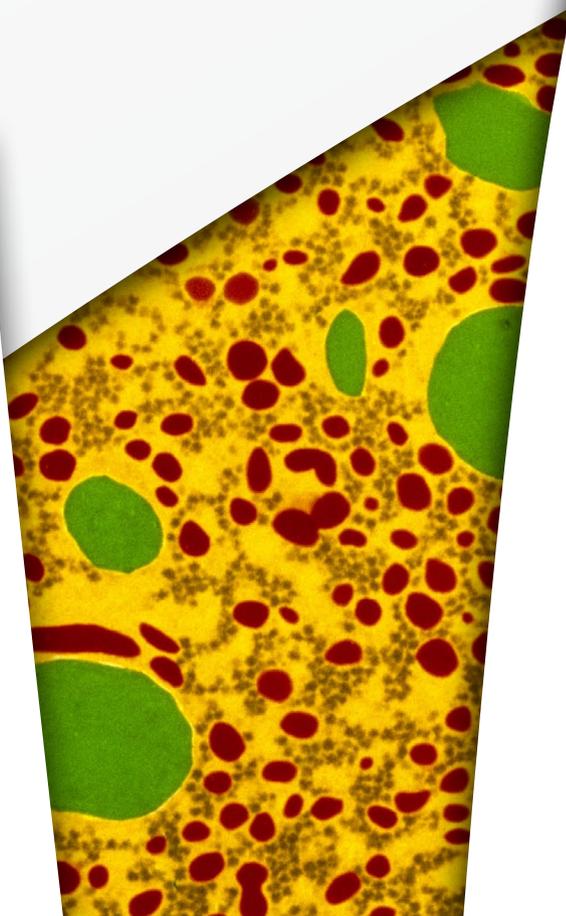


DIABETES PEPTIDES BACHEM

LEADING PARTNER IN TIDES



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

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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 occurrence 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 prohormone 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 disul-

fide 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)).

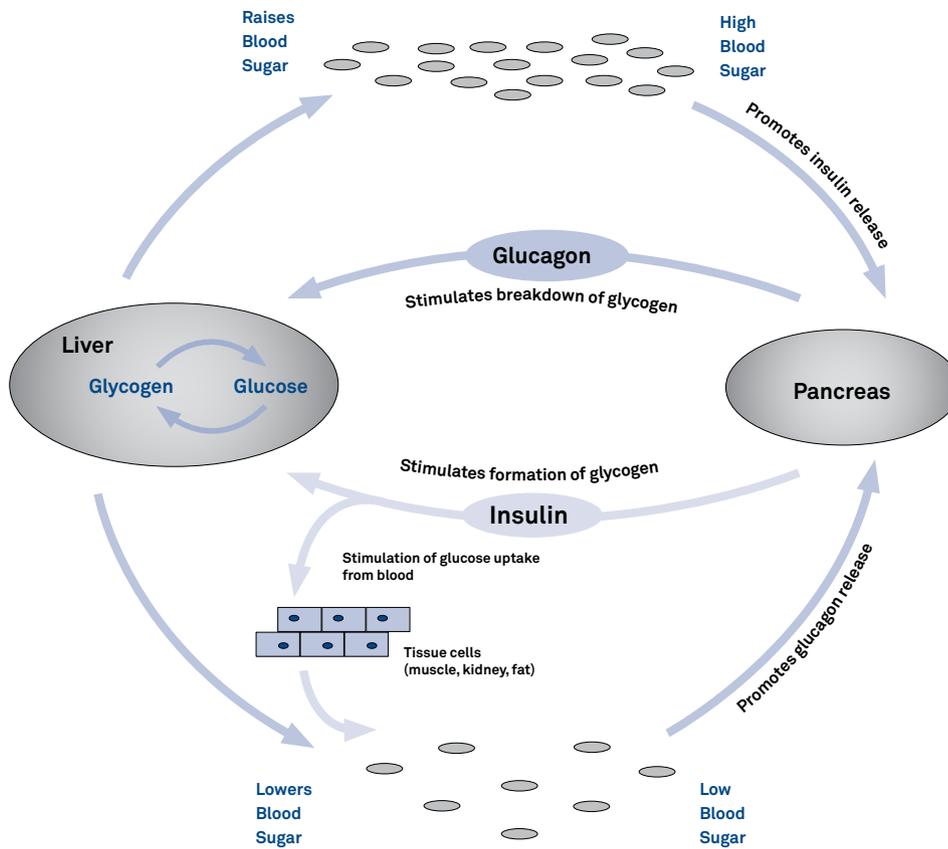


Fig. 1. Opposing effects of insulin and glucagon

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.

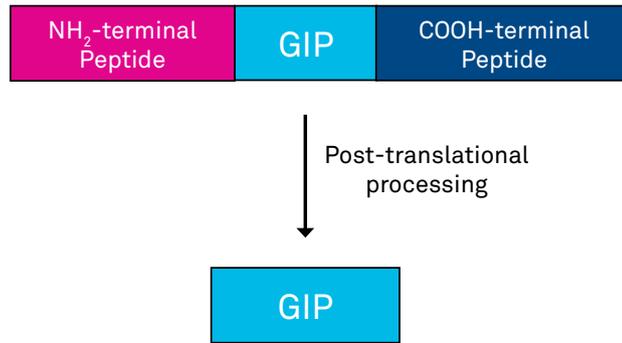
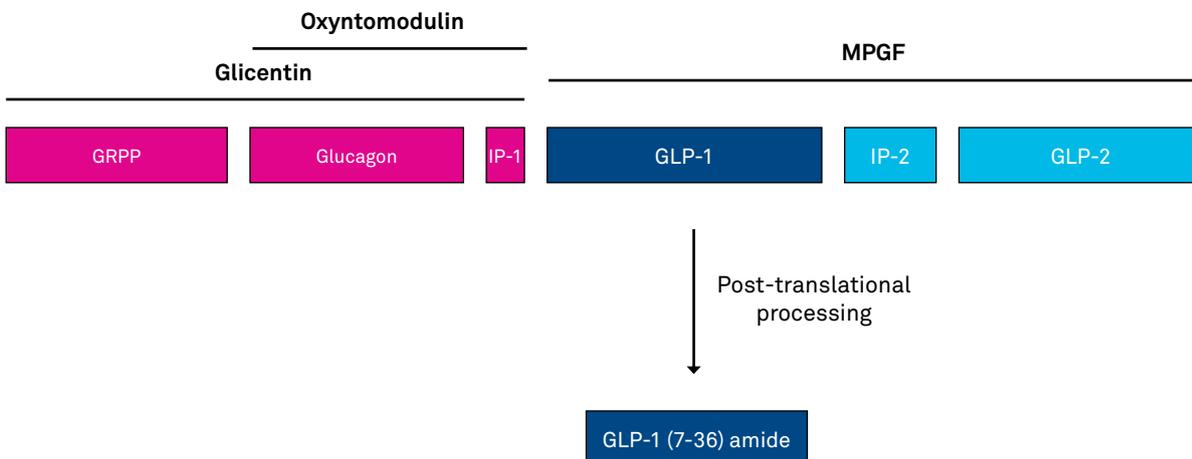


Fig. 2.
Structure of prepro-GIP

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 (NN2211, a fatty acid-linked DPP IV-resistant derivative of GLP-1) or exendin-4 (ex-

Fig. 3.
Structure of proglucagon: 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.



enatide). 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 53% identical to human GLP-1 at the amino acid level. The main advantage of exenatide

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.

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-lives, 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 Asn²¹ (A-chain) by glycine and addition of two arginine residues (insulin glargine) or acylation of lysine²⁹ (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 PKB β) 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)

4030200

KCNTATCATQRLANFLVHSSN-
NFGAILSSTNVGSNTY-NH₂

Amylin (free acid) (human) NEW

4073878

KCNTATCATQRLANFLVHSSN-
NFGAILSSTNVGSNTY

Biotinyl-Amylin (human)

4059629

Biotinyl-KCNTATCATQRLANFLVHSSN-
NFGAILSSTNVGSNTY-NH₂

5-FAM-Amylin (human)

4089771

Fluorescein-5-carbonyl-KCNTATCATQR-
LANFLVHSSNFGAILSSTNVGSNTY-NH₂

Amylin (1-13) (human)

4039860

KCNTATCATQRLA

Amylin (8-37) (human)

4030202

ATQRLANFLVHSSNFGAILSSTNVGSN-
TY-NH₂

Acetyl-Amylin (8-37) (human)

4030345

Ac-ATQRLANFLVHSSNFGAILSSTNVG-
SNTY-NH₂

Amylin (14-20) (human) NEW

4099428

NFLVHSS

Amylin (20-29) (human)

4030350

SNNFGAILSS

Amylin (mouse, rat)

4030201

KCNTATCATQRLANFLVRSSNNLGPV-
LPPTNVGSNTY-NH₂

Biotinyl-Amylin (mouse, rat)

4089772

Biotinyl-KCNTATCATQRLANFLVRSSNN-
LGPVLPPTNVGSNTY-NH₂

5-FAM-Amylin (mouse, rat)

4089773

Fluorescein-5-carbonyl-KCNTATCATQR-
LANFLVRSSNNLGPVLPPTNVGSNTY-
NH₂

Amylin (8-37) (mouse, rat)

4030346

ATQRLANFLVRSSNNLGPVLPPTNVGSN-
TY-NH₂

C-PEPTIDE

(Tyr⁰)-C-Peptide (dog)

4030533

YEVEDLQVRDVELAGAPGEGGLQPLALE-
GALQ

C-Peptide (human) NEW

(Acetate salt)

4068086

EAEDLQVGQVELGGGPGAGSLQPLALEG-
SLQ (Acetate salt)

C-Peptide (human)

(Trifluoroacetate salt)

4009494

EAEDLQVGQVELGGGPGAGSLQPLALEG-
SLQ (trifluoroacetate salt)

(Tyr⁰)-C-Peptide (human)

4034546

YEAEDLQVGQVELGGGPGAGSLQPLA-
LEGLSQ

([D₈]Val⁷⁻¹⁰)-C-Peptide (human)

4028385

EAEDLQ[D₈]VGQ[D₈]VELGGGPGAGSLQ-
PLALEGLSQ

**Proinsulin C-Peptide (55-89)
(human)**

4011662

RREAEDLQVGQVELGGGPGAGSLQPLA-
LEGLSQKR

C-PEPTIDE (CONTINUED)

**Tyr-Proinsulin C-Peptide (55-89)
(human)**
4015509
YRREAEDLQVGVQVELGGGPGAGSLQPLA-
LEGSLQKR

C-Peptide 1 (rat)
4045921
EVEDPQVPQLELGGGPEAGDLQTLAL-
EVARQ

C-Peptide 2 (rat)
4035984
EVEDPQVAQLELGGGPGAGDLQTLAL-
EVARQ

EXENDIN

Exenatide
(Exendin-4)
4019602
HGEGTFTSDLSKQMEEEEAVRL-
FIEWLKNGGPSSGAPPPS-NH₂

Acetyl-Exenatide
4072222
Ac-HGEGTFTSDLSKQMEEEEAVRL-
FIEWLKNGGPSSGAPPPS-NH₂

(D-Asn²⁸)-Exenatide
4084643
HGEGTFTSDLSKQMEEEEAVRL-
FIEWLKNGGPSSGAPPPS-NH₂

(Asp²⁸)-Exenatide
4085312
HGEGTFTSDLSKQMEEEEAVRLFIEWLK
nGGPSSGAPPPS-NH₂

(D-Asp²⁸)-Exenatide
4085313
HGEGTFTSDLSKQMEEEEAVRLFIEWLK-
dGGPSSGAPPPS-NH₂

(β-Asp²⁸)-Exenatide
4085314
HGEGTFTSDLSKQMEEEEAVRLFIEWLK
D(GGPSSGAPPPS-NH₂)

(β-D-Asp²⁸)-Exenatide NEW
4085315
HGEGTFTSDLSKQMEEEEAVRLFIEWLK
d(GGPSSGAPPPS-NH₂)

(Des-Gly²)-Exenatide
4072221
HEGTFTSDLSKQMEEEEAVRLFIEWLKNG-
GPSSGAPPPS-NH₂

Endo-38a-Pro-Exenatide
4072223
HGEGTFTSDLSKQMEEEEAVRL-
FIEWLKNGGPSSGAPPPS-NH₂

(D-His¹)-Exenatide
4072224
hHGEGTFTSDLSKQMEEEEAVRL-
FIEWLKNGGPSSGAPPPS-NH₂

(Met(O)¹⁴)-Exenatide
(Exendin-4 sulfoxide)
4082706
HGEGTFTSDLSKQM(O)EEEEAVRL-
FIEWLKNGGPSSGAPPPS-NH₂

(Glu⁹)-Exenatide (2-39) NEW
4095258
GEGTFTSELSKQMEEEEAVRLFIEWLKNG-
GPSSGAPPPS-NH₂

Exendin-3
4015051
HSDGTFTSDLSKQMEEEEAVRL-
FIEWLKNGGPSSGAPPPS-NH₂

Exendin-4 (1-8)
4051740
HGEGTFTS-NH₂

Exendin-4 (3-39)
4027457
EGTFTSDLSKQMEEEEAVRLFIEWLKNGG-
PSSGAPPPS-NH₂

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GLUCAGON, GRPP, OXYNTO- MODULIN (CONTINUED)

(Glu²⁰)-Glucagon (1-29)
(human, rat, porcine) NEW
4079055
HSQGTFTSDYSKYLDSRRAED-
FVQWLMNT

((Glu²⁴)-Glucagon (1-29)
(human, rat, porcine) NEW
4071253
HSQGTFTSDYSKYLDSRRAQDFVEW-
LMNT

(Des-His¹,Glu⁹)-Glucagon (1-29) amide
(human, rat, porcine))
4030635
SQGTFTSEYSKYLDSRRAQDFVQWLMNT-
NH₂

(Des-Thr⁵)-Glucagon
4045345
HSQGTFTSDYSKYLDSRRAQDFVQWLMNT

(Des-Thr⁷)-Glucagon
4045365
HSQGTFTSDYSKYLDSRRAQDFVQWLMNT

(Met(O)²⁷)-Glucagon (1-29)
(human, rat, porcine)
4043506
HSQGTFTSDYSKYLDSRRAQDFVQWLM
(O)NT

Glucagon (19-29)
(human, rat, porcine)
4030650
AQDFVQWLMNT

GRPP (human)
(Glicentin-Related Polypeptide
(human))
4044528
RSLQDTEEKSRFSASQADPLSDP-
DQMNE

Oxyntomodulin (human, mouse, rat)
(Glucagon-37 (human, mouse, rat))
4044527
HSQGTFTSDYSKYLDSRRAQD-
FVQWLMNTKRNRNNIA

Oxyntomodulin (30-37)
(bovine, dog, porcine)
4012614
KRKNKNIA

GLUCAGON- LIKE PEPTIDES

**GLP-1 (1-36) amide (human, bovine,
guinea pig, mouse, rat)**
4030651
HDEFERHAEGTFTSDVSSYLEGQAAKE-
FIAWLVKGR-NH₂

**GLP-1 (1-37) (human, bovine,
guinea pig, mouse, rat)**
4037542
HDEFERHAEGTFTSDVSSYLEGQAAKEFI-
AWLVKGRG

GLP-1 (7-36) amide
(chicken, common turkey)
4040190
HAEGTYTSDITSYLEGQAAKEFIWLVN-
GR-NH₂

**GLP-1 (7-36) amide (human, bovine,
guinea pig, mouse, rat)**
4030663
HAEGTFTSDVSSYLEGQAAKEFIWLVK-
GR-NH₂

**GLP-1 (7-36)-Lys(biotinyl) amide (hu-
man, bovine, guinea pig, mouse, rat)**
4042611
HAEGTFTSDVSSYLEGQAAKEFIWLVK
RK(biotinyl)-NH₂

**GLP-1 (7-36)-Lys(6-FAM) amide (hu-
man, bovine, guinea pig, mouse, rat)**
4042610
HAEGTFTSDVSSYLEGQAAKEFIWLVK
RK(fluorescein-6-carbonyl)-NH₂

GLUCAGON-LIKE PEPTIDES (CONTINUED)

(Ser⁸)-GLP-1 (7-36) amide (human, bovine, guinea pig, mouse, rat)
4029130
 HSEGTFTSDVSSYLEGQAAKEFIAWLVK-GR-NH₂

GLP-1 (7-37) (human, bovine, guinea pig, mouse, rat)
(Acetate salt)
4043014
 HAEGTFTSDVSSYLEGQAAKEFIAWLVK-GRG
 (Acetate salt)

GLP-1 (7-37) (human, bovine, guinea pig, mouse, rat)
(Trifluoroacetate salt)
4034865
 HAEGTFTSDVSSYLEGQAAKEFIAWLVK-GRG
 (Trifluoroacetate salt)

GLP-1 (9-36) amide (human, bovine, guinea pig, mouse, porcine, rat)
4027697
 EGTFTSDVSSYLEGQAAKEFIAWLVKGR-NH₂

Semaglutide* NEW
 (NN9535, (Aib², Lys(γ-Glu-AEEAc-AEEAc-17-carboxy-heptadecanoyl)²⁶, Arg³⁴)-GLP-1 (7-37))
4091661
 H-Aib-EGTFTSDVSSYLEGQAAK(γE(AEEAc-AEEAc-17-carboxyheptadecanoyl))EFIAWLVRGRG

GLP-2 (1-33) (human)
(Ammonium acetate salt) NEW
4095874
 HADGSFSDDEMNTILDNLAARDFIN-WLIQTKITD
 (Ammonium acetate salt)

GLP-2 (1-33) (human)
(Trifluoroacetate salt)
4039611
 HADGSFSDDEMNTILDNLAARDFIN-WLIQTKITD
 (Trifluoroacetate salt)

GLP-2 (1-34) (human)
4029353
 HADGSFSDDEMNTILDNLAARDFIN-WLIQTKITDR

GLP-2 (rat)
4034866
 HADGSFSDDEMNTILDNLATRDFIN-WLIQTKITD

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INSULIN, INSULIN-LIKE GROWTH FACTOR (IGF)

rec IGF-I (human)
[4030778](#)

IGF-I Analog
[4018631](#)
CYAAPLKPAKSC
(Disulfide bond)

IGF-I (1-3)
[4026104](#)
GPE

IGF-I (24-41)
[4030780](#)
YFNKPTGYGSSRRAPQT

rec IGF-II (1-67) (human)
[4030639](#)
AYRPSETLCGGELVDTLQFVCGDRGFYFS-
RPASRVSRRSRGIVECCFRSDLALLE-
TYCATPAKSE

IGF-II (33-40)
[4030781](#)
SRVSRRSR

**Lys-Lys-IRS-1 (891-902)
(dephosphorylated) (human)**
[4046873](#)
KKKSPGEYVNIEFG

Insulin B (22-25)
[4004735](#)
RGFF

RELATED PRODUCTS: DPP IV SUBSTRATES AND INHIBITORS

H-Gly-Pro-AMC · HBr
[4002520](#)
GP-AMC · HBr

H-Gly-Pro-4MβNA
[4000721](#)
GP-MNA

H-Gly-Pro-βNA
[4000551](#)
GP-bNA

H-Gly-Pro-pNA · HCl
[4025614](#)
GP-pNA · HCl

H-Gly-Pro-pNA · p-tosylate
[4003654](#)
GP-pNA · p-tosylate

Diprotin A
[4009723](#)
IPI

Diprotin B
[4009528](#)
VPL

RELATED PRODUCTS: PEPTIDES

Adropin (34-76) (human, mouse, rat)

4064212

CHSRADVDLSLSESSPNSSPGPCPE-KAPPPQKPSHEGSYLLQP

(Pyr¹)-Apelin-13 (human, bovine, mouse, rat)

4029110

<ERPRLSHKGPMPF

Calcitonin (8-32) (salmon I)

4037182

VLGKLSQELHKLQTYPRNTGSGTP-NH₂

Acetyl-(Asn³⁰,Tyr³²)-Calcitonin (8-32) (salmon I)

(AC187)

4034543

Ac-VLGKLSQELHKLQTYPRNTGSNTY-NH₂

L-Carnosine

4030364

Cyclo(-His-Prol)

4003655

c(HP)

Endotrophin (mouse)

4085553

TEPLFLTDTDICKLSRDAGTCVDFKLL-WHYDLESKSKRFWYGGCGNENRFH-SQEECEKMCPELTV

(Disulfide bonds, air oxidized)

Osteocalcin (1-49) (human)

4034491

YLYQWLGAPVPYPDPPL-Gla-PRR-Gla-VC-Gla-LNPDCDELADHIGFQEAYRRFYGPV

(Disulfide bond)

(Glu^{17,21,24})-Osteocalcin (1-49)

(human) NEW

(Osteocalcin (1-49) (human)

(decarboxylated))

4063516

YLYQWLGAPVPYPDPLEPRREVCELNP-DCDELADHIGFQEAYRRFYGPV

(Disulfide bond)

Pancreastatin (33-48) (human)

4055812

EEEEEMAVVPQGLFRG-NH₂

Preptin (human)

4059088

DVSTPPTVLPDNFPRYPVGKFFQYDT-WKQSTQRL

Preptin (rat)

4050843

DVSTSQAVLPDDFPRYPVGKFFKFDT-WRQSAGRL

Pseudin-2

4060547

GLNALKKVFGQIHEAIKLINNHVQ

TRH

(Protirelin)

4038214

<EHP-NH₂

(His(3-Me)²)-TRH NEW

4095712

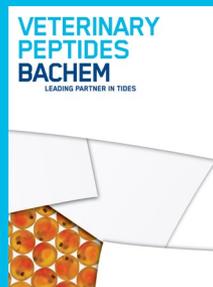
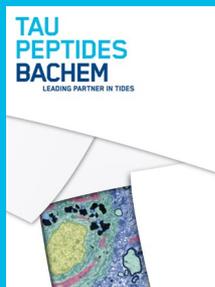
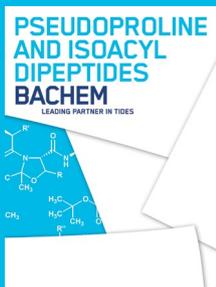
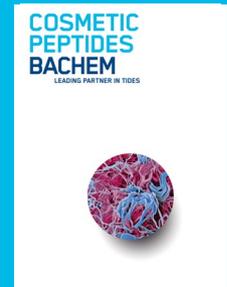
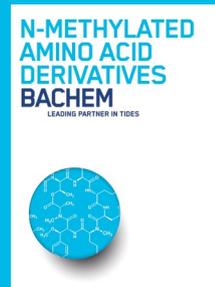
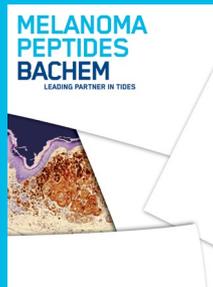
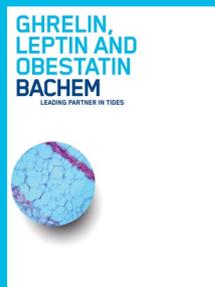
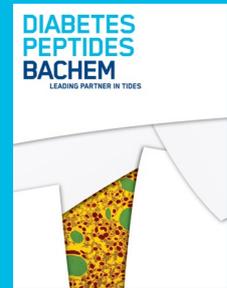
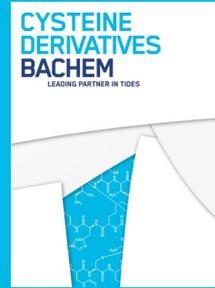
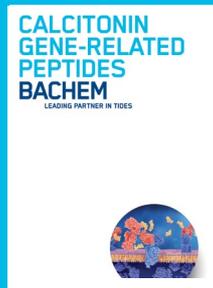
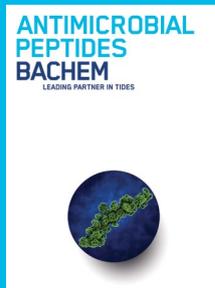
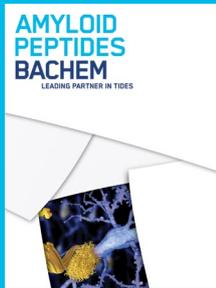
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Xenin 25

4031355

MLTKFETKSARVKGLSFHPKRPWIL

PRODUCT BROCHURES



GENERIC APIs

Exenatide Acetate

4044219

HGEGTFTSDLSKQMEEEAVRL-
FIEWLKNGGPSSGAPPPS-NH₂

Lixisenatide*

4041774

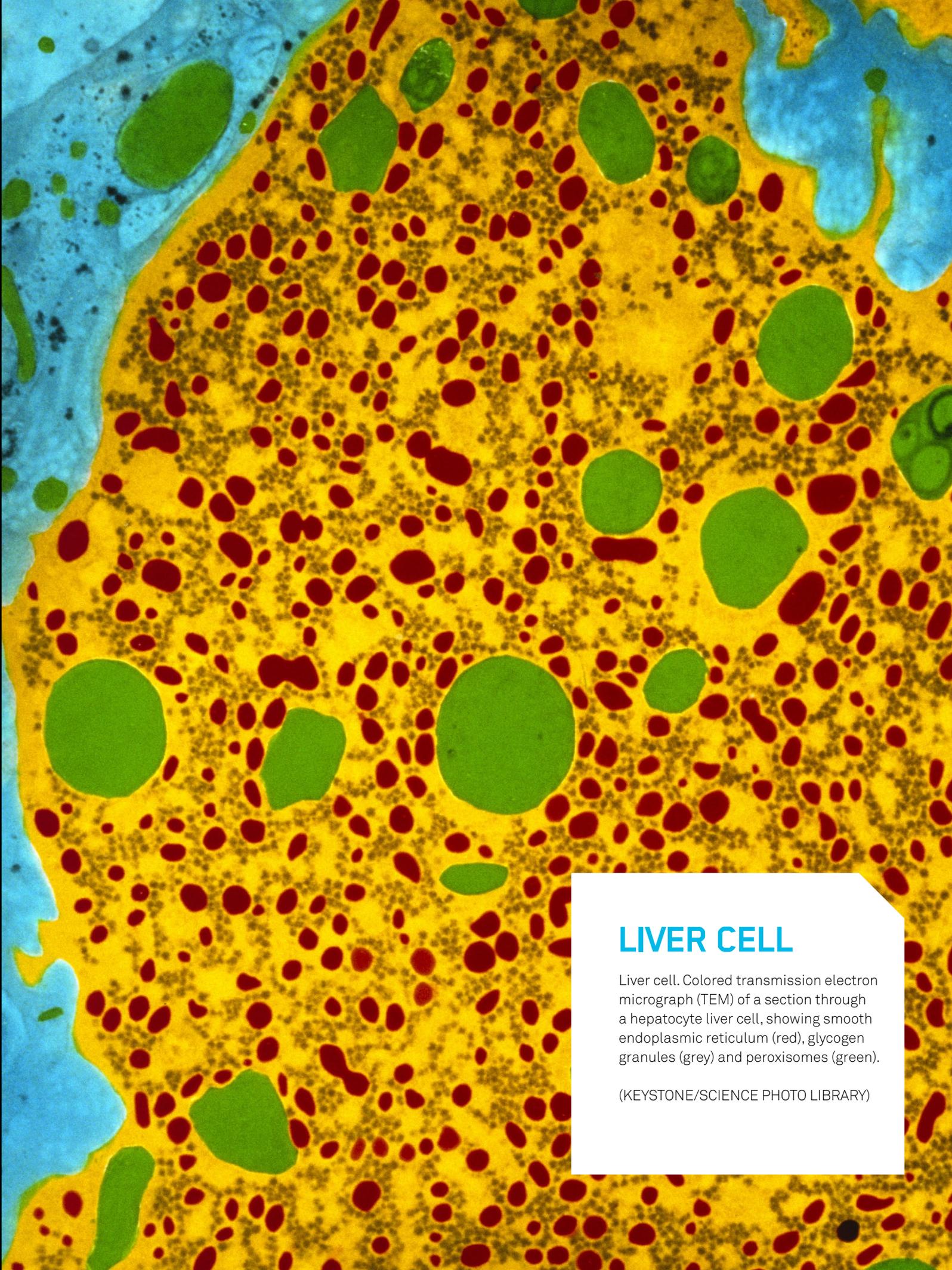
HGEGTFTSDLSKQMEEEAVRL-
FIEWLKNGGPSSGAPPSKKKKKK-NH₂

Glucagon

4033017-GMP

HSQGTFTSDYSKYLDSRRAQD-
FVQWLMNT

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LIVER CELL

Liver cell. Colored transmission electron micrograph (TEM) of a section through a hepatocyte liver cell, showing smooth endoplasmic reticulum (red), glycogen granules (grey) and peroxisomes (green).

(KEYSTONE/SCIENCE PHOTO LIBRARY)

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