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Gene Section
Review

GRPR (Gastrin-Releasing Peptide Receptor)

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Abstract

Bombesin (BB) and gastrin-releasing peptide (GRP) bind with high affinity to the GRP-receptor (GRP-R) which regulates release of gastrointestinal hormones, smooth muscle contraction and proliferation of epithelial as well as cancer cells. The GRP-R is a G-protein coupled receptor (GPCR) which activates phospholipase C signaling pathways. The GRP-R is expressed in numerous cancers including breast, colon, lung and prostate cancer.

Identity

HGNC (Hugo): GRPR

Location: Xp22.2

DNA/RNA

Note

The human GRP-R gene has 3 exons and is localized to chromosome Xp22.2.

Description

The gene has 3 exons. The GRP-R gene spans 30218 bases.

Transcription

The GRP-R gene has 9 and 3.1 kb transcripts in human stomach as well as NCI-H345 lung cancer cells, T47D breast cancer cells and HuTu 80 duodenal carcinoma cells.

The pancreas has 9, 4.6, 3.1 and 2.1 kb transcripts. Polymorphisms are observed at 794 (G-A), 851 (C-T) and 1061 (C-T) but these do not alter the GRP-R sequence (Xiao et al., 2001).

The GRP-R gene has 1155 bp.

Protein

Note

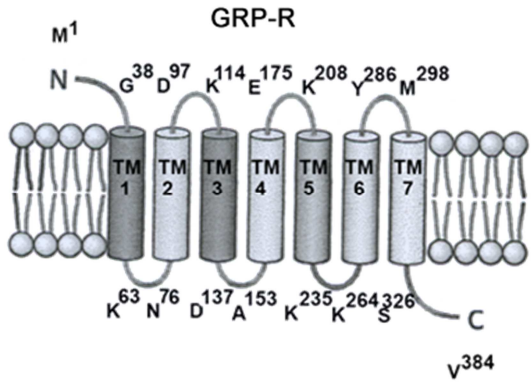
Bombesin, a 14 amino acid peptide (Anastasi et al., 1974) and gastrin-releasing peptide (GRP), a 27 amino acid peptide (McDonald et al., 1979), bind with high affinity to receptors initially characterized in the rat brain (Moody et al., 1978) and guinea pig pancreatic acini (Jensen et al., 1978).

The GRP-R was cloned (Battey et al., 1991; Spindel et al., 1990) and found to be a G-protein coupled receptor (GPCR) containing 384 amino acids.

The human GRP-R gene is localized to the X chromosome and the GRP-R has 7 transmembrane (TM) domains, an extracellular N-terminal and intracellular C-terminal.

Exon 1 codes for TM 1, 2 and 3 domains with splice site in IC loop 2 (Asp^{137}). Exon 2 codes for TM 4 and 5 with a Gln^{255} splice site. Exon 3 codes for TM 6-7 domains and the cytoplasmic C-terminal. Exon 1, 2 and 3 have 413 bp, 352 bp and 390 bp respectively whereas introns 1 and 2 are 23 kb and 1.6 kb respectively (Xiao et al., 2001).

The human GRP-R is glycosylated at Asn^{20}, palmitoylated at Cys^{339} and has a disulfide between Cys^{113} and Cys^{196} (Jensen et al., 2008). For GRP-R agonist binding Gln^{120}, Pro^{198}, Arg^{287} and Ala^{307} are essential (Akeson et al., 1997). For GRP-R antagonist binding Thr^{296}, Phe^{301} and Ser^{304} are essential (Tokita et al., 2001). GRP-R antagonists include ($Psi^{13,14}$, Leu^{14})BB, ($D\text{-}Phe^{6}$)BB^{6-13}propylamide and PD176,252 (Gonzalez et al., 2009).



Human GRP-R protein. The GRP-R, which is a glycoprotein embedded in the plasma membrane, contains 384 amino acids with 7 TM domains, an extracellular N-terminal and intracellular C-terminal. The amino acids at the N- and C-terminal are indicated. The amino acids before and after each of the 7 TM domains are indicated. Numerous amino acids in or near TM 2, 3, 4, 6 and 7 domains are essential for agonist binding, whereas amino acids in or near TM 6 and 7 domains are important for antagonist binding.

Description

The GRP-R interacts with Gq causing phosphatidylinositol turnover (Rozengurt, 1998). As a result, BB addition to small cell lung cancer (SCLC) cells causes increased protein kinase C activity and elevation of cytosolic Ca^{2+} (Moody et al., 1987). Also, BB causes tyrosine phosphorylation of EGFR, ERK, FAK, paxillin, and Src leading to increased cellular proliferation (Jensen et al., 2008).

Expression

The GRP-R is localized to the normal brain especially the periventricular nucleus (PVN) of the hypothalamus (Wolf et al., 1983) where activation by BB causes satiety (Gibbs et al., 1979). The GRP-R, which regulates insulin secretion, is present in the pancreatic islets (Persson et al., 2002). The GRP-R is present in colonic villi and may play a role in villi development (Carroll et al., 2002). The GRP-R is present on small cell lung cancer (SCLC) cells and BB stimulates whereas (Psi^{13,14}, Leu^{14})BB or PD176252 inhibits cellular proliferation (Mahmoud et al., 1991; Moody et al., 2003). The GRP-R is present on squamous cell carcinoma of the head and neck cancer cells and PD176252 inhibits the growth of these cells (Zhang et al., 2007). In colon cancer the transcription factor CREB is a regulator of GRP-R expression (Chinnappan et al., 2008).

Localisation

The GRP-R is localized to the plasma membrane of normal and cancer cells.

Homology

Other receptors of the BB family include neuromedin B (NMB) which contains 390 amino acids (Wada et al., 1991) and has 55% sequence homology with the GRP-R.
An orphan receptor named BB receptor subtype 3 (BRS-3) was cloned which contains 399 amino acids and has 51% sequence homology with the GRP-R (Fathi et al., 1993).
The GRP receptor binds BB and GRP with high affinity whereas the NMB receptor binds NMB with high affinity.
BRS-3 does not bind BB, GRP or NMB with high affinity (Jensen et al., 2008).

Mutations

Note
The GRP-R gene has 4 point mutations in biopsy specimens from patients with autism spectrum disorders, 2 of which result in amino acid changes (C6S and L181F).
The mutated GRP-R had normal agonist binding and second messenger production (Seidita et al., 2008).
Also an X-8 translocation occurs in intron 1 of the GRP-R gene in a patient with infantile autism (Ishikawa-Brush et al., 1997).

Implicated in

Lung cancer

Note
High densities of GRP-R are present in SCLC and NSCLC biopsy specimens and cell lines (Mattei et al., 2014). BB stimulates whereas GRP-R antagonists such as PD176252 inhibit lung cancer cellular proliferation (Moody et al., 2003).

Prostate cancer

Note
Numerous radioligands have been developed to image the GRP-R in prostate cancer patients (Mansi et al., 2013; Sancho et al., 2011). GRP-R antagonists have been radiolabeled with (111)In, (99m)Tc, (68)Ga or (64)Cu (Abiraj et al., 2011). High tumor/background ratios were obtained as PET and SPECT images.

Breast cancer

Note
Cytotoxic BB conjugates of 2-pyrrolinodoxorubicin inhibit the growth of breast cancer xenografts in nude mice (Engel et al., 2005). The GRP-R was detected in 41/57 breast carcinoma biopsy specimens (Reubi et al., 2002).

Colon cancer

Note
The GRPR regulates colon cancer cellular differentiation and impairs cellular metastasis (Carroll et al., 1999).

Head and neck cancer

Note

The GRP-R regulates transactivation of the epidermal growth factor receptor in head and neck squamous cell carcinoma (Lui et al., 2003). The mitogenic effects of GRP require the activation of an EGFR-dependent MEK/ERK-dependent pathway.

Diabetes

Note

GRP-R knockout mice had impaired glucose tolerance due to a defect in insulin release (Persson et al., 2000).

Satiety

Note

GRP-R blockade antagonizes feeding suppression by peripherally administered GRP (Ladenheim et al., 1996).

Hormone secretion

Note

The GRP-R regulates the secretion of numerous hormones including gastrin, glucagon, insulin, pancreatic polypeptide, prolactin and somatostatin (Westendorf and Schonbrunn, 1982; Jensen et al., 2008).

Pruritus

Note

GRP-R containing spinal cord neurons, which are present in lamina I, mediate itch sensation (Sun et al., 2009). Addition of GRP-R antagonists inhibited scratching behavior in 3 mouse models of itching.

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