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<p>(21) International Application Number: PCT/US89/01121 (22) International Filing Date: 20 March 1989 (20.03.89)</p> <p>(71) Applicant: THE GENERAL HOSPITAL CORPORATION [US/US]; Fruit Street, Boston, MA 92114 (US). (72) Inventor: HABENER, Joel, F. ; 217 Plymouth Road, Newton Highlands, MA 02161 (US). (74) Agents: FOX, Samuel, L. et al.; Saidman, Sterne, Kessler & Goldstein, 1225 Connecticut Avenue, N.W., Suite 300, Washington, DC 20036 (US). (81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent). + </p>		<p>Published <i>With international search report.</i></p>
<p>(54) Title: INSULINOTROPIC HORMONE</p> <p>(57) Abstract</p> <p>Derivatives of glucagon-like peptide I (GLP-1) have been found to have insulinotropic activity. The invention pertains to such derivatives, and to the use of such derivatives as a potential therapy for <i>Diabetes Mellitus</i>.</p>		

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INSULINOTROPIC HORMONE

Cross-Reference to Related Applications

This application is a continuation-in-part of United States Patent Application Serial No. 859,928, filed on May 5, 1987.

BACKGROUND OF THE INVENTION

Field of the Invention

This invention is directed to the discovery that certain peptide fragments of the prehormone, proglucagon, possess hormonal activities and can be used to stimulate the synthesis and secretion of the hormone, insulin. These peptide fragments are useful in therapy for the disease Diabetes mellitus.

Description of the Background Art

The endocrine secretions of the pancreatic islets are under complex control not only by blood-borne metabolites (glucose, amino acids, catecholamines, etc.), but also by

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local paracrine influences. The major pancreatic islet hormones (glucagon, insulin, and somatostatin) interact among their specific cell types (A, B, and D cells, respectively) to modulate secretory responses mediated by the metabolites. Although insulin secretion is predominantly controlled by blood levels of glucose, glucagon and somatostatin stimulate and inhibit glucose-mediated insulin secretory responses, respectively. In addition to the proposed interislet paracrine regulation of insulin secretion, there is evidence to support the existence of insulintropic factors in the intestine. This concept originates from the observations that glucose taken orally is a much more potent stimulant of insulin secretion than is a comparable amount of glucose given intravenously.

The human hormone, glucagon, is a 29-amino acid peptide hormone produced in the A-cells of the pancreas. The hormone belongs to a multi-gene family of structurally related peptides that include secretin, gastric inhibitory peptide, vasoactive intestinal peptide, and glicentin. These peptides variously regulate carbohydrate metabolism, gastrointestinal mobility, and secretory processing. The principal recognized actions of pancreatic glucagon, however, are to promote glycogenolysis and gluconeogenesis, resulting in an elevation of blood sugar levels. In this regard, the actions of glucagon are counter-regulatory to those of insulin and may contribute to the hyperglycemia that accompanies Diabetes mellitus (Lund, P.K., et al., Proc. Natl. Acad. Sci., USA 79:345-349 (1982)).

Glucagon has been found to be capable of binding to specific receptors which lie on the surface of insulin-producing cells. Glucagon, when bound to these receptors, stimulates the rapid synthesis of cAMP, by these cells.

cAMP, in turn, has been found to stimulate insulin expression (Korman, L.Y., et al., Diabetes 34:717-722 (1985)). Insulin acts to inhibit glucagon synthesis (Review of Medical Physiology, Ganong, W.F., 1979, Lang Publications, Los Altos, California (p. 273)). Thus, the expression of glucagon is carefully regulated by insulin, and ultimately by the serum glucose level.

The glucagon gene is initially translated from a 630-base pair precursor to form the polypeptide, preproglucagon (Lund et al. (1982)). This polypeptide is subsequently processed to form proglucagon. Patzelt, C., et al. (Nature 282:260-266 (1979)) demonstrated that proglucagon was subsequently cleaved into glucagon and a second polypeptide. Subsequent work by Lund, P.K., et al. (Proc. Natl. Acad. Sci. USA 79:345-349 (1982)); Lopez, L.C., et al. (Proc. Natl. Acad. Sci. USA 80:5485-5489 (1983)) and Bell, G.I., et al. (Nature 302:716-718 (1983)) demonstrated that the proglucagon molecule was cleaved immediately after lysine-arginine dipeptide residues. Studies of proglucagon produced by channel catfish (Ictalurus punctata) indicated that glucagon from this animal was also proteolytically cleaved after adjacent lysine-arginine and arginine-arginine dipeptide residues (Andrews, P.C., et al., J. Biol. Chem. 260:3910-3914 (1985)). Lopez, L.C., et al. (Proc. Natl. Acad. Sci. USA 80:5485-5489 (1983)), and Bell, G.I., et al., discovered the mammalian proglucagon was cleaved at lysine-arginine or arginine-arginine dipeptides and demonstrated that the proglucagon molecule contained three discrete and highly homologous peptide molecules which were designated glucagon, glucagon-like protein 1 (GLP-1), and glucagon-like protein 2 (GLP-2). Lopez et al. concluded that glucagon-like protein 1 was 37 amino acid residues long

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