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(54) Title: ANTAGONISTS OF INTESTINOTROPHIC GLP-2 PEPTIDES

(57) Abstract

Antagonists of glucagon-like peptide 2 have been identified. Their effects on the growth of gastrointestinal tissue are described. Its formulation as a pharmaceutical, and its therapeutic and related uses in treating bowel tissue, are described. Also described are methods of identifying antagonists of glucagon-like peptide 2.

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ANTAGONISTS OF INTESTINOTROPHIC GLP-2 PEPTIDES

I. FIELD OF THE INVENTION

This invention relates to glucagon-related peptides which are functional antagonists of glucagon-like peptides-2, and to their use therapeutically to counter hyperplasia or induce hypoplasia particularly in intestinal tissue.

II. BACKGROUND TO THE INVENTION

Expression of the glucagon gene yields a tissue-determined variety of peptide products that are processed from the 160 residue proglucagon product. The organization of these peptides within the proglucagon precursor was elucidated by the molecular cloning of preproglucagon cDNAs from the anglerfish, rat, hamster and bovine pancreas. These analyses revealed that preproglucagon contains not only the sequence of glucagon and glicentin, but also two additional glucagon-like peptides (GLP-1 and GLP-2) separated from glucagon and each other by two spacer or intervening peptides (IP-I and IP-II). These peptides are flanked by pairs of basic amino acids, characteristic of classic prohormone cleavage sites, suggesting they might be liberated after posttranslational processing of proglucagon (Drucker, Pancreas, 1990, 5(4):484). Analysis of the peptides liberated from proglucagon in the pancreatic islets of Langerhans, for instance, suggests the primary pancreatic peptide liberated is the 29-mer glucagon, whereas glicentin, oxyntomodulin, IP-II and the glucagon-like peptides are more prevalent in the small and large intestines. This demonstration that the glucagon-like peptides are found in the intestine has prompted research into the precise structure and putative function(s) of these newly discovered gut peptides. Most studies have focussed on GLP-1, because several lines of evidence suggested that GLP-1 may be an important new regulatory peptide. Indeed, it has been determined that GLP-1 is the most potent known peptidergic stimulus for insulin release, an action mediated in a

glucose-dependent manner through interaction with receptors on pancreatic ß cells. GLP-1 and its derivatives are in development for use in the treatment of diabetics.

With respect to the biological role of GLP-2, co-pending U.S. Application Serial No. 08/422,540 (PCT Publ. No. WO 96/32414), incorporated in its entirety herein by reference, discloses that mammalian GLP-2 acts as a trophic agent, to promote growth of intestinal tissue. The effect of GLP-2 is marked particularly by increased growth of the small intestine. Furthermore, co-pending U.S. Application Serial No. 08/631,273 and PCT Application No. PCT/CA 97/00252, both of which are incorporated in its entirety herein by reference, disclose that analogs of vertebrate GLP-2 can have enhanced intestinotrophic activity.

III. SUMMARY OF THE INVENTION

It has now been discovered that alteration of GLP-2 peptide structure can yield peptides capable of inhibiting the intestinotrophic activity of GLP-2. More particularly, and according to one aspect of the invention, there are provided antagonists comprising an amino acid sequence corresponding to that of a first reference mammalian GLP-2 which has been mutated so that from one to four of any of the first four N-terminal residues are deleted. In another aspect of the invention, the antagonists correspond to a reference mammalian GLP-2 that has been mutated so that at least one amino acid selected from the amino acid positions corresponding to the amino acid positions of human GLP-2 at Asp^{15}, Phe^{22}, Thr^{29}, Thr^{32} and Asp^{33} is substituted with an amino acid which does not naturally occur at that position in the reference GLP-2. In another aspect of the invention, position Ala^{2} is substituted with an amino acid selected from the group consisting of Leu, Cys, Glu, Arg, Trp, and PO_3-Tyr^{2}. In yet another aspect of the invention, the antagonist corresponds to a polypeptide with any combination of the above substitutions and deletions mutated relative to the reference mammalian GLP-2.

Also provided as an aspect of the invention are methods of producing and identifying GLP-2 antagonists.

For use in medical or veterinary treatment, there is further provided by the present invention a pharmaceutical or veterinary composition comprising an amount of a GLP-2 antagonist effective to antagonize GLP-2 activity in vivo, and a pharmaceutically or veterinarily acceptable carrier.

The GLP-2 antagonist activity of the present GLP-2 antagonists is manifest in vivo as a reduction in the mass of small bowel tissue or as an ability to inhibit the intestinotrophic activity of GLP-2 or intestinotrophic analogs thereof. Accordingly, there is provided, in another aspect of the invention, a method for reducing the mass or suppressing the proliferation of small bowel tissue in a subject, including an animal or a human, which comprises the step of delivering to that subject an amount of a GLP-2 antagonist of the invention effective to cause a reduction in the mass of small bowel tissue.

Subjects for whom such treatment would be useful include those suffering from hyperplastic conditions of the small intestine, for example, as a result of GLP-2 overdose or of GLP-2 overproducing tumors, and conditions wherein prophylactic inducement of small bowel hypoplasia would be useful, for example, in the treatment of clinical obesity as a non-surgical alternative to resection of the small intestine.

IV. DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to therapeutic and related uses of a novel class of GLP-2 antagonists, particularly for decreasing the growth rate of gastrointestinal tissue, most particularly small bowel. The biological effect of the present GLP-2 antagonists manifests as a decrease in small bowel weight, relative to a mock treated control or as an ability to inhibit the intestinotrophic activity of GLP-2 or an intestinotrophic analog of GLP-2, relative to a control

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