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(54) Title: INSULINOTROPIC HORMONE

(57) Abstract

A fragment of glucagon-like peptide I (GLP-1) has been found to be an insulinotropic hormone. This insulinotropic hormone comprises amino acid residues 7-37 of GLP-1. The insulinotropic hormone is useful as a potential therapy for *Diabetes Mellitus.*

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INSULINOTROPIC HORMONE

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, catecholemines, etc.), but also by local paracrine influences. The major pancreatic islet hormones (glucagon, insulin and somatostatin) interact amongst 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 pro-

posed interislet paracrine regulation of insulin secretion, there is evidence to support the existence of insulinotropic 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 counterregulatory 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 Lange 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 tranlated 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., Lopez L. C. et al., 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 discreet 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 and that glucagon-like peptide 2 was 34 amino acid residues long. Analogous studies on the structure of rat preproglucagon revealed a similar pattern of proteolytic cleavage between adjacent lysine-arginine or arginine-arginine dipep-

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