PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 :
C07K 7/10, 7/34, 7/40
A61K 37/02, 37/24

A1

(11) International Publication Number: WO 90/11296

(43) International Publication Date: 4 October 1990 (04.10.90)

(21) International Application Number: PCT/US89/01121

(22) International Filing Date: 20 March 1989 (20.03.89)

(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).

Published
With international search report.

(54) Title: INSULINOTROPIC HORMONE

(57) Abstract

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 *Diabetes Mellitus*.

DESIGNATIONS OF "DE"

Until further notice, any designation of "DE" in any international application whose international filing date is prior to October 3, 1990, shall have effect in the territory of the Federal Republic of Germany with the exception of the territory of the former German Democratic Republic.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MR	Mauritania
BE	Belgium	GA	Gabon	MW	Malawi
BF	Burkina Faso	GB	United Kingdom	NL	Netherlands
BG	Bulgaria	HU	Hungary	NO	Norway
BJ	Benin	IT	Italy	RO	Romania
BR	Brazil	JP	Japan	SD	Sudan
CA	Canada	KP	Democratic People's Republic of Korea	SE	Sweden
CF	Central African Republic			SN	Senegal
CG	Congo	KR	Republic of Korea	SU	Soviet Union
CH	Switzerland	LI	Liechtenstein	TD	Chad
CM	Cameroon	LK	Sri Lanka	TG	Togo
DE	Germany, Federal Republic of	LU	Luxembourg	US	United States of America
DK	Denmark	MC	Monaco		

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

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 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 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, preproglycagon (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

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.