

Signal Transduction Section

G proteins are involved in signal transduction in many cell types. In the small intestine, in the intestinal epithelial cells, the transport of water through membrane proteins is regulated by a G protein. The effect of drugs, and toxins on the G protein can cause aberrant conditions in which water and electrolytes leave the underlying blood capillaries, going through the epithelial cells and exit into the intestinal tract. This water is eliminated by the body in the form of diarrhea.

a) *Vibrio cholerae* is a bacterium that one ingests through contaminated water or food. Once swallowed the vibrios swim to the surface of the intestinal epithelium where they colonize. Upon colonization, the bacteria elaborate cholera toxin. The toxin is transported across the epithelial cell plasma membrane into the cytoplasm, where the toxin proceeds to irreversibly modify the $G\alpha$ subunit of the G protein. This modified $G\alpha$ subunit continues to stimulate adenylate cyclase. The result of cholera toxin is a sudden and severe (and fatal if not treated) diarrhea, where a person can lose all fluids (and lots of electrolytes) from their body in less than 24 hours. Death is due to severe dehydration and shock.

i) What function of $G\alpha$ subunit is altered by cholera toxin so that adenylate cyclase is always active?

ii) What would be the effect of cholera toxin on cAMP levels in the intestinal epithelial cells?

iii) Can you suggest a mechanism for how cAMP may function in intestinal cells to result in massive diarrhea?

b) An analogue of GTP, called $GTP-\gamma S$, when bound to the G protein, cannot be hydrolyzed to GDP.

i) If $GTP-\gamma S$ is fed to an individual, what would its effect on the intestinal epithelial cells?

ii) Would you expect the effects of $GTP-\gamma S$ to be limited to the intestinal epithelial cells?

c) What are the 3 key attributes, as taught by Professor Jacks, concerning signal transduction?