Cholecystokinin and cholecystokinin-A receptor: An attractive treatment strategy for biliary dyskinesia?

Chang et al. Attractive treatment strategy for biliary dyskinesia?

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Abstract
Biliary dyskinesia is a relatively common gastrointestinal disease that is increasing in incidence as living standards improve. However, its underlying pathogenesis remains unclear, hindering the development of therapeutic drugs. Recently, Xu et al demonstrated that cholecystokinin (CCK) regulates the contractile function of the common bile duct through interaction with the cholecystokinin-A receptor (CCK-A receptor) in interstitial Cajal-like cells, contributing to improving the academic understanding of biliary tract dynamics and providing emerging directions for the pathogenesis and clinical management of biliary dyskinesia. This letter provides a brief overview of the role of CCK and CCK-A receptors in biliary dyskinesia from the perspective of animal experiments and clinical studies, and discusses prospects and challenges for the clinical application of CCK and CCK-A receptors as potential therapeutic targets.

Key Words: Cholecystokinin; Cholecystokinin-A receptor; Biliary dyskinesia; Interstitial Cajal-like cell; therapeutic target


Core Tip: Biliary dyskinesia has an estimated 10% morbidity rate and its cause is unknown, hindering the development of appropriate treatments. Traditional surgical treatments have side effects and there is thus an urgent need to identify safe and effective therapeutic targets. This letter agrees with the findings of Xu et al and provides a brief overview of the prospects and challenges of CCK and CCK-A receptors as potential targets in biliary dyskinesia from the perspective of animal experiments and clinical studies.
TO THE EDITOR

We were interested to read an original article "Expression and functional study of cholecystokinin-A receptors on the interstitial Cajal-like cells of the guinea pig common bile duct" by Xu et al. [1]. We agree with the authors' findings that CCK-A receptors are highly expressed by common bile duct (CBD) interstitial Cajal-like cells (ICLC) and that CCK interacts with ILC CCK-A receptors to regulate CBD smooth muscle contraction in a dose-dependent manner. We are grateful to the authors for their commitment to the study of CCK and CCK-A receptors in biliary dyskinesia, as this will assist in the elucidation of the key cells and receptors involved in biliary dyskinesia and thus provide promising directions for the development of clinical treatments for the disorder.

Gallbladder motility is regulated by hormonal interactions. CCK is a peptide hormone found in neurons and the gastrointestinal tract that regulates digestive, cardiovascular, and neurological functions by binding to CCK receptors on target cells. In the digestive system, CCK regulates cholecystic contraction, pancreatic enzyme secretion, and gastrointestinal peristalsis. CCK binds to CCK receptors to induce gallbladder contraction and promote cholecystic emptying and bile release [2] and also mediates rhythmic contraction of the gallbladder and diastole of the sphincter of Oddi, resulting in the release of bile from the gallbladder into the duodenum to participate in food digestion. An animal study found that increased levels of CCK enhanced cholecystic contractile function, while on the contrary, reduced CCK levels led to cholecystic contractile dysfunction and ultimately led to gallstone formation [3]. Notably, Xu et al found that in guinea pigs, CCK interacted with ILC CCK-A receptors to regulate CBD smooth muscle contractility in a dose-dependent manner [1], suggesting that CCK and CCK-A receptors play a key role in regulating CBD smooth muscle contraction. The CCK-A receptor is a major mediator of gallbladder smooth muscle contraction and is highly expressed by guinea pig CBD ICLCs [1]. Reduced expression of the CCK-A receptor in the mouse gallbladder is an important cause of cholelithiasis [4].
These animal studies suggest that both CCK and CCK-A receptors may be attractive targets for combating biliary dyskinesia.

However, there have been few studies on the safety and efficacy of targeting CCK and CCK-A receptors in humans. A clinical study explored whether a CCK-A agonist (GI181771X) was beneficial in reducing body weight in obese patients. GI181771X was found to have no significant effect on body weight and waist circumference, nor on hepatobiliary, pancreatic, and other cardiometabolic markers, but had mild side effects in the gastrointestinal tract \[5\]. In contrast, another clinical study analyzed the role of CCK-A receptors in patients with functional dyspepsia and found that a CCK-A antagonist (dexloxiglumide) reduced gastric volume and dyspepsia during duodenal lipid infusion, and also reduced gastric compliance during gastric distension \[6\], which implies that CCK-A receptors play a significant role in gastric distension and duodenal lipid-induced symptoms of dyspepsia. Similarly, clinical studies used a CCK-A antagonist (loxiglumide) to assess the role of CCK-A receptors in postprandial satiety and nausea and their influence on duodenal lipids, and found that loxiglumide reduced both postprandial satiety and nausea \[7\], indicating the involvement of CCK-A receptors in inducing these symptoms. Despite these findings, research on the effectiveness and safety of targeting CCK-A receptors in the treatment of organic digestive diseases is still in the preliminary stage, and more in-depth exploration is required to provide a scientific basis for the prevention and treatment of these diseases and biliary dyskinesia in particular.

As an important hormone that affects the contraction of gallbladder tissue, CCK plays a unique role in the maintenance of physiological homeostasis in the body. However, current animal and clinical studies have not fully elucidated its biological effects, and its safety and effectiveness warrant further investigation. It has been reported that while CCK promotes gastric motility in guinea pigs, it has the opposite effect in both humans and dogs \[8\], indicating that the effect of CCK on gastric motility is species-dependent. Further investigation into species differences in the effects of CCK on biliary motility is required. In addition, the biological mechanisms underlying the
interaction between CCK and the CCK-A receptors, which mediate the cholecystic contractile function, require further study. Once the safety and effectiveness of targeting the CCK-CCK-A receptor interaction have been clarified in animal studies, it will be necessary to conduct large-scale clinical trials to promote the clinical transformation of basic research results and better serve patients.

In conclusion, while biliary dyskinesia is traditionally treated with cholecystectomy, this can cause side effects such as diarrhea, dyspepsia, and duodenal gastrointestinal reflux, as well as damage to the patient’s immune system. Thus, in recent years, treatment involving gallbladder conservation has tended to be used for biliary dyskinesia-related disorders, which makes the search for potential targets for the prevention and treatment of biliary dyskinesia particularly important. The study of biliary tract dynamics represents a research hotspot in extra-biliary science. Evidence from in-depth basic and clinical research on biliary tract dynamics is expected to clarify the key cells and receptors together with their functions and regulatory mechanisms, allowing the identification of therapeutic targets for biliary dyskinesia and the design of drugs against these targets, which will, in turn, provide a theoretical basis for the standardized treatment of biliary dyskinesia.

FOOTNOTES
Conflict-of-interest statement: The authors have no conflict-of-interests.

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