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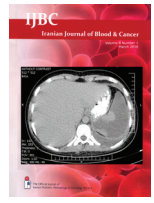

Review Article

Role of Ghrelin in Cancer

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ABSTRACT

Cancer is one of the most fatal diseases in human beings which annually leads to death of 30000 individuals in Iran. Prevention, diagnosis and treatment of cancer is one of the major scientific challenges all around the world. It seems that increased incidence of several cancers such as colon and prostate and their mortality are connected with obesity. It is suggested that obesity and metabolic syndrome are associated with endocrine related cancers and ghrelin pathway may play a role in cancer progression. Ghrelin is a potent regulator of the growth hormone (GH)/ insulin-like growth factor-1 (IGF-1) axis, which is frequently implicated in the development of several neoplasms, including colon cancer. It has been reported that changed ghrelin level as a main regulator of energy homeostasis plays an important role in carcinogenesis. Also, antiproliferative effects of ghrelin in lung and breast carcinoma cell lines have been detected in some studies . In this paper, ghrelin and its role and function in cancer is discussed.

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Introduction

One of the most fatal diseases in human beings is cancer which annually leads to the death of about 30000 persons in Iran.[1] This incurable disease continues to be a major problem in recent years.[1-3] It seems that increased risk of the expansion of several cancers such as colon and prostate cancers, and their risk with mortality are connected to obesity.[4] Hormonal abnormalities in obese people such as low ghrelin level may play a key role in cancer development. Moreover, the undesirable side effects of currently standard therapies for colon and androgen independent prostate cancers lead to persistent need for new and more powerful therapeutic options.[4]

Ghrelin

Ghrelin is a 28-amino acid peptide[5-7] mainly produced in the stomach[8] of humans and rodents.[3] It is also produced by a wide variety of tissues and acts as a paracrine/ autocrine factor.[8] About 60–70% of circulating ghrelin is originated by stomach, while about up to 30% is produced in the small intestine.[9] Moreover, other tissues including pancreas and cardiovascular system could produce ghrelin.[10] Albeit ghrelin expressed in heart is lower than that in the stomach, but it exerts a cardioprotective effect via unknown mechanisms.[11] Ghrelin known as a brain-gut peptide can induce changes such as increased food intake and body fat through altered appetite and amount of food intake.[12,13]

Ghrelin plays a significant role in release of GH and triggers secretion of hepatic IGF-1. Both GH and IGF-1 as anabolic hormones can increase lean body mass via stimulating skeletal muscle growth and inhibiting skeletal muscle protein breakdown.[14] It has been reported that ghrelin causes positive energy balance via decreasing fat utilization by GH-independent mechanisms.[15] Moreover, the secretion of ghrelin is stimulated via energy restriction and acetylcholine and reduced via gastrectomy, food intake, glucose, insulin and somatostatin releasing

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inhibitory factor (SRIF).[10] Also it plays an important role in metabolic response to starvation via modulating insulin secretion, glucose metabolism and amino acid uptake.[3] Ghrelin stimulates the differentiation of preadipocytes and inhibit lipolysis. Therefore it has a main role in the process of adipogenesis.[16] It increases anxiety-like behavior and memory retention in rodents and may promote sleep in human beings.[16] Inhibition of insulin secretion and regulation of gluconeogenesis/glycogenolysis was accomplished in the presence of ghrelin; therefore, it regulates glucose homeostasis in many aspects.[17] Ghrelin is pertained to G protein-coupled receptor family.[18,19] Ghrelin could cause weight gain through growth hormone secretion and as a result increasing food intake and reducing fat utilization in rodents.[20] It also moderates some actions of gastrointestinal tract and alters the growth processes of neoplastic tissues.[2]

Ghrelin exists in two molecular forms: acylated or octanoylated and unacylated or desoctanoylated.[2] Unacylated ghrelin via ghrelin O-acyltransferase (GOAT) enzyme can be acylated[8] and yields the natural ligand of the only known ghrelin receptor.[8] Figures 1 and 2 show unacylated and acylated ghrelin, respectively.

Endocrine activity of ghrelin is dependent on its acylation mediated by GH secretagogue (GHS) receptor and des-acyl ghrelin has no endocrine activity and does not bind to GHSR-1a; however, its mechanism of action is not defined well.[11]

Ghrelin and Cancer

Gastrointestinal cancers, especially colorectal cancers are associated with obesity and strong relationship is observed between these cancers and environmental factors in addition to genetic factors. Obesity is associated with hyperisulinemia or insulin resistance with elevated leptin and decreased ghrelin serum levels. Obesity and metabolic syndrome are associated with endocrine related cancers and ghrelin has proposed to have some influencial role in cancer development or progression.[21] Ghrelin is a potent regulator of the GH/IGF-I axis which is frequently implicated in the development of several neoplasms, including colon cancer.[2] It has been observed that circulating changes in leptin and ghrelin levels as two main regulators of energy homeostasis could play important role in carcinogenesis.[2] Clear-cut data about

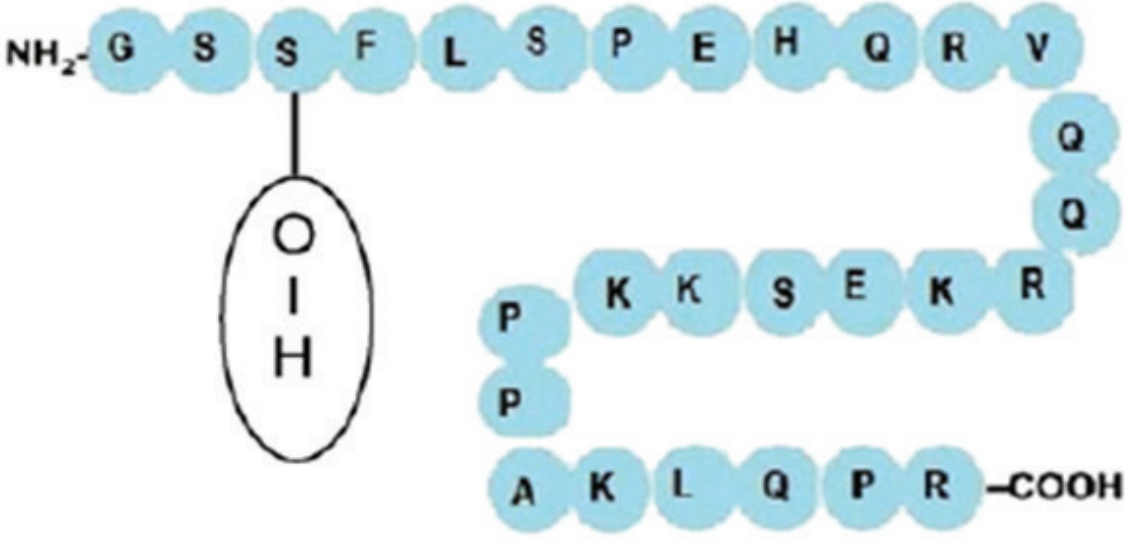

Figure 1: Unacylated ghrelin[9]

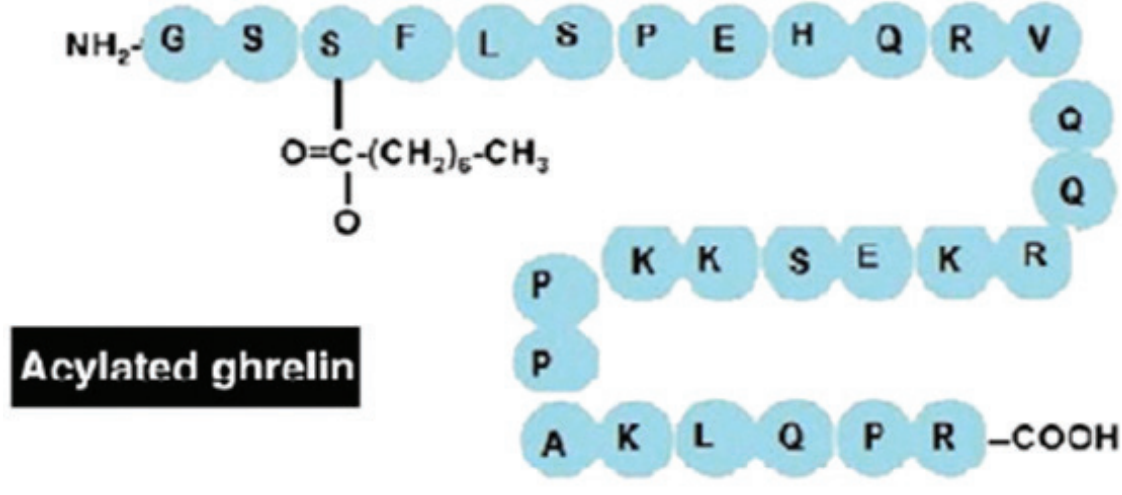

Figure 2: Acylated ghrelin[9]

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ghrelin and its effects on proliferative pathologies is contradictory for now.[3]

Ghrelin and its receptors exist in many endocrine and non-endocrine tumor cell types such as gastroenteropancreatic, pituitary, prostate, breast and other related cancer cell lines.[8] Ghrelin controls neoplastic cell proliferation, but precise role of ghrelin still is not clear.[8] Some studies have reported that ghrelin has proliferative properties in cancers. Study in canine mammary carcinoma showed that there are high levels of ghrelin and GHS-R in metastatic tumors.[17]

Ghrelin has shown antiproliferative effects in lung and breast carcinoma cell line and proliferative effects in prostate, pancreatic and adrenal cancer cell lines.[3] Another study reported that ghrelin may inhibit growth of breast, thyroid and lung cancer cell lines independent of the GH releasing effect. In contrast, ghrelin may induce a proliferative response in some other cell lines via IGF-1 and GH with tumorigenic potential.[16]

The effect of ghrelin on breast cancer cell proliferation is discovered by Jeffery et al. in their study.[22] They evaluated proliferation of breast cancer cell lines MDAMB-231 and MDA-MB-435 and observed that growth rate of MDA-MB-231 cells was significantly increased in the presence of ghrelin.[9]

Volante et al. in another study reported that high concentrations of ghrelin (100 nmol/ l–1 µmol/l) has anti-proliferative actions in thyroid cancer cells. They also suggested that autocrine circuits of ghrelin may be operating in the growth control of thyroid follicular tumors.[23]

De Vriese et al. evaluated the autocrine proliferative effect of ghrelin on human leukemic HL-60 and THP-1 cell lines.[24] The human leukemic cell lines did not express the functional GHS-R1a, but expressed GHSR1b. They observed that addition of octanoylated or des-acyl ghrelin did not exert any effect on leukemic cell proliferation. Another study has shown that ghrelin levels in gastric cancer tissues were significantly lower than normal tissues and a significant difference was observed according to the degree of cell differentiation.[9]

Researchers also examined the proliferative effect of ghrelin and its mechanisms of action on pituitary cell line (GH3). They showed that ghrelin, at 10−10 to 10−6 M concentrations exerts GH3 pituitary somatotroph cell proliferation. In addition, activation of the MAPK pathway and inhibitors of the extracellular signal-regulated kinase 1 and 2 (ERK 1/2), protein kinase C (PKC) and tyrosine phosphatase pathways were evaluated. The results showed that PKC-MAPK-dependent and tyrosine kinase-dependent pathways are mediators of proliferation of GH3 cells in the presence of ghrelin.[9]

Other studies have indicated expression of ghrelin in leydig cell tumors and dysgenetic sertoli cells. They described that differentiated leydig cell tumors were associated with ghrelin expression;[25] Whereas, poorly differentiated types were negative for ghrelin expression.[9] Karapanagiotou et al. evaluated the role of ghrelin in advanced non-small cell lung cancer patients and observed significantly higher ghrelin serum levels in these patients.[26]

A starting role of ghrelin in cancer cell migration and invasion has also been detected. Ghrelin concentrations of 100 nM could cause increment of migration ability of canine carcinoma cell lines.[18]

Conclusion

The existing knowledge regarding ghrelin and its effect on proliferation processes is contradictory. However, ghrelin abnormalities in obese population may have contribution in tissue growth and cancer development.

Conflict of Interest: None declared.

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