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Review

Ghrelin and cancer

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ABSTRACT

Ghrelin is a peptide hormone that was originally isolated from the stomach as the endogenous ligand for the growth hormone secretagogue receptor (GHSR). Ghrelin has many functions, including the regulation of appetite and gut motility, growth hormone release from the anterior pituitary and roles in the cardiovascular and immune systems. Ghrelin and its receptor are expressed in a number of cancers and cancer cell lines and may play a role in processes associated with cancer progression, including cell proliferation, apoptosis, and cell invasion and migration.

Contents

1. Introduction

Ghrelin is a multifunctional peptide hormone originally isolated from the stomach as the endogenous ligand for the growth hormone secretagogue receptor (GHSR) (Kojima et al., 1999). Ghrelin has a number of functions, including roles in the regulation of growth hormone release, metabolism, appetite, the cardiovascular system and insulin secretion (Kojima et al., 1999). There is also growing evidence that ghrelin plays an autocrine/paracrine role in a number of processes related to cancer progression, including cell proliferation (Jeffery et al., 2002; Jeffery et al., 2003), cell migration (Dixit et al., 2006), and apoptosis (Fung et al., 2010). This review will focus on the autocrine/paracrine role of ghrelin in cancer, and the actions of ghrelin that may promote cancer progression.

2. Paracrine/autocrine ghrelin

2.1. Local expression of the ghrelin-axis

While ghrelin was originally discovered in the rat and human stomach (Kojima et al., 1999), the expression of ghrelin and its receptor, the growth hormone secretagogue receptor (GHSR), has been demonstrated in a range of tissues. This includes the small and large intestine, the hypothalamus and pituitary (Korbonits et al., 2001) and a number of other peripheral tissues, including

Abbreviations: NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

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the endocrine pancreas (Volante et al., 2002) and placenta (Gualillo et al., 2001). Local production of ghrelin has been shown in a range of cancers including pituitary adenomas (Kim et al., 2001; Korbonits et al., 2001; Wasko et al., 2006; Wasko et al., 2008), and colorectal (Papotti et al., 2001; Waseem et al., 2008), gastric (An et al., 2007; Aydin et al., 2005; Ekeblad et al., 2006; Papotti et al., 2001), prostate (Cassoni et al., 2004; Jeffery et al., 2002; Yeh et al., 2005), breast (Jeffery et al., 2005), thyroid (Volante et al., 2003), endocrine pancreatic (Ekeblad et al., 2007; Iwakura et al., 2002; Volante et al., 2002), ovarian (Gaytan et al., 2005), endometrial (Fung et al., 2010), testicular (Gaytan et al., 2004), adrenocortical (Ueberberg et al., 2008), renal (Dagli et al., 2009) and lung cancer (Cassoni et al., 2006). Ghrelin is highly expressed in the stomach and ghrelin secretion is greatly reduced in atrophic gastritis associated with *Helicobacter pylori* infection, as ghrelin-producing cells are damaged in this precancerous condition (Zub-Pokrowiecka et al., 2010). Treatment for gastric cancer, where the whole stomach is removed, therefore, greatly reduces plasma ghrelin levels (Zub-Pokrowiecka et al., 2010).

The growth hormone secretagogue receptor (GHSR) isoforms, GHSR 1a and GHSR 1b, are also widely expressed (Gnanapavan et al., 2002; Ueberberg et al., 2009). Many of the endocrine functions of ghrelin appear to be mediated by the GHSR 1a isoform, which is known as the functional ghrelin receptor. GHSR 1a expression was initially characterised in the pituitary and the hypothalamus (Howard et al., 1996) and it is also expressed in numerous peripheral tissues including the stomach, intestine, pancreas, spleen, thyroid, gonads, adrenal gland, kidney, heart, lung, liver, adipose tissue, bone and prostate (Camina, 2006; Gnanapavan et al., 2002; Jeffery et al., 2002; Kojima and Kangawa, 2005; Soares and Leite-Moreira, 2008). The GHSR is expressed in a range of tumours, including pituitary tumours, prostate, breast and ovarian cancer and in astrocytoma (Adams et al., 1998; Dixit et al., 2006; Gaytan et al., 2005; Jeffery et al., 2002, 2005; Korbonits et al., 1998; Skinner et al., 1998). GHSR 1a expression is absent in some cases of colorectal cancer, adrenocortical tumours, non-small cell lung cancer, leukaemia and some breast cancer cell lines (Barzon et al., 2005; Cassoni et al., 2001; Ghe et al., 2002; Takahashi et al., 2006). GHSR1a expression is not required for all ghrelin functions, however, and many of the effects of ghrelin could be mediated by an alternative receptor that has not yet been identified (for review, see Seim et al., 2011).

The truncated, 5-transmembrane domain, ghrelin receptor isoform, GHSR 1b, is believed to be a non-functional isoform of the receptor (Howard et al., 1996; Kojima et al., 1999). In a number of cancers, GHSR 1a expression is downregulated or absent (Barzon et al., 2005; Cassoni et al., 2001; Ghe et al., 2002; Takahashi et al., 2006), while the non-functional, truncated form of the receptor, GHSR 1b is widely expressed in cancer and expression may be upregulated compared to normal tissues (Waseem et al., 2008).

2.2. Paracrine/autocrine actions of the ghrelin axis in cancer progression

2.2.1. Ghrelin in cell proliferation

As ghrelin is synthesised locally in many tissues, it could act as an autocrine/paracrine growth factor in normal and cancer tissues (Jeffery et al., 2002). While most studies indicate that ghrelin stimulates cell proliferation in normal cell lines (Andreis et al., 2003; Maccarinelli et al., 2005; Nanzer et al., 2004; Pettersson et al., 2002; Wang et al., 2009; Xia et al., 2004), the effect of ghrelin in cancer cell lines has proven more controversial.

Ghrelin may act as a growth factor in a range of cancers and increase cell proliferation, a hallmark of cancer (Hanahan and Weinberg, 2000; Jeffery et al., 2003; Soares and Leite-Moreira, 2008). Ghrelin stimulates proliferation in a number of cancer cell lines, including the HepG2 human hepatoma cell line (Murata et al., 2002), human erythroleukaemic (De Vriese et al., 2005), and leukaemic cell lines (De Vriese and Delporte, 2008), in adrenocortical carcinoma (Barzon et al., 2005), in pancreatic adenocarcinoma cell lines (Duxbury et al., 2003), colorectal cancer (Waseem et al., 2008), the JEG-3 choriocarcinoma cell line (Rak-Mardyla and Gregoraszczuk, 2010) and in prostate (Jeffery et al., 2002; Yeh et al., 2005), breast (Jeffery et al., 2005) and endometrial cell lines (Fung et al., 2010). Ghrelin-induced proliferation is mediated by the ERK1/2 MAPK pathway in a number of cell lines, including prostate cancer cells lines (Yeh et al., 2005), the rat normal pituitary-derived GH3 cell-line (Nanzer et al., 2004), and the rat thyrocyte FRTL-5 cell line (Park et al., 2008).

While a number of studies have demonstrated that ghrelin stimulates cell proliferation, some reports indicate that ghrelin may inhibit proliferation. This includes thyroid (Volante et al., 2003), prostate (Diaz-Lezama et al., 2010) and breast cancer (Cassoni et al., 2001) and small cell lung carcinoma (Cassoni et al., 2006) cell lines. Studies in the ARO anaplastic thyroid carcinoma and the N-PAP papillary follicular thyroid carcinoma cell lines demonstrated a modest inhibition of cell growth using crystal violet staining-based assay (Volante et al., 2003). In the N-PAP cell line, a statistically significant decrease in cell proliferation was seen with 100 nM and 1 μM concentrations of ghrelin after 96 h. In the ARO cell line, a significant decrease in cell number was only seen with 1 μM ghrelin treatments and no effect was seen in cells treated with 10 nM ghrelin (Volante et al., 2003). In contrast, no change in cell proliferation was seen in the ARO cell line treated with ghrelin, or in this cell line stimulated with thyroid stimulating hormone in another study (Park et al., 2008). It is unclear if ghrelin was replenished during the assay in these studies.

The role of ghrelin in stimulating cell proliferation in prostate cancer remains controversial. Studies performed by our research group have shown that ghrelin stimulates proliferation of the PC-3 prostate cancer cell line at levels within the physiological range (5–10 nM) using a metabolic, colourimetric MTT assay (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) to estimate changes in cell number (Jeffery et al., 2002; Yeh et al., 2005). A similar response in the PC3 cell line has been reported, where low concentrations of ghrelin (10–100 pM) stimulated cell proliferation, but higher concentrations (1 μM) inhibited proliferation (Cassoni et al., 2004). In contrast, a recent study demonstrated that ghrelin treatment (10–50 nM) decreased the incorporation of ^{3}H thymidine in the PC3 cell line, indicating that it decreased cell proliferation (Diaz-Lezama et al., 2010). Ghrelin treatment stimulated an increase in intracellular free calcium and the decrease in cell number was inhibited by treatment with T-type calcium channel blockers (Diaz-Lezama et al., 2010). We have also demonstrated that ghrelin stimulates cell proliferation in the LNCaP prostate cancer cell line (Yeh et al., 2005). In contrast to our findings, Cassoni et al. (2004) demonstrated no effect on LNCaP prostate cancer cell line proliferation. In the androgen-independent DU145 prostate cancer cell line, ghrelin and des-ghrelin alone had no effect on cell proliferation (measured by ^{3}H thymidine incorporation), but they inhibited cell proliferation stimulated by IGF-I treatment (Cassoni et al., 2004).

Although the reasons for these discrepancies are not immediately apparent, these studies varied in the concentrations of ghrelin used and in the assay method applied. The application of supraphysiological doses of ghrelin could have an inhibitory effect, while physiological levels could stimulate cell proliferation (Lanfranco et al., 2008; Nikolopoulos et al., 2010). In our assays, ghrelin was replenished every 24 h, while Cassoni et al., treated the cells with ghrelin every 48 h. Ghrelin has been reported to have a short half-life and it is rapidly de-acetylated and also protelytically cleaved (De Vriese et al., 2004; Hosoda et al., 2004) and therefore, chronic