ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2024 January 21; 30(3): 199-285

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 30 Number 3 January 21, 2024

EDITORIAL

199 Toward less invasive coloproctology: The future is out there

Emile SH, Ragheb J

OPINION REVIEW

204 Garg incontinence scores: New scoring system on the horizon to evaluate fecal incontinence. Will it make a difference?

Tsarkov P, Tulina I, Sheikh P, Shlyk DD, Garg P

REVIEW

211 Why is early detection of colon cancer still not possible in 2023?

Tonini V, Zanni M

225 Relationship among Parkinson's disease, constipation, microbes, and microbiological therapy

Yuan XY, Chen YS, Liu Z

ORIGINAL ARTICLE

Retrospective Cohort Study

238 Effectiveness of antibiotic prophylaxis for acute esophageal variceal bleeding in patients with band ligation: A large observational study

Ichita C, Shimizu S, Goto T, Haruki U, Itoh N, Iwagami M, Sasaki A

Basic Study

252 SLC6A14 promotes ulcerative colitis progression by facilitating NLRP3 inflammasome-mediated pyroptosis

Gu Q, Xia H, Song YQ, Duan J, Chen Y, Zhang Y, Chen HP, Zhang L

268 Calcium/calcimimetic *via* calcium-sensing receptor ameliorates cholera toxin-induced secretory diarrhea in mice

Tang LQ, Fraebel J, Jin S, Winesett SP, Harrell J, Chang WH, Cheng SX

LETTER TO THE EDITOR

280 Use of curcumin and its nanopreparations in the treatment of inflammatory bowel disease

Meng ZW, Chang B, Sang LX

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

Chang J, Liu Y, Jiang TC, Zhao L, Liu JW

World Journal of Gastroenterology

Weekly Volume 30 Number 3 January 21, 2024

Contents

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The primary aim of *World Journal of Gastroenterology* (*WJG*, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJG* mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The *WJG* is now abstracted and indexed in Science Citation Index Expanded (SCIE), MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJG* as 4.3; Quartile category: Q2. The *WJG*'s CiteScore for 2021 is 8.3.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yi-Xuan Cai*; **Production Department Director:** *Xu Guo*; **Editorial Office Director:** *Jia-Ru Fan*.

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

PUBLICATION DATE
January 21, 2024

PUBLISHING PARTNER
Shanghai Pancreatic Cancer Institute and Pancreatic Cancer Institute, Fudan University
Biliary Tract Disease Institute, Fudan University

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

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World Journal of Gastroenterology

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World J Gastroenterol 2024 January 21; 30(3): 283-285

DOI: 10.3748/wjg.v30.i3.283

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LETTER TO THE EDITOR

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

Jun Chang, Yan Liu, Ting-Can Jiang, Lan Zhao, Jian-Wei Liu

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Cerwenka H, Austria

Received: October 28, 2023
Peer-review started: October 28, 2023
First decision: December 5, 2023
Revised: December 16, 2023
Accepted: January 9, 2024
Article in press: January 9, 2024
Published online: January 21, 2024

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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, "Expression and functional study of cholecystokinin-A receptors on the interstitial Cajal-like cells of the guinea pig common bile duct" demonstrated that cholecystokinin (CCK) regulates the contractile function of the common bile duct through interaction with the 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 "Expression and functional study of cholecystokinin-A receptors on the interstitial Cajal-like cells of the guinea pig common bile duct" and provides a brief overview of the prospects and challenges of cholecystokinin (CCK) and CCK-A receptors as potential targets in biliary dyskinesia from the perspective of animal experiments and clinical studies.

Citation: Chang J, Liu Y, Jiang TC, Zhao L, Liu JW. Cholecystokinin and cholecystokinin-A receptor: An attractive treatment strategy for biliary dyskinesia? *World J Gastroenterol* 2024; 30(3): 283-285
URL: https://www.wjgnet.com/1007-9327/full/v30/i3/283.htm
DOI: https://dx.doi.org/10.3748/wjg.v30.i3.283

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 cholecystokinin (CCK)-A receptors are highly expressed by common bile duct (CBD) interstitial Cajal-like cells (ICLC) and that CCK interacts with ICLC 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*[1] found that in guinea pigs, CCK interacted with ICLC 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

Author contributions: Chang J drafted the manuscript; Liu Y and Jiang TC edited and revised the manuscript; Zhao L and Liu JW revised the letter and approved the final version of the manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country/Territory of origin: China

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S-Editor: Li L
L-Editor: A
P-Editor: Li L

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