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4 Part Research Project: Cholecystokinin

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Biological Molecule: Cholecystokinin

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Cholecystokinin or CCK is a peptide hormone that plays a key role in Digestion. According to records of the American Journal of Physiology, CCK was discovered around 1928 by scientists Ivy and Oldberg. They had predicted the potential for a hormone in the small intestine that could stimulate the gall bladder. These predictions were aroused, “on the basis of the ability of intestinal extracts to stimulate gallbladder contraction in dogs. Later it was recognized that CCK was a potent stimulant of pancreatic enzyme secretion. However, it was not until 1966, when CCK was purified and the primary sequence was then determined” (Little 903).

CCK is made up of amino acids. It was originally found in the form of a 33-amino acid peptide but further discoveries have identified many other structures for the molecule. CCK is similar to gastrin, which is another type of hormone found in the stomach. The two homones are similar because they share one common group, “COOH-terminal amino acids (Gly-Trp-Met-Asp-Phe-CO-N[H.sub.2])” (Dufresne Intro.). This group is similar to the two molecules along with the characteristics that they are formed and secreted by G and I cells in the upper intestine and in the gastric antrum.

Cholecystokinin is a group of amino acids with the formula Gly-Trp-Met-Asp-Phe-CO-N[H.sub.2]. This formula makes CCK an amide because at the end of its molecular formation there is NH2 functional group. It is a small peptide chain with amino acids bonded by peptide bonds.

Cholecystokinin is a hormone whose primary action is to stimulate the enzyme release from pancreatic acinar cells. After food is consumed and broken down in the stomach, chyme then moves to the small intestine. There are varying amounts of fat in the chyme; this fat triggers the release of hormone Cholecystokinin. The peptide hormone CCK then sends chemical signals to the brain and pancreas where it reaches specific receptors. Cholecystokinin has two types of

receptors, CCK1 and CCK2. Type 1 is alimentary and found primarily on pancreatic acinar cells. Type 2 is found in the brain and the stomach. “CCK-stimulated enzyme secretion is initiated by the binding of CCK to CCK_1 receptors localized on pancreatic acinar cells” (Noble et al).

The CCK receptors are believed to be G protein-coupled receptors (GPCRs) because of the structures of seven trans-membrane spanning domains, these types of receptors play an important role in the hormone signaling process. Ligands bind and activate the g- coupled protein receptors which send a message through signal transduction pathways which will relay the message from the protein receptor. The ligands activate the g- coupled protein receptors which trigger the signal for the pancreatic duct to release gastric juices into the duodenum; it stimulates CCK2 in the brain to trigger then sensation of satiety. “The pancreatic duct adjoins with the bile duct which is connected to the gallbladder. When the pancreatic duct is triggered to release pancreatic enzymes, bile is also released in this process. Bile and pancreatic enzymes, aid in digestion and the breakdown of fat in the duodenum” (Mahan 18).

Sulfated ligands have a higher affinity or strength of binding for both types of CCK receptors, “The natural ligand with the highest affinity for CCK1R is the sulfated octapeptide of CCK (CCK-8).

Other natural molecular variants of CCK such as CCK-33, CCK39, and CCK-58 bind to CCK1R with similar affinity to CCK-8 (396, 490). The two natural ligands with the highest affinities for CCK2R are sulfated gastrin-17 (often abbreviated G-17II) and sulfated CCK-8 (140, 214). Non-sulfated gastrin-17 (G-17I) exhibits a 3- to 10-fold lower affinity than sulfated gastrin-17” (Dufresne). There is a noticeable decrease in affinity when the ligands are not sulfated. If the binding strength or affinity is weak in the ligands, they cannot activate the g-

coupled receptors which then in turn will not relay messages to the pancreatic acinar cells or to the brain.

Certain residues which are located inside the ligand binding site in g- protein coupled receptors, are a major contributor in the GPCR activation process. The residues are amino acid residues, “Amino acid residues are the portion of an amino acid structure that remains, after the release of H_20, when an amino acid participate in peptide bond formation as it becomes part of a peptide chain” (Stoker 665). Once g- protein receptors are activated by the binding with ligands, messages are sent through signal transduction pathways. “Signal transduction pathways involving the G-protein coupled receptors have specific steps in the signaling process. When a ligand binds to the GPCR it causes a conformational change in the GPCR which allows it to act as a guanine nucleotide. The GPCR can then activate an associated g-protein by exchanging its bound GDP (guanosine diphosphate) for a GTP (guanosine triphosphate). The G-protein's α subunit, together with the bound GTP, can then dissociate from the β and γ subunits to further affect intracellular signaling proteins or target functional proteins directly depending on the α subunit type ($G_{\alpha s}$,$G_{\alpha i}$, $G_{\alpha q/11}$, $G_{\alpha 12/13}$)”(Dufresne). The g-protein acts as a molecular switch. In the guanine nucleotide exchange factor, the g-protein is “off” or deactivated and they are bound to guanosine diphosphate where no messages are transferred. When the g-protein is “on” or activated, guanosine diphosphate is dissociated and the g-proteins are bound to guanosine triphosphate; signals are relayed to the pancreas and brain.

There are many different signaling pathways that CCK receptors activate such as: “The JAK/STAT pathway Janus kinases (JAKs) are a family of non-receptor tyrosine kinases. They are known to phosphorylate and activate the STAT family of transcription factors (signal transducers and activators of transcription). Pathways such as focal adhesion kinase and

associated proteins, phospholipases/calcium mobilization and protein kinase C activation E. As well as phosphatidylinositol 3-kinase D, mitogen-activated kinase cascades C, nitric oxide and cGMP pathway" (Dufresne**)**. Although CCK1 and CCK2 receptors react with all of these signaling transduction pathways, the main pathways that are affected in the pancreas acinar cells are the phosphatidylinositol, calcium mobilization and protein kinase pathways.

These pathways are said to be the most affected because they carry most of the biological responsibility in the body. The CCK1 receptors, located on the acinar cells of the pancreas, play the key role of the release of pancreatic enzymes and bile that are essential for regular digestion; "It has been shown that the breakdown of phosphatidylinositol 4, 5-biphosphate, which thereby produces both diacylglycerol and inositol trisphosphate (IP_3), is activated by CCK_1 receptor stimulation. Subsequent activation of Ca^{2+}phospholipid-dependent protein kinase by diacylglycerol and intracellular Ca^{2+} mobilization induced by IP_3 have been considered to act synergistically to cause digestive enzyme secretion" (Pandol et al). The binding of CCK and CCK1 receptors sends messages through those pathways which cause the release of pancreatic enzymes in to the duodenum. If CCK did not affect those signaling pathways regular digestion would not occur.

Cholecystokinin is a small peptide hormone that helps regulate many different functions in the body. CCK is located in the duodenum, the first part of the small intestine. CCK receptors however are located in various locations of the body, in order to conduct different biological functions in the body. CCK receptors are located on the brain, gallbladder, liver, pancreas acinar cells, and in the central nervous system.

CCK lends a hand to many responses in the body but certain CCK receptors define the primary actions CCK has in the body. The first primary action that Cholecystokinin does for the body is to help aid in the digestion process.

Food is digested mechanically and chemically from the mouth and the stomach which then forms a semi liquid substance called chyme. “The chyme travels from the stomach to the small intestine through gastric emptying” (Mahan 18). The chyme enters the duodenum, the first part of the small intestine which is also where CCK is located. Depending on the nutritional makeup of the chym will depend on how much CCK is released. A chyme high in fat and protein will trigger a sufficient amount of CCK to be released. “CCK is released by epithelial cells in the duodenum” (Mahan 18).

After CCK is released into the blood stream it travels to it different receptors. Once CCK reaches CCK receptors, they send signals to the liver, gallbladder, pancreas, brain, central nervous system and stomach. CCK receptors trigger the signal for the stomach to stop emptying chyme into the small intestine, “The hormone instructs the stomach to stop emptying by contracting the pyloric sphincter. CCK signals the liver to create more bile and for the pancreas to release digestive enzymes. It also signals the gallbladder to spasm and secretes stored bile into the small intestine. The combination of bile and pancreatic enzymes then breaks down the chyme and facilitates the absorption of nutrients” (Pendleton). All of the CCK1 receptors bind with the ligands, in order to signal the specific organs that aid with digestion.

The second major biological function that CCK has is to create the feeling of satiety. CCK receptors located in the central nervous system play a key role in this operation. Once CCK is released the CCK receptors pick up the ligands and act as a neurotransmitter. These signal the reactions in the body to stop eating, “CCK increase after eating to reduce hunger and

subsequently food intake in the short term" (Wood 17). While not proven, it is an intriguing though that CCK, or lack of it may be a key factor in obesity and over eating in the United States.

These biological roles would not be possible if the ligands did not bind to the CCK receptors. "Ligands bind and activate the g- coupled protein receptors which send a message through signal transduction pathways which will relay the message from the protein receptor. The ligands activate the g- coupled protein receptors which trigger the signal for the pancreatic duct to release gastric juices into the duodenum; it stimulates CCK2 in the brain to trigger then sensation of satiety"(Tasker). The chemical reactions are essential for CCK to do its job of signaling organs and central nervous system for proper bodily functions.

Cholecystokinin is very important for normal bodily functions. It is well known in the digestive system to help break down protein and fat in chyme. CCK is also linked to functions in the central nervous system. A major role that Cholecystokinin plays in the body is to trigger a feeling of satiety.

Satiety occurs when a person feels full and no longer has the desire to eat. Cholecystokinin has been known to trigger the feeling of satiety through signals sent through the central nervous system to the brain and stomach. These signals return back to the brain and relay a message to the person to stop eating. This is a very simple concept and gives the reasoning that everyone should have the ability to stop eating, because the CCK hormone will tell their bodies to stop. Studies have shown this is not always the case.

These studies bring up an interesting thought that CCK could have something to do with the problem of obesity in our world today. The question has come up, "What would happen if CCK did not function properly, would this explain why someone could not stop eating?"

Researchers have been doing their best to try and answer these questions. The facts are known that, “Since the initial discovery of its property as a food-intake inhibitor, CCK was demonstrated to be a short-term, meal-reducing signal in most mammalian species including humans” (Dufresne IIV). This is significant because there is evidence that CCK has the potential to be a contributing factor in obese people. According to Mr. B.A. Baldwin and his colleagues, “there have been many studies demonstrating that exogenous CCK has been shown to significantly decrease meal size” (Baldwin). The only way for satiety to occur under the presence of CCK is for CCK1 receptors to be present on vagus nerves, “Which relays to the hypothalamus via brain stem areas such as the nucleus tractus solitarius and the area postrema” (Dufresne IIV). The CCK messages are received by these regions on the brain stem and they will react by slowing gastric emptying. This relays a message from the stomach to the brain for a person to stop eating because they are satiated.

Normal bodily function allows all of these messages to be transmitted from the duodenum where CCK is released, to the CCK receptors, to the messenger path ways, then onto the brain which triggers different functions in the body to occur. If all of these reactions occur flawlessly a person should not have an over eating issue. Any flaws in this system however will not allow the proper messages to be relayed.

There are two theories of why the messages of CCK are not relayed. One theory is determined by Akihiro Funakoshia, a very well known scientist in the department of endocrinology. He and his team operated a study which resulted in evidence that “Polymorphisms in the promoter region of the human CCK1R gene were detected in 1.9% of individuals in a cohort study and were related to increased body fat content” (Funkoshia). By

this study there is evidence that an abnormal shape of the CCK1 receptor is linked to excess body fat in a person. This could cause a person to become obese.

The second theory of why CCK messages are not relayed is abnormal plasma CCK levels. “Basal and postprandial CCK was found to be reduced in women with polycystic ovary syndrome secretion who tend to binge eat and become overweight. Lack of a CCK response to a high-fat meal was reported to contribute to obesity” (Dufresne IIV). The plasma CCK levels are lower than normal possibly signifying that these overweight patients do not produce enough CCK which is weakening the messages of satiety.

Cholecystokinin is a major biological molecule because it performs many important tasks in the body. When it functions properly the body can operate normally in digestion and its other normal functions. It is when CCK does not function properly that there can be serious consequences. Obesity may not seem like a serious consequence to many, but it is certainly taking the world by storm. Further research on this connection could do amazing things for the health and wellness of the population.

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