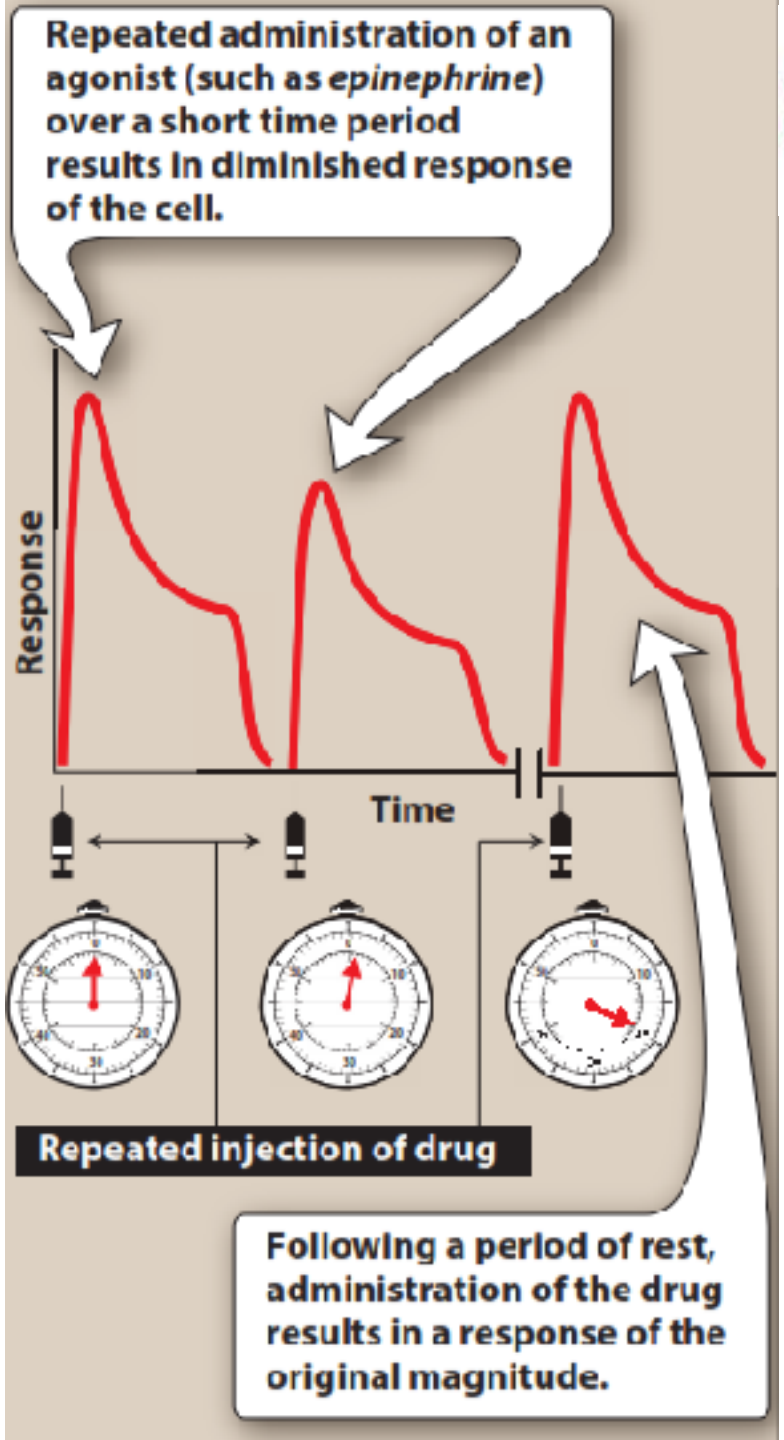
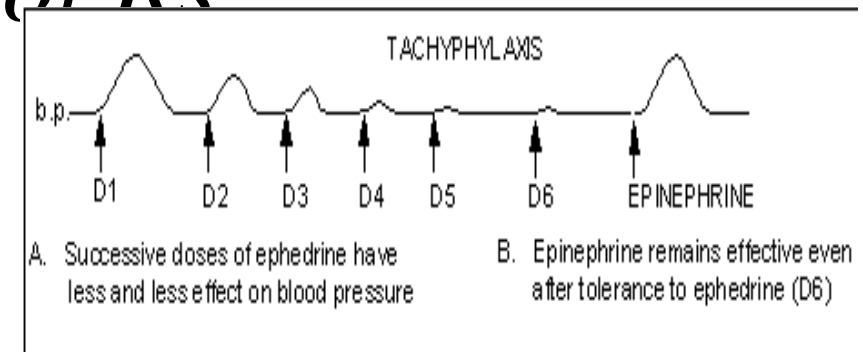
Characteristics of Signal Transduction

- ✓ *Signal Amplification*
  - *e.g. albuterol*
- ✓ *Spare receptors*
  - *insulin spare Rs = 99%*
  - *B-adrenoceptors = 5-10%*



Desensitization, & Down-Regulation of Receptors

- ***tachyphlaxis:*** *repeated administration of the agonist lead to decrease in responsiveness of Rs*



- ***Refractory***
- ***Up-regulation of receptors***

Dose-Response Relationships

- *Graded dose-response curve (DRC)*

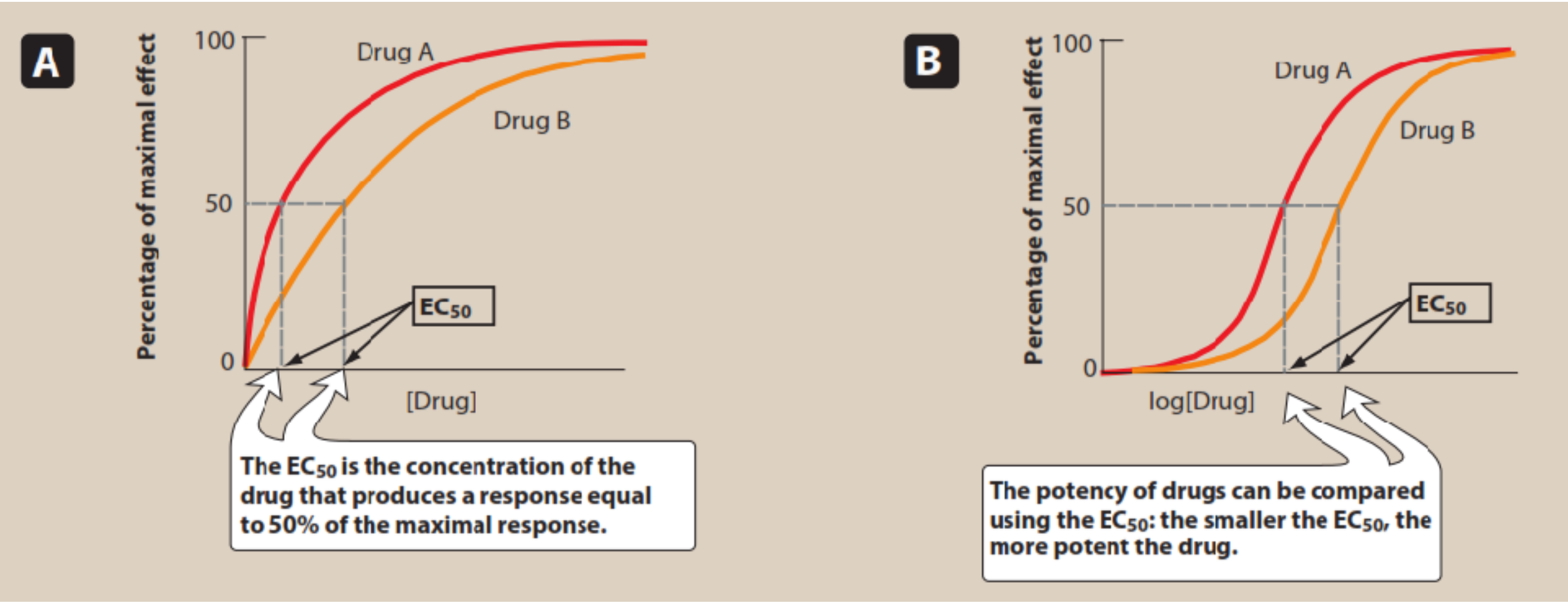
- *Potency amount of drug required to produce a given response & used to determine* ED_{50}

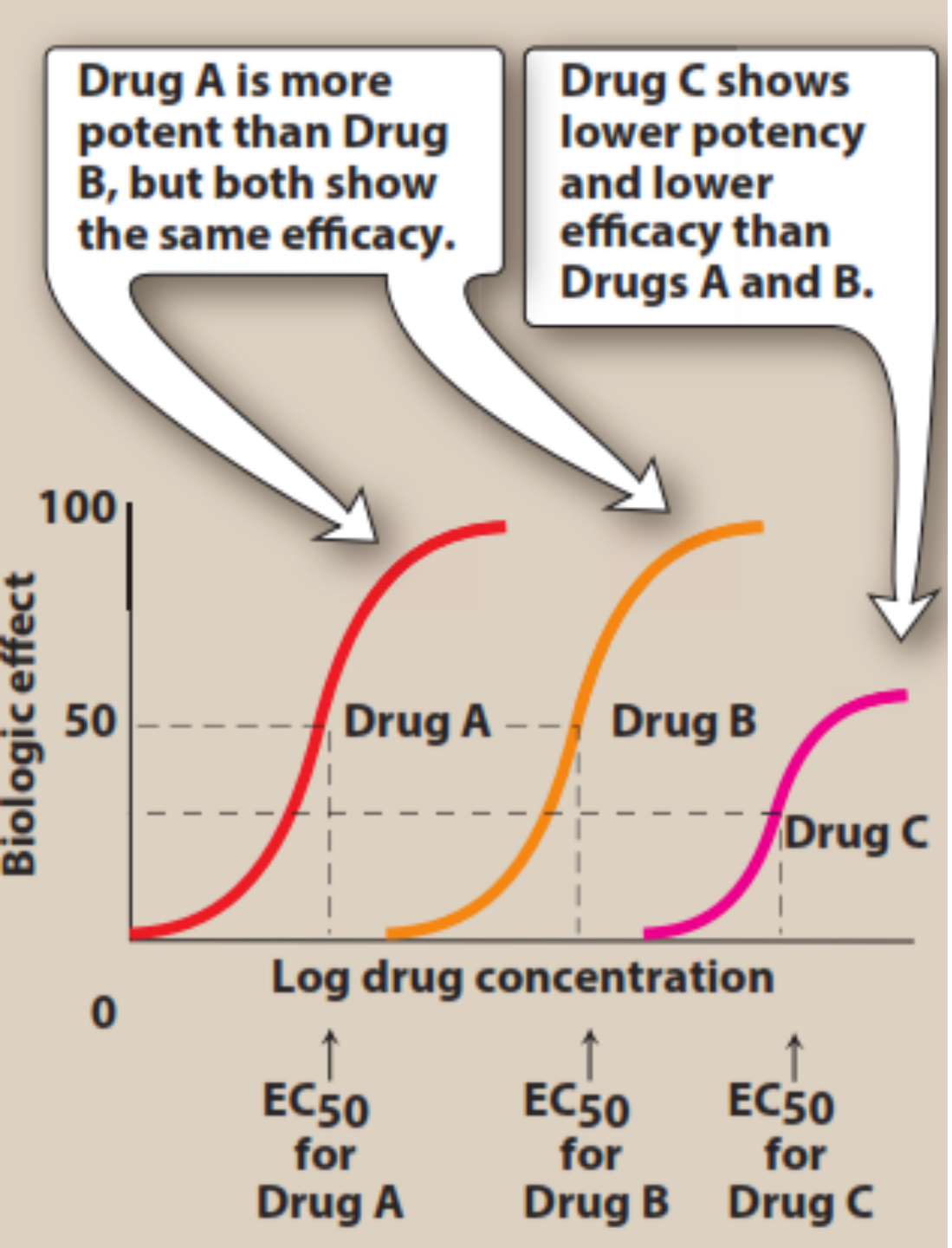
  Candesartan 4 - 32 mg

  Irbisartan 75 – 300 mg

- *Efficacy: the magnitude of response*
- *Maximal efficacy* E_{max}

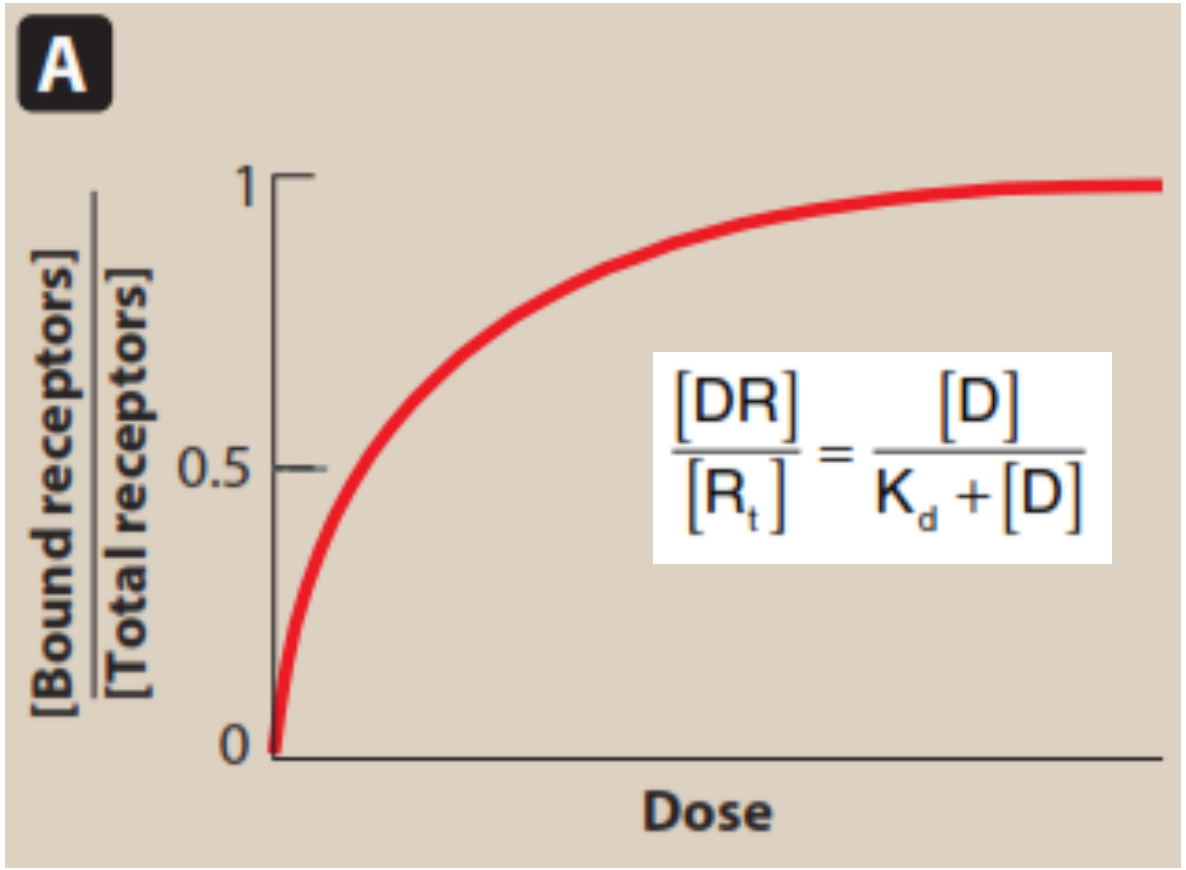
Dose-Response Relationships

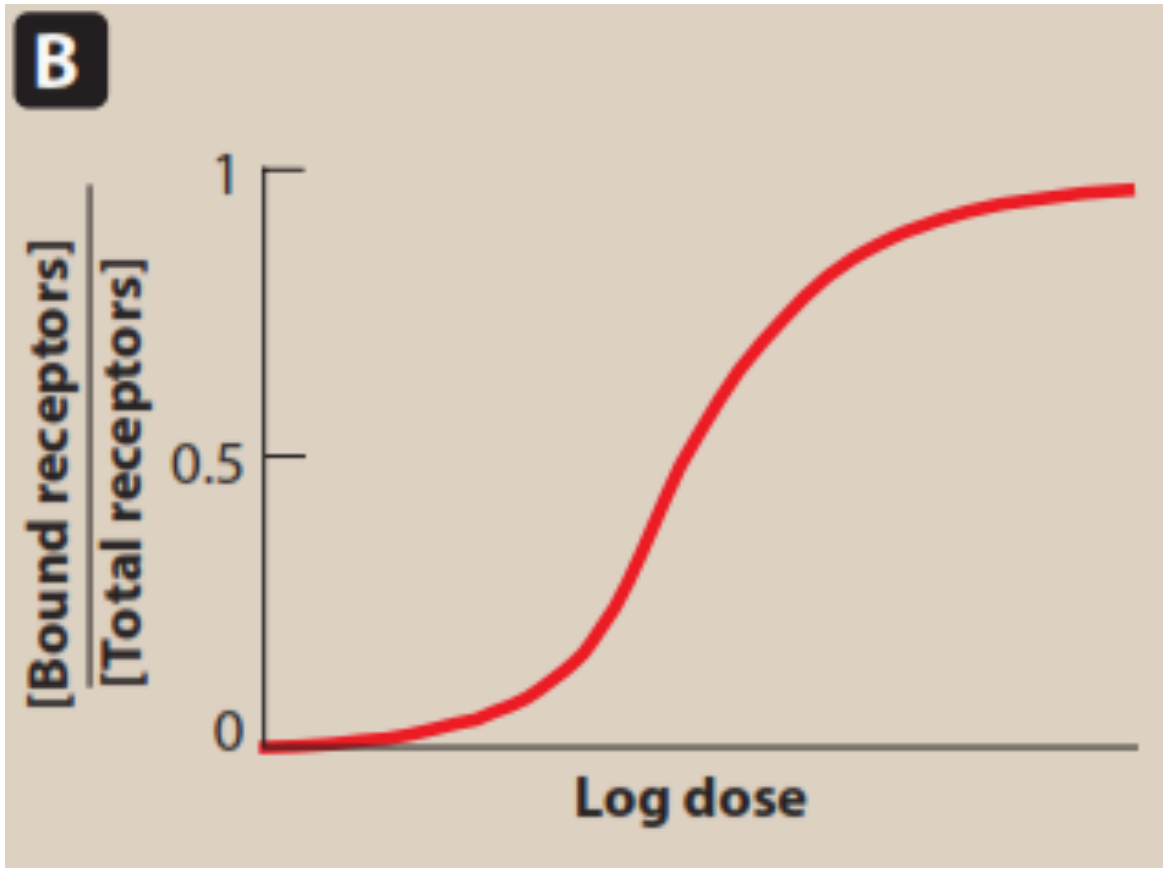



Drug A is more potent than Drug B, but both show the same efficacy.
Drug C shows lower potency and lower efficacy than Drugs A and B.
100
50
0
Biologic effect
Drug A
Drug B
Drug C
Log drug concentration
EC50 for Drug A
EC50 for Drug B
EC50 for Drug C

Effect of Drug Concentration on Receptor Binding

$$\text{Drug} + \text{Receptor} \rightleftarrows \text{Drug–receptor complex} \rightarrow \text{Biologic effect}$$



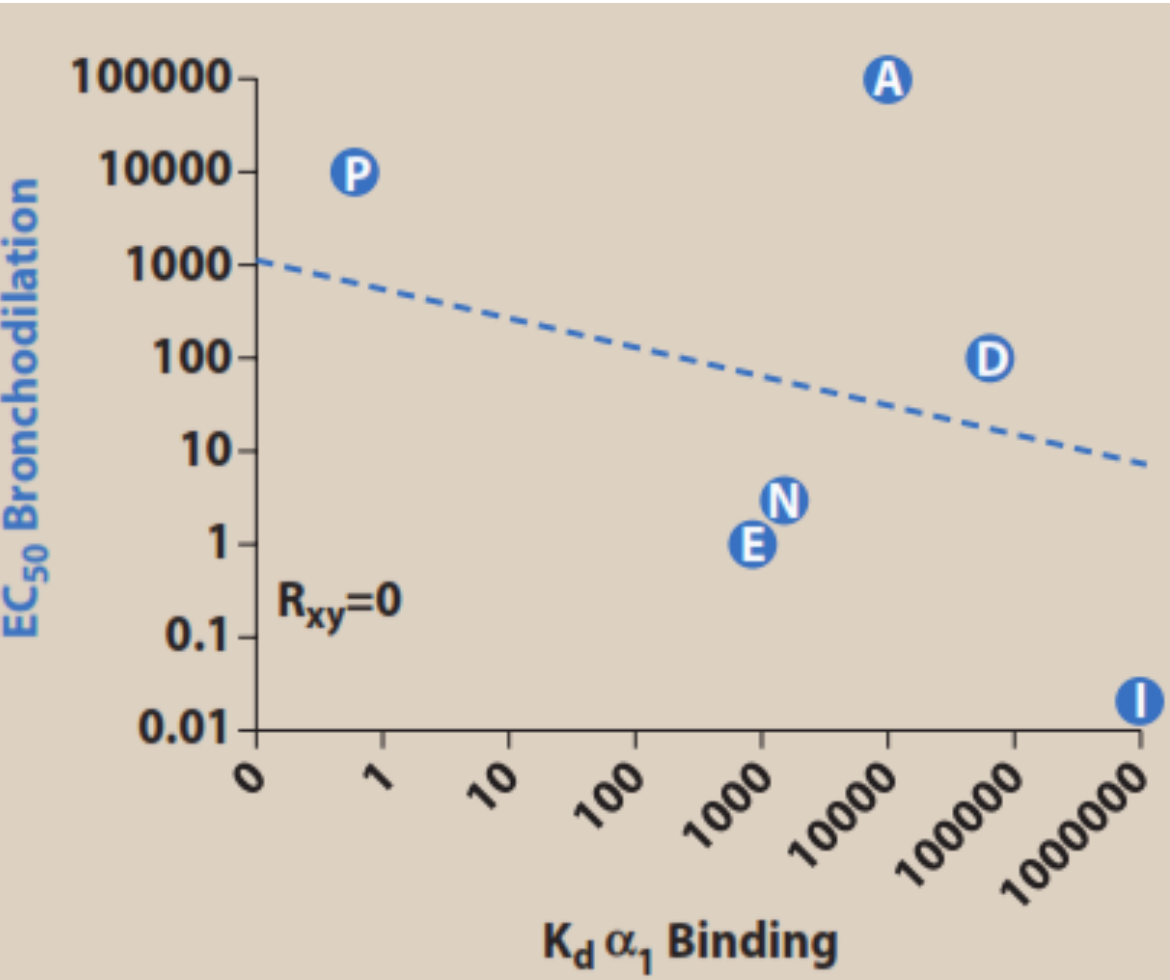


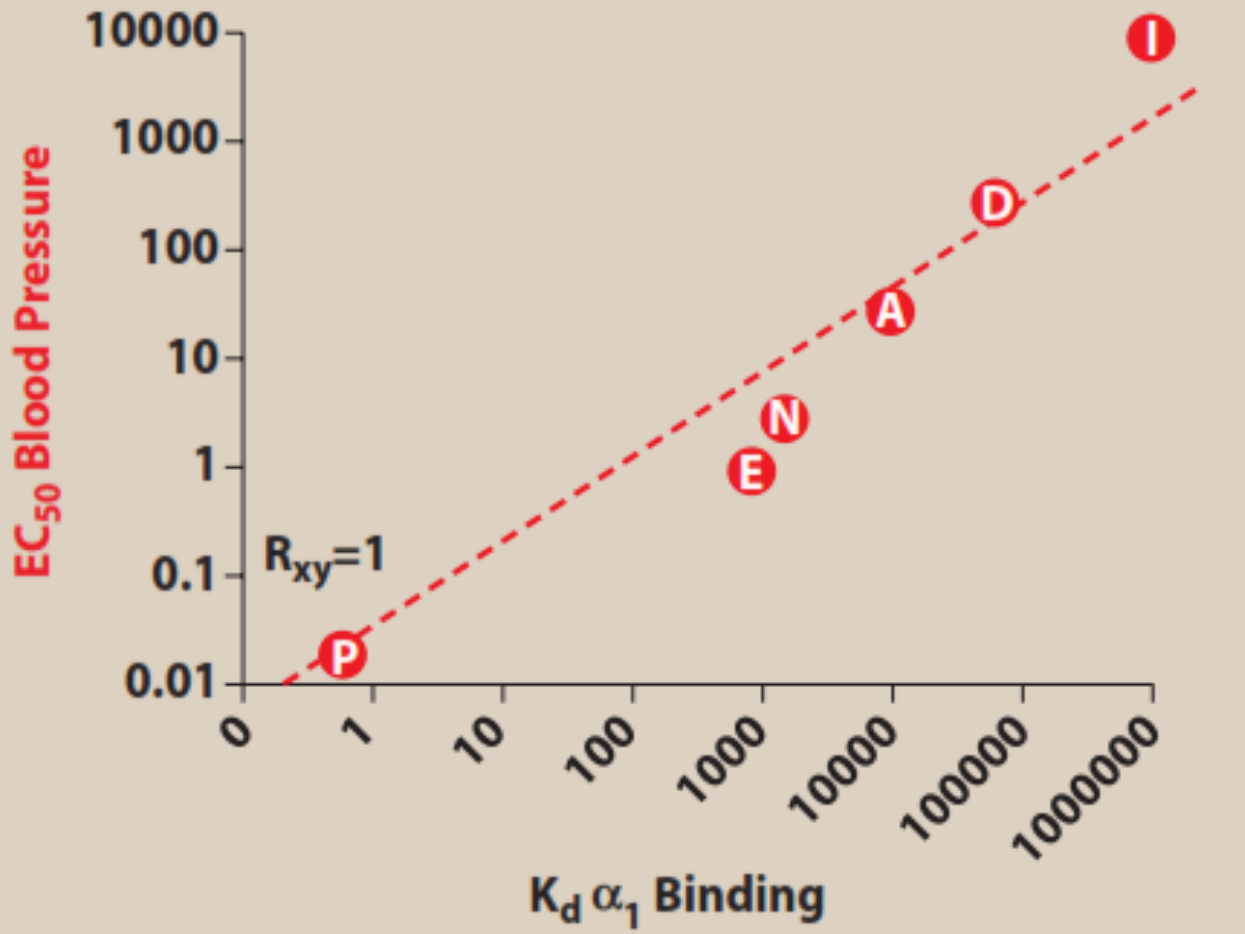
Relationship of Drug Binding to Pharmacologic Effect

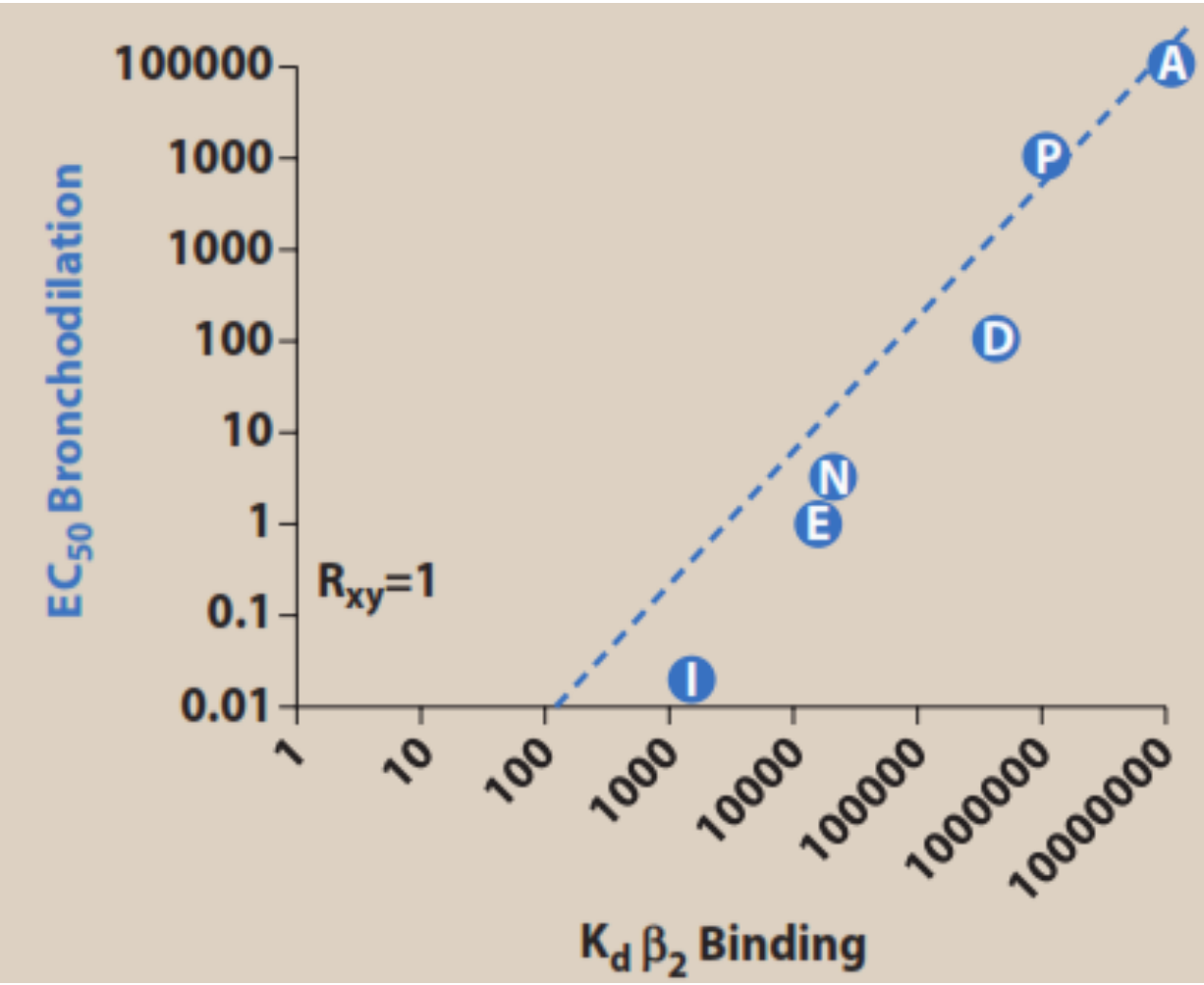
- *K_d value used to determine affinity*
- *The higher the K_d, the weaker the interaction, the lower the affinity*
- *The magnitude of response is proportional to the amount of Rs bound*
- *E_{max} represent full occupation of Rs*

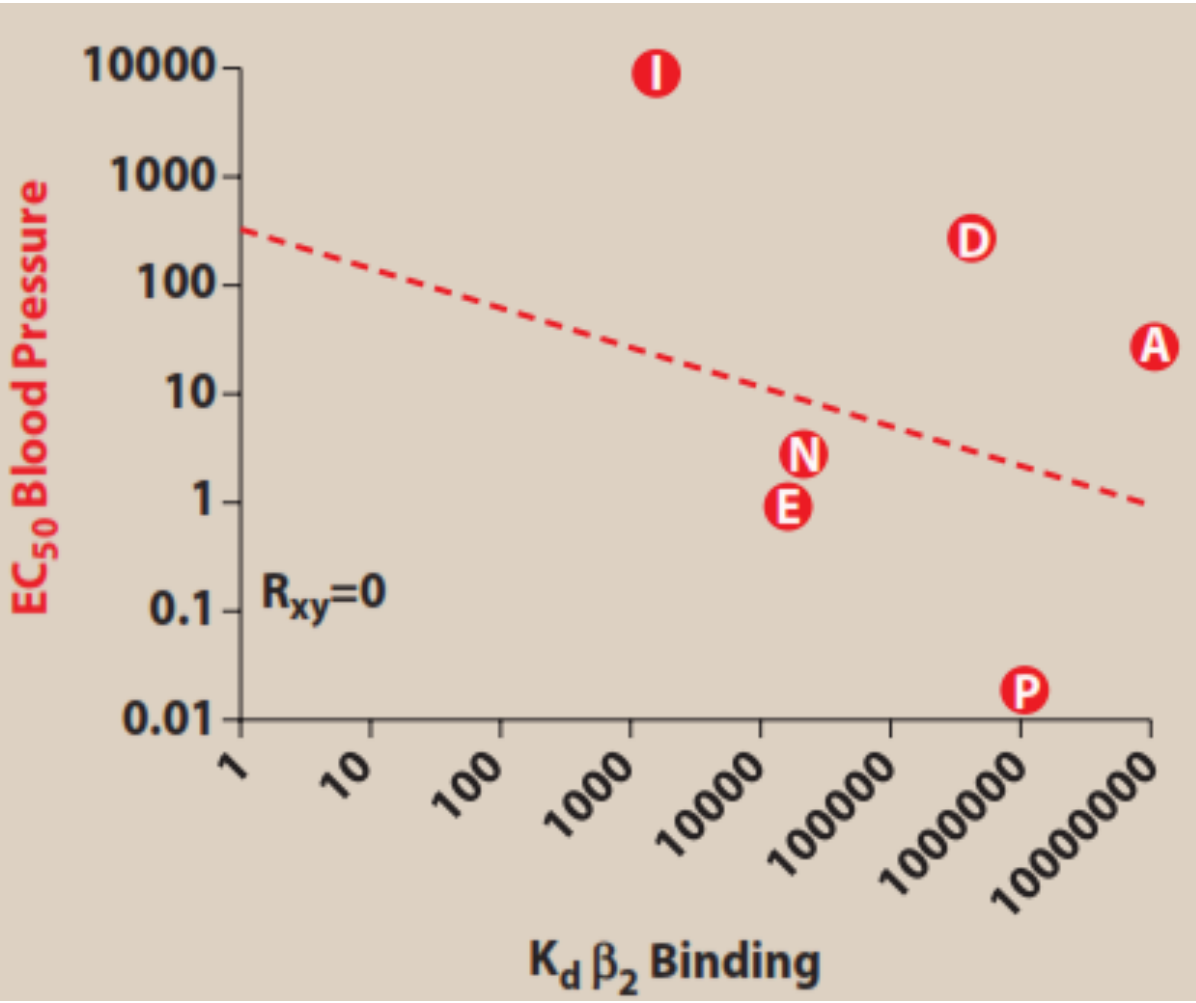
$$\frac{[E]}{[E_{max}]} = \frac{[D]}{K_d + [D]}$$

- **Affinity should be related to potency of drug for causing physiologic response**


100000
10000
1000
100
10
1
0.1
0.01
A
P
D
N
E
I
R_{xy}=0
EC_{50} Bronchodilation
0
1
10
100
1000
10000
100000
1000000
K_d α_1 Binding


10000
1000
100
10
1
0.1
0.01
I
D
A
N
E
P
R_{xy}=1
EC_{50} Blood Pressure
0
1
10
100
1000
10000
100000
1000000
K_d α_1 Binding


100000
1000
1000
100
10
1
0.1
0.01
EC50 Bronchodilation
Rxy=1
A
P
D
N
E
I
1
10
100
1000
10000
100000
1000000
10000000
Kd β2 Binding


10000
1000
100
10
1
0.1
0.01
EC50 Blood Pressure
Rxy=0
I
D
A
N
E
P
1
10
100
1000
10000
100000
1000000
10000000
Kd β2 Binding

Intrinsic activity represents the ability of a D to act as:

I- Full Agonists

$intrin.activity = 1$

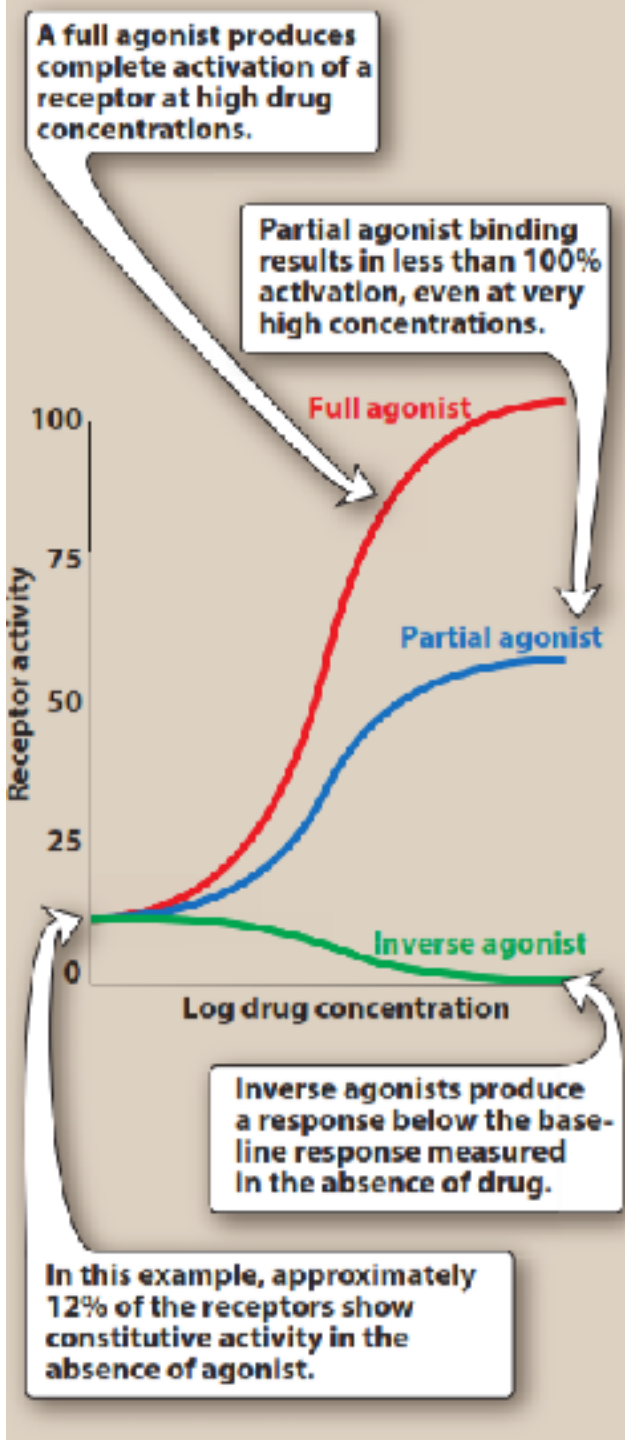
II- Partial Agonists

$intrin.activity > 0 \ \& < 1$

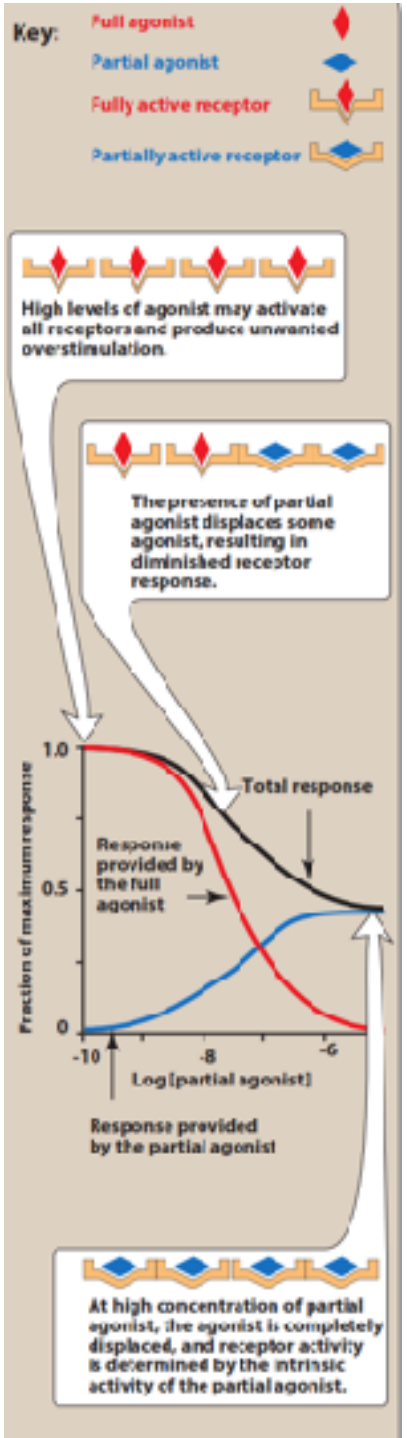
III- Inverse Agonists

*Spontaneous conversion from R to R**

$intrin.activity < 0$

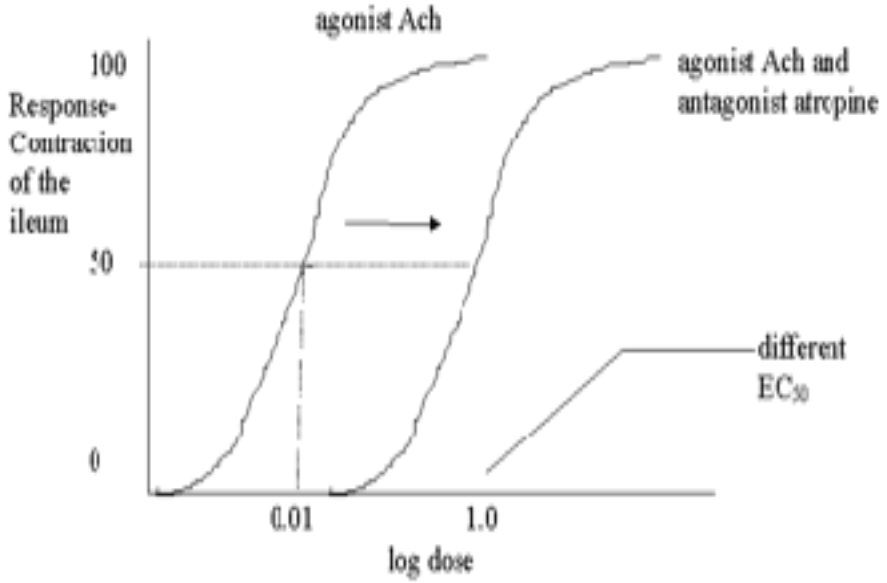


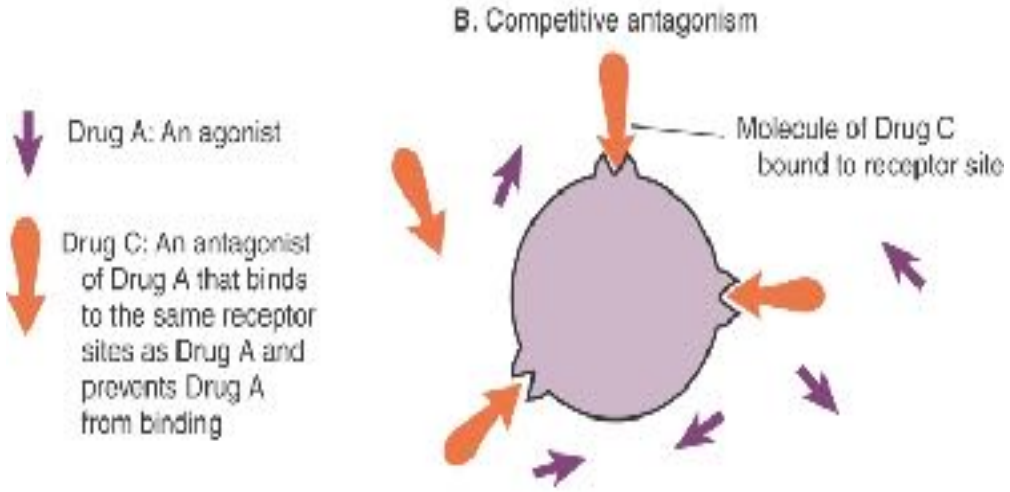
Effects of Partial Agonists



Competitive antagonism

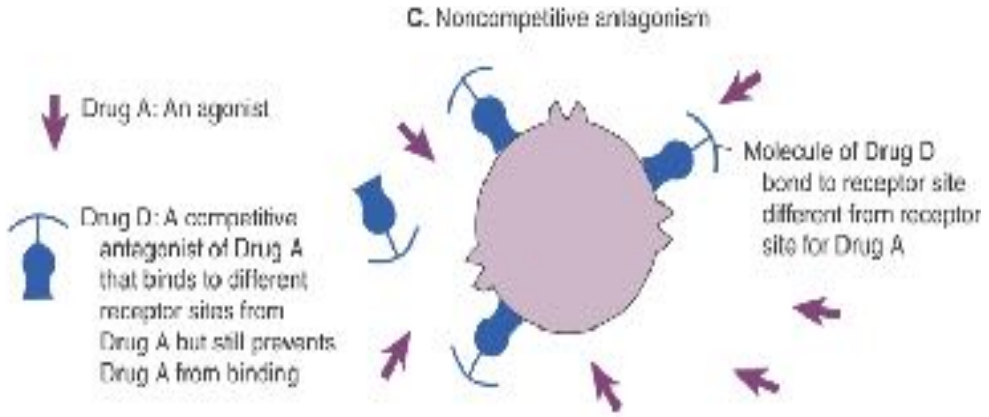
- *Competitive --- Surmountable*
- *Competes with agonist in **reversible** fashion for same receptor site*
- *Necessary to have higher concentration of agonist to achieve same response*

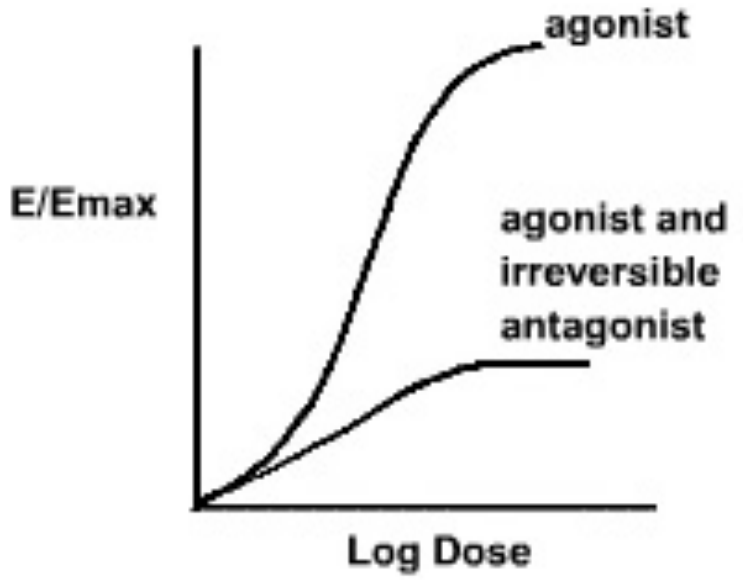




Noncompetitive antagonism

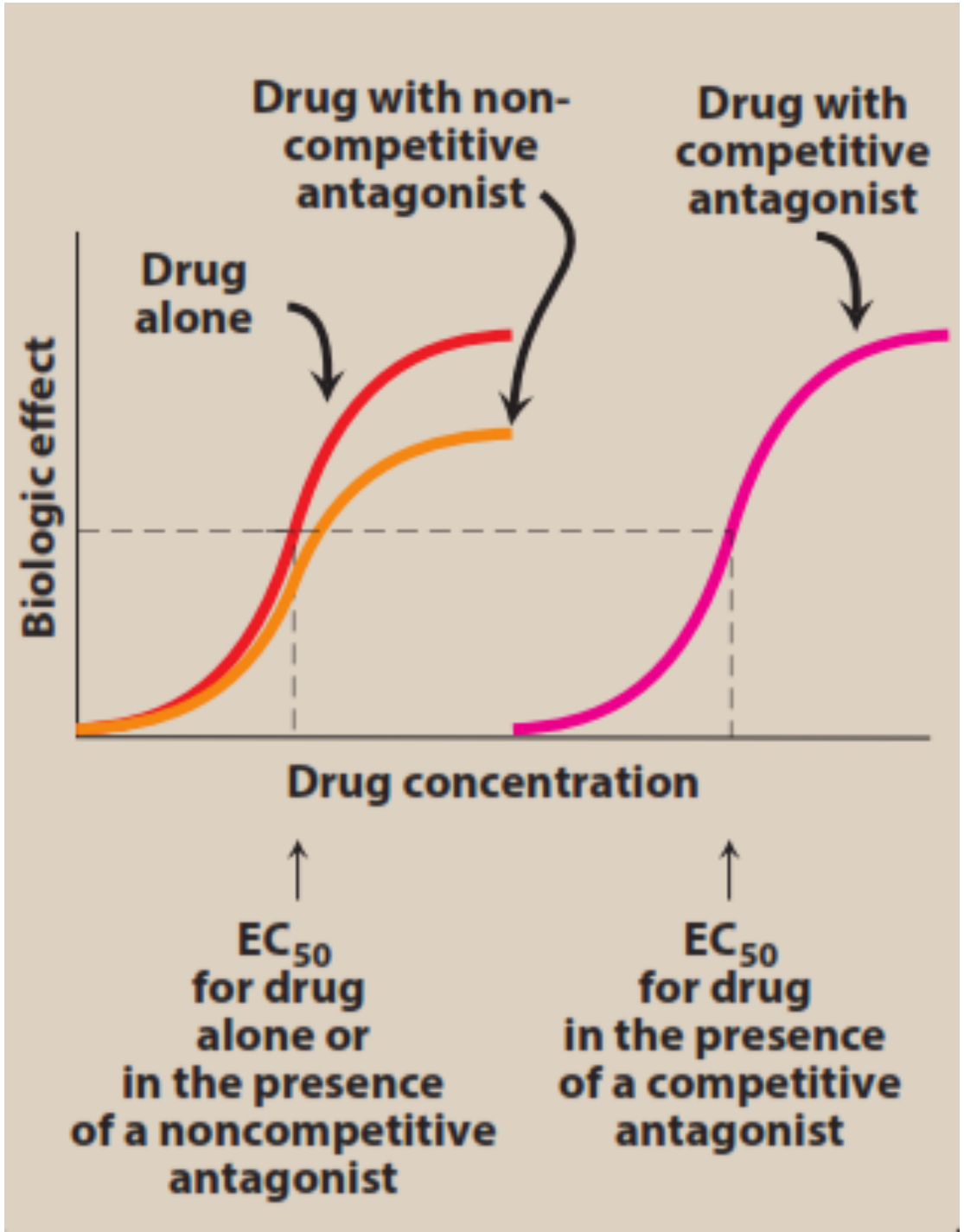
- *Noncompetitve --- Insurmountable*
- *Antagonist binds to a site different to that of an agonist*
- *No matter how much agonist -- antagonism cannot be overcome*





Antagonists

I- Competitive Antagonists
II- Irreversible Antagonists
III- Allosteric Antagonists
IV- Functional or Chemical Antagonists



Therapeutic Index