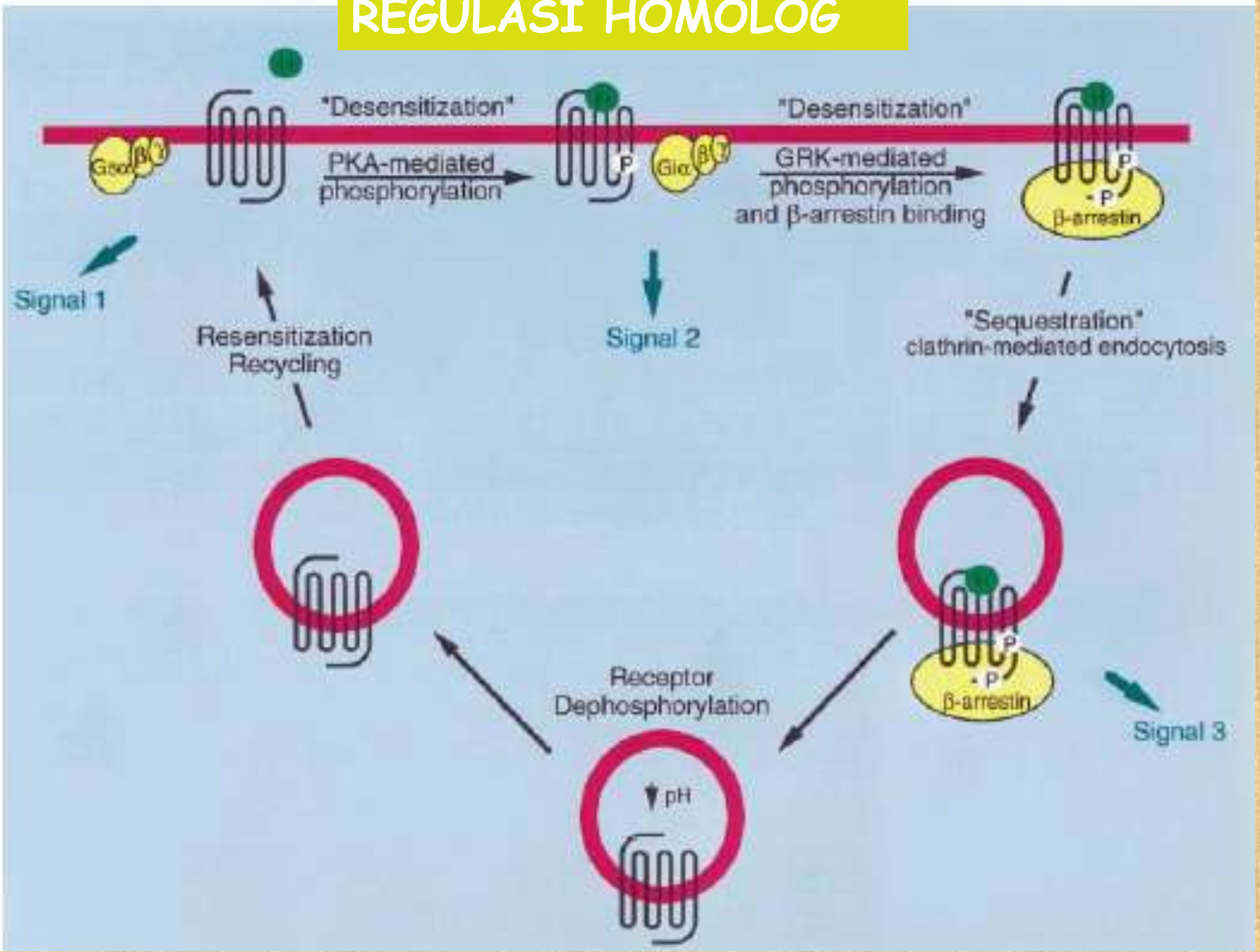
Fig. 2-37. A diagrammatic scheme for the life cycle of membrane receptors. Certain morphologic components of the scheme are shown but are not drawn to scale. See text for explanation.

From Taylor, P and Insel PA. Molecular Basis of Drug Action, in *Principles of Drug Action*, 3rd edition, W Pratt and P Taylor, editors, p 103-200, 1990, Churchill Livingstone

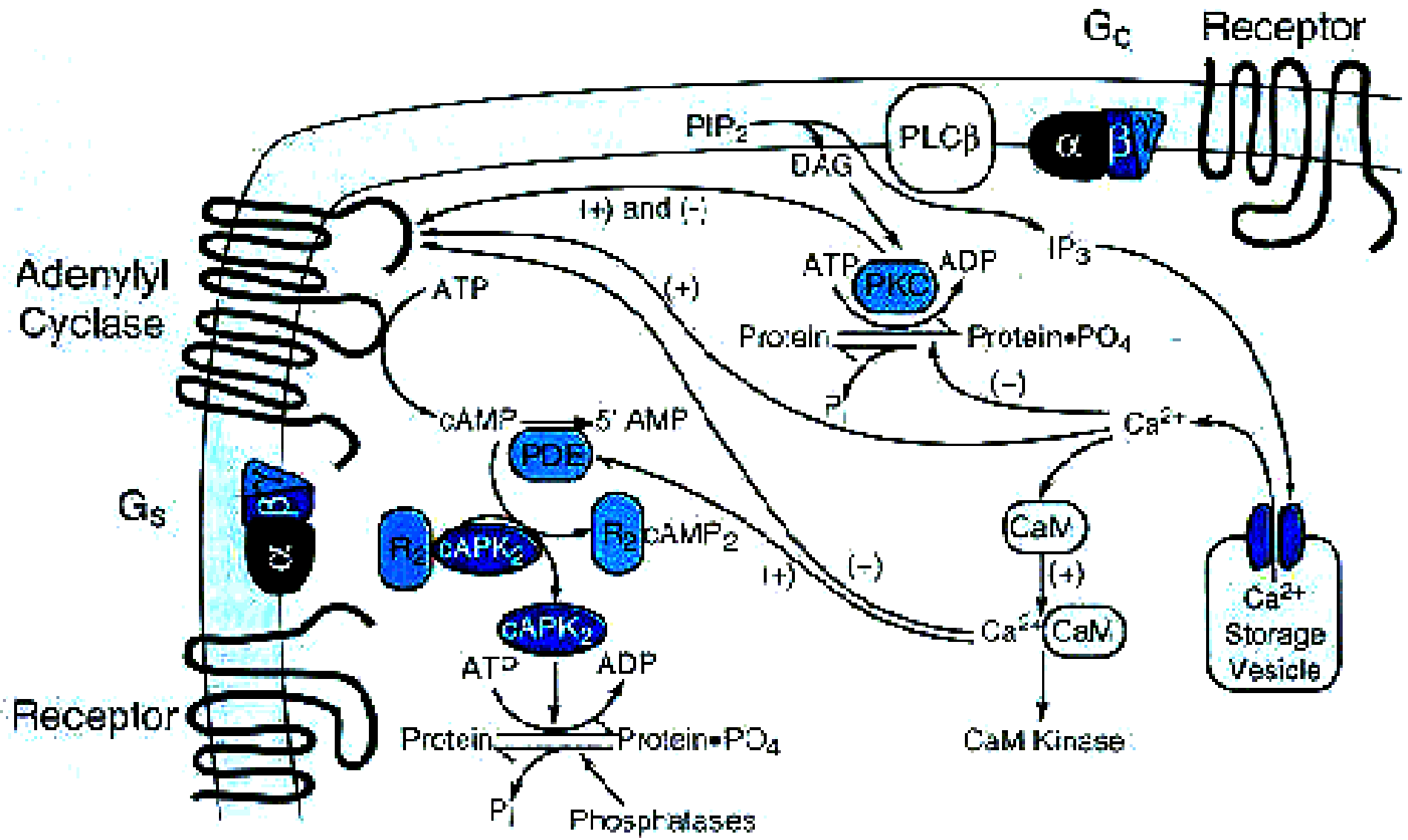
Desensitization

- Homologous: “affecting responses elicited only by the stimulated receptor.”
- Heterologous: “acting on several receptors or on a pathway common to many receptors.”

REGULASI HOMOLOG



REGULASI HETEROLOG



Causes of Variability in Drug Response

A. Those related to the biological system

1. Body weight and size
2. Age and Sex
3. Genetics - pharmacogenetics
4. Condition of health
5. Placebo effect

Causes of Variability in Drug Response

B. Those related to the conditions of administration

1. Dose, formulation, route of administration.
2. Resulting from repeated administration of drug:
   drug resistance; drug tolerance-tachyphylaxis; drug allergy
3. Drug interactions:
   chemical or physical;
   GI absorption;
   protein binding/distribution;
   metabolism (stimulation/inhibition);
   excretion (ph/transport processes);
   receptor (potentiation/antagonism);
   changes in pH or electrolytes.

Monitoring Dose-Effect

- Level
  - Molecular (e.g, enzyme inhibition)
  - Cellular (*in vitro* tissue culture, blood cells)
  - Tissue or organ (*in vitro* or *in vivo*)
  - Organism
- Endpoint used to measure effect may be different at each level
- Overall effect = sum of multiple drug effects and physiological response to drug effects

Endpoints to Monitor Drug Effect

Mis. Farnesyltransferase Inhibitors for Cancer

LEVEL	ENDPOINT
Molecular	Farnesyltransferase inhibition
Cellular	Proliferation rate, apoptosis
Tumor	Response (change in tumor size)
Organism	Survival, quality of life

Toleransi

Efek suatu obat mungkin berubah dengan pemberian yang berulang

Toleransi

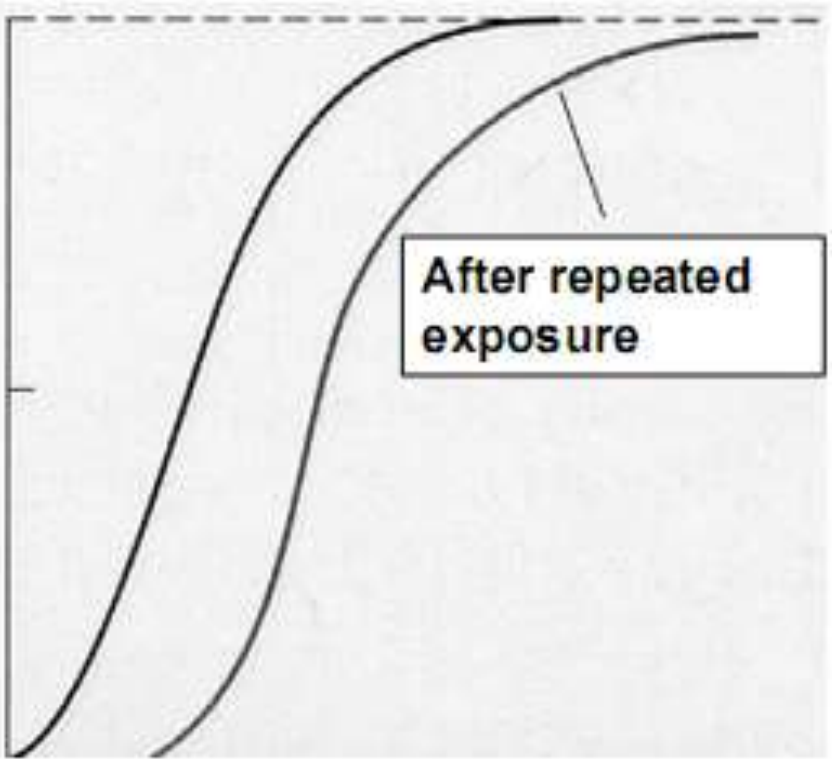
- Penurunan respon pada pemberian obat yang berulang, atau
- Dosis lebih tinggi dibutuhkan untuk mendapatkan efek yang sama (kurva bergeser ke kanan)

Cross-tolerance

Chronic drug use:

Can result in drug tolerance: a diminished response to the drug after repeated exposure to that drug. That is, larger doses are needed to obtain same magnitude of response.

Tolerance to a drug can cause cross-tolerance to another drug.



Sensitisasi

Sensitisasi

- Peningkatan respon pada penggunaan yang berulang, atau
- Diperlukan dosis yang lebih kecil untuk menghasilkan efek yang sama (kurva bergeser ke kiri)

- Cross sensitization

- Conditioned Tolerance:

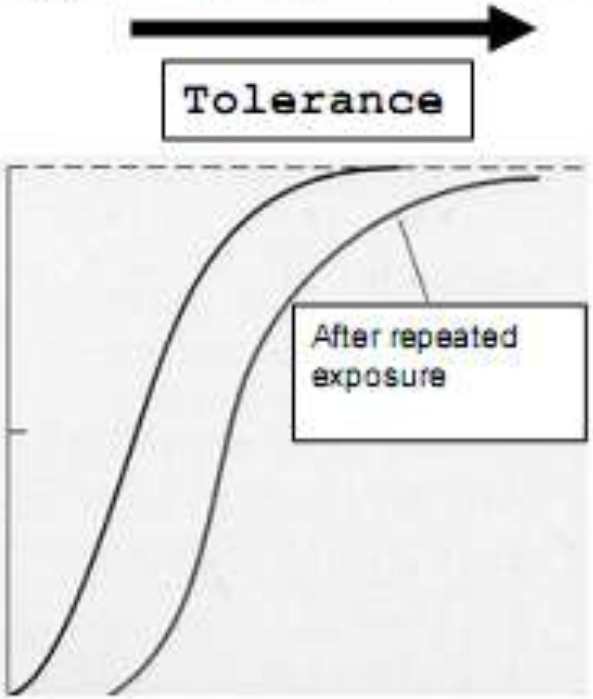
✓ Lethal dose of heroin in normal individual = 200-500mg. Heroin addicted individuals can tolerate 1800mg without ill effects.

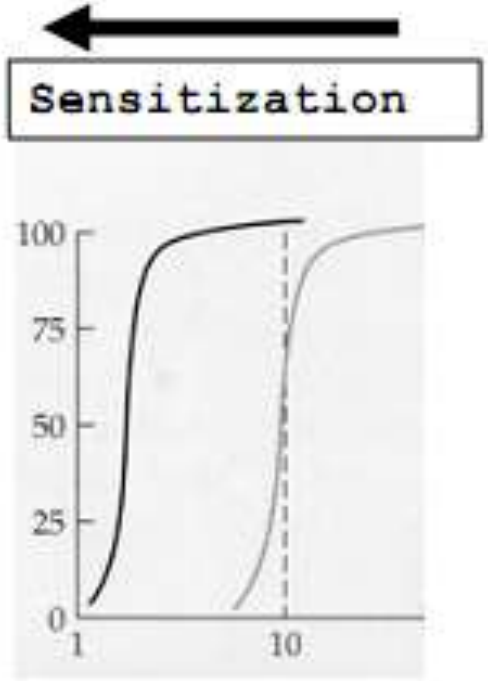
✓ Addicts have been killed by a dose that was readily tolerated before. A possible explanation is that perhaps there is a loss of 'conditioned tolerance.'

✓ If drug is consumed in novel environment (altered drug-taking routine) may result in much greater effect and death.

- Sensitization:

The opposite of tolerance -- sometimes called reversed tolerance. The enhancement of drug effect(s) following repeated administration of same drug dose.





Terima kasih atas perhatiannya...