Role of cholecystokinin in appetite regulation: A review

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Abstract: Cholecystokinin (CCK) acts on the peripheral or central nervous system and generates a large number of satiety signals, regulating food intake and body mass. CCK also plays a role in promoting digestion and nutrient absorption throughout the gastrointestinal tract. There are many hormones that affect the secretion of CCK, such as leptin, ghrelin and insulin. Because CCK is related to energy metabolism, it also affects the occurrence of cancer and other diseases to a certain extent. In a word, CCK has many functions, and its role in appetite regulation is crucial. The peripheral mechanism of CCK involved in appetite regulation has been studied thoroughly, while the central mechanism needs further study. It is worth noting that CCK is also related to the occurrence of a variety of diseases. Therefore, CCK in the study of energy metabolism related diseases deserves more in-depth research. The fundamentals, the method of secretion, the variables influencing CCK secretion, and its critical function in appetite regulation are covered in this article, laying the groundwork for future studies on the energy metabolism of mammals by combining hormones like CCK.

Keywords: Cholecystokinin; Appetite regulation; Neuropeptides; Metabolic disease

Although we still don't fully understand how the body achieves and maintains energy balance, the evidence we do have suggests that a sophisticated physiological control system is involved. This system incorporates both the outbound signals that influence energy intake and expenditure as well as the incoming signals from the periphery that describe the level of energy storage (Sandoval et al., 2008). Additionally, we are aware that the mutual changes between the positive and negative energy balances will have an impact on the energy balance's constituent parts. If the energy balance system is out of balance and is only impacted by food intake and usage of energy, the majority of people typically experience significant weight changes quickly (Stubbs et al., 2004).

Diet gives us the nutrition we need to survive. However, eating insufficiently, eating excessively, or eating too much at the wrong time will all have negative effects. These factors lead to stringent control over appetite (Andermann & Lowell, 2017). There are many factors that promote diet, including the availability of food, individual preferences, circadian rhythm and the time between meals. By contrast, the gut primar-

ily regulates feelings of satiety. Through vagal afferent neurons (VAN), the stomach and small intestine send numerous satiety signals to the hindbrain (Steinert et al., 2017). Cholecystokinin (CCK), leptin, insulin, glucagon-like peptide-1 (GLP-1), peptide YY (PYY), 5-hydroxytryptamine, pancreatic polypeptide (PP), and amylin are examples of paracrine signals released by intestinal endocrine cells. In order to control appetite, these chemicals stimulate neurons in the nucleus tractus solitarius (NTS) (Freire & Alvarez Leite, 2020).

1. Overview of CCK

Gibbs, Young, and Smith shown in 1973 that exogenous cholecystokinin might decrease rats' food consumption. Thousands of studies have been inspired by this initial report. CCK activity in animals was discovered in tissues for the first time in 1906 (Edkins, 1906), and it was then isolated as an intestinal hormone in 1928.This peptide was first discovered to be a material produced from the small intestine of pigs and cats, which can, respectively, induce gallbladder contraction and cause pancreatic enzyme secretion. Its structural formula is shown in Figure 1 (Fig. 1).
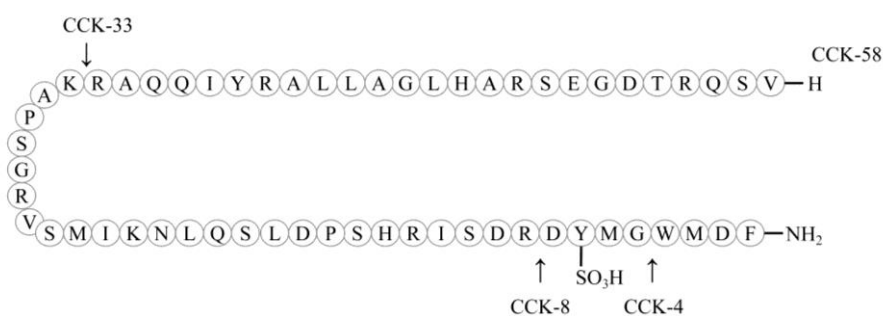

Figure1 CCK structure

CCK has a number of functions in animals and is generated by intestinal endocrine cells and brain neurons (Nä ssel & Wu, 2022). Male rats' total calorie consumption and body weight are unaffected by long-term infusion of CCK, although it can decrease the amount of food they consume, indicating a role for CCK in energy maintaining (Crawley & Beinfeld, 1983). However, abnormal weight gain results from a damaged CCK system. The rise in calorie consumption and increased body weight in mice fed a high-fat diet are related to the decreased effectiveness of acute exogenous CCK treatment to reduce food intake. Chronic CCK intervention has minimal impact on weight loss or food intake in obese rodents. The weakening of the CCK response, as well as the inhibition, fusion, and synergy between CCK and other energy balancing and extraction-related signals, show the complex regulatory role of CCK (Savastano & Covasa, 2005).

Further functions of CCK related to feeding and metabolism include inducing the synthesis of amylase (Reidelberger & Solomon, 1986), lipase (Greengard et al., 1944), trypsin (Beglinger et al., 1985) and chymotrypsin (Einarsson et al., 1997) through paracrine, endocrine and neuronal pathways, which are crucial regulators of the entire digestive problems. tract's digestive function. For the breakdown of proteins, lipids, and car-

bohydrates, respectively, these enzymes are crucial. As crucial regulators of metabolic balance, calcitonin, insulin, and glucagon are also stimulated by CCK (Rehfeld, 2017).

It also proposed the role of CCK in rat and mouse aggression. Neurons expressing CCK have been found in the limbic system, brain stem and cerebral cortex. The neural circuits that control anxiety, fear, and aggressiveness are known to cross these regions (Zwanzger et al., 2012). The research results show that hyperactivity and aggressive behavior can be induced by CCK signal transduction of CCK1R in the brain (Li et al., 2007). Additionally, mice lacking CCK2R exhibit more exploratory behavior and experience less anxiety than mice with overexpressed CCK2R in the brain (Li et al., 2007). It was also found that other regulatory functions mediated by CCK in the brain include the role in sleep, nociception, memory and learning, panic and anxiety (Dockray, 2009).

2. The role of CCK in appetite regulation
2.1 Satiety

The period of time during which eating is continuously inhibited and the time between meals are referred to as the sense of satiety. Rodents who are satiated exhibit a succession of ordered actions, such as combing their hair for a while before resting (Antin et al., 1975). In rodents (Lee et al., 2020), monkeys (Gibbs et al., 1976), and humans (Kissileff et al., 1981), exogenous CCK has been shown to lower food intake in a dose-dependent way. This result provides crucial evidence of the physiological role of endogenous CCK, which is located in the gastrointestinal system, in controlling food intake. The cause of this impact is external CCK's capacity to promote satiety. In conclusion, consuming meal can trigger the production of CCK, and the amount of CCK in the blood may be enough to produce temporary satiety (Gibbs et al., 1976). The greatest inducers of CCK release are dietary fat and protein, and fatty acids with more than 12 carbons are more efficient (McLaughlin et al., 1999). In human studies, it was found that after a high-fat or high protein diet, compared with an equal calorie food with high carbohydrate content, cells' perception of protein or fatty acid would lead to an increase in intracellular Ca2+and CCK release through different signal pathways, and then lead to an increase in plasma CCK levels (Gibbons et al., 2016).

One of the most extensively researched and significant brain regions is the hypothalamus. It is essential in the regulation of satiety and takes part in the central control of food intake and energy consumption. According to Myers et al. (2012), the hypothalamic arcuate nucleus (ARC) is crucial in controlling metabolism related to leptin and food intake. Different groups of nerve cells, particularly in the hypothalamic ARC, sense the body's nutritional status and combine signals from peripheral hormones (like insulin from the pancreas and leptin from fat cells) in order to regulate calorie intake, glucose metabolism, and energy expenditure. The ability to coordinate behavioral responses is provided by the strong connections that the arcuate neurons have with other neuronal subgroups in the hypothalamus as well as with other brain regions outside of the hypothalamus. Neurons that express anorexia (appetite inhibition), opiomelanocortin (POMC), cocaine and aminophenamine regulated transcription peptide (CART), and neurons that express appetite (appetite stimulation), neuropeptide Y (NPY), and

agouti related protein (AgRP), are two antagonistic types of neurons in this process (Gropp et al., 2005).

2.2 Peripheral mechanism

Peripheral CCK plays a role in many aspects related to food regulation, and studies have shown that exogenous injection of CCK will show satiety without meals, which indicates that this hormone can evoke satiety without internal food stimulation. The identification of CCK1R in VAN partially explains the mechanism of CCK in satiety and its connection with other systems in controlling eating (Antin et al., 1975). The activation of the vagus nervous system is essential in mediating CCK-induced satiety.

During food intake and subsequent gastric dilatation, CCK is released from intestinal endocrine cells (EEC) in the gastrointestinal tract and acts on adjacent VAN. These VANs express CCK1R. At the same time, their axons are connected to neurons in the brain stem NTS. The combination of CCK and CCK1R in VAN leads to the activation of these neurons. The food intake is regulated through gastric emptying, thus triggering the feedback after feeding to the hindbrain (Fig. 2) (Cawthon et al., 2021). VAN integrates several signals and some sensory inputs to fine tune food intake. It was proposed that, according to the expression of these peptides and receptors, VAN can take two states, one is related to eating (hunger), and the other is related to eating inhibition (satiety). CCK acts as the gatekeeper to determine these states (Dockray et al., 2009). In terms of mechanism, the CCK induced signal in VAN propagates to the brain stem and leads to the efferent signal to the gastrointestinal tract. These efferent satiety signals regulate (inhibit) gastric emptying, thus leading to reduced food intake (Cawthon et al., 2021).
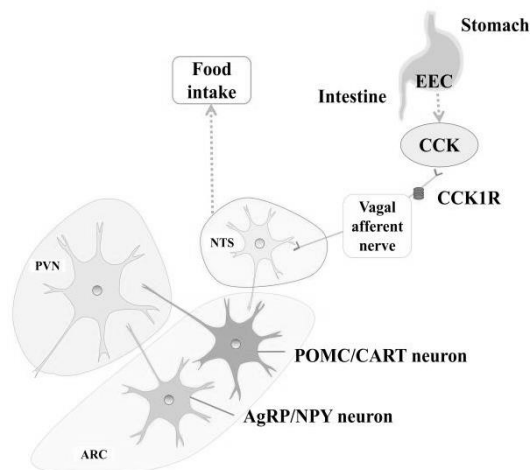

Figure 2 Synthesis of CCK and feeding signal pathway in peripheral mechanism

Additionally, VAN communicates with NTS in the brainstem to activate secondary neurons that express NPY, POMC, dopamine, and other chemicals. Several neural circuits in the hypothalamus (or elsewhere) receive the information from these secondary neurons, which further process it, resulting in a thorough response to energy intake and consumption. As a result, CCK-mediated satiety signals from the gut not only engage direct feedback to the GI tract but also indirectly activate brain signals that may mediate longer-lasting impacts on behavior (Roh et al., 2016).

In addition to expressing CCK receptors, VAN also expresses receptors for tension, mucosal percussion, and other feeding signals, such as anorexia-related signals like leptin, insulin, GLP-1, PYY, and urinary corticosteroids, as well as signals that promote appetite, like ghrelin and endogenous cannabinoids. To precisely regulate food intake and control eating, the VAN's capacity to integrate signals from these several chemicals and receptors is essential (Cawthon et al., 2021).

2.3 Central mechanism

The central nervous system (CNS) is essential for regulating the dynamic equilibrium of glucose and energy, claim Myers et al. (2012). The hypothalamus, specifically, is home to the principal CCK receptor, or CCK2R, which controls the body's energy balance (Barrachina et al., 1997). The dopaminergic system regulates behavioral reactions and significantly influences how much food is consumed, and it is also known that CCK2R interacts with opioids and dopaminergic systems (Noble et al., 1999). The brain also contains CCK1R, despite the fact that it is typically thought of as a peripheral receptor type (Boden et al., 1991; Alén et al., 2013).

Studies on mammals over the years have demonstrated that CCK released from the small intestine directly acts on VAN, and that this neuronal activity terminates in NTS and activates the upstream pathway regulating eating behavior. It has long been of great interest to understand the mechanism of the central nervous system's reaction to circulating CCK. Peripheral mechanisms and the central nervous system may both contribute to the satiety effect of CCK. Although it appears that the activation of the hypothalamus pituitary adrenal axis by fasting is mediated by the expression of the CCK receptor, the primary mechanism by which CCK may regulate food intake is still in part unknown (Baldwin et al., 1998). After eating, the hypothalamus releases CCK (Schick et al., 1987), and giving CCK to certain hypothalamic nuclei appears to reduce appetite (Inuiet al., 1987). Additionally, it is understood that CCK receptors exist in brain areas involved in controlling appetite. (Alén et al., 2013). Rats' reduced appetite is caused by CCK injection into the dorsomedial hypothalamus and is mediated by CCK2R (Carlberg et al., 1992). This CCK-8-mediated neural substrate of the satiety signal innervates the paraventricular nucleus of the hypothalamus in mice. Long-term effects on hunger and weight loss will result from the activation of these CCK neurons. Contrarily, the short-term consequences of ingesting food are associated to CCK input through the VAN/brainstem (Rust et al., 2021). According to D'Agostino et al. (2016), the CCK-mediated satiety signal in insects is known to alter taste neurons' perception of carbohydrates through neural circuits in the brain, which in turn affects food intake.

3. Hormones that affect CCK secretion

There are many factors that can affect the secretion of CCK, and complex interactions will occur through many feeding and anorexia signals generated in the brain and peripheral tissues. In addition to CCK1R and CCK2R, VAN also expresses Ghrelin 1 receptor, orexin 1 receptor, cannabinoid CB1 receptor and leptin receptor. However, in order to maintain energy balance, metabolic state information must be effectively transmitted to the brain (Burdyga et al., 2006).

Gastric X/A-like cells produce the peptide ghrelin, which has 28 amino acids (Kojima et al., 1999). Ghrelin functions as a hunger signal in energy metabolism and

promotes food intake in a dose-dependent way (Naznin et al., 2018). Plasma ghrelin will rise during a fast and peak just before meals (Toshinai et al., 2001). According to the research, ghrelin greatly reduced the ability of rats (Date et al., 2002) and mice (Page et al., 2007) to release vagal afferent fibers. In vitro, ghrelin can successfully block CCK's activity. Additionally, it was discovered that ghrelin and CCK1R receptors are co-located in the ganglia, raising the possibility that they could block the transmission of signals produced by one another (Date et al., 2005).

Through its synergistic interactions with leptin and other long-term obesity signals, CCK also appears to play a significant role in weight regulation. White adipose tissue produces the anorexic hormone leptin. Rodents and people who lack leptin develop extreme obesity (Schwartz et al., 2000). Leptin activates the paraventricular nucleus neurons in the hypothalamus arcuate nucleus, which sends signals that control food intake. Through an early growth response 1 (EGR 1) dependent pathway, leptin can also improve CCK signal transduction in VAN, increasing its sensitivity to CCK. The satiety effect of CCK will be diminished by a long-term high-fat diet because it will cause VAN to produce leptin resistance and decrease its sensitivity to CCK (Morton et al., 2006). These results imply that leptin signaling is necessary for satiety induction and CCK signaling in VAN. By raising CART and thyrotropin releasing hormone (TRH) and lowering AMPK phosphorylation in the hypothalamus, a combination injection of CCK and leptin reduces the consumption of food, at least in part (Barrachina et al., 1997). More research is required to determine the integration mode and location of CCK and leptin signal because leptin signal in the hypothalamus is unlikely to augment CCK signal either alone or by CCK signal.

The adaptive response of pancreatic islets may be influenced by CCK. It functions as a paracrine or autocrine factor to boost the survival of islet B cells and extend the quality of B cells, thereby compensating for insulin resistance brought on by obesity (Lavine et al., 2010; Alén et al., 2013). It is up-regulated by islet cells during obesity.

A cannabis CB1 receptor agonist pretreatment could counteract the rat satiety caused by CCK-8. The satiety generated by CCK-8, however, was enhanced by pretreatment with cannabinoid CB1 receptor antagonist/reverse agonist. In addition to influencing satiety and appetite, endogenous cannabinoids and CCK also play a role in the intricate process of nutritional perception and control of nutrient intake. From this perspective, cannabinoid CB1 receptor antagonist and CCK1 receptor agonist combination therapy may be an extremely helpful method to suppress appetite. This is because they both work to reduce food intake, but also due to the impact on the state of nutrition and the activity of other intermediaries like leptin, ghrelin, and PYY may affect how effective CCK is (Alén et al., 2013). The change trend of each index is shown in Table 1.

Table 1. The change trend between ghrelin and some index about food intake.

Index	Trend
Ghrelin	↓
Leptin	↑
Cannabinoid CB1 receptor	↓

· ↑means increasing; · ↓means decreasing

4. CCK related energy metabolism diseases

4.1 Tumor

5. Multicellular organisms have perfected an efficient system of cell regulation to keep the balance of cell division, proliferation, and death. Carcinogenesis results from abnormal cellular control, such as unrestricted cell proliferation and metastatic invasion. The biggest endocrine organ in the body, the intestines have a variety of bioactive peptides and more than 30 genes for intestinal hormones that can be expressed (Holst et al., 1996). CCK is one of the earliest gastrointestinal peptides identified and is crucial to digestion. But accumulating in vitro and in vivo research has revealed that CCK integrates and orchestrates complex information networks during cell proliferation and apoptosis. They occasionally aid in the pathophysiology and development of specific tumor types (Rozengurt et al., 2001). The CCK regulation system is complicated, though, as a result of the widespread distribution of hormone genes, cell-specific alternative splicing, and post-translational modification. In actuality, various forms of adenocarcinomas originating from the stomach, colon, pancreas, esophagus, and gallbladder, as well as some cancers in the brain, express CCK and its cognate receptors (CCK1R and CCK2R) and are associated with them. Additionally, it was found that human gastric adenocarcinoma, colorectal cancer, and pancreatic cancer all expressed CCK at levels that were higher than in the corresponding normal tissues, suggesting that CCK contributed to the promotion of carcinogenesis (Rai et al., 2012).

4.2 Obesity

6. Can obesity be prevented by continuously extending the CCK signal duration? Can the CCK signal's recovery help with metabolic health and weight loss? Although weight loss treatments involving CCK have been tried, the majority of this research has only been done on rodents, and further research is necessary to evaluate whether these treatments are suitable for usage in humans and are also safe (Christoffersen et al., 2020). At least one positive allosteric CCK1R regulator is currently known, but much more research is required to ascertain whether the process of preserving the action time of CCK1R may be employed to treat obesity. Therefore, it is yet to be seen whether the CCK-focused treatment can result in weight loss (Christoffersen et al., 2019; Cawthon et al., 2021).

5. Conclusion

CCK is an important regulator of human appetite and energy intake. Current research shows that CCK plays a role in appetite regulation mainly through peripheral and central mechanisms, of which the peripheral mechanism is more in-depth. In the peripheral mechanism, VAN is the main target of CCK, which is now considered to be an important part of the peripheral signal integration regulating food intake. CCK stimulates VAN in a paracrine manner, which is related to the inhibition of gastric emptying in a short time, and the expression changes of receptors and neuropeptides in these neurons are also related to it. Ghrelin inhibits many of these effects, while leptin enhances

them. The fat uptake of the central nervous system is largely mediated by the release of CCK. In obese patients, VAN shows CCK resistance, and CCK also plays an important role in the pathogenesis of cancer in the process of cell proliferation and apoptosis. However, obesity, cancer and other diseases as well as the role of the central axis mechanism in energy metabolism need to be further studied.

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