Receptors

and Anesthetics

Anesthetics

Without feeling or sensation

Local Anesthetics

local
numbs
small
area of
body

General Anesthetics

effect
the whole
body

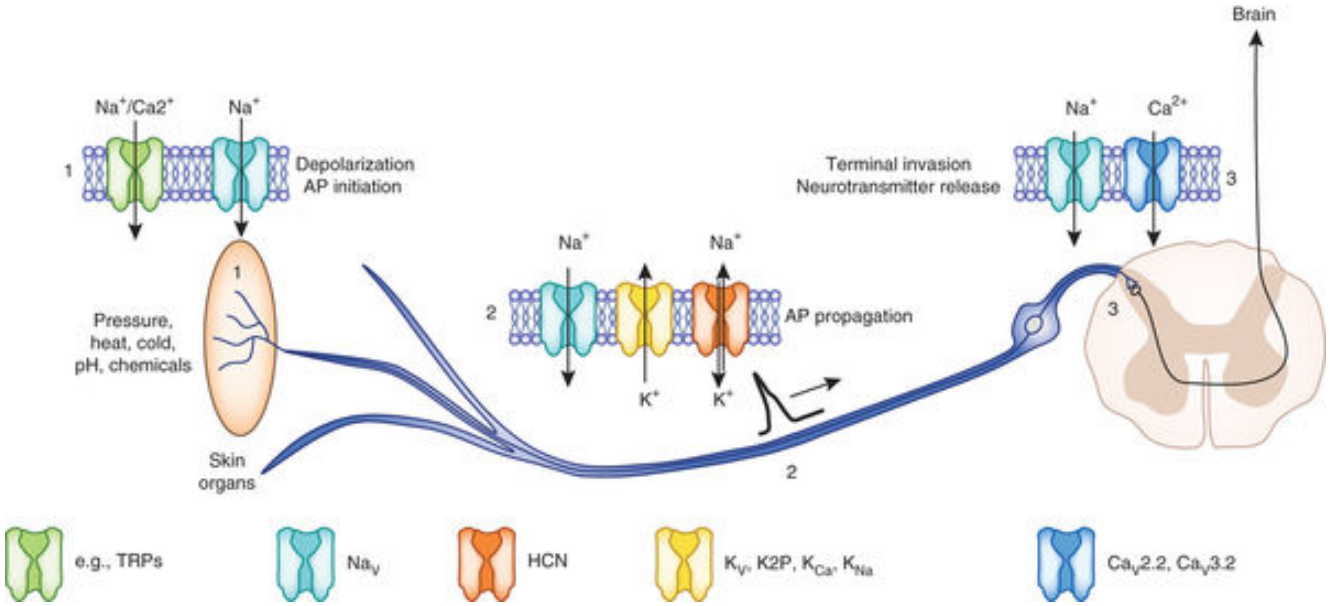
Analgesics

↑
relief of
pain
without
loss of
feeling

1 of Earliest recorded example of local anesthetic

hypothermia

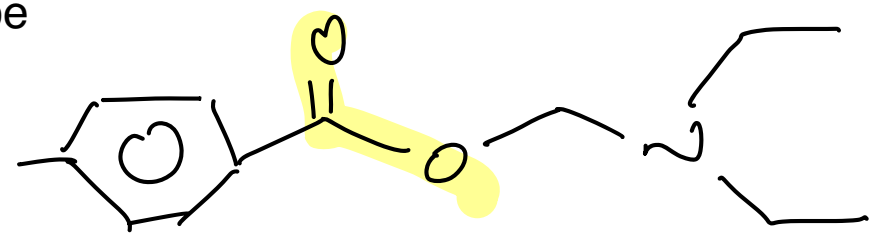
used to use
evaporative cooling
ether, EtBr, EtCl


Brain
Na+/Ca2+
Na+
1
Depolarization
AP initiation
Terminal invasion
Neurotransmitter release
Na+
Ca2+
3
Na+
Na+
2
AP propagation
K+
K+
1
Pressure,
heat, cold,
pH, chemicals
Skin
organs
2
3
e.g., TRPs
Nav
HCN
KV, K2P, KCa, KNa
CaV2.2, CaV3.2

Structures of Local Anesthetics

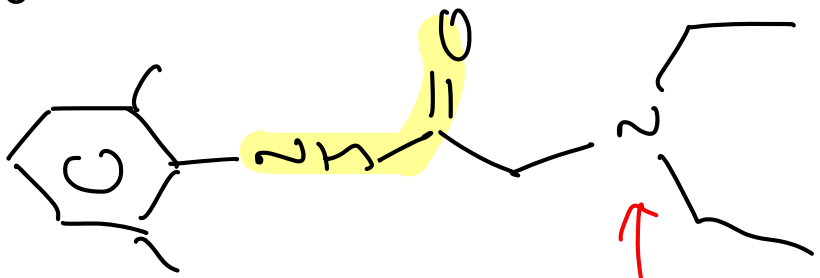
-caine

Ester Type



procaine

Amide Type



lidocaine

hydrophobic benzene rings

3° amine protonate becomes hydrophilic

1900 Meyer and Overton

Lipid Theory :

general anesthetics act through interact by nonspecific mechanisms by dissolving in membrane to change fluidity

1984 Franks and Lieb

Anesthetics interact directly with proteins

Isomers have different potencies which supports a non nonspecific mode

general volatile anesthetics act on different receptors

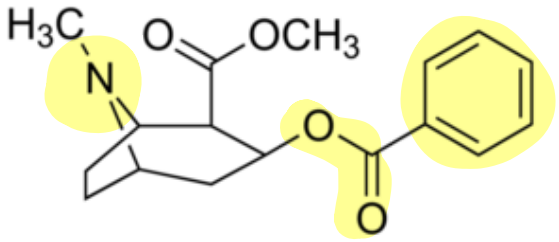
	GABA	Glycine	nACh muscle	nACh neural	5-HT
etomidate	X	/	/	/	
propofol	X	X	/	/	
barbiturates	X	/	/	X	/
ketamine	/		/	X	/
isoflurane	X	X	/	X	X
sevoflurane	X	X	/	X	
Nitrous oxide	/	/	X	X	X

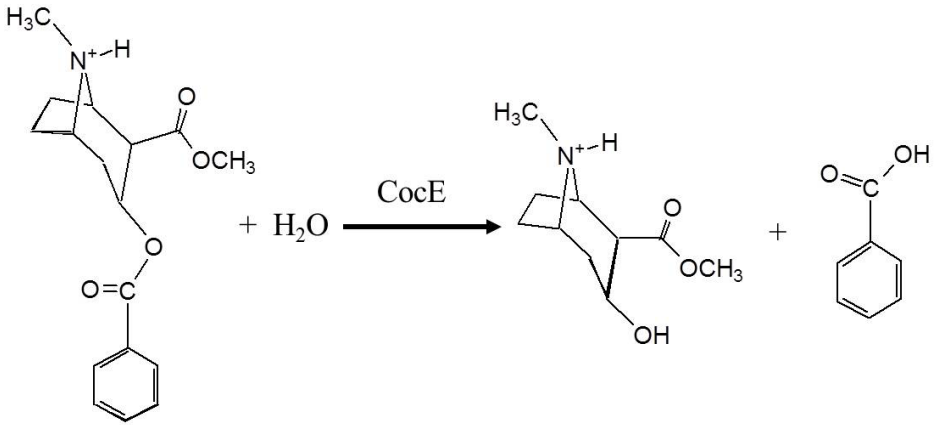
Coca leaves – traditionally used for pain or wounds

began to be used as anesthetic in 1880s

Structure found in 1924

Cocaine





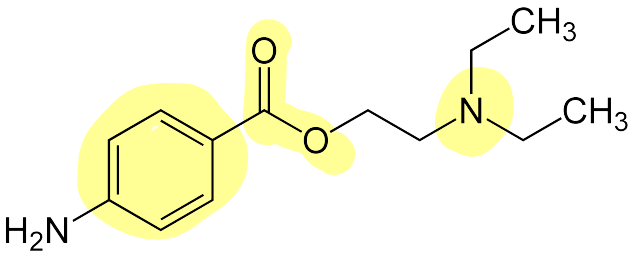
– addicting

– can cause allergic reactions

– not stable in solution

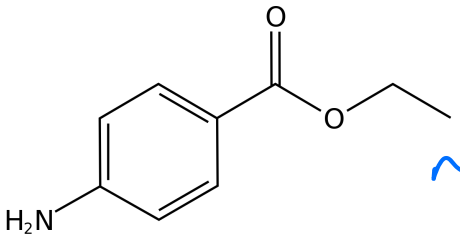
novacaine 1904

Procaine



- doesn't have cocaine's side effects
- prototype for whole class of local anesthetics
- short acting, not very potent

Benzocaine



no amine

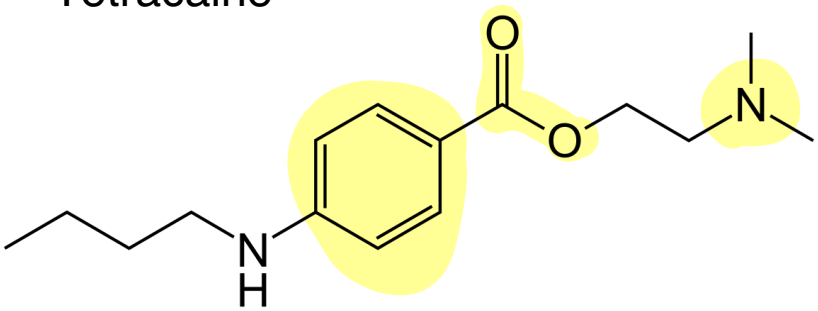
- usually combined with epinephrine

Vaso constrictor

lower H_2O solubility

not as potent

Tetracaine



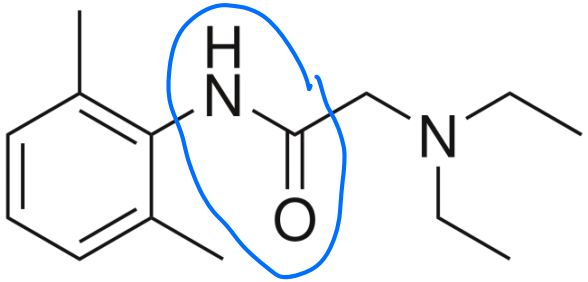
long lasting

potent

spinal anesthesia

Amide type local anesthetic

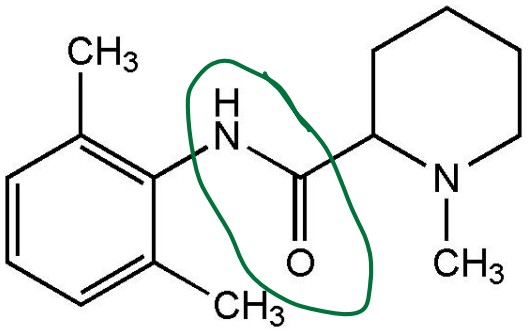
Lidocaine



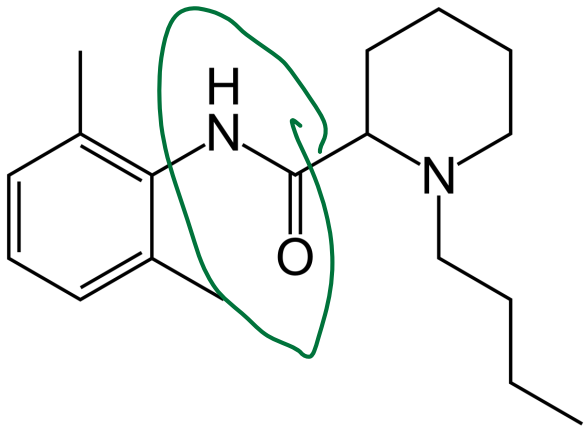
Xylocaine

open chain analogue of isogramine

Carbocaine



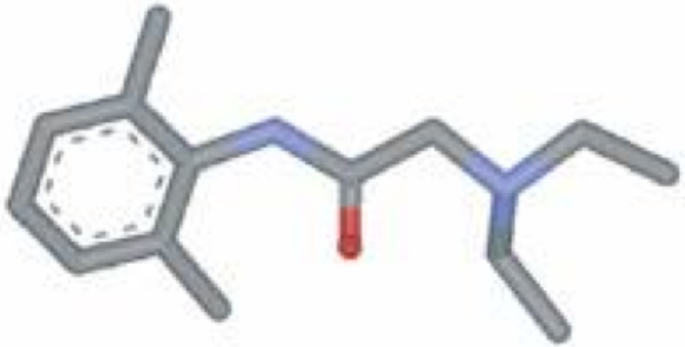
Bupivacaine



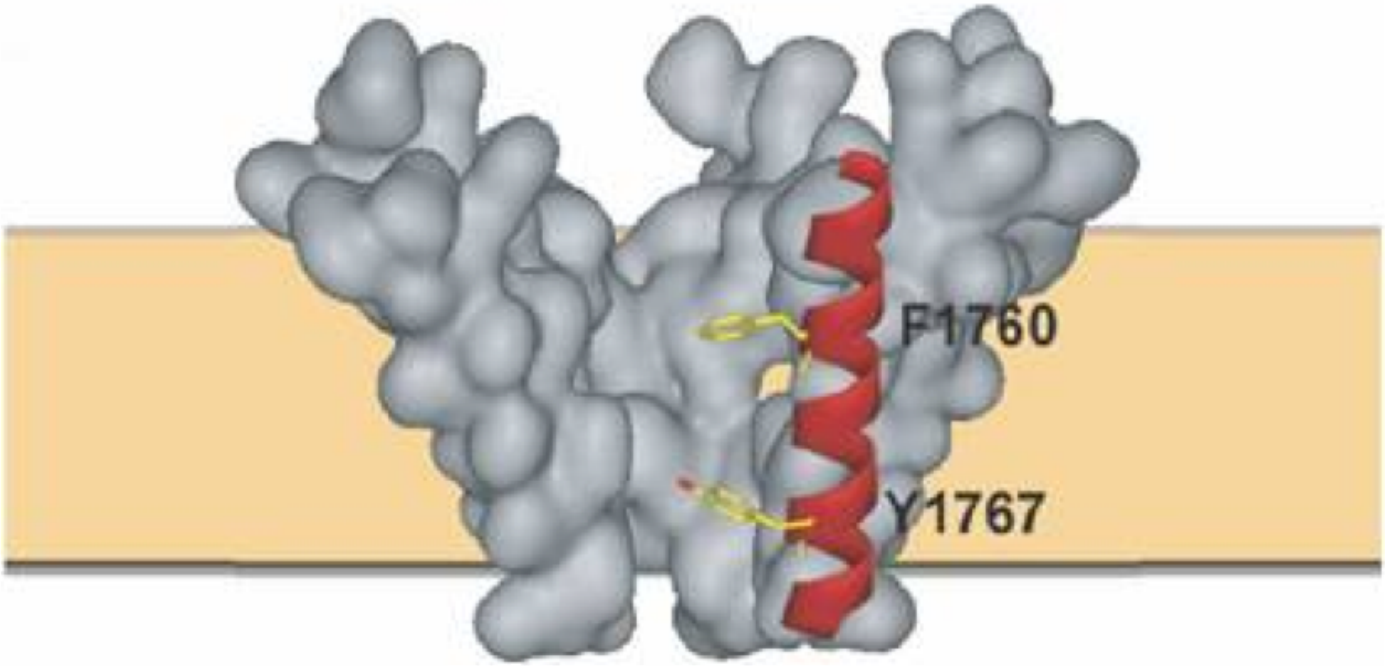
longer lasting

up to 8 hrs

Lidocaine



Binds Na+ channels to interfere with nerve transmission



Receptor Vocabulary

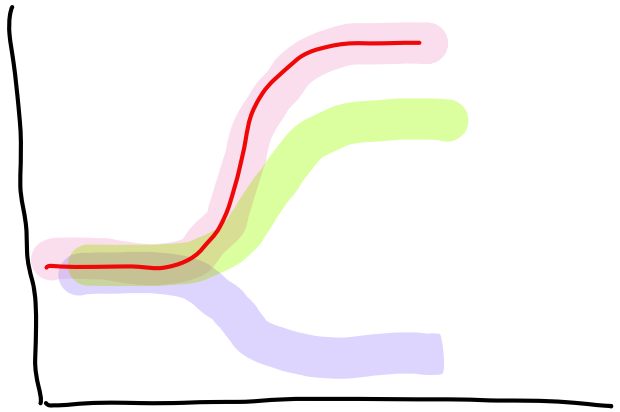
Agonist: – produce same response as the usual ligand

Partial Agonist: – interacts but doesn't give full response

Inverse Agonist: – Inhibit basal activity

Pleiotropic: –

agonist that produces multiple biochemical effects



Antagonist: Bind a receptor and keep a response from occuring

Competitive: – compete with agonist for same binding site

Noncompetitive: – bind some other place an allosteric binding site

Binding of Ligands to Receptors

Simplest model for binding of L to R

↑

or D for drug

Occupancy Theory (Clark, 1920's)

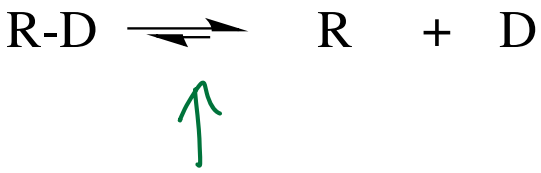
Ligand (D) binds independent receptors

response ∝ to # of receptors occupied

$$R + D \rightleftharpoons R\text{-}D \longrightarrow \text{Effect}$$

$E + S \rightleftharpoons E \cdot S \longrightarrow P$ looks like m-m

↑



there is an K_{eq} for this step

$$K_D = \frac{[R][D]}{[R \cdot D]}$$

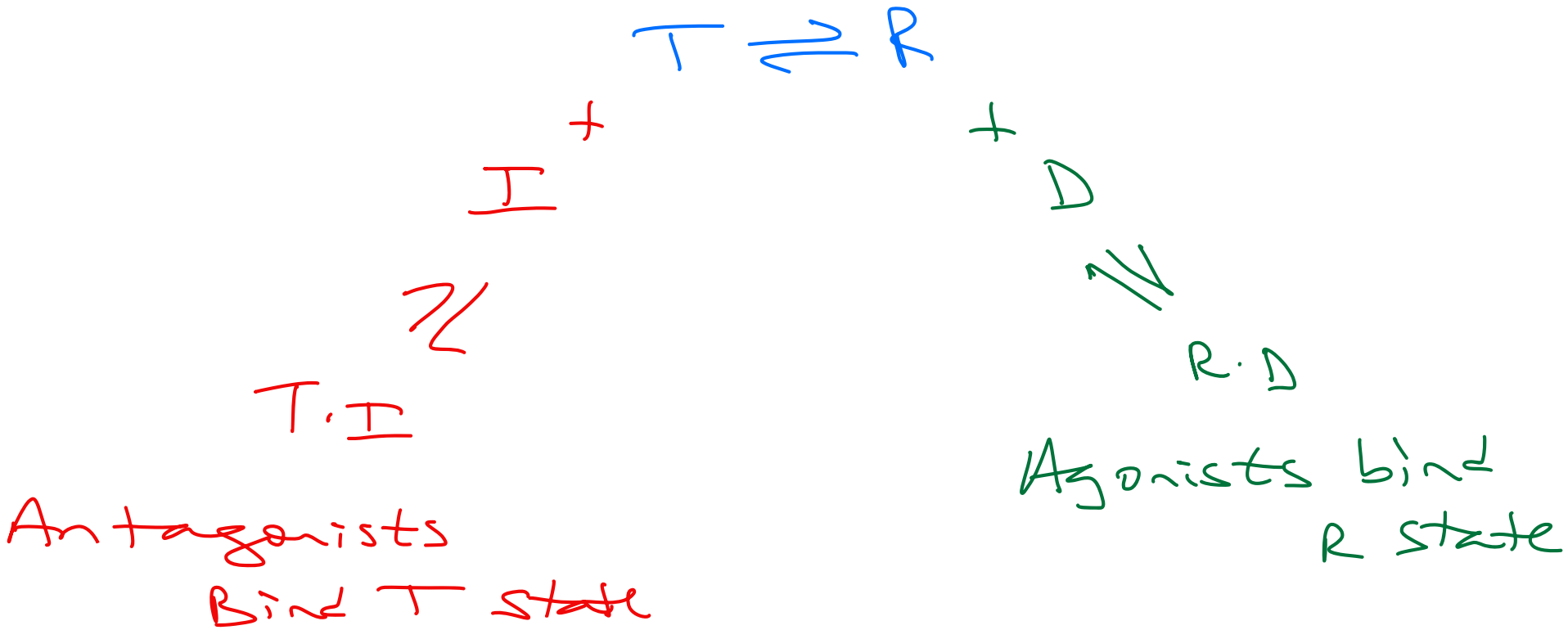
$$K_a = \frac{1}{K_D}$$

smaller dissociation constants mean better binding

K_D's for most agonist $10^{-10} - 10^{6}$ M

Other Models: 2 State Receptor Model

R = relaxed, active, on
T = tense, inactive, off



This explains why # occupied ≠ #

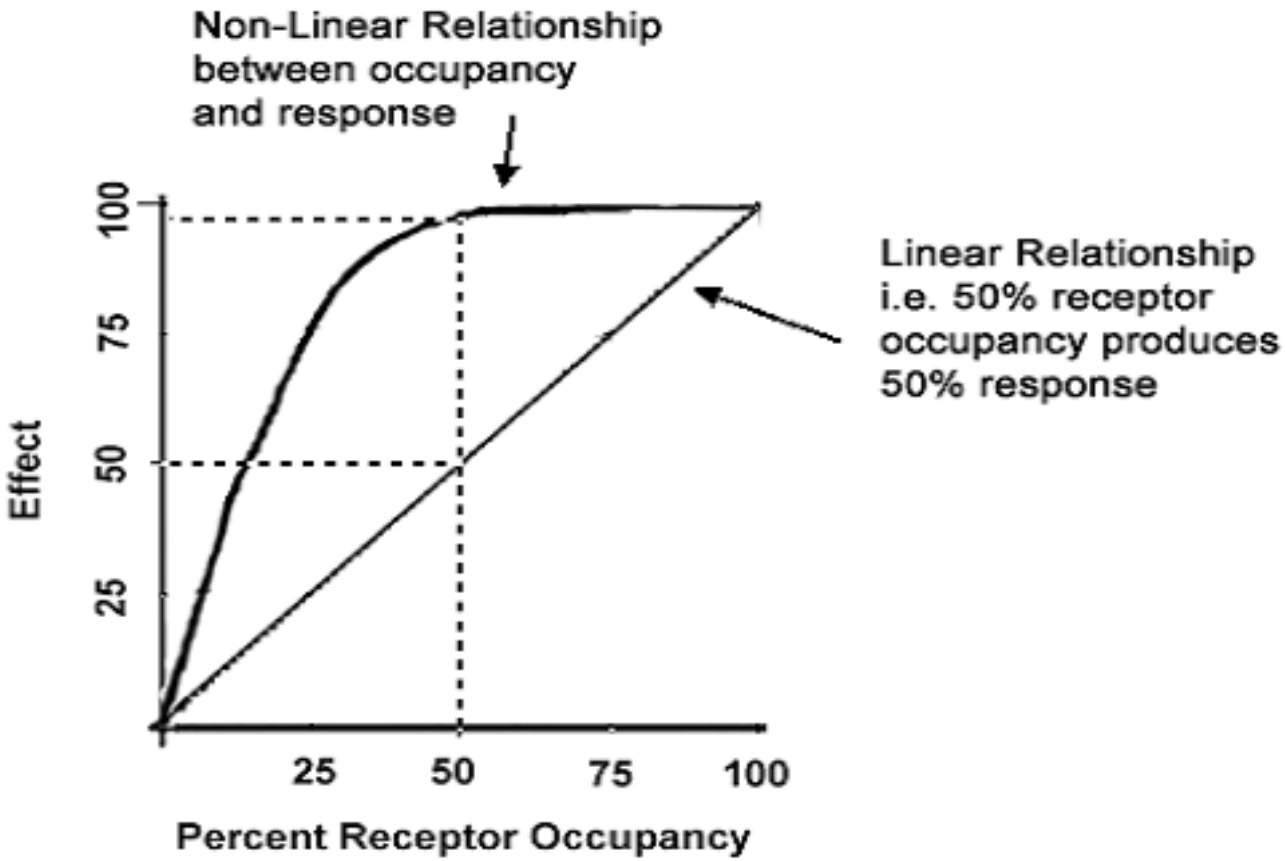
receptors activated receptors

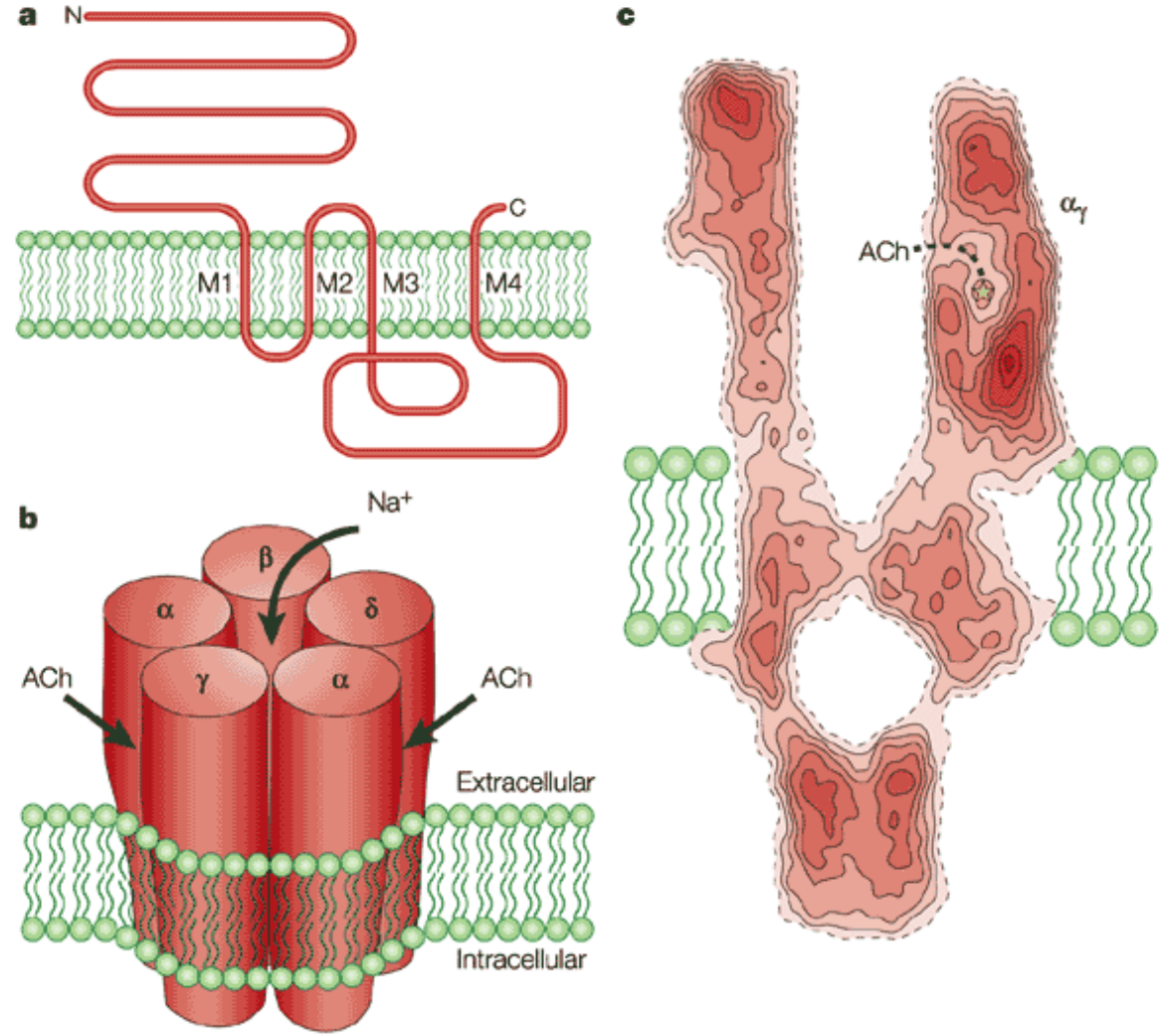
Spare Receptor Model

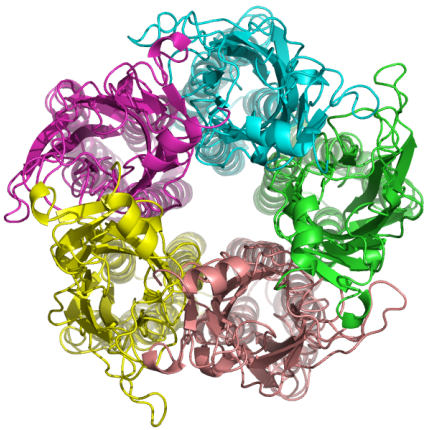
don't always need all receptors bound to get a full respons

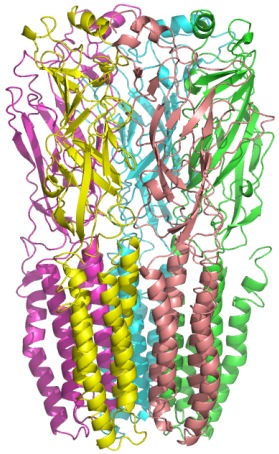
only 5-10% of adrenergic receptors need NE bound to get response

Other Models: Spare Receptor Model









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