DIABETES PEPTIDES

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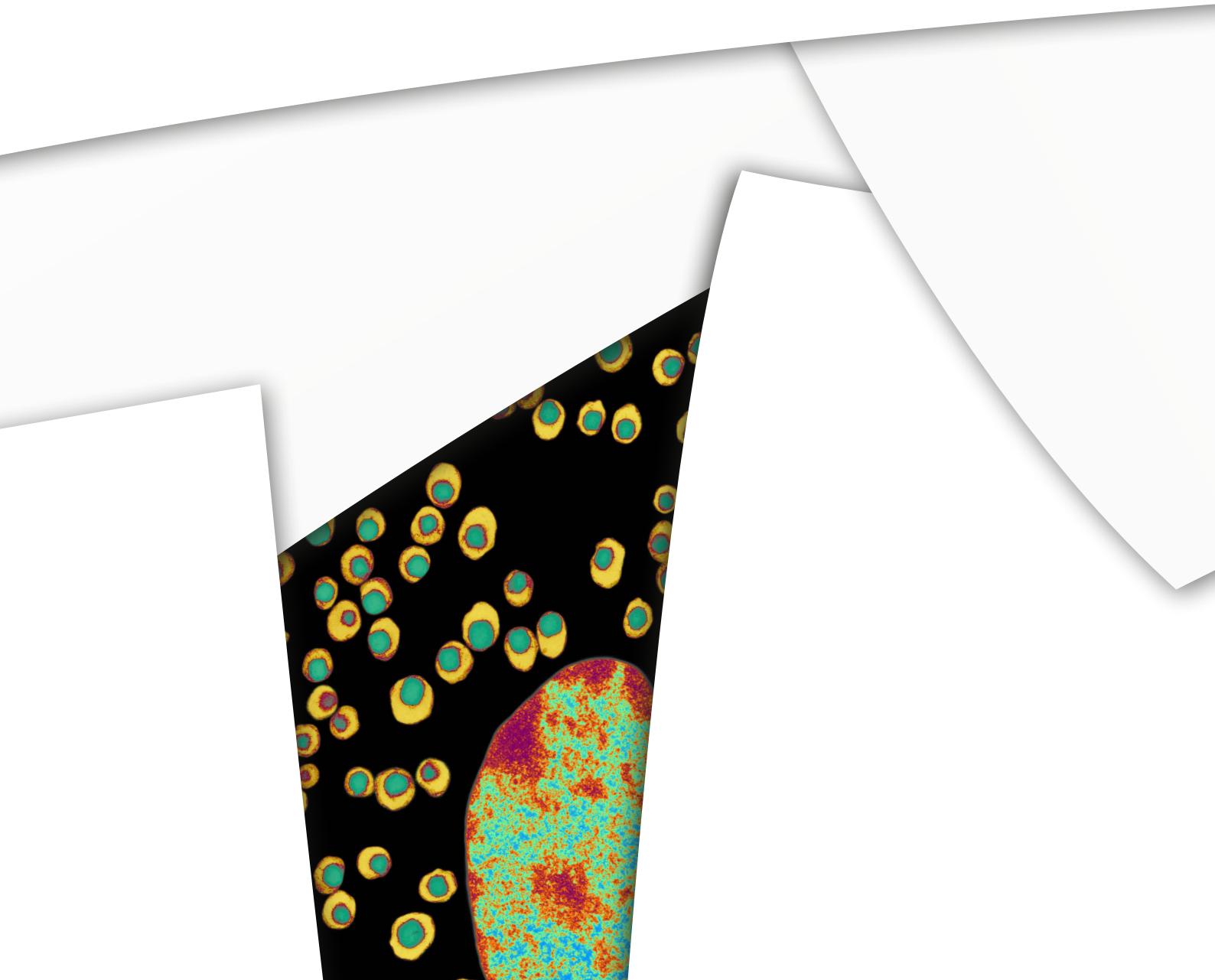

PEPTIDES FOR DIABETES RESEARCH

In 2014, according to data from the WHO, 422 million adults (or 8.5% of the population) had diabetes mellitus, a chronic metabolic disorder characterized by hyperglycemia, compared with 108 million (4.7%) in 1980. Diabetes mellitus can be divided into two main types, type 1 or insulin-dependent diabetes mellitus (IDDM) and type 2, or non insulin-dependent diabetes mellitus (NIDDM). The absolute lack of insulin, due to destruction of the insulin producing pancreatic β-cells, is the particular disorder in type 1 diabetes. Type 2 diabetes is mainly characterized by the inability of cells to respond to insulin. The condition affects mostly the cells of muscle and fat tissue, and results in a condition known as „insulin resistance".

Introduction

Diabetes was already known in ancient times. The name of this disease was created by the Graeco-Roman physician Aretaeus of Cappadocia (approx. 80 - 130 AD) and is derived from the Greek word *diabainein* that means 'to flow through'. The adjective *mellitus*, which comes from Latin and means 'honey-sweet', was added by the German physician Johann Peter Frank (1745-1821). It was introduced in order to distinguish diabetes mellitus, also called 'sugar diabetes', from diabetes insipidus, where an excessive amount of urine is produced as a result of a disturbance of the hormonal control of reabsorption of water in the kidneys. In 1889, pancreatic secretions were shown to control blood sugar levels. However, it took another 30 years until insulin was purified from the islets of Langerhans. In the following 50 years scientists detected the system-wide effects of insulin in liver, muscle, and adipose tissues. In the 1970s, the insulin receptor was discovered, and 10 years later, its tyrosine kinase activity was demonstrated. Despite this steady progress, one of the most challenging health problems of the 21st century remains the dramatic increase in diabetes mellitus that

EFFECTS OF DIABETES

Over time, diabetes mellitus can lead to blindness, kidney failure, and nerve damage. Diabetes mellitus is also an important factor in accelerating the hardening and narrowing of the arteries (atherosclerosis), leading to stroke, coronary heart diseases, and other blood vessel disorders.

is occurring throughout the world. Today diabetes mellitus is one of the main causes of death in most developed countries. According to data from the International Diabetes Federation, more than 382 million people around the world suffered from diabetes in 2013. This alarming number could reach 592 million by 2035. Further 316 million people have impaired glucose tolerance, a condition that can signal oncoming diabetes. 85 - 95 % of the diabetics have type 2 diabetes, a chronic disease associated with insulin deficiency and insulin resistance. Complications seen with diabetes range from heart disease (2 to 4 times higher occurence than in non-diabetics) to blindness, kidney disease, amputations, nerve damage and erectile dysfunction. As obesity spreads, the number of type 2 diabetics rises. Over 80% of diabetics are obese. Consequently, the treatment of risk factors such as obesity, hypertension, and hyperlipidemia assumes major importance and must be coordinated with a good glycemic control for the reduction in total mortality in type 2 diabetes mellitus. In this monograph, we describe the pancreatic and gastrointestinal peptide hormones that are involved in the control of blood glucose, the classification, and the treatment of diabetes mellitus.

Pancreatic Peptide Hormones

The islets of Langerhans contain four main cell types: β-cells secreting insulin, α-cells secreting glucagon, δ-cells secreting somatostatin and γ-cells secreting pancreatic polypeptide (PP). The core of each islet contains mainly the β-cells surrounded by a mantle of α-cells interspersed with δ-cells or γ-cells. Insulin is synthesized as a preprohormone in the β-cells of the islets of Langerhans. Removal of its signal peptide during insertion into the endoplasmic reticulum generates proinsulin which consists of 3 domains: an amino-terminal B-chain, a carboxy-terminal A-chain and a connecting peptide known as C-peptide. Within the endoplasmic reticulum proinsulin is exposed to several specific endopeptidases. These enzymes excise the C-peptide, thereby generating the mature form of insulin, a small protein consisting of an A-chain of 21 amino acids (containing an internal disulfide bridge) linked by two disulfide bridges to a B-chain of 30 amino acids. β-Cells secrete insulin in response to a rising level of circulating glucose. The normal fasting blood glucose concentration in humans and most mammals is 80 to 90 mg per 100 ml, associated with very low levels of insulin secretion. After a meal, excess sugars must be stored so that energy reserves will be available later on. Excess glucose is sensed by β-cells in the pancreas, which respond by secreting insulin into the bloodstream. Insulin causes various cells in the body to store glucose (see Fig. 1):

- Insulin stimulates skeletal muscle fibers to convert glucose into glycogen. It also induces the synthesis of proteins from amino acids circulating in the blood.
- Insulin acts on liver cells. It stimulates them to take up glucose from the blood converting it into glycogen while inhibiting the production of the enzymes involved in glycogenolysis.
- Insulin acts on fat cells to stimulate the uptake of glucose and the synthesis of fat.

In each case, insulin triggers these effects by binding to the insulin receptor, a heterotetramer of two extracellular α-subunits that are bonded by disulfides to two transmembrane β-subunits. Insulin receptor activation leads to specific phosphorylation events followed by an increase in glucose storage and a concomitant decrease in hepatic glucose release.

C-Peptide is applied as a diagnostic tool. It is released in amounts equal to insulin, so the level of C-peptide in the blood indicates how much insulin is being produced by the pancreas. The concentration of C-peptide is measured in diabetics to differentiate between endogenous (produced by the body) and exogenous (injected into the body) insulin, since synthetic insulin does not contain the C-peptide. Inappropriate use of insulin in persons with a low blood sugar level results in a low C-peptide level. The C-peptide level can also be determined in patients with type 2 diabetes showing how much insulin is produced by the β-cells. Abnormal high amounts of C-peptide can indicate the presence of a tumor called insulinoma which secretes insulin.

β-Cells also secrete a peptide hormone known as islet amyloid polypeptide (IAPP)

Glucose homeostasis is accomplished by complex physiological mechanisms. Control of blood glucose levels involves insulin, glucagon and other peptide hormones such as glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (gastric inhibitory polypeptide (GIP)).

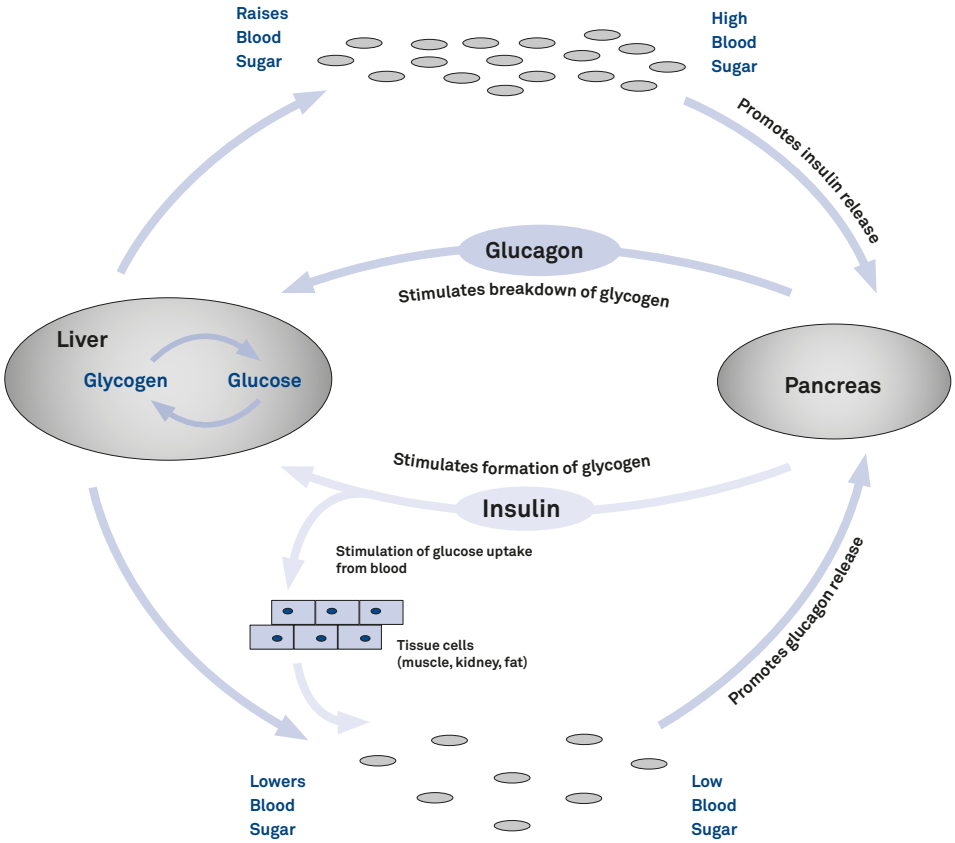

Fig. 1.
Opposing effects of insulin and glucagon

or amylin. This 37 amino acid peptide is structurally related to calcitonin and has weak calcitonin-like effects on calcium metabolism and osteoclast activity. Amylin shows about 50% sequence identity with calcitonin gene-related peptide (CGRP). It is stored together with insulin in the secretory granules of β-cells and is co-secreted with insulin. Amylin's most potent actions include the slowing of gastric emptying and the suppression of postprandial glucagon secretion. The hormone also reduces food intake and inhibits the secretion of gastric acid and digestive enzymes.
Thus, there is therapeutic potential of IAPP agonists for the treatment of patients with absolute amylin deficiency (type 1 diabetes) or relative amylin deficiency (type 2 diabetes).
In addition, amylin is the major component of the pancreatic amyloid deposits occurring in the pancreas of patients with type 2 diabetes.
Glucagon secretion is stimulated by low, and inhibited by high concentrations of glucose and fatty acids in the plasma (see Fig. 1). It counterbalances the action of insulin, increasing the levels of blood glucose and stimulating the protein breakdown in muscle. Glucagon is a major catabolic hormone, acting primarily on the liver. The peptide stimulates glycogenolysis (glycogen breakdown) and gluconeogenesis (synthesis of glucose from non-carbohydrate sources), inhibits glycogenesis (glycogen synthesis) and glycolysis, overall increasing hepatic glucose output and ketone body formation. In people suffering from diabetes, excess secretion of glucagon plays a primary role in hyperglycemia (high blood glucose concentration). Glucagon is clinically used in the treatment of hypoglycemia in unconscious patients (who can't drink).
Somatostatin release from the pancreas and gut is stimulated by glucose and amino acids. In diabetes, somatostatin levels are increased in pancreas and gut, presumably as a consequence of insulin deficiency. Somatostatin inhibits secretion of growth hormone, insulin and glucagon.

Gastrointestinal Peptide Hormones

Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) have significant effects on insulin secretion and glucose regulation. They are released after ingestion of carbohydrate- and fat-rich meals and stimulate insulin secretion postprandially. Both gut hormones constitute the class of incretins and share considerable sequence homology. GIP is a single 42 amino acid peptide derived from a larger 153 amino acid precursor (see Fig. 2). The peptide was originally observed to inhibit gastric acid secretion (hence it was designated gastric inhibitory polypeptide). Subsequent studies have demonstrated potent glucose-dependent insulin stimulatory effects of GIP administration in dogs and rodents. GIP also regulates fat metabolism in adipocytes, including stimulation of lipoprotein lipase activity, fatty acid incorporation, and fatty acid synthesis. Unlike GLP-1, GIP does not inhibit glucagon secretion or gastric emptying. The peptide promotes β-cell proliferation and cell survival in islet cell line studies.

GLP-1 is derived from the product of the proglucagon gene. This gene encodes a preproprotein (see Fig. 3) that is differentially processed dependent on the tissue in which it is expressed. In pancreatic α-cells, prohormone convertase 2 action leads to the release of glucagon. In the gut, prohormone convertase 1/3 action leads to the release of several peptides including GLP-1. Bioactive GLP-1 consists of two forms: GLP-1 (7-37) and GLP-1 (7-36) amide. The latter form constitutes the majority (80%) of the circulating GLPs.

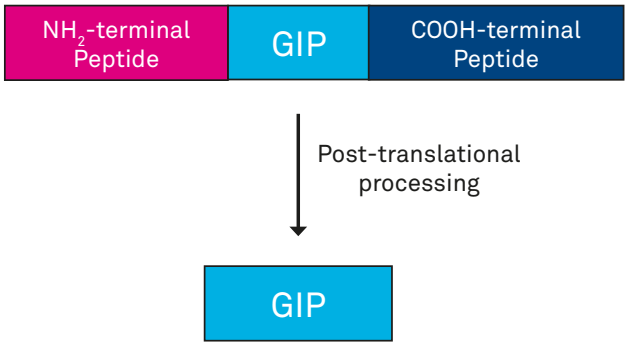

Fig. 2.
Structure of prepro-GIP

The primary physiological responses to GLP-1 are glucose-dependent insulin secretion, inhibition of glucagon secretion and inhibition of gastric acid secretion and gastric emptying. All effects of GLP-1 are exerted by activation of the GLP-1 receptor, a seven transmembrane spanning G-protein-coupled receptor (GPCR), leading to increased cAMP production and enhanced protein kinase A (PKA) activity.

The potential use of GLP-1 for the treatment of diabetes has been considered. GLP-1 exerts antidiabetogenic properties in subjects with type 2 diabetes by stimulating insulin secretion, increasing β-cell mass, inhibiting glucagon secretion, delaying gastric emptying, and inducing satiety, thus slowing the entry of sugar into the blood. However, GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase IV (DPP IV), making it unattractive as a therapeutic agent. Successful strategies to overcome this difficulty are the use of DPP IV-resistant GLP-1 receptor agonists, such as liraglutide

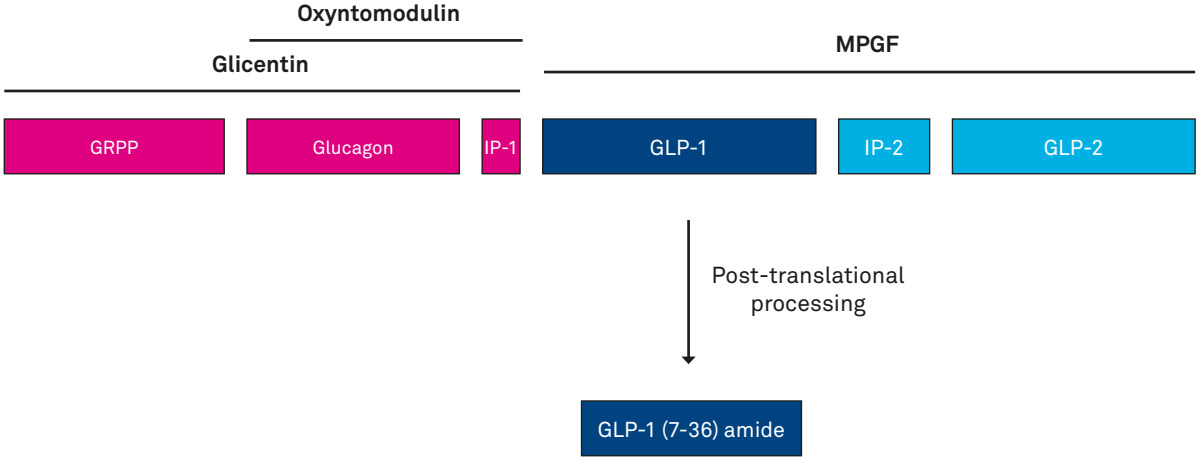

Fig. 3.
Structure of preproglucagon: GRPP, glicentin-related pancreatic peptide; IP, intervening peptides. Further peptides derived from the preproprotein include glicentin which is composed of amino acids 1-69, oxyntomodulin (glucagon-37) consisting of amino acids 33-69, and the major proglucagon fragment (MPGF) comprising amino acids 72-158.

(NN2211, a fatty acid-linked DPP IV-resistant derivative of GLP-1) or exendin-4 (exenatide). An alternative approach is the use of inhibitors of DPP IV, such as sitagliptin, P32/98 (H-Ile-thiazolidide hemifumarate), NVP DPP 728 (N-[2-(5-Cyanopyridin-2-yl-amino)ethyl]-Gly-Pro-nitrile) and the Gly-Pro-nitrile-derived compounds vildagliptin and saxagliptin.
Exendin-4 is a peptide hormone found in the saliva of the Gila monster, a lizard native to several Southwestern American states. Like GLP-1 exendin-4 exerts its effects through the GLP-1 receptor but is much more potent than GLP-1. Exenatide, a synthetic form of exendin-4 has been approved by the FDA as an antidiabetic drug. In contrast to most drugs that work by only one mechanism, exendin-4 acts by multiple mechanisms, such as stimulation of insulin secretion, slowing gastric emptying, and inhibiting the production of glucose by the liver. Furthermore, exendin-4 was shown to suppress appetite and promote weight loss.

Classification of Diabetes Mellitus
The International Diabetes Federation distinguishes between three main types of diabetes mellitus. This division is based upon whether the 'blood sugar problem' is caused by insulin deficiency or insulin resistance:
Type 1 diabetes (formerly known as insulin-dependent diabetes mellitus or juvenile-onset diabetes) is a β-islet cell specific, T-lymphocyte-mediated autoimmune disorder. It is characterized by a failure of the pancreas to produce sufficient insulin. Without insulin to promote the cellular uptake of glucose, the blood glucose concentrations reach high levels. At concentrations above 10 mM, renal tubular reabsorption is saturated and glucose is passed into the urine. The classic symptoms are excessive secretion of urine, thirst, weight loss and tiredness.
It is known that multiple genes contribute to the familial clustering of this disease, the major histocompatibility complex (MHC) being the most important of these. The MHC class 2 genotype is one of the strongest genetic factors determining disease susceptibility.
Type 2 diabetes (formerly named non-insulin-dependent diabetes mellitus or maturity-onset diabetes) is associated with insulin resistance rather than the lack of insulin as seen in type 1 diabetes. This lack of insulin sensitivity results in higher than normal blood glucose levels.
Type 2 diabetes is not HLA-linked and no autoimmune destruction of the pancreatic cells is observed. The development of type 2 diabetes seems to be multifactorial. Genetic predisposition appears to be the strongest factor. Other risk factors are obesity and high caloric intake. Pancreatic α-cell mass is increased, followed by an exaggerated response of glucagon to amino acids and an impaired suppression of glucagon secretion by hyperglycemia. Increased hepatic production of glucose with a failure of the pancreas to adapt to this situation and resistance to the action of insulin are characteristic features of this disorder. Another important morphological feature is the amyloid deposition in islets. These deposits consist of islet amyloid polypeptide or amylin, that is believed, to originate in the β-cell secretory granule.
Type 2 diabetes occurs most frequently in adults, but is being noted increasingly in adolescents as well. Type 2 diabetes develops slowly and the symptoms are usually less severe than in type 1. Sometimes the disease is only diagnosed several years after its onset, when complications are already present. Common late microvascular complications include retinopathy, nephropathy, and peripheral and autonomic neuropathies. Macrovascular complications include atherosclerotic coronary peripheral arterial disease.
Gestational diabetes may be observed in non-diabetic women during late pregnancy. They develop a resistance to insulin and, subsequently, high blood glucose. This type of diabetes is probably caused by hormones produced by the placenta. The blood glucose level has to be carefully controlled as to minimize risks for mother and child, it will return to the normal value after birth.

Treatment of Diabetes Mellitus
Insulin is essential for the treatment of type 1 diabetes. The effects of insulin and its mechanism of action are described above. For clinical application, either porcine or bovine insulin was given formerly. Today,

human insulin (produced recombinantly) is used. A new approach is the production of orally active insulin using modifications to make insulin resistant to enzymatic breakdown, facilitating absorption.
Most of the vascular consequences of insulin resistance are due to the hyperglycemia seen in type 2 diabetes. For this reason a major goal of therapeutic intervention in type 2 diabetes is to reduce circulating glucose levels. There are many pharmacological strategies to accomplish these goals:
1) The use of α-glucosidase inhibitors (e.g. acarbose) leads to a reduction in digestion and thereby minimizes the consequent absorption of glucose into the systemic circulation. The reduction in glucose uptake allows the pancreatic β-cells to regulate the insulin secretion more effectively. The advantage of α-glucosidase inhibitors is that they function locally in the intestine and have no major systemic action. Plants are rich sources of α-glucosidase inhibitors, some of which are being evaluated for their therapeutic potential.
2) The sulfonylureas (e.g. glibenclamide) are referred to as endogenous insulin secretagogues because they induce the pancreatic release of insulin and thus reduce plasma glucose. Sulfonylureas function by binding to and inhibiting the pancreatic ATP-dependent potassium channels normally involved in the glucose-mediated insulin secretion. Unwanted side-effects of sulfonylureas are appetite stimulation, probably via their effects on insulin secretion and blood glucose, often leading to weight gain.
3) The biguanides (e.g. metformin) are a class of drugs that lower blood glucose levels by enhancing insulin-mediated suppression of hepatic glucose production (gluconeogenesis) and by enhancing insulin-stimulated glucose uptake by skeletal muscle. Metformin is currently the most widely prescribed insulin-sensitizing drug in clinical use. The major site of action for metformin is the liver. Its use can be contraindicated in patients with liver dysfunction.
4) The thiazolidinediones (e.g. pioglitazone) have been proven useful in treating the hyperglycemia associated with insulin resistance in both type 2 diabetes and non-diabetic conditions. These products function as agonists for the peroxisome proliferator-activated receptor-γ (PPAR-γ). PPARs are members of a nuclear receptor superfamily that has important roles in carbohydrate and lipid metabolism. Thiazolidinediones enhance peripheral sensitivity to insulin and, to a lesser degree, decrease hepatic glucose production by binding to and activating the PPAR-γ. Adverse effects of thiazolidine-diones include weight gain, anemia, and abnormalities in liver and enzyme levels. Resistin, an adipocyte-derived peptide, first identified during a search for targets of thiazolidinediones, has been found to be downregulated by thiazolidinediones.
5) GLP-1 analogs stimulate insulin release, inhibit glucagon secretion, slow gastric emptying and stimulate β-cell proliferation. One of the most promising GLP-1 receptor agonists is exenatide (exendin-4) which is

Advances in genomics, proteomics and metabolomics will help us to further understand the causes of type 1 and type 2 diabetes and might eventually lead to novel therapeutic approaches.

ACCORDING TO THE WHO, THE NUMBER OF PEOPLE LIVING WITH DIABETES HAS ALMOST QUADRUPLED SINCE 1980 TO 422 MILLION ADULTS.

In the 1970s, the insulin receptor was discovered, and 10 years later, its tyrosine kinase activity was demonstrated.

53% identical to human GLP-1 at the amino acid level. The main advantage of exenatide is its resistance to cleavage and inactivation by dipeptidyl-peptidase IV (DPP IV).
In 2005, the FDA approved exenatide as adjunctive therapy to improve blood sugar control in patients with type 2 diabetes who have not achieved adequate control with metformin and/or a sulfonylurea. Use of the peptide as primary monotherapy was approved in 2009, and a sustained release formulation in 2014.
The long-acting GLP-1 agonist liraglutide was approved by the authority for the treatment of type 2 diabetes in 2010.
Albiglutide, a DPP IV-resistant GLP-1 dimer bound to albumin was approved by both FDA and European authorities in 2014.
FDA-approved dulaglutide is a GLP-1 dimer linked to human immunoglobulin G4. Their half-lifes, 4 - 7 days, are in the same range as the half-life of the recently developed GLP-1 analog semaglutide, These peptides are considerably more stable than exenatide,

6) DPP IV inhibitors represent another approach for the treatment of diabetes. Sitagliptin is the first candidate of this novel class of antihyperglycemic agents that has been approved by the FDA. Alogliptin, linagliptin, saxagliptin, and vildagliptin have been approved in the USA and in various countries worldwide. These DPP IV inhibitors can be used either alone or in combination with other oral antihyperglycemic agents (such as metformin or a thiazolidine -dione) for treatment of diabetes mellitus type 2.

7) Pramlintide, a soluble amylin analog, has gained FDA approval as an adjunct to insulin therapy in type 1 and type 2 diabetes. Like amylin, pramlintide acts centrally and decreases glucagon secretion, slows gastric emptying and induces satiety.

8) Insulin therapy is also indicated in the treatment of type 2 diabetes for the management of severe hyperglycemia after failure of oral agents. Long-acting insulin analogs could be obtained by replacement of Asn^{21} (A-chain) by glycine and addition of two arginine residues (insulin glargine) or acylation of $lysine^{29}$ (B-chain) with long-chain fatty acids. Insulin degludec is obtained by palmitoylation, which distinctly improves the metabolic stability of the peptide hormone by hexamer formation. Insulin degludec was approved in Europe in 2015 for treatment of children and adolescents with diabetes.

9) C-Peptide is biologically active. Clinical studies showed that administration of C-peptide to diabetes type 1 patients lacking the peptide alleviates nerve and renal dysfunctions associated with the disease. A long-acting analog, PEGylated C-peptide, is under evaluation.

Prospects

Although some of the agents described above are still in the early phases of investigation, there is little doubt that the therapy of diabetes will undergo major changes in the near future. It is important to diagnose all type 2 diabetics at an earlier stage (for example by making self monitoring of blood glucose easier) and begin treatment in an attempt to minimize the diabetes-associated complications.
The identification of the genetic components of type 1 and type 2 diabetes is an important area of research, because elucidation of the diabetes genes will influence all efforts towards an understanding of the disease, its complications, and its treatment, cure, and prevention. For this reason, genomic DNA from subjects with severe insulin resistance has been screened for mutations in genes that are implicated in insulin signaling. Indeed, a mutation in the gene encoding the serine/threonine kinase AKT2 (also known as PKBβ) could be identified. AKT2 is highly expressed in insulin-sensitive tissues and has been implicated in insulin-regulated glucose uptake into muscle and fat cells by promoting the translocation of glucose transporter 4 (GLUT4) to the cell surface.
Advances in genomics, proteomics and metabolomics will help us to further understand the causes of type 1 and type 2 diabetes and could eventually lead to novel therapeutic approaches.

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PEPTIDES FOR DIABETES RESEARCH

Bachem offers peptidic active pharmaceutical ingredients (generic APIs) and Clinalfa® basic ready-to-use formulations, sterile products for approved clinical studies, please see page 22 or go to www.bachem.com

AMYLIN (IAPP)

Amylin (human)
H-7905
KCNTATCATQRLANFLVHSSN-NFGAILSSTNVGSNTY-NH_2

Amylin (free acid) (human) NEW
H-7692
KCNTATCATQRLANFLVHSSN-NFGAILSSTNVGSNTY

Biotinyl-Amylin (human)
H-7398
Biotinyl-KCNTATCATQRLANFLVHSSN-NFGAILSSTNVGSNTY-NH_2

5-FAM-Amylin (human)
H-7392
Fluorescein-5-carbonyl-KCNTATCATQR-LANFLVHSSNNFGAILSSTNVGSNTY-NH_2

Amylin (1-13) (human)
H-5708
KCNTATCATQRLA

Amylin (8-37) (human)
H-2742
ATQRLANFLVHSSNNFGAILSSTNVGSN-TY-NH_2

Acetyl-Amylin (8-37) (human)
H-2744
Ac-ATQRLANFLVHSSNNFGAILSSTNVG-SNTY-NH_2

Amylin (14-20) (human) NEW
H-8094
NFLVHSS

Amylin (20-29) (human)
H-3746
SNNFGAILSS

Amylin (mouse, rat)
H-9475
KCNTATCATQRLANFLVRSSNNLGPV-LPPTNVGSNTY-NH_2

Biotinyl-Amylin (mouse, rat)
H-7394
Biotinyl-KCNTATCATQRLANFLVRSSNN-LGPVLPPTNVGSNTY-NH_2

5-FAM-Amylin (mouse, rat)
H-7396
Fluorescein-5-carbonyl-KCNTATCATQR-LANFLVRSSNNLGPVLPPTNVGSNTY-NH_2

Amylin (8-37) (mouse, rat)
H-2746
ATQRLANFLVRSSNNLGPVLPPTNVGSN-TY-NH_2

Acetyl-Amylin (8-37) (mouse, rat)
H-8665
Ac-ATQRLANFLVRSSNNLGPVLPPTNVG-SNTY-NH_2

C-PEPTIDE

(Tyr^0)-C-Peptide (dog)
H-2914
YEVEDLQVRDVELAGAPGEGGLQPLALE-GALQ

C-Peptide (human) NEW
(Acetate salt)
H-7722
EAEDLQVGQVELGGGPGAGSLQPLALEG-SLQ (Acetate salt)

C-Peptide (human)
(Trifluoroacetate salt)
H-2470
EAEDLQVGQVELGGGPGAGSLQPLALEG-SLQ (trifluoroacetate salt)

(Tyr^0)-C-Peptide (human)
H-4934
YEAEDLQVGQVELGGGPGAGSLQPLA-LEGSLQ

([D_8]$Val^{7,10}$)-C-Peptide (human)
H-4242
EAEDLQ[D_8]VGQ[D_8]VELGGGPGAGSLQ-PLALEGSLQ

Proinsulin C-Peptide (31-63) (porcine)
H-2142
RREAENPQAGAVELGGGLGGLQALA-LEGPPQKR

C-PEPTIDE (CONTINUED)

Proinsulin C-Peptide (55-89) (human)
H-1800
RREAEDLQVGQVELGGGPGAGSLQPLA-LEGSLQKR

Tyr-Proinsulin C-Peptide (55-89) (human)
H-2465
YRREAEDLQVGQVELGGGPGAGSLQPLA-LEGSLQKR

C-Peptide 1 (rat)
H-6136
EVEDPQVPQLELGGGPEAGDLQTLAL-EVARQ

C-Peptide 2 (rat)
H-6122
EVEDPQVAQLELGGGPGAGDLQTLAL-EVARQ

EXENDIN

Exenatide
(Exendin-4)
H-8730
HGEGTFTSDLSKQMEEEAVRL-FIEWLKNGGPSSGAPPPS-NH_2

Acetyl-Exenatide
H-7488
Ac-HGEGTFTSDLSKQMEEEAVRL-FIEWLKNGGPSSGAPPPS-NH_2

(D-Asn^{28})-Exenatide
H-8192
HGEGTFTSDLSKQMEEEAVRL-FIEWLKNGGPSSGAPPPS-NH_2

(Asp^{28})-Exenatide
H-7496
HGEGTFTSDLSKQMEEEAVRLFIEWLK nGGPSSGAPPPS-NH_2

(D-Asp^{28})-Exenatide
H-8184
HGEGTFTSDLSKQMEEEAVRLFIEWLK-dGGPSSGAPPPS-NH_2

(β-Asp^{28})-Exenatide
H-8186
HGEGTFTSDLSKQMEEEAVRLFIEWLK D(GGPSSGAPPPS-NH_2)

(β-D-Asp^{28})-Exenatide NEW
H-8188
HGEGTFTSDLSKQMEEEAVRLFIEWLK d(GGPSSGAPPPS-NH_2)

(Des-Gly^2)-Exenatide
H-7486
HEGTFTSDLSKQMEEEAVRLFIEWLKNG-GPSSGAPPPS-NH_2

Endo-38a-Pro-Exenatide
H-7492
HGEGTFTSDLSKQMEEEAVRL-FIEWLKNGGPPSSGAPPPS-NH_2

(D-His^1)-Exenatide
H-7494
hGEGTFTSDLSKQMEEEAVRL-FIEWLKNGGPSSGAPPPS-NH_2

(Met(O)^{14})-Exenatide
(Exendin-4 sulfoxide)
H-7498
HGEGTFTSDLSKQM(O)EEEAVRL-FIEWLKNGGPSSGAPPPS-NH_2

(Glu^9)-Exenatide (2-39) NEW
H-7544
GEGTFTSELSKQMEEEAVRLFIEWLKNG-GPSSGAPPPS-NH_2

Exendin-3
H-8735
HSDGTFTSDLSKQMEEEAVRL-FIEWLKNGGPSSGAPPPS-NH_2

Exendin-4 (1-8)
H-6454
HGEGTFTS-NH_2

Exendin-4 (3-39)
H-3864
EGTFTSDLSKQMEEEAVRLFIEWLKNGG-PSSGAPPPS-NH_2

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EXENDIN (CONTINUED)

Exendin (9-39)
H-8740
DLSKQMEEEAVRLFIEWLKNGGPSS-GAPPPS-NH_2

Lixisenatide*
((Des-Pro^{38})-Exendin-4(-Lys)$_6$ amide)
H-7426
HGEGTFTSDLSKQMEEEAVRL-FIEWLKNGGPSSGAPPSKKKKKK-NH_2

GLUCOSE-DEPENDENT INSULINO-TROPIC POLYPEPTIDE (GIP)

Gastric Inhibitory Polypeptide (human)
(Glucose-Dependent Insulinotropic Polypeptide (human), GIP (human))
H-5645
YAEGTFISDYSIAMDKIHQQDFVNWL-LAQKGKKNDWKHNITQ

(D-Ala^2)-Gastric Inhibitory Polypeptide (human) NEW
H-7586
YaEGTFISDYSIAMDKIHQQDFVNWL-LAQKGKKNDWKHNITQ

(Pro^3)-Gastric Inhibitory Polypeptide (human) NEW
H-7584
YAPGTFISDYSIAMDKIHQQDFVNWL-LAQKGKKNDWKHNITQ

Gastric Inhibitory Polypeptide (6-30) amide (human)
H-6102
FISDYSIAMDKIHQQDFVNWLLAQK-NH_2

Gastric Inhibitory Polypeptide (porcine)
H-6220
YAEGTFISDYSIAMDKIRQQDFVNWL-LAQKGKKSDWKHNITQ

Gastric Inhibitory Polypeptide (1-30) amide (porcine)
(Glucose-Dependent Insulinotropic Polypeptide (porcine), GIP (porcine))
H-3824
YAEGTFISDYSIAMDKIRQQDFVNWL-LAQK-NH_2

Gastric Inhibitory Polypeptide (3-42) (human)
H-6614
EGTFISDYSIAMDKIHQQDFVNWLLAQK-GKKNDWKHNITQ

GLUCAGON, GRPP, OXYNTO-MODULIN

Glucagon (1-29) (human, rat, porcine)
H-6790
HSQGTFTSDYSKYLDSRRAQD-FVQWLMNT

Glucagon (1-29) (human, rat, porcine) (Acetate salt) NEW
H-7754
HSQGTFTSDYSKYLDSRRAQD-FVQWLMNT
(Acetate salt)

([$^{13}C_6$]Leu^{14})-Glucagon (1-29) (human, rat, porcine)
H-7236
HSQGTFTSDYSKY[$^{13}C_6$]LDSRRAQD-FVQWLMNT

Biotinyl-Glucagon (1-29) (human, rat, porcine)
H-5676
Biotinyl-HSQGTFTSDYSKYLDSRRAQD-FVQWLMNT

(Asp^{28})-Glucagon (1-29) (human, rat, porcine) NEW
H-8264
HSQGTFTSDYSKYLDSRRAQDFVQWLMDT

(Glu^3)-Glucagon (1-29) (human, rat, porcine) NEW
H-8258
HSEGTFTSDYSKYLDSRRAEDFVQWLMNT

GLUCAGON, GRPP, OXYNTO-MODULIN (CONTINUED)

(Glu^{20})-Glucagon (1-29) (human, rat, porcine) NEW
H-8262
HSQGTFTSDYSKYLDSRRAED-FVQWLMNT

((Glu^{24})-Glucagon (1-29) (human, rat, porcine) NEW
H-8266
HSQGTFTSDYSKYLDSRRAQDFVEW-LMNT

(Des-His^{1},Glu^{9})-Glucagon (1-29) amide (human, rat, porcine))
H-2754
SQGTFTSEYSKYLDSRRAQDFVQWLMNT-NH_2

(Des-Thr^{5})-Glucagon
H-6156
HSQGFTSDYSKYLDSRRAQDFVQWLMNT

(Des-Thr^{7})-Glucagon
H-6158
HSQGTFSDYSKYLDSRRAQDFVQWLMNT

(Met(O)^{27})-Glucagon (1-29) (human, rat, porcine)
H-6148
HSQGTFTSDYSKYLDSRRAQDFVQWLM(O)NT

Glucagon (19-29) (human, rat, porcine)
H-2758
AQDFVQWLMNT

GRPP (human)
(Glicentin-Related Polypeptide (human))
H-6062
RSLQDTEEKSRSFSASQADPLSDP-DQMNED

Oxyntomodulin (bovine, dog, porcine)
(Glucagon-37 (bovine, dog, porcine))
H-6880
HSQGTFTSDYSKYLDSRRAQD-FVQWLMNTKRNKNNIA

Oxyntomodulin (human, mouse, rat)
(Glucagon-37 (human, mouse, rat))
H-6058
HSQGTFTSDYSKYLDSRRAQD-FVQWLMNTKRNRNNIA

Oxyntomodulin (30-37) (bovine, dog, porcine)
H-5910
KRNKNNIA

GLUCAGON-LIKE PEPTIDES

GLP-1 (1-36) amide (human, bovine, guinea pig, mouse, rat)
H-6025
HDEFERHAEGTFTSDVSSYLEGQAAKE-FIAWLVKGR-NH_2

GLP-1 (1-37) (human, bovine, guinea pig, mouse, rat)
H-5552
HDEFERHAEGTFTSDVSSYLEGQAAKEFI-AWLVKGRG

GLP-1 (7-36) amide (chicken, common turkey)
H-5824
HAEGTYTSDITSYLEGQAAKEFIAWLVN-GR-NH_2

GLP-1 (7-36) amide (human, bovine, guinea pig, mouse, rat)
H-6795
HAEGTFTSDVSSYLEGQAAKEFIAWLVK-GR-NH_2

GLP-1 (7-36)-Lys(biotinyl) amide (human, bovine, guinea pig, mouse, rat)
H-5956
HAEGTFTSDVSSYLEGQAAKEFIAWLVKG RK(biotinyl)-NH_2

GLP-1 (7-36)-Lys(6-FAM) amide (human, bovine, guinea pig, mouse, rat)
H-5954
HAEGTFTSDVSSYLEGQAAKEFIAWLVKG RK(fluorescein-6-carbonyl)-NH_2

GLUCAGON-LIKE PEPTIDES (CONTINUED)

(Ser^{8})-GLP-1 (7-36) amide (human, bovine, guinea pig, mouse, rat)
H-4592
HSEGTFTSDVSSYLEGQAAKEFIAWLVK-GR-NH_2

GLP-1 (7-37) (human, bovine, guinea pig, mouse, rat)
(Acetate salt)
H-9560
HAEGTFTSDVSSYLEGQAAKEFIAWLVK-GRG
(Acetate salt)

GLP-1 (7-37) (human, bovine, guinea pig, mouse, rat)
(Trifluoroacetate salt)
H-5102
HAEGTFTSDVSSYLEGQAAKEFIAWLVK-GRG
(Trifluoroacetate salt)

GLP-1 (9-36) amide (human, bovine, guinea pig, mouse, porcine, rat)
H-4012
EGTFTSDVSSYLEGQAAKEFIAWLVKGR-NH_2

Liraglutide*
(Acetate salt) **NEW**
(NN2211, (Lys(γ-Glu-palmitoyl)^{26},Arg^{34})-GLP-1 (7-37))
H-8148
HAEGTFTSDVSSYLEGQAAK(γE(Pam))EFIAWLVRGRG
(Acetate salt)

Liraglutide*
(Trifluoroacetate salt)
(NN2211, (Lys(γ-Glu-palmitoyl)^{26},Arg^{34})-GLP-1 (7-37))
H-6724
HAEGTFTSDVSSYLEGQAAK(γE(Pam))EFIAWLVRGRG
(Trifluoroacetate salt)

Semaglutide* **NEW**
(NN9535, (Aib^{2}, Lys(γ-Glu-AEEAc-AEEAc-17-carboxy-heptadecanoyl)^{26},Arg^{34})-GLP-1 (7-37))
H-7894
H-Aib-EGTFTSDVSSYLEGQAAK(γE(AEEAc-AEEAc-17-carboxyheptadecanoyl))EFIAWLVRGRG

GLP-2 (1-33) (human)
(Ammonium acetate salt) **NEW**
H-7742
HADGSFSDEMNTILDNLAARDFIN-WLIQTKITD
(Ammonium acetate salt)

GLP-2 (1-33) (human)
(Trifluoroacetate salt)
H-5662
HADGSFSDEMNTILDNLAARDFIN-WLIQTKITD
(Trifluoroacetate salt)

GLP-2 (1-34) (human)
H-4766
HADGSFSDEMNTILDNLAARDFIN-WLIQTKITDR

GLP-2 (rat)
H-5002
HADGSFSDEMNTILDNLATRDFIN-WLIQTKITD

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INSULIN, INSULIN-LIKE GROWTH FACTOR (IGF)

H-Asn-Pro-Glu-Tyr(PO_3H_2)-OH
H-2706
NPEpY

rec IGF-I (human)
H-5555

IGF-I Analog
H-1356
CYAAPLKPAKSC
(Disulfide bond)

IGF-I (1-3)
H-2468
GPE

IGF-I (24-41)
H-3098
YFNKPTGYGSSSRRAPQT

IGF-I (30-41)
H-7460
GYGSSSRRAPQT

rec IGF-II (1-67) (human)
H-7020
AYRPSETLCGGELVDTLQFVCGDRGFYFS-
RPASRVSRRSRGIVEECCFRSCDLALLE-
TYCATPAKSE

IGF-II (33-40)
H-7250
SRVSRRSR

Lys-Lys-IRS-1 (891-902) (dephosphorylated) (human)
H-6178
KKKSPGEYVNIEFG

Insulin B (22-25)
H-6005
RGFF

RELATED PRODUCTS: DPP IV SUBSTRATES AND INHIBITORS

H-Gly-Pro-AMC · HBr
I-1225
GP-AMC · HBr

H-Gly-Pro-4MβNA
J-1210
GP-MNA

H-Gly-Pro-βNA
K-1335
GP-bNA

H-Gly-Pro-pNA · HCl
L-1880
GP-pNA · HCl

H-Gly-Pro-pNA · p-tosylate
L-1295
GP-pNA · p-tosylate

Diprotin A
H-3825
IPI

Diprotin B
H-5290
VPL

RELATED PRODUCTS: PEPTIDES

Adropin (34-76) (human, mouse, rat)
H-6686
CHSRSADVDSLSESSPNSSPGPCPE-KAPPPQKPSHEGSYLLQP

(Pyr^{1})-Apelin-13 (human, bovine, mouse, rat)
H-4568
<ERPRLSHKGPMPF

Calcitonin (8-32) (salmon I)
H-5502
VLGKLSQELHKLQTYPRTNTGSGTP-NH_2

Acetyl-(Asn^{30},Tyr^{32})-Calcitonin (8-32) (salmon I)
(AC187)
H-4922
Ac-VLGKLSQELHKLQTYPRTNTGSNTY-NH_2

L-Carnosine
G-1250

Cyclo(-His-Pro)
G-1745
c(HP)

Endotrophin (mouse)
H-7382
TEPLFLTKTDICKLSRDAGTCVDFKLL-WHYDLESKSCKRFWYGGCGGNENRFH-SQEECEKMCSPELTV
(Disulfide bonds, air oxidized)

Galanin (1-13)-Mastoparan
(Galparan)
H-4188
GWTLNSAGYLLGPINLKALAALAKKIL-NH_2

Osteocalcin (1-49) (human)
H-4912
YLYQWLGAPVPYPDPL-Gla-PRR-Gla-VC-Gla-LNPDCDELADHIGFQEAYRRFYGPV
(Disulfide bond)

(Glu^{17,21,24})-Osteocalcin (1-49) (human) **NEW**
(Osteocalcin (1-49) (human) (decarboxylated))
H-7534
YLYQWLGAPVPYPDPLEPRREVCELNP-DCDELADHIGFQEAYRRFYGPV
(Disulfide bond)

Pancreastatin (33-48) (human)
H-6506
EEEEEMAVVPQGLFRG-NH_2

Pancreastatin (dephosphorylated) (porcine)
(Chromogranin A (240-288) (dephosphorylated) (porcine))
H-6165
GWPQAPAMDGAGKTGAEEAQPPEGK-GAREHSRQEEEEETAGAPQGLFRG-NH_2

Phylloseptin-L2
H-6704
FLSLIPHVISALSSL-NH_2

Preptin (human)
H-6568
DVSTPPTVLPDNFPRYPVGKFFQYDT-WKQSTQRL

Preptin (rat)
H-6572
DVSTSQAVLPDDFPRYPVGKFFKFDT-WRQSAGRL

Pseudin-2
H-6586
GLNALKKVFQGIHEAIKLINNHVQ

(Lys^{18})-Pseudin-2
H-6588
GLNALKKVFQGIHEAIKKINNHVQ

TRH
(Protirelin)
H-4915
<EHP-NH_2

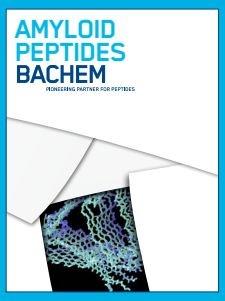
(His(3-Me)^{2})-TRH **NEW**
H-7652
<EH(3-Me)P-NH_2

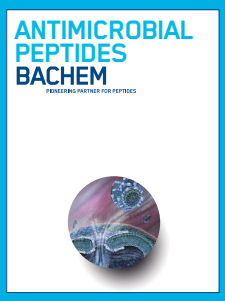
Xenin 25
H-8860
MLTKFETKSARVKGLSFHPKRPWIL

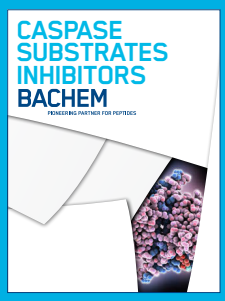
BACHEM

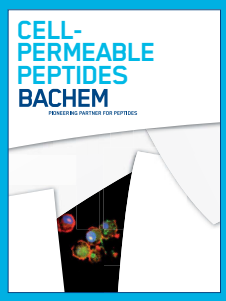
PIONEERING PARTNER FOR PEPTIDES

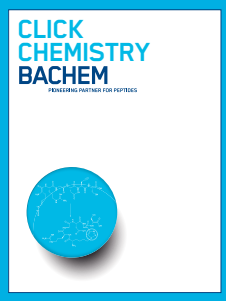
PRODUCT BROCHURES

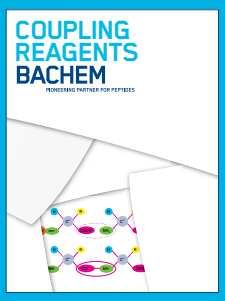


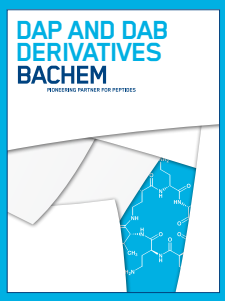


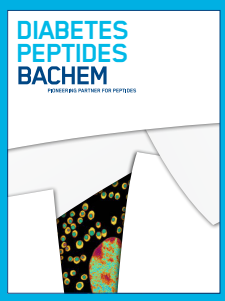


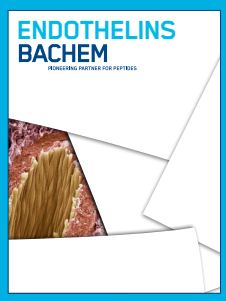


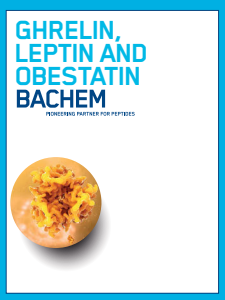


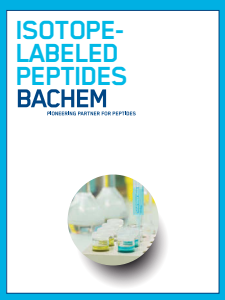


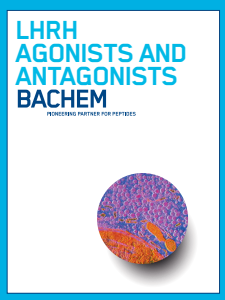


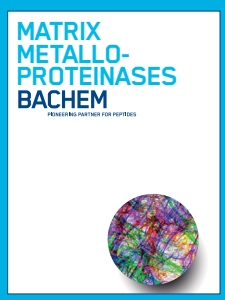


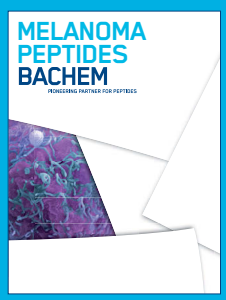


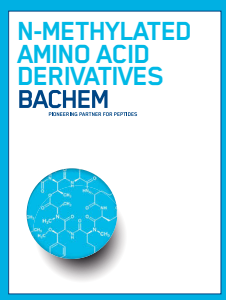


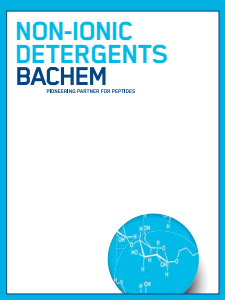


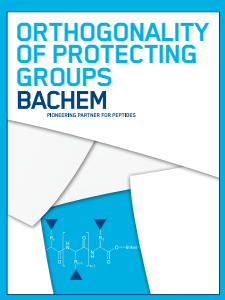


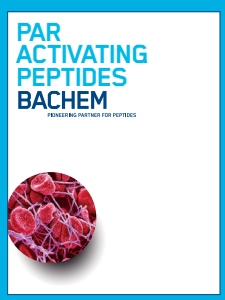


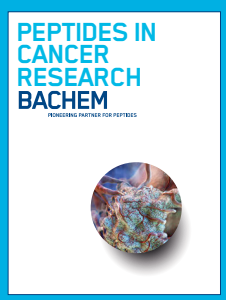


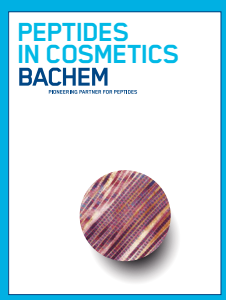


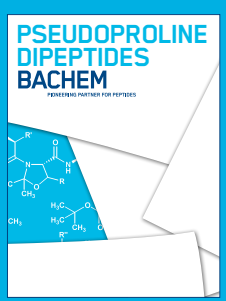


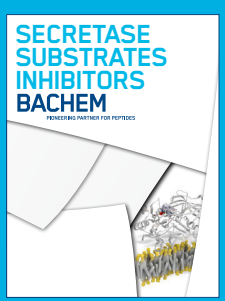


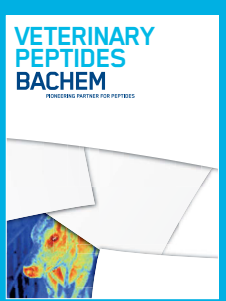












GENERIC APIs

Exenatide Acetate
4044219
HGEGTFTSDLSKQMEEEAVRL-FIEWLKNGGPSSGAPPPS-NH_2

Glucagon
H-6790-GMP
HSQGTFTSDYSKYLDSRRAQD-FVQWLMNT

Lixisenatide*
4041774
HGEGTFTSDLSKQMEEEAVRL-FIEWLKNGGPSSGAPPSKKKKKK-NH_2

CLINALFA® BASIC

(Pyr¹)-Apelin-13 Acetate
1 mg/vial (Clinalfa basic)
U-1270
<ERPRLSHKGPMPF

Exendin (9-39) Acetate
10 mg/vial (Clinalfa basic)
U-1160
DLSKQMEEEAVRLFIEWLKNGGPSS-GAPPPS-NH_2

GIP Acetate
500 µg/vial (Clinalfa basic)
U-1240
YAEGTFISDYSIAMDKIHQQDFVNWL-LAQKGKKNDWKHNITQ

GLP-1 (7-36) amide Acetate
100 µg/vial (Clinalfa basic)
U-1190
HAEGTFTSDVSSYLEGQAAKEFIAWLVK-GR-NH_2

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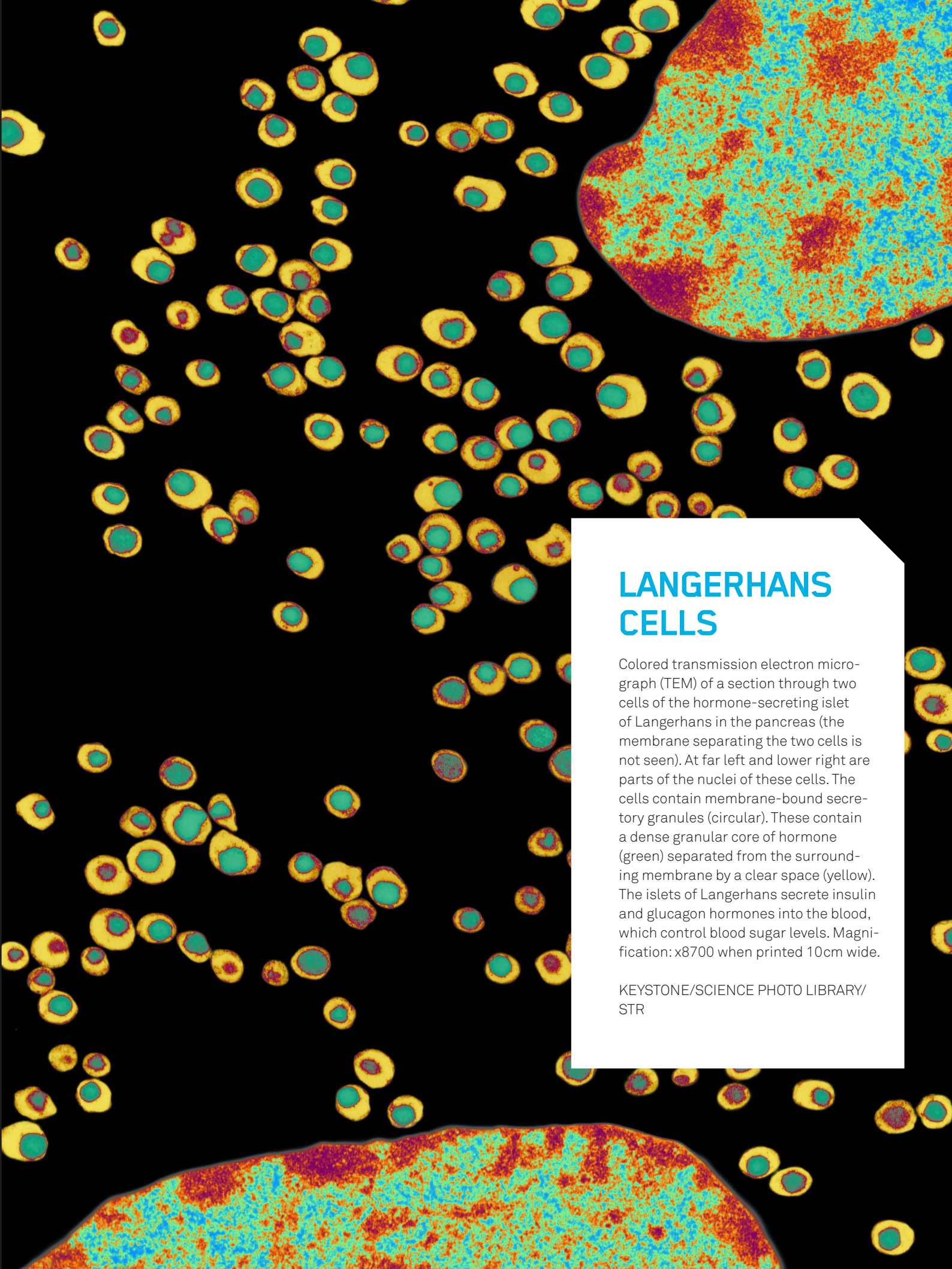

LANGERHANS CELLS

Colored transmission electron micrograph (TEM) of a section through two cells of the hormone-secreting islet of Langerhans in the pancreas (the membrane separating the two cells is not seen). At far left and lower right are parts of the nuclei of these cells. The cells contain membrane-bound secretory granules (circular). These contain a dense granular core of hormone (green) separated from the surrounding membrane by a clear space (yellow). The islets of Langerhans secrete insulin and glucagon hormones into the blood, which control blood sugar levels. Magnification: x8700 when printed 10cm wide.

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PIONEERING PARTNER FOR PEPTIDES

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