

Influences of Gut Hormones on Hepatocellular Carcinoma

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Abstract

Hepatocellular Carcinoma (HCC) is worldwide the fifth most common cancer in men and represents the third most frequent cause of cancer death. Development of new therapeutic agents is of paramount importance in the management of HCC patients. Known studies indicated that most gut hormones were the promoter in HCC, including ghrelin, Cholecystokinin (CCK), gastrin, secretin, growth factor and leptin. Although these hormones have the different functions in digestion, most of them increase or have active expression in HCC. Presently, Gastrointestinal (GI) imaging is not good tips and traps in the diagnosis of small HCC. How to use the analysis of gut hormones to examine the liver function or detect the HCC is important. We hope that these findings can serve a good knowledge to therapy HCC.

Keywords: Hepatocellular Carcinoma; Gastrin; Cholecystokinin; Gut hormones; Catenin pathway

Background in Hepatocellular Carcinoma (HCC)

In 2014, HCC is worldwide the fifth most common cancer in men and the seventh one in women, and it represents the third most frequent cause of cancer death [1]. Most patients with HCC have elevated serum alpha fetoprotein (AFP) levels. The incidence of HCC is highest in Asia and Africa, where the major risk factors are hepatitis B and C, cirrhosis, and exposure to environmental carcinogens, such as aflatoxin [1]. The pathogenesis of HCC is a multistep process. The molecular pathways involved include p53, β -catenin, NF- κ B [2], MAPK [3], ERK [4], JNK [5], WNT/beta - catenin pathway [6] and PI3K/Akt [7], but the detailed molecular mechanisms of HCC are still poorly understood. It is more interesting to find the roles of hormones in HCC molecular mechanisms. In clinical, HCC patients have a poor prognosis unless treated surgically by resection or liver transplantation. HCC is potentially curable by surgical resection, but surgery is the treatment of choice for only the small fraction of patients with localized disease [8]. Although surgical resection and various tumor ablation methods can cure disease or prolong survival, the outcomes for most HCC patients remain grave. Prognosis depends on the degree of local tumor replacement and the extent of liver function impairment. Therapy other than surgical resection includes systemic or infusional chemotherapy [9], hepatic artery ligation [10] or embolization [11], percutaneous ethanol injection [12,13], radiofrequency ablation [14], cryotherapy [15], and radiolabeled antibodies [16], often in conjunction with surgical resection and/or radiation therapy. HCC is a chemo-refractory malignancy and most patients with unresectable HCC died soon despite aggressive treatment. In some studies of these approaches, long remissions have been reported. A few patients may be candidates for liver transplantation, but the limited availability of livers for transplantation restricts the use of this approach [17]. Presently, sorafenib is the only effective systemic therapeutic agent n, but its effect is only marginal [18]. Therefore, development of new therapeutic agents, as hormone therapy, may be an importance in the management of HCC patients.

Gut Hormones

Gastrointestinal (GI) endocrinology has since 1970. These regulatory gut peptides originally defined as three classifications - hormones, peptide transmitters, and growth factors. Gut hormones mean which were produced from stomach, pancreas, liver, or intestinal gland. These gut regulatory peptide groups including ghrelin, Cholecystokinin (CCK), gastrin, secretin, growth factor, leptin, Vasoactive Intestinal Polypeptide (VIP), Gastric Inhibitory Polypeptide (GIP), Neuropeptide

Y(NPY), substance P, etc. There are six GI hormones that are generally recognized as the primary hormones. Secretin and GIP are parts of the secretin family. Ghrelin and motilin are parts of the motilin family. The gastrin-CCK family includes gastrin and CCK. They exert autocrine and paracrine actions that integrate all of the GI function. Many studies indicated that most of the gut hormones are associated with liver cancer, due to the existence of them in GI system; it is interesting to integrate these findings in HCC.

GI environment in HCC

In GI tract, intestinal microflora, as a main source of portal-vein LPS, might play a critical role in hepatofibrogenesis and carcinogenesis [19]. Besides, intestinal microbiota and Toll-like Receptors (TLRs), which are long-term consequence of chronic liver injury, inflammation, and fibrosis, can promote HCC [20]. Gut-derived norepinephrine also plays a critical role in producing hepatocellular dysfunction during early sepsis [21]. As above, it means that gut environment may be connected with liver carcinogenesis. The gut hormones are acted on this GI environment.

Ghrelin

Ghrelin, secreted in hunger, is a peptide hormone released from the stomach, liver and hypothalamus. There are two major forms: n-octanoyl-modified ghrelin (acylated ghrelin) and des-acyl ghrelin. The active form acylated ghrelin, even called Growth Hormone (GH) secretagogues, was a GH-releasing peptide and promoted the GH release [22]. In GH-STAT5 pathway, GH may regulate the liver, and the GH receptor expression decreases in HCC tissues. Few findings shown that ghrelin levels in cirrhosis and HCC, which due to hepatitis B and D viruses were association with TNF-alpha, IL-6 and the severity of the disease [23]. Serum ghrelin levels were significantly increased in cirrhosis and HCC, and significantly decreased with AFP [23]. Moreover, cisplatin-based transcatheter arterial infusion (TAI) chemotherapy was indicated to reduce plasma ghrelin levels and food intake in HCC patients [24].

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CCK

CCK, previously called pancreozymin, is synthesized by I-cells in the mucosal epithelium of the small intestine and secreted in the duodenum. The C-terminal 8 amino acid peptide has been found in inhibition of GI motility [25] and in suppression of plasma total ghrelin [26]. Most CCK peptides have a sulfate-group attached to the tyrosine in position 7 in the C-terminus. Up to now, there are still few studies about the relationship between CCK and HCC. Only one study has shown the internalisation of anti-CCK-B receptor into the nucleus of live cancer cell lines of colonic, pancreatic and hepatic origin [27]. Nuclear expression of the CCK-B receptor was observed in human resection specimens of HCC, pancreatic carcinoma, and gastric carcinoid [28].

Gastrin

Gastrin is a peptide hormone that released by G cells in the pyloric antrum of the stomach, duodenum, and the pancreas. Gastrin binds to CCK-B receptors to stimulate the release of histamines in enterochromaffin-like cells. Gastrin is a trophic factor within the normal GI tract, and is also a mitogen for a number of GI and non-GI tumours [28]. Endocytosis of gastrin has been demonstrated in tumor cell lines expressing gastrin receptor, and this has raised the possibility of receptor targeted therapy [27].

Secretin

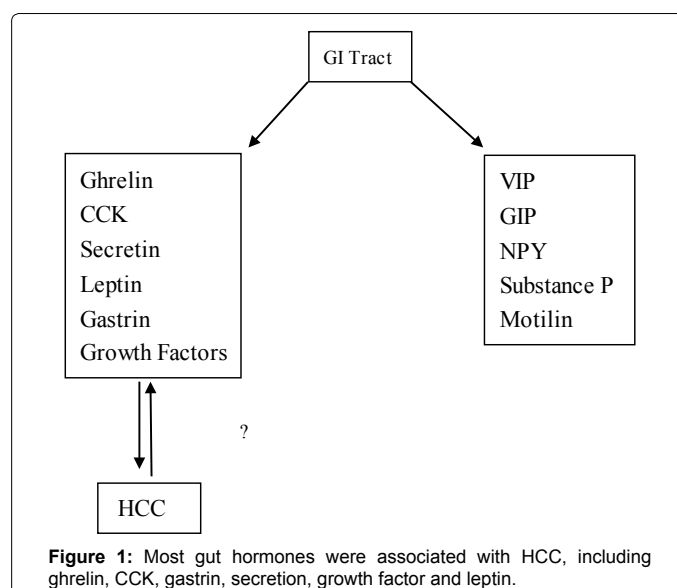
Secretin is a peptide hormone which is composed of 27 amino acids and regulates pancreatic secretion of HCO_3^- , reduces gastric motility and inhibits gastrin release. The expression of secretin receptors in the biliary tract are the molecular basis of the secretin-induced bicarbonate-rich choleresis in man. Due to the secretin receptors are expressed in biliary tract and cholangiocarcinoma, but not in hepatocytes or hepatocellular carcinoma, the high receptor expression in cholangiocarcinomas may be used for in vivo secretin receptor-targeting of these tumors and for the differential diagnosis with HCC [29].

Growth Factors

Growth factors are important for regulating a variety of cellular processes, including cytokines and hormones that bind to specific receptors on the surface of their target cells. Due to the importance for regulating a variety of cellular processes, many kinds of growth factors have different roles in HCC. In 2013, known studies have shown that Fibroblast Growth Factor 21 (FGF21), an endocrine factor secreted mainly by the liver, exerts a protective action against cardiac hypertrophy. The liver is considered the main site of production of FGF21 under the starvation, stress, or some disease. Inhibition of fibroblast growth factor receptor signaling impairs metastasis of HCC [30]. On the other hand, pre-LT plasma Vascular Endothelial Growth Factor (VEGF) level > 44 pg/ml may be a predictor of tumor vascular invasion in patients with chronic end stage liver disease and HCC, [31]. Moreover, insulin-like growth factor-2 (IGF-2) genes polymorphisms and their combinations are defined as the associated factors in risk of HCC [32].

Leptin

Leptin, a appetite control, is mainly secreted from adipose tissue. Leptin, as ghrelin, participates in the complex process of energy homeostasis. Leptin and its receptors were proved to be associated with many human cancers. Some findings indicated that leptin administration induces a significant suppression of human HCC [33],



at the same time, the serum leptin levels were significantly decreased in cirrhosis and HCC [23]. Leptin levels in cirrhosis and HCC under hepatitis B and D viruses were associated with leptin in TNF-alpha, IL-6 and the severity of the disease [23]. Moreover, leptin inhibits HCC cell growth in vitro via a p38-MAPK-dependent signalling pathway [34]. Leptin is also a key regulator of the malignant properties of HCC cells through modulation of hTERT, a critical player of oncogenesis [35].

Other Gut Hormones

VIP is a peptide hormone containing 28 amino acid residues. It relaxes smooth muscle of gut, blood, and genitourinary system as well as increases water and electrolyte secretion from pancreas and gut. However, the relationship between VIP and HCC is still unknown, as the roles of neuropeptide Y, substance P, GIP, motilin in HCC.

Conclusion

Known studies indicated that most gut hormones were associated with HCC, including ghrelin, CCK, gastrin, secretion, growth factor and leptin. Although these hormones have the different functions in digestion, most of them increase or have active expression in HCC. As shown in Figure 1 we integrate the similar characteristics of gut hormones according to the connection with HCC or unknown. We think some gut hormones, like ghrelin, CCK, gastrin, secretion, growth factor and leptin, may be the key roles in HCC. Because the dietary habits are connected to the gut hormone secretion, we broadly hypothesize that when people were hungrier, or overall full, it may bring the negative effects on cell growth or carcinogenesis. Moreover, during the cancer cell proliferation, the hormone secretion may be different. Discussing the relationship between gut hormone and HCC in detail will be the important future work. We conclude that, presently, GI imaging is not good tips and traps in the diagnosis of small HCC [36]. How to use the analysis of gut hormones to examine the liver function or detect the HCC is important. We hope that these finding can serve a good knowledge to therapy HCC.

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