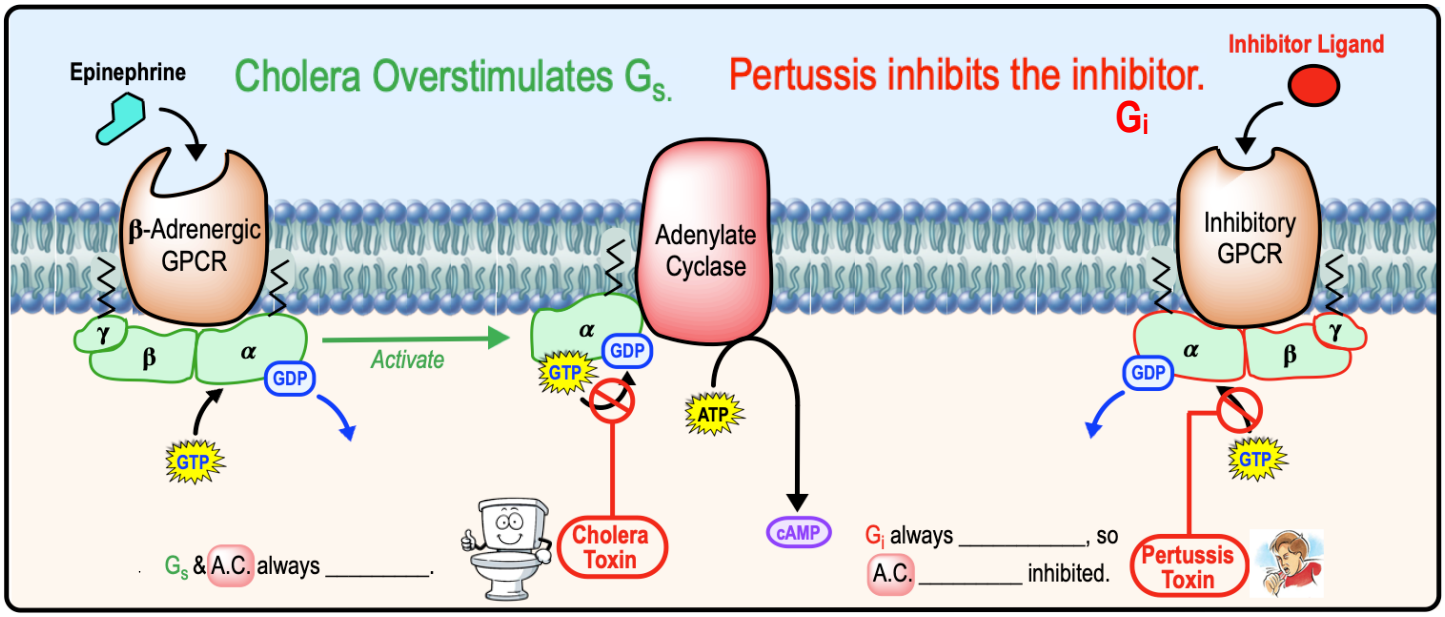
CONCEPT: DRUGS & TOXINS AFFECTING GPCR SIGNALING

- _____ bacterial toxins target G-proteins & indirectly *increase* activity of the effector enzyme (*adenylate cyclase*).
  - 1) _____ *Toxin*: inhibits GTPase activity of G_s (*stimulating* G protein α subunit), causing *cholera*.
    - □ Permanently _____ G protein α subunit & thus *overstimulates* adenylate cyclase activity.
  - 2) _____ *Toxin*: inhibits GDP-GTP exchange in G_i (*inhibiting* G protein α subunit), causing *whooping cough*.
    - □ Permanently _____ G_i protein α subunit (preventing adenylate cyclase *inhibition*).



EXAMPLE: Cholera toxin blocks GTP hydrolysis of the stimulating G_s protein α subunit, whereas pertussis toxin prevents the interaction of the inhibiting G_i protein α subunit with adenylate cyclase. What is the effect of these toxins on the intracellular concentration of cAMP?

a) Cholera toxin increases cAMP concentration, while pertussis toxin decreases cAMP concentration.
b) Cholera toxin decreases cAMP concentration, while pertussis toxin decreases cAMP concentration.
c) They both would lead to an increase in cAMP concentration.
d) They both would lead to a decrease in cAMP concentration.

PRACTICE: Cholera toxin increases the cellular cAMP levels by:

a) Binding to and activating GPCRs.
b) Altering the activity of stimulatory G_s proteins.
c) Inhibiting phosphodiesterase activity.
d) Binding to and inhibiting adenylyl cyclase.
e) Altering the activity of inhibitory G_i proteins.

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PRACTICE: Pertussis toxin is produced by *Bordetella pertussis,* the bacterium that causes whooping cough. Pertussis toxin catalyzes the addition of ADP-ribose to G_i which 'locks' it in the GDP-bound state. If the uninhibited, toxin free GPCR pathway normally results in decreased glycogen synthesis, then what would be the effect of pertussis toxin?

a) It would decrease contraction.
b) It would decrease glucose production.
c) It would further decrease glycogen production.
d) It would increase the rate of endocytosis.

Agonists vs. Antagonists

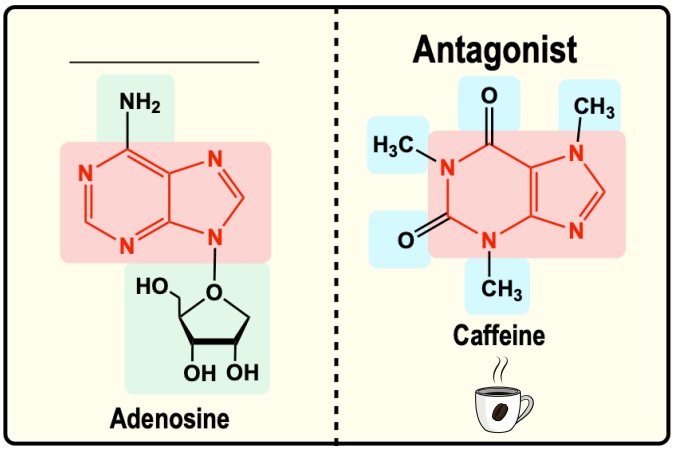
●Many clinical drugs are developed to act either as _____ or _____-agonists to various receptors.

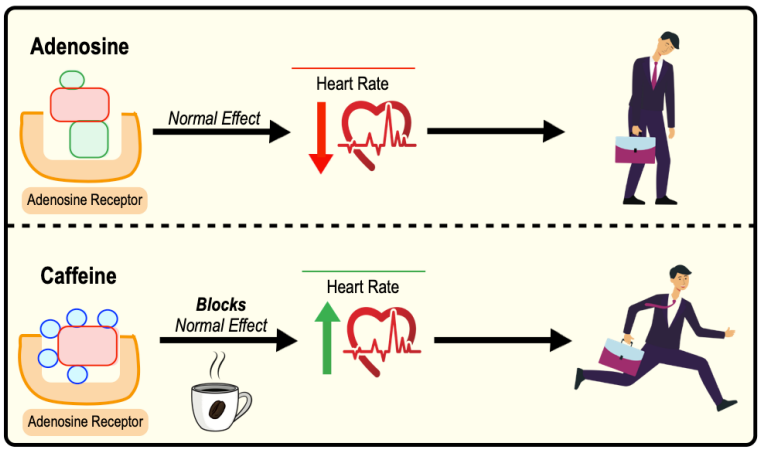
□ *Agonist*: structural analogs that bind receptors & _____ the effect of the original/natural ligand.

□ *Antagonist*: analogs that bind receptor without triggering normal effect & thus _____ effects of agonists/ligands.

□ Antagonists function similarly to _____ enzyme inhibitors (*blocking* the "active site").

EXAMPLE: Caffeine acts as an Antagonist to the Adenosine Receptor.





PRACTICE: Caffeine is a molecule that binds to _____ receptors, inhibiting their response.

a) Tyrosine. c) Adenine. e) Asparagine.
b) Adenosine. d) Cytosine. f) Dopamine.

PRACTICE: Caffeine is a(n) _____ of adenosine that blocks its receptors from activation.

a) Inhibitor. b) Antagonist. c) Agonist. d) Activator.