DOWNLOAD PDF STRUCTURAL AND FUNCTIONAL STUDIES OF THE GLUCAGON-LIKE PEPTIDE-1 (GLP-1 RECEPTOR

Chapter 1 : Glucagon-like peptide-1 - Wikipedia

Glucagon-like peptide-1()amide (GLP-1) is a residue peptide hormone released from intestinal L cells following nutrient consumption. It potentiates the glucose-induced secretion of insulin from pancreatic beta cells, increases insulin expression, inhibits beta-cell apoptosis, promotes beta.

Novo Nordisk Park G8. However, the molecular details that govern ligand binding and specificity of nGLP-1R remain undefined. Here we report the crystal structure of human nGLP-1R in complex with the antagonist Exendin-4 9â€”39 solved by the multiwavelength anomalous dispersion method to 2. The structure provides for the first time detailed molecular insight into ligand binding of the human GLP-1 receptor, an established target for treatment of type 2 diabetes. Previous Section Next Section G protein-coupled receptors represent the largest protein family encoded by the human genome, and they are defined by the presence of seven transmembrane helices, an extracellular N terminus, ligand binding via the extracellular face, an intracellular C terminus, G protein coupling, and signaling via the intracellular face. Receptors of the B1 subfamily are specifically characterized by three conserved disulfide bonds in the N-terminal extracellular domain Nt-domain 2 1 â€” 4 and by their structurally related peptide hormone ligands, such as glucagon-like peptide-1 GLP-1 , glucagon-like peptide-2 GLP-2 , glucagon, glucose-dependent insulinotropic polypeptide GIP , secretin, vasoactive intestinal polypeptide, pituitary adenylate cyclase-activating polypeptide PACAP , growth hormone-releasing hormone, parathyroid hormone, calcitonin, and corticotropin-releasing factor CRF 5. Peptide hormone binding of cloned Family B1 receptors has been investigated for 15 years by pharmacological and biochemical approaches. The current binding model is a two-step mechanism where initially the C-terminal part of the peptide ligand interacts with the Nt-domain of the receptor 6 â€” 8. In the second step, the N-terminal part of the ligand interacts with the core domain of the receptor transmembrane helices and connecting loops , which leads to activation and signal transduction 9 â€” More recently, it was proposed that the Nt-domain of the secretin receptor was involved in the activation mechanism, but such an endogenous agonist mechanism has not been confirmed for GLP-1R The isolated soluble Nt-domains are able to bind their cognate ligands, although the affinity is often reduced compared with the full-length receptors 1 , 3 , 4 , 6. This is physiologically important, given the essentially opposite effects of glucagon and GLP-1 on blood glucose. The structures confirmed both the existence of a common structural fold and the interaction with the C-terminal part of their cognate ligands. Ex4 has a C-terminal extension of nine amino acid residues known as the Trp cage, which is absent in GLP However, recent results suggest that the Trp cage plays only a minor role in receptor binding Therefore, the role of the Trp cage in receptor binding is not crystal clear. Briefly, N-terminal His6-tagged nGLP-1R was expressed in Escherichia coli inclusion bodies, isolated as inclusion body protein, solubilized in guanidine HCl and dithiothreitol, dialyzed against guanidine HCl to remove the dithiothreitol, and refolded using L-Arg and a 1: Refolded nGLP-1R was purified by hydrophobic interaction chromatography and size exclusion chromatography. The His6 tag was removed by thrombin cleavage. Native Ex4 9â€”39 -amide was synthesized as previously described The product was crystallized from ethyl acetate and n-heptan as off-white crystals with a slight odor of selenide. The crystallization conditions was identified initially using the Crystal Screen and Detergent Screen from Hampton Research and subsequently optimized to 0. Data Collection and Structure Determinationâ€”Diffraction data were collected from a single crystal at three different wavelengths peak, remote, inflection at the MAX-lab beamline Iâ€”3 Lund, Sweden. The final SeMet model has residues in allowed and six residues in disallowed regions of the Ramachandran plot, a working R-factor of Data collection, phasing, and refinement statistics are summarized in Table 1. Coordinates and structure factors are deposited in the Protein Data Bank under accession code 3C Molecular graphics were prepared in PyMOL. Rmsd, root mean square deviation. FOM, figure of merit. We synthesized a selenium derivative of the ligand, where Met14 and Leu21 were substituted by SeMet: The intrinsic Trp fluorescence properties of the eluted protein suggested a 1: The complex was crystallized in

hanging drops, and the structure was solved by the multiwavelength anomalous dispersion method to 2. Subsequently, we crystallized and solved the structure of the complex with native Ex4 9â€”39 to 2. The two structures were essentially identical except for Met14 and Leu21 of Ex4 9â€” Data collection and refinement statistics are summarized in Table 1 , and all the figures illustrate the structure with the native ligand. There was no detectable electron density for residues ArgGln27 and GlyTyr Trp is not involved in ligand binding but appears to play a structural role by forming a well defined surface-exposed hydrophobic cluster together with Phe80, Tyr, Phe, and Leu Here, the side chain of Asp67 interacts indirectly via a water molecule with the side chain of Arg and directly with the side chain of Trp72 and Arg Fig. The importance of Asp67, Trp72, and Trp for ligand binding was previously documented by receptor mutagenesis 33 , Pro86 at the beginning of loop 2 plays a structurally important role for the formation of the ligand binding site of nGLP-1R see below.

Chapter 2 : Crystal Structure of the Ligand-bound Glucagon-like Peptide-1 Receptor Extracellular Domain

GLP-1 is clearly an important hormone linking nutrient consumption with blood sugar control, and therefore knowledge of its structure, function and mechanism of action is of great importance. LINKED ARTICLES This article is part of a themed section on Secretin Family (Class B) G Protein-Coupled Receptors.

Advanced Search Glucagon-like peptide 1 GLP-1 analogs are increasingly being used in the treatment of type 2 diabetes. It is clear that these drugs lower blood glucose through an increase in insulin secretion and a lowering of glucagon secretion; in addition, they lower body weight and systolic blood pressure and increase heart rate. Using a new monoclonal antibody for immunohistochemistry, we detected GLP-1 receptor GLP-1R in important target organs in humans and monkeys. Pancreatic ductal epithelial cells did not express GLP-1R. In the kidney and lung, GLP-1R was exclusively expressed in smooth muscle cells in the walls of arteries and arterioles. In the heart, GLP-1R was localized in myocytes of the sinoatrial node. No GLP-1R was seen in primate liver and thyroid. In conclusion, these results give important new insight into the molecular mode of action of GLP-1 analogs by identifying the exact cellular localization of GLP-1R. Liraglutide and exenatide are approved for treatment of type 2 diabetes, and apart from lowering blood glucose, these glucagon-like peptide 1 GLP-1 analogs also have a beneficial effect on body weight and blood pressure BP. Furthermore, liraglutide is in phase 3 clinical development for the induction and maintenance of weight loss in people without diabetes who are obese. The expression of GLP-1R has been described in many tissues with the highest expression reported in the lung and pancreas and less expression in the stomach, intestine, kidney, heart, and brain 2 â€” 6. The liver has been reported to express GLP-1R, but recent publications do not show expression in hepatocytes in a study having rigorous controls 7. Several studies indicate that C-cells in the thyroid gland express GLP-1R; however, expression levels appear to be higher in rodents than in humans 8 , 9. The exact cellular localization of the GLP-1R is poorly understood. One of the main reasons for the sparse and conflicting information in the literature of the identity of GLP-1Râ€”expressing cell types in vivo is the general problem with generating specific anti-GPCR antibodies that reliably detect such receptors in tissue sections using immunohistochemistry IHC 14 â€” Here, extensive validation of a monoclonal GLP-1R antibody for IHC is reported, and this antibody is used for the specific and highly sensitive detection of GLP-1R in formalin-fixed and paraffin-embedded samples of primate pancreas, kidney, lung, heart, gastrointestinal GI tract, liver, and thyroid. The strain is not commercially available. Spleens from mice with positive serum titers were removed aseptically and dispersed to a single cell suspension. Spleen and myeloma cell fusions P3X63Ag8. A total of 11 positive clones were selected for testing by IHC. Pancreas samples were included from two normal cynomolgus monkeys and 7 normal and 7 diabetic rhesus monkeys. A similarly thorough sampling was performed for the ampulla of Vater regions from both cynomolgus monkeys. Samples from kidney, lung, stomach, duodenum, jejunum, ileum, colon, liver, and thyroid from the 7 normal rhesus monkeys were included. For the studies of cynomolgus monkey heart tissue, paraffin-embedded sections were used, representing all areas from a male and a female monkey heart, as well as frozen sections, representing all areas from a male monkey. The sampling and histological use of all human tissues were ethically approved by local authorities. Untransfected BHK cells were used as negative controls. The agar cylinders were removed from the plastic tubing and embedded in paraffin. Slides were washed in TBS with 0. Slides were washed and then were incubated with the biotin-free catalyzed system amplification system CSA II with anti-mouse horseradish peroxidase Dako for 10 minutes. After washing, sections were stained with Hoechst nuclear stain for 10 minutes and rinsed in water for 1 minute before mounting. All sections were scanned in a NanoZoomer 2. The tracer was used at a concentration of 0. We then screened 11 MAb clones for binding to the full-length human GLP-1R expressed in BHK cells, both as fresh frozen cells and as formalin-fixed and paraffin-embedded cells. We identified 4 clones that showed reactivity to human GLP-1Râ€”transfected cells, with no reactivity to nontransfected cells. The same 4 clones also showed membrane-associated reactivity with

islet cells in formalin-fixed and paraffin-embedded monkey pancreas, and one clone, MAb 3F52, was selected for further studies because of its superior signal to noise ratio in both transfected cells and pancreas tissue When tested on cells transfected with rabbit and mouse GLP-1R, no reactivity with MAb 3F52 was detected, indicating that this antibody is primate specific Supplemental Figure 1 B and data not shown. With this information and using the National Center for Biotechnology Information protein blast tool, we determined that the only published GLP-1R sequences with tryptophan in position 33 are from primate species. Normal primate kidney IHC with MAb 3F52 on frozen sections of cynomolgus monkey kidney yielded a distinct signal exclusively in the preglomerular vascular compartment, ie, in vas afferens arterioles, interlobular arteries, and arcuate arteries Supplemental Figure 2 , Aâ€”C. This binding was specific as determined by the absence of reactivity with an isotype control antibody at the same concentration Supplemental Figure 2 , Dâ€”F. IHC with MAb clone 3F52 on paraffin-embedded normal monkey kidney sections showed the exact same pattern of immunoreactivity with selective labeling of vas afferens arterioles, interlobular arteries, and arcuate arteries in the kidney. The immunoreactivity was located exclusively in the smooth muscle cells SMCs in the wall of the GLP-1Râ€”positive arterioles and arteries, whereas the endothelial cell layer was negative Figure 1 A. The staining was both membrane-associated and cytoplasmic. No other cells or compartments in the kidney, including glomeruli and tubuli, showed a signal Figure 1 A.

Chapter 3 : OMIM Entry - * - GLUCAGON-LIKE PEPTIDE 1 RECEPTOR; GLP1R

The glucagon-like peptide-1 receptor (GLP1R) is a receptor protein found on beta cells of the pancreas. It is involved in the control of blood sugar level by enhancing insulin secretion. In humans it is synthesised by the gene GLP1R, which is present on chromosome 6.

Pancreatic proglucagon gene expression is promoted upon fasting and hypoglycaemia induction and inhibited by insulin. Conversely, intestinal proglucagon gene expression is reduced during fasting and stimulated upon food consumption. In mammals, the transcription gives rise to identical mRNA in all three cell types, which is further translated to the amino acid precursor called proglucagon. However, as a result of tissue-specific posttranslational processing mechanisms, different peptides are produced in the different cells. Initially, GLP-1 was thought to correspond to proglucagon 72â€" suitable with the N-terminal of the MGPF, but sequencing experiments of endogenous GLP-1 revealed a structure corresponding to proglucagon 78â€" from which two discoveries were found. Secondly, the glycine corresponding to proglucagon was found to serve as a substrate for amidation of the C-terminal arginine resulting in the equally potent GLP-1 7â€"36 amide. The L-cells are open-type triangular epithelial cells directly in contact with the lumen and neuro-vascular tissue and are accordingly stimulated by various nutrient , neural and endocrine factors. As the majority of L-cells are located in the distal ileum and colon, the early phase is likely explained by neural signalling, gut peptides or neurotransmitters. Other evidence suggest that the amount of L-cells located in the proximal jejunum is sufficient to account for the early phase secretion through direct contact with luminal nutrients. Less controversially, the second phase is likely caused by direct stimulation of L-cells by digested nutrients. The rate of gastric emptying is therefore an important aspect to consider, as it regulates the entry of nutrients into the small intestines where the direct stimulation occurs. One of the actions of GLP-1 is to inhibit gastric emptying , thus slowing down its own secretion upon postprandial activation. Individual nutrients, such as fatty acids , essential amino acids and dietary fibre have also shown to stimulate GLP-1 secretion. The mechanisms of protein-triggered GLP-1 secretion are less clear, but the amino acid proportion and composition appear important to the stimulatory effect. DPP-4 is widely expressed in multiple tissues and cell types and exists in both a membrane-anchored and soluble circulating form. Notably, DPP-4 is expressed on the surface of endothelial cells , including those located directly adjacent to GLP-1 secretion sites. However, the activity only becomes apparent once the degradation of DPP-4 has been prevented, as the majority of GLP-1 reaching the kidneys have already been processed by DPP Similarly, renal clearance appear more significant for the elimination of already inactivated GLP Physiological functions[edit] Functions of GLP-1 GLP-1 possesses several physiological properties making it and its functional analogs a subject of intensive investigation as a potential treatment of diabetes mellitus , as these actions induce long-term improvements along with the immediate effects. During the process, influx of glucose ensures sufficient ATP to sustain the stimulatory effect. Critically, this does not affect the glucagon response to hypoglycaemia as this effect is also glucose-dependent. The inhibitory effect is presumably mediated indirectly through somatostatin secretion, but a direct effect cannot be completely excluded. Consequently, diabetic subjects treated with GLP-1 receptor agonists often experience weight loss as opposed to the weight gain commonly induced with other treatment agents. By decelerating gastric emptying GLP-1 reduce postprandial glucose excursion which is another attractive property regarding diabetes treatment. However, these gastrointestinal activities are also the reason why subjects treated with GLPbased agents occasionally experience nausea.

Chapter 4 : Glucagon-like peptide-1 receptor - Wikipedia

A better understanding of the molecular mechanism of ligand-receptor interaction of glucagon-like peptide 1 (GLP-1) receptors (GLP-1Rs) is useful for the design of potent GLP-1 analogs that could potentially be used as a treatment for diabetic patients.

This is an open access article distributed under the Creative Commons Attribution License , which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. Glucagon-like peptide 1 GLP-1 bestows protective effects upon the cardiovascular system through direct cardiovascular interactions or by improvements to metabolic function. This case-controlled study investigated whether polymorphisms in the GLP-1R gene affect the risk of cardiovascular disease in type 2 diabetic patients in the Chinese Han population. Eleven haplotype-tagging single nucleotide polymorphisms SNPs , distributed across 22 kb of the 39 kb GLP-1R gene, were selected and genotyped in diabetic patients from a Chinese Han population. Patients were classified based on the severity of coronary artery stenosis. Allele and genotype frequencies were compared between the two groups at all 11 SNPs. Introduction Coronary artery disease CAD is a life-threatening condition that is a frequently occurring complication in patients with type 2 diabetes mellitus T2DM , with diabetic patients being 2â€”4 times more likely to develop CAD than nondiabetics [1]. Determination of genetic variants associated with CAD development in T2DM patients may assist in the identification of at-risk individuals and allow targeting of primary prevention and early intervention measures. In recent years, glucagon-like peptide 1 receptor GLP-1R agonists such as exenatide and liraglutide have been widely studied because of their glucose-dependent insulinotropic effects [2] and their other physiological effects such as decrease in fatty acid absorption, increase in satiety, and reduction in body weight [3]. Previous studies demonstrated that GLP-1 agonists could reduce the rate of the first occurrence of death from cardiovascular causes and nonfatal myocardial infarction among patients with T2DM [5 , 6]. Materials and Methods 2. Written informed consents were acquired from all subjects participating in this study, in agreement with the Helsinki Declaration. Subjects Diabetes mellitus was diagnosed according to World Health Organization criteria [9] as follows: Patients with type 1 diabetes and subjects with active inflammatory conditions, autoimmune diseases, malignancies, usage of immunosuppressive drugs, and known hematological disorders were excluded. Diagnostic procedures were carried out at Peking University First Hospital. Demographic data and patient cardiovascular risk factor data were collected for all subjects from medical records. The GLP-1R gene is located at chromosome 6p21, is Target regions were amplified by PCR. Genotype distributions described departure from Hardy-Weinberg equilibrium at each polymorphic locus. Linkage disequilibrium LD and haplotype analysis were performed using Haploview 4. Allele frequencies were determined by gene counting. Qualitative variables were compared using a test, and quantitative variables were compared using an independent samples -test or a Mannâ€”Whitney test. Associations between CAD and genotype were analyzed using multiple logistic regression with adjustment for the following potential confounders: Bonferroni correction was used to correct for multiple comparisons. Power and Sample Size Calculation software version 3. HbA1c and FPG measurements were acquired after antidiabetic treatment. Genotype distributions at all 11 loci were in agreement with Hardy-Weinberg equilibrium data not shown. Statistical power was 0. In dominant inheritance mode, no significant difference in genotype distribution was found between the CAD-positive and control groups Supplementary Material 1. The protective effect of the homozygous GG minor allele genotype at rs was also observed in additive codominant inheritance mode using logistic regression analysis Table 2. The other ten SNPs tested in this study displayed similar allele frequencies between the CAD-positive and control groups, and no significant associations were noted between genotype and CAD risk Tables 2 and 3. Haplotype Analysis Haploview plotting was used to construct haplotypes depending on the physical position and the value of between each pair of SNPs in one block. Three blocks were delineated as follows: LD block 1 rs, rs,

rs, rs, and rs , block 2 rs and rs , and block 3 rs, rs, and rs GLP-1R is a classic seven-transmembrane protein; the C-terminus of GLP-1R interacts with a signaling G protein, and the large N-terminal extracellular domain plays an important role in ligand binding [13 , 14]. Systematically, GLP-1R transmits signals that prompt insulin secretion increases, appetite reduction, metabolism improvement, and lower blood pressure and, as a result, decreases the severity of atherosclerotic lesions [5]. The mechanisms through which this allele confers protection are unclear. For example, 3 UTRs can influence chromosome structure, regulate transcription, stabilize mRNA, and modulate translation, thus affecting the stability and transport of the encoded proteins [16]. We therefore speculate that variations at rs may differentially affect the function of GLP-1R through one or more of these mechanisms, but this remains to be confirmed. In , Scott et al. We acknowledge some limitations of this study. Sample size was relatively small, for in the cases were only 26 type 2 diabetes patients with one CAD vessel affected, 83 and for two and three CAD vessels affected, respectively, so we did not stratify the cases and analyze the association with the number of affected vessels. And clinical features were not perfectly matched, and urine albumin creatinine ratio ACR was not collected, between the case and control groups. Both of them may introduce bias. Moreover, further functional studies on genetic variations at the GLP-1R locus would be beneficial. Consent Written informed consents were acquired from all subjects participating in this study, in agreement with the Helsinki Declaration. Conflicts of Interest We declare that we have no conflict of interest. Xiaowei Ma edited the manuscript. Xiaohui Guo reviewed the manuscript and contributed to the discussion. Xiaowei Ma accepts responsibility for the article. Acknowledgments The authors are very grateful to the staff of the Departments of Cardiology, Radiology, Statistics, and others, from Peking University First Hospital, for excellent contributions to data collection. We also wish to thank all the patients who participated in this study. Supplementary Materials Supplementary Material 1: Supplementary Materials References W. View at Google Scholar P.

Chapter 5 : Structure-activity studies of glucagon-like peptide

The glucose-dependent insulinotropic polypeptide (GIP) receptor and the glucagon-like peptide-1 (GLP-1) receptor are homologous G-protein-coupled receptors (GPCRs). Incretin receptor agonists stimulate the synthesis and secretion of insulin from pancreatic Î²-cells and are therefore promising agents for the treatment of type 2 diabetes.

Advanced Search Abstract A better understanding of the molecular mechanism of ligand-receptor interaction of glucagon-like peptide 1 GLP-1 receptors GLP-1Rs is useful for the design of potent GLP-1 analogs that could potentially be used as a treatment for diabetic patients. Changes in the ligand and receptor sequences during evolution provide invaluable clues to evaluate the functional motifs of the receptor that are responsible for ligand interaction. For these reasons, in the present study, we have isolated and functionally characterized a GLP-1R from goldfish. Its amino acid sequence shows These results indicate that the gfGLP-1R is structurally more flexible than its mammalian counterpart and that its binding pocket can accommodate a wider spectrum of peptide ligands. Previous studies demonstrated that the charged residues in the extracellular domains of mammalian GLP-1R, particularly those found in the N-terminal domain and the first exoloop, are important for ligand binding. We investigated the roles of the conserved charged residues in the function of the gfGLP-1R. Eleven mutant receptors were constructed, and the effects of mutations were determined by functional assays. Our results demonstrated that three charged residues D, R, and D present in the extracellular domains are critical for receptor function. In mammals, some of its actions include stimulation of glucose-dependent insulin secretion, inhibition of glucagon secretion and gastric emptying, and possibly promotion of glycogenesis 1 â€” 3. The action of GLP-1 is mediated via a specific cell surface receptor, which has been cloned and characterized in rat 4 and human 5 â€” 7. These GPCRs activate adenylyl cyclase for signal transduction. Mechanisms involving calcium for signaling have also been reported for the GLP-1 receptor 13 â€” The GLP-1 receptor is widely distributed in tissues, including brain, pancreas, intestine, lung, stomach, heart, and kidney 16 , Apparently, there is a functional switch of GLP-1 from having glucagon-like activities in fish to being an insulinotropic secretagogue in mammals. Thus, fish and mammalian GLP-1s seem to be interchangeable in their functions. These early findings indicated that a putative GLP-1 receptor should be present in fish and that the fish GLP-1 receptor should be able to interact with the mammalian GLP-1 peptide. In addition, there was evidence suggesting that fish glucagon [goldfish gf GLU] and GLP-1, though having similar biological function, act via different receptors We have previously characterized a proglucagon cDNA from goldfish Carassius auratus, which encodes both glucagon and GLP-1 sequences In the present study, we have isolated and functionally characterized a GLP-1 receptor from goldfish, with a goal to understand the molecular mechanisms governing the interaction of GLP-1 receptors both with its specific ligands and with the intracellular G proteins. This understanding is essential for future design of potent GLP-1 analogs for the treatment of diabetes mellitus. Several studies have been performed previously and have identified the structural features in the sequence of the mammalian GLP-1 receptors that play a role in the interaction with the ligand 23 , 24 and in signal transduction 25 â€” They have demonstrated that the extracellular domains, especially the large N-terminal NT domain and the first exoloop, are important for ligand binding. To gain insights into the role of particular amino acid residues in the function of the gfGLP-1R, we constructed and characterized, in the present study, 11 receptor mutants. These mutations were located within the putative ligand-binding domains of the gfGLP-1R. Functional characterization of the mutants indicated that 3 charged residues at positions , , and are critical for function of the gfGLP-1R. The clone was sequenced from both strands using a T7 sequencing kit Amersham Pharmacia Biotech, Arlington Heights, IL by synthetic primers and by subcloning of restriction fragments. Louis, MO for 30 min at 37 C. Peptides were added to stimulate the cells for 45 min. After stimulation, the cells were lysed by 1 ml cold ethanol. Human peptides were purchased from Bachem California, Inc. Tissue distribution of the gfGLP-1R Total RNA from various tissues, including brain, gall bladder, gill, male gonad, female gonad, lower intestine,

upper intestine, kidney, liver, heart, pituitary, muscle, and spleen, were prepared using the acid guanidinium thiocyanate-phenol-chloroform extraction method The expected size of the amplified fragment was bp. The reaction conditions were 40 sec at 94 C, 1 min 30 sec at 68 C, and 1 min 30 sec at 72 C, respectively, for 30 cycles. To detect the expression pattern of the receptor in the brain, the tissue was dissected into eight parts, including olfactory bulbs and tracts, telencephalon, hypothalamus, optic tectum-thalamus, cerebellum, medulla, spinal cord, and pituitary, as previously described Mutagenic primers were purchased from Life Technologies, Inc. The sequences of these primers are listed in Table 1. Mutants were sequenced to confirm their identities and cloned back to the pBK-CMV expression vector for subsequent functional studies. The sequences of mutagenic primers used in the present study Name of mutant.

Chapter 6 : Glucagon-like peptide-1 receptor | Revolvy

Isolation and Structure-Function Studies of a Glucagon-Like Peptide 1 Receptor from Goldfish Carassius auratus: Identification of Three Charged Residues in Extracellular Domains Critical for.

This receptor, which functions at the cell surface, becomes internalized in response to GLP-1 and GLP-1 analogs, and it plays an important role in the signaling cascades leading to insulin secretion. It also displays neuroprotective effects in animal models. Polymorphisms in this gene are associated with diabetes. The protein is an important drug target for the treatment of type 2 diabetes and stroke. Alternative splicing of this gene results in multiple transcript variants. Co-treatment with glucagon and exendin-4 Ex-4 , a GLP-1 receptor agonist, additively increased glucose-stimulated insulin secretion in INS-1 cells genetic association studies in population in Republic of Korea: Studies were also conducted in primary human and mouse beta-cells and in rat insulinoma cell line. The GLP-1R was abundantly expressed in numerous regions, including the septal nucleus, hypothalamus, and brain stem. Changes in GLP-1 levels are associated with weight loss in newly diagnosed Chinese diabetes patients receiving acarbose the present study revealed that overexpression of GLP1R significantly reduces proliferation, migration and cytokine release in ASM cells from COPD patients; this involved a significant increase in ABCA1 expression levels. GLP-1 receptor agonists affect gut homeostasis in both proximal and distal parts of the gut. Our work uncovers GLPinduced signaling pathways in the exocrine pancreas and suggests that increases in amylase and lipase levels in subjects treated with GLP-1 receptor agonists reflect adaptive growth rather than early-stage pancreatitis. Dapagliflozin, when added in real life to patients with T2DM treated with GLP1-R agonists, induced a further significant, albeit modest improvement in A1C and a further weight loss. Our studies show that GLP-1R is widely expressed throughout the human hypothalamus. The effects of GLPbased therapies on blood glucose in type 2 diabetics are not mediated through microvascular responses. In conclusion, exenatide significantly improves coronary endothelial function in patients with newly diagnosed type 2 diabetes. Immunohistochemistry of human ileum tissues was performed in this study, which showed that TAS2R38 was co-localized with glucagon-like peptide 1 GLP-1 in enteroendocrine L-cells. Data suggest that three conserved positively charged residues located at extracellular ends of transmembrane helices 3, 4 and 5 of GLP1R are essential for high affinity agonist binding and conformational transitions linked to pleiotropic effector coupling through stabilisation of extracellular domains. The rate of homologous desensitization and internalization of the GLP-1R has been determined in a transgenic cell line system. In the glucagon receptor GCGR and glucagon-like peptide-1 receptor GLP-1R , the extracellular domain is required for signaling even when the hormone is covalently linked to the transmembrane domain. We aimed to investigate whether genetic variations in glucagon-like peptide receptor are associated with responses to dipepdityl peptidase-4 inhibitors in patients with type 2 diabetes. Results suggest that pancreatic ductal adenocarcinoma PDAC cells or their precursor lesions do not overexpress glucagon-like peptide-1 receptor GLP-1R compared with non-neoplastic pancreatic cells. The molecular dynamics simulations of wild-type and mutant GLP-1R. NMR-determined structure of a high-potency cyclic conformationally-constrained residue analogue of GLP-1 was also docked into the receptor-binding site. Lack of association of rs GLP-1 R polymorphism with weight loss. An association was found between the rs GLP-1 receptor polymorphism and basal GLP-1 levels in diabetes mellitus type 2 patients. GLP-1R rs polymorphism explained some of the inter-individual differences in response to liraglutide regarding weight loss in obese PCOS women. Hyperglycemia decreases GLP-1R expression in retinal pigment epithelial cells. Data indicate that the role of the SP signal peptide sequence is to promote the expression of GLP-1R glucagon-like peptide-1 receptor. The potency of GLP-1 is enhanced by the endocannabinoid-like lipids oleoylethanolamide and 2-oleoylglycerol. Our study showed a higher weight loss 12 and 18 months after bariatric surgery in GG variant than A allele carriers. The biochemical parameters and cardiovascular comorbidity rates improved similarly in both genotypes. The GLP-1 receptor variant rs was

found to be associated with decreased weight and anthropometric parameters in A allele carriers with and without MS. MS or its components were not associated with this polymorphism in obese adults. Lack of association of rs GLP-1 R polymorphism with weight loss after hypocaloric diets; better anthropometric parameters in obese subjects with the mutant allele A of rs GLP-1 R polymorphism. The significant gene-gene interaction between rs and rs in GLP1R. Our aim was to analyze the effects of rs GLP-1 receptor polymorphism on body weight, cardiovascular risk factors and serum adipokine levels in morbid obese patients GLP-1R expression is not a risk prognostic factor in intrahepatic cholangiocarcinoma. These data demonstrate that the defective function of the incretin axis in type 2 diabetes may also result from decreased GLP-1R expression in its extrapancreatic target organs. GLP1R activation modulated food related responses in appetite and reward areas of the brain in humans. Data indicate that glucagon-like peptide 1 receptor GLP-1R might become a molecular target for treatment of metastatic pancreatic neuroendocrine tumors PNETs. Determined is the expression of GLP-1R in different regions of human stomach mucosa and its specific cellular association and distribution within gastric glands. GLP-1R may have a role in different subtypes of thyroid cancer [review] analysis of how a pentapeptide agonist at interacts with the glucagon-like peptide-1 receptor Functional expression of a GIP receptor mutant lacking N-glycosylation is rescued by co-expressed wild type GLP1 receptor, which suggests formation of a GIP-GLP1 receptor heteromer. Suggest a possible direct effect of glucagon-like peptide-1 receptor agonist exenatide on intestinal lipoprotein particle production. Most of the somatostatin receptor-negative neuroendocrine tumors and GLP-1 receptor-negative malignant insulinomas are GIP receptor positive. Evolutionarily conserved residues at glucagon-like peptide-1 GLP-1 receptor core confer ligand-induced receptor activation a critical role of ECL2 of the GLP-1R in the activation transition s of the receptor and the importance of this region in the determination of both GLP-1 peptide- and pathway-specific effects. Glucagon-like peptide-1 receptor activation stimulates hepatic lipid oxidation and restores hepatic signalling alteration induced by a high-fat diet in nonalcoholic steatohepatitis. GLP-1 signaling through GLP-1 receptor modulates cytokine production in natural killer T-cells; GLP-1 signaling appears to be important in psoriasis patients with type 2 diabetes mellitus e. In humans, neoplastic and hyperplastic lesions of thyroid C cells express the GLP-1 receptor. In contrast to insulinoma, hyperinsulinaemic hypoglycaemia after gastric bypass surgery is not accompanied by overexpression of GLP-1 receptor in individual islets. Low molecular weight pyrimidine-based compounds can activate the GLP-1 receptor and stimulate glucose-dependent insulin secretion. Exendin-4 stimulates proliferation of coronary artery endothelial cells via a GLP-1R dependent mechanism. HuGE Navigator In prolonged ventricular fibrillation followed by resuscitation, myocardial microcirculatory function was enhanced with administration of GLP Treatment was not associated with significant improvement in post-resuscitation myocardial function. The data of this study confirmed that GLP-1R agonists have clinical potential in treating neuronal stresses relevant to neurodegenerative conditions. GLP-1R is present on human hepatocytes. In vivo GLP-1R imaging is an innovative, noninvasive diagnostic approach that successfully localizes small insulinomas. GFP-GLP-1 receptor is weakly expressed in the plasma membranes and is functionally coupled to adenylyl cyclase via heterotrimeric G-proteins, similarly as its wild type. GLP-1 receptor scintigraphy is a novel tool to facilitate the detection of insulinomas. Observational study of gene-disease association and gene-gene interaction. Structural basis of endogenous agonist activation of family B G protein-coupled receptors. HuGE Navigator For GLP-1 receptor scintigraphy, a low-background signal can be expected, on the basis of the low receptor expression in the normal tissues surrounding tumors. In vitro folding, functional characterization, and disulfide pattern of the extracellular domain glucagon-like peptide-1 receptor polymorphism results in reduced agonist responsiveness Missenses mutations in Japaneses type 2 diabetes patients. Experimental evidence indicates that the GLP-1 receptor gene is expressed in human brain as a protein, with binding properties similar to those of the GLP-1R located in peripheral tissues. GLP-1R stimulation does not modify the growth or survival of human pancreatic cancer cells.

Chapter 7 : GLP1R glucagon like peptide 1 receptor [(human)]

The GLP-1 receptor and its peptide ligands. Glucagon-like peptide 1 () amide (GLP-1) is a 30 amino acid peptide produced in intestinal L cells and released into the bloodstream in response to food intake.

It is the most potent stimulator of glucose-induced insulin secretion and also suppresses in vivo acid secretion by gastric glands. Transfected into COS cells, the receptor bound GLP1 with high affinity and was coupled to activation of adenylate cyclase. The receptor is amino acids long and contains 7 transmembrane domains. The peptide is clasped between the N-terminal domain and the transmembrane core of the receptor, and further stabilized by extracellular loops. Conformational changes in the transmembrane domain result in a sharp kink in the middle of transmembrane helix 6, which pivots its intracellular half outward to accommodate the alpha-5 helix of the Ras-like domain of Gs. At the extracellular surface, the organization of extracellular loop 3 and proximal transmembrane segments differed between the exendin-P5-bound structure and the GLP1 -bound GLP1 receptor structure reported by Zhang et al. At the intracellular face, there was a 6-degree difference in the angle of the G-alpha-s-alpha-5 helix engagement between structures, which was propagated across the G protein heterotrimer. In addition, the structures differed in the rate and extent of conformational reorganization of the G-alpha s protein. Crystal Structure Jazayeri et al. The peptide agonist retained an alpha-helical conformation as it sat deep within the receptor-binding pocket. The arrangement of the transmembrane helices revealed hallmarks of an active conformation similar to that observed in class A receptors. The receptor is in an inactive conformation with compounds that restrict movement of the intracellular tip of helix VI, a movement that is generally associated with activation mechanisms in class A GPCRs. Molecular modeling and mutagenesis studies indicated that agonist-positive allosteric modulators target the same general region, but in a distinct subpocket at the interface between helices V and VI, which may facilitate the formation of an intracellular binding site that enhances G-protein coupling. They concluded that the basal activity of the GLP1R gene is mediated by 2 proximal SP1-binding sites and that a more distal site acts as a repressor. Glp1r homozygous knockout mice showed a contextual fear learning deficit which was restored after hippocampal Glp1r gene transfer. Rats overexpressing Glp1r showed improved learning and memory. Glp1r-deficient mice also had enhanced seizure severity and neuronal injury after kainate administration, which was reduced after Glp1r hippocampal gene transfer. The findings suggested a role for GLP1R in learning and neuroprotection. Cloning and functional expression of the human glucagon-like peptide-1 GLP-1 receptor. Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. Crystal structure of the GLP-1 receptor bound to a peptide agonist. Localization of a CA n repeat in glucagon-like peptide-1 receptor gene Glp1r to proximal mouse chromosome 17 and its linkage to other markers. Human GLP-1 receptor transmembrane domain structure in complex with allosteric modulators. Human glucagon-like peptide-1 receptor gene: Expression cloning of the pancreatic beta cell receptor for the gluco-incretin hormone glucagon-like peptide 1. Gene expression of the human glucagon-like peptide-1 receptor is regulated by Sp1 and Sp3.