

# Cholera and Cystic Fibrosis

Cholera is a bacterial disease caused by a toxin released by the bacterium, *Vibrio cholerae* (*V. cholerae*). The most common mode of infection is through the consumption of contaminated food or water. Cholera toxin physiologically affects the body by blocking the activity of the G-enzyme protein, this in turn, causes there to be a constant stimulation of adenylyl cyclase producing an excessively high amount of cyclic AMP (Cassel, 1977). The resulting condition is a massive exodus of ions into the lumen of the intestine, causing the infected person to have significant amounts of rice water-like diarrhea (Silverthorn, 2016). The mechanism by which *V. cholerae* infects an individual to disrupt their homeostasis is simple and takes advantage of an ion channel necessary in certain cells to maintain homeostasis.

Once inside of the body, *V. cholerae* releases the cholera toxin—a protein complex with six subunits. The toxin attaches to the epithelial cells of the intestine and through the process of endocytosis, the A subunit is taken into the enterocytes (Silverthorn, 2016). When inside the intestinal cell, the A subunit transfers ADP-ribose from the coenzyme, NAD, to the  $\alpha$ -subunit of a stimulatory G protein (Gs) (O'Neal, 2005). The  $\alpha$ -subunit has an intrinsic GTPase activity that the bound ATP-ribose inhibits (Cassel, 1977). This inhibition of GTPase activity means that the GTP-coupled form of the protein is permanently activated. Activation of Gs results in the  $\alpha$ -subunit attaching to the catalytic subunit of adenylyl cyclase, which becomes permanently activated as well, causing a continuous elevation of the intracellular levels of cAMP (Cassel, 1977).

All cell membranes have mechanisms that help regulate transportation through them. Enterocytes have cAMP-gated cystic fibrosis transmembrane conductance regulator (CFTR) channels. CFTR channels are located in the epithelial cells of many organs, such as the lungs, sweat glands, the digestive tract, and the pancreas (Silverthorn, 2016). One of the major effects of cholera is the opening of the CFTR channel and keeping them open due to the constant production of cAMP caused by the released cholera toxin (Silverthorn, 2016). This is the mechanism by which Cholera ultimately disrupts homeostasis within the infected individual.

Normally, CFTR channels, open when the nucleotide ATP binds to the protein and the open channel allows for the transport of  $\text{Cl}^-$  out of the cell. However, when the cholera toxin is present in the body, that channel is continuously open to the transport of  $\text{Cl}^-$  out of the cell (Silverthorn, 2016). This means that as the  $\text{Cl}^-$  leaves the cell, water will follow to compensate for the imbalance in the chemical gradient. The increased secretion of salt and water into the lumen leads to massive amounts of watery diarrhea. Since the water and salt come from the extracellular fluid, their loss through diarrhea causes significant dehydration within the infected patient (Silverthorn, 2016).

Cholera takes advantage of the cyclic AMP-gated channel, cystic fibrosis transmembrane conductance regulator, ultimately causing a disruption to the homeostasis of the infected person that could cause death if not treated. As devastating as the affects of cholera are, there is a hypothesis that the effects of its toxin could counteract the symptoms of cystic fibrosis. Cystic fibrosis is a genetic disease that affects the CFTR channels, ultimately negatively affecting the mucosal functions of multiple organs. Since it affects multiple organ systems the abnormalities can be easily observed at autopsy, where those multiple organs systems can be examined together. At autopsy there is usually focal biliary cirrhosis, obstructive lesions of the male genital tract, pancreatic atrophy, bacterial colonization within the respiratory secretions and obstructive bronchopulmonary disease (Vawter & Shwachman, 1979).

One of the most significantly affected organs are the lungs, the disease causes an excess of mucus to be produced impairing the individual's ability to effectively breath. Azimi (2015) states that the cholera toxin could dilute the thickened mucus suffered by those with cystic fibrosis. This dilution would then lend itself to assisting the mucociliary clearance naturally experienced in the body and thus improve any airway obstruction experienced by those with cystic fibrosis (Azimi, 2015). Ultimately, while the effects of the cholera toxin and cystic fibrosis are devastating, the way cholera interacts with CFTR channels could provide for a new direction of treatment for cystic fibrosis.



## References

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