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NEUROMEDIN U: A BIOACTIVE PEPTIDE AND ITS ROLE IN PANCREATIC CANCER

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ABSTRACT

Neuromedin U (NmU) is a neuropeptide belonging to the neuromedin family and is found in the brain of humans and other mammals. They have number of diverse functions and a highly conserved neuropeptide present in many species, existing as multiple isoforms. Neuromedin U is exerting its biological response mediated via two receptors, peripheral NmUR1 and central nervous system NmUR2. Both receptors are examples of Class A G-protein coupled receptors (or GPCRs) with a distinct distributional pattern. The activation of NmU receptors leads to intracellular signal transduction via calcium mobilization, phosphoinositide (or PI) signaling, and the inhibition of cAMP production. Several other peptide and non-peptide ligands are also available for the NMU receptors for example Neuromedin S is NmUR2 selective. The exact role of neuromedin- u in cancer is not yet fully understood. The research output revealed that, theNmU and its receptor NMUR2 have been shown to be over-expressed in human pancreatic cancers compared to normal cells. Studies also showed NmU serum levels decreased after the tumors were removed, as NmU and its receptor are localized predominantly in cancer cells. So in this article we have tried to summarize the mechanism of over-expression of neuromedin U receptors in pancreatic cancer via different signal transduction mechanism.

KEYWORDS: Neuromedin U, Pancreatic cancer, G-protein coupled receptors, Signal transduction.

INTRODUCTION

Pancreatic cancer

Pancreatic cancer is a disease in which healthy cells in the pancreas stop working correctly and grow out of control. These cancerous cells can build up and form a mass called a tumor. A cancerous tumor is malignant, meaning it can grow and spread to other parts of the body. As it grows, a pancreatic tumor can affect the function of the pancreas, grow into nearby blood vessels and organs, and eventually spread through a process called metastasis to other parts of the body.[1]

Types of pancreatic cancer

- Insulinoma
- Glucagonoma
- Somatostatinoma

Insulinoma

Insulinoma forms in your pancreas, however, it will continue to produce insulin, even when your blood sugar is too low. This can lead to severe hypoglycemia.[2]

Symptoms

- Double vision or blurred vision
- Confusion
- Anxiety and irritability
- Dizziness
- Mood swings
- Weakness
- Sweating
- Hunger
- Tremors
- Sudden weight gain[3]

Causes

When eat food, the pancreas creates insulin. Insulin is a hormone that helps your body store the sugar from your food the sugar has been absorbed, the pancreas stops producing insulin.[4] This process usually keeps blood sugar levels stable. it can be disrupted when an insulinoma

develops. The tumor continues to produce insulin even when your blood sugar drops too low. This can lead to hypoglycemia, a serious condition characterized by low blood sugar levels.[5]

Diagnosis

The test can check for

- proteins that block the production of insulin
- medications that cause the pancreas to release more insulin
- Other hormones that affect insulin production including an MRI or CT scan. These imaging tests help your doctor determine the location and size of the insulinoma.[6]

Treatement

The best treatment for an insulinoma is surgical removal of the tumor. A small part of the pancreas may also be removed if there's more than one tumor. This typically cures the condition.

Treatments for cancerous insulinomas include

- Radiofrequency ablation, which uses radio waves to kill cancerous cells in the body
- Cry therapy, which involves the use of extreme cold to destroy cancerous cells
- Chemotherapy, which is an aggressive form of chemical drug therapy that helps destroy cancerous cells.[7]

Glucagonoma

Glucagonoma is a rare tumor involving the pancreas. Glucagon is a hormone produced by the pancreas that works with insulin to control the amount of sugar in your blood.[8] Glucagonomatumor cells produce large amounts of glucagon, and these high levels create severe, painful, and life-threatening symptoms. About 5 to 10 percent of neuroendocrine tumors that develop in the pancreas are glucagonomas.[9]

Symptoms

Glucagonoma leads to diabetes-like symptoms and other painful and dangerous symptoms, including

- High blood sugar
- Excessive thirst and hunger due to high blood sugar
- Frequently waking up at night to urinate
- Diarrhea

- A skin rash, or dermatitis, on the face, belly, buttocks, and feet that's often crusty or filled with pus
- Unintentional weight loss
- Blood clots in the legs, which is also called deep vein thrombosis.[10]

Causes

There are no known direct causes of glucagonoma. If you have a family history of a syndrome called multiple endocrine neoplasia type 1 (MEN1) you have a greater risk of developing glucagonoma.[11] Glucagonomas are cancerous, or malignant, about 75 percent of the time. Malignant glucagonomas spread into other tissues, usually the liver, and start interfering with the function of other organs.[12]

Diagnosis

Diagnosis is initially made with several blood tests. High glucagon levels are the hallmark of this condition. Other signs include high blood sugar, high levels of chromogranin A, which is a protein often found in carcinoid tumors, and anemia, which is a condition in which you have a low level of red blood cells.[13] A CT scan of the abdomen to look for the presence of tumors.

Treatment

Treating glucagonoma involves removing tumor cells and treating the effects of an excess of glucagon on your body.[14] It's best to begin treatment by stabilizing the effects of excess glucagon. This often involves taking a somatostatinanalog drug, such as an injection of octreotide (Sandostatin). Octreotide helps to counteract the effects of glucagon on your skin and improve skin rash. Exploratory surgery of the abdomen may be done either laparoscopically, with small cuts to allow for cameras, lights, and tools, or by creating a larger open incision.[15] Most glucagonomas occur on the left side or tail of the pancreas. Removal of this section is called a distal pancreatectomy. In some people, the spleen is also removed. When the tumor tissue is examined under a microscope, it's difficult to tell whether it's cancerous. If it's cancerous, your surgeon will remove as much of the tumor as possible to prevent it from spreading further. This may include part of the pancreas, local lymph nodes, and even part of the liver.[16]

Somatostatinoma

Somatostatinoma is a rare type of neuroendocrine tumor that grows in the pancreas and sometimes the small bowel. A neuroendocrine tumor is one that is made up of hormone-producing cells.[17] These hormone-producing cells are called islet cells. A somatostatinoma develops specifically in the delta islet cell, which is responsible for producing the hormone somatostatin. The tumor causes these cells to produce more of this hormone. When your body produces extra somatostatin hormones, it stops producing other pancreatic hormones.[18] When those other hormones become scarce, it eventually leads to symptoms appearing.

The symptoms caused by a somatostatinoma may include the following

- Pain in the abdomen (most common symptom)
- Diabetes
- Unexplained weight loss
- Gallstones
- Steatorrhea, or fatty stools
- Bowel blockage
- Diarrhea
- Jaundice, or yellowing skin (more common when a somatostatinoma is in the small bowe.[19]

Causes

What causes a somatostatinoma is currently unknown. However, there are some risk factors that may lead to a somatostatinoma. A family history of multiple endocrine neoplasia type 1 (MEN1), a rare type of cancer syndrome that is hereditary.[20]

- Neurofibromatosis
- Von Hippel-Lindau disease
- Tuberous sclerosis

Diagnosis

Diagnosis must be made by a medical professional. It will usually start the diagnosis process with a fasting blood test. This test checks for an elevated somatostatin level.[21] The blood test is often followed by one or more of the following diagnostic scans or X-rays

- Endoscopic ultrasound
- CT scan

- Octreoscan (which is a radioactive scan)
- MRI scan

These tests allow to the tumor, which may be either cancerous or noncancerous. The majority of somatostatinomas are cancerous. The only way to determine whether tumor is cancerous is with surgery.[22]

Treatment

A somatostatinoma is most often treated by removing the tumor through surgery. If the tumor is cancerous and the cancer has spread (a condition referred to as metastasis), surgery may not be an option.[23]

How pancreatic cancer forms

Pancreatic cancer occurs when cells in your pancreas develop mutations in their DNA. These mutations cause cells to grow uncontrollably and to continue living after normal cells would die. These accumulating cells can form a tumor. Untreated pancreatic cancer spreads to nearby organs and blood vessels.Most pancreatic cancer begins in the cells that line the ducts of the pancreas. This type of cancer is called pancreatic adenocarcinoma or pancreatic exocrine cancer. Rarely, cancer can form in the hormone-producing cells or the neuroendocrine cells of the pancreas. These types of cancer are called islet cell tumors, pancreatic endocrine cancer and pancreatic neuroendocrine tumors.[24]

Pathophysiology

Activating mutations in K-ras, mostly codon 12 but also affecting codons 13 or 61, occur in 75–90% of pancreatic cancers.10 11 Ras is a 21 kDa membrane-bound GTP-binding protein involved in growth factor-mediated signal transduction pathways. The mutations result in a constitutively activated form of Ras in which the protein is locked in the GTP-bound state, capable of stimulating a multitude of downstream signalling cascades. 6 Post-translational modification of Ras protein involves farnesylation of the C terminus, mediated by farnesyl protein transferase and is a major therapeutic target (16 17 although farnesyltransferase inhibitors up to now have not been successful in phase III trials, downstream of Ras also offer therapeutic targets such as the Raf-MEK ERK 1134 www.gutjnl.com Downloaded from gut.bmj.com on 6 July 2008 pathway. Sorafenib, an inhibitor of Raf-1 kinase and vascular endothelial growth factor receptor-2, it is inactive in patients with advanced pancreatic cancer.[25]

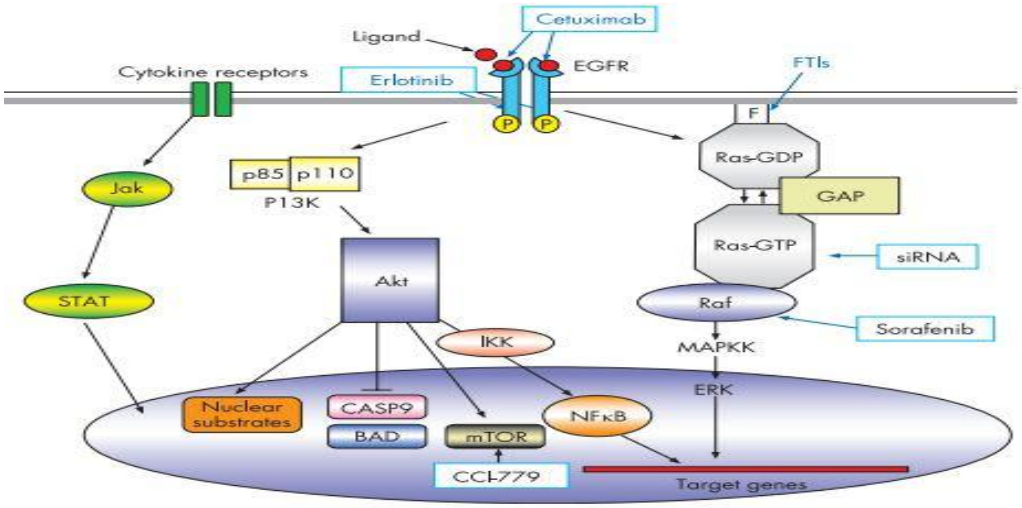

Fig. 1: Schematic representation of molecular oncogenic signalling pathways in pancreatic cancer.

Diagnosis

Tumor markers and proteomic signatures: The most commonly used marker in practice such as- CA19-9 has a sensitivity of 70–90% and specificity of 90%, and is better than other markers, including CA-50 and DU-PAN-2 and CEA. under evaluation, but radically newer approaches that hold real promise are new proteomic techniques identifying unique panels of proteins associated with pancreatic cancer and protein profiles providing a distinctive pancreatic signature. Diagnostic biopsy: Percutaneous FNA cytology has a sensitivity and specificity of 69% and 100%, respectively, for tissue diagnosis the incidence of carcinomatosis is much less after EUS-guided biopsy than percutaneous biopsy.[26]

Neuromedin U

Neuropeptide

Neuropeptides are the largest and most diverse class of signalling molecules in thebrain. Neuropeptides production occurs within the ribosomes in the neuronal cell body.

Neuromedin

Neuromedin U (NmU) is amembers of the neuropeptidefamily known as the neuromedins. NmU was isolated from porcine cord in the early 1980s due to its ability to contract smooth muscle of rat uterus or guinea pig ileum (the suffix U represents the ability to contract uterus smooth muscle).[5] NMU is widely distributed in the CNS, with high levels in the arcuate nucleus of the hypothalamus, the pituitary, the medulla oblongata of the brain stem, and the spinal cord.[27]

Types of Neuromedin U

Two G-protein-coupled receptors, NMUR1 and NMUR2, have been identified as the receptors for NMU.

- NMUR1 is expressed predominantly in the periphery, with highest levels in the gastrointestinal tract.
- NMUR2 is predominantly expressed in the central nervous system, with greatest expression in regions of hypothalamus, medulla, and spinal cord.[28]

Activation of GPCR

GPCRs are polypeptides of 300-1200 amino acids, sharing seven transmembrane α-helices (7TM) and possessing an extracellular *N*-terminus and cytoplasmic *C*-terminus constituting the largest family of plasma membrane receptors.[29] Three main sub-families of GPCRs is A, B and C.

- Family A is the largest family belongs to this sub-family including opsin receptors and adrenoreceptors and they are known as rhodopsin-like receptors.
- Family B receptors are smaller than family A and include peptide hormones such as secretin and glucagon and therefore they are called secretin/glucagon receptors.
- Family C is the smallest family with a long extracellular *N* terminal containing "venus flytrap" module that is the ligand binding site.

Neuromedin u is types of class A G-protein coupled receptors with a distinct distributional pattern. The activation of NmU receptors leads to interacellular signal transduction via calcium mobilization, phosphoinositide (or PI), signaling, and the inhibition of cAMP production.[30] several other peptide and non-peptide ligand are also available for the NmU receptor for example: Neuromedin S in NmUR2 selective.

Physiological role of Neuromedin U in pancreatic cancer

NmU can, for instance, stimulate the secretion of the somatostatin hormone from δ-cell of rat pancreatic islets. It has also been indicated that NmU has the ability to inhibit bone formation and remodelling. It has also been indicated that NmU plays a role in specific types of cancer. Since treatment of leukemic cancer cell-line expressing dominant negative c-Myb may promote leukemogenesis.[31]

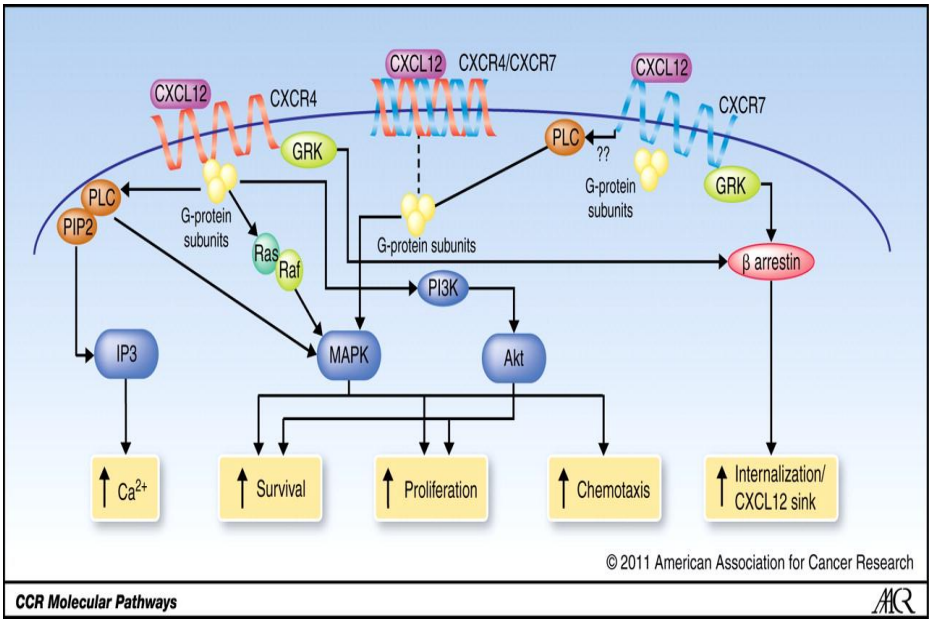

Fig. 2: Physiological role of Neuromedin U in pancreatic cancer.

CONCLUSION

NmU is a multifunctional neuropeptide with multiple roles in different cell and tissue types, relaying central nervous system signals and stimulating organ functions, but also directly affecting certain cell types in many ways, from increasing proliferation and migration to inducing release of hormones and autocrine/paracrine factors. Most of its functions appear to be carried out through receptors NMUR1 and NMUR2, although alternative receptors have been described. It is also possible that NmU may bind and signal through other, yet undescribed, receptors as well. Perhaps NmU will become an ideal target for the therapy of certain disorders, particularly obesity and cancer, although the multiple roles of this neuropeptide should be taken into account when attempting to block its functions for therapeutic uses.

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