

5 Zusammenfassung

Die enteroendokrinen K-Zellen sind geeignete Kandidaten zur Herstellung von β -Ersatzzellen zur Therapie des Typ I Diabetes mellitus. Aus diesem Grund wurden sie am Modell der Ratte zunächst mittels immunhistochemischer Methoden lokalisiert. Sowohl über die gesamte Darmlänge als auch innerhalb der Villus-Krypt-Achse existiert ein Verteilungsgradient: die Anzahl der K-Zellen nimmt vom proximalen Jejunum zum Ileum und von den Villi zu den Krypten hin ab.

Nach Lokalisation der K-Zellen wurden Methoden zur Isolation und Anreicherung der Zellen entwickelt. Zur Isolation wurde der Darm kleingeschnitten und in einem hyperosmolaren, natriumcitratthaltigen Puffer inkubiert, mit dem Darmzellen schonend aus dem Zellverband gelöst werden konnten. Zur anschließenden Anreicherung der K-Zellen wurden Dynabeads (Dynal, Hamburg) genutzt, ein immunomagnetisches Verfahren, das eine zellschonende und hochspezifische Anreicherung der K-Zellen ermöglichte. Hierbei wurde ein humanspezifischer Kaninchen IgG₁-Antikörper als primärer Antikörper und ein an diesen bindender Dynabead-gekoppelter zweiter Antikörper verwendet.

Es konnte gezeigt werden, daß die durch Anreicherungsversuche gewonnenen K-Zell-Suspensionen auf eine Glucose-Stimulation (20 mmol/l) mit der Ausschüttung ihres Zellproduktes Glucose-dependent Insulinotropic Polypeptide (GIP) reagieren.

Für zukünftige Versuche zur Transfektion der K-Zellen mit dem Proinsulingen und anschließender Kultur oder auch der Transfektion direkt in Suspension steht nun eine K-Zellsuspension zur Verfügung, die in dieser Reinheit bisher noch nicht gewonnen werden konnte. Damit ist die Grundlage zur Herstellung von β -Ersatzzellen aus den enteroendokrinen K-Zellen gelegt.

6 Literatur

- [1] KASPER H
Ernährungsmedizin und Diätetik. 8. Auflage. Urban & Schwarzenberg, München, 1996: 248-252
- [2] THE DCCT RESEARCH GROUP
The Diabetes Control and Complications Trial (DCCT) - Design and Methodologic Considerations for the Feasibility Phase.
Diabetes 1986; 35: 530-545
- [3] THE DIABETES CONTROL AND COMPLICATIONS TRIAL RESEARCH GROUP
Lifetime Benefits and Costs of Intensive Therapy as Practiced in the Diabetes Control and Complications Trial.
JAMA 1996; 276: 1409-1415
- [4] DEUTSCHE GESELLSCHAFT FÜR ERNÄHRUNG
DGE-Beratungsstandards V/2. Diabetes mellitus. 2. Auflage. Deutsche Gesellschaft für Ernährung, Frankfurt, 1998
- [5] SCHNEDL WJ, HOHMEIER HE, NEWGARD CB
Insulinsezernierende Zellen zur Therapie des Diabetes mellitus.
Naturwissenschaften 1996; 83: 1-5
- [6] NEWGARD CB, CLARK S, BELTRANDELRIO H, HOHMEIER HE, QUADE C, NORMINGTON K
Engineered cell lines for insulin replacement in diabetes: current status and future prospects.
Diabetologia 1997; 40: S42-S47
- [7] LACY PE
Inselzell-Verpflanzung bei Diabetes.
Spektrum der Wissenschaft 1995; Heft 9: 72-78
- [8] HUGHES SD, JOHNSON JH, QUADE C, NEWGARD CB
Engineering of glucose-stimulated insulin secretion and biosynthesis in non-islet cells.
Proc. Natl. Acad. Sci. USA. 1992; 89: 688-692
- [9] MOTOYOSHI S, SHIROTANI T, ARAKI E, SAKAI K, MOTOSHIMA H, YOSHIZATO A, SHIRAKAMI A, KISHIKAWA H, SHICHIRI M
Cellular characterization of pituitary adenoma cell line (AtT20 cell) transfected with insulin, glucose transporter type 2 (GLUT2) and glucokinase genes: Insulin secretion in response to physiological concentrations of glucose.
Diabetologia 1998; 41:1492-1501

-
- [10] HAKES DJ, BIRCH NP, MEZEY A, DIXON JE
Isolation of Two Complementary Deoxyribonucleic Acid Clones from a Rat Insulinoma Cell Line Based on Similarities to Kex2 and Furin Sequences and the Specific Localization of Each Transcript to Endocrine and Neuroendocrine Tissues in Rats.
Endocrinology 1991; 129:3053-3063
- [11] HUGHES SD, QUADE C, MILBURN JL, CASSIDY L, NEWGARD CB
Expression of Normal and Novel Glucokinase mRNAs in Anterior Pituitary and Islet Cells.
J. Biol. Chem. 1991; 266: 4521-4530
- [12] MOORE HPH, WALKER MD, LEE F, KELLY RB
Expressing a Human Proinsulin cDNA in a Mouse ACTH-secreting Cell. Intracellular Storage, Proteolytic Processing and Secretion on Stimulation.
Cell 1983; 35:531-538
- [13] DAVIES EL, SHENNAN KIJ, DOCHERTY K, BAILEY CJ
Expression of GLUT2 in insulin-secreting AtT20 pituitary cells.
J. Mol. Endocrinol. 1998; 20: 75-82
- [14] OOMURA Y, SASAKI K, SUZUKI, K, MUTO, T, LI A, OGITA ZI, HANAI K, TOOYAMA I, KIMURA H, YANAIHARA N
A new brain glucosensor and its physiological significance.
Am. J. Clin. Nutr. 1992; 55: 278S-282S
- [15] HEBEL R, STROMBERG M
Anatomy and Embryology of the Laboratory Rat. Biomed-Verlag, Wörthsee, 1986:51
- [16] THEWS G, MUTSCHLER E, VAUPEL P
Anatomie, Physiologie, Pathophysiologie des Menschen. 4. Auflage, Wissenschaftliche Verlagsgesellschaft, Stuttgart, 1991: 283-285
- [17] WEISS L
Cell and Tissue Biology - A Textbook of Histology. 6. Auflage. Urban & Schwarzenberg, München, 1988: 652-683
- [18] LEONHARDT H
Histologie, Zytologie und Mikroanatomie des Menschen. 8. Auflage, Georg Thieme Verlag, Stuttgart, 1990: 394-395
- [19] CHENG H, LEBLOND CP
Origin, Differentiation and Renewal of the Four Main Epithelial Cell Types in the Mouse Small Intestine - III Entero-endocrine Cells.
Am. J. Anat. 1974; 141: 503-520

-
- [20] BUCHAN AMJ, POLAK JM, CAPELLA C, SOLCIA E, PEARSE AGE
Electroimmunocytochemical Evidence for the K Cell Localization of Gastric Inhibitory Polypeptide (GIP) in Man.
Histochemistry 1978; 56: 37-44
- [21] MOODY AJ, THIM L, VALVERDE I
The isolation and sequencing of human gastric inhibitory peptide (GIP).
FEBS Lett. 1984; 172: 142-148
- [22] HIGASHIMOTO Y, SIMCHOCK J, LIDDLE RA,
Molecular cloning of rat glucose-dependent insulinotropic peptide (GIP).
Biochim. Biophys. Acta 1992; 1132: 72-74
- [23] TAKEDA J, SEINO Y, TANAKA KI, FUKUMOTO H, KAYANO T,
TAKAHASHI H, MITANI T, KURONO M, SUZUKI T, TOBE T, IMURA H
Sequence of an intestinal cDNA encoding human gastric inhibitory polypeptide precursor.
Proc. Natl. Acad. Sci. USA 1987; 84: 7005-7008
- [24] TSENG CC, JARBOE LA, LANDAU SB, WILLIAMS EK, WOLFE MM
Glucose-dependent insulinotropic peptide: Structure of the precursor and tissue-specific expression in rat.
Proc. Natl. Acad. Sci. USA 1993; 90: 1992-1996
- [25] KIEFFER TJ, BUCHAN AMJ, BARKER H, BROWN JC, PEDERSON RA
Release of gastric inhibitory polypeptide from cultured canine endocrine cells.
Am. J. Physiol. 1994; 267: E489-E496
- [26] GROMADA J, BOKVIST K, DING WG, HOLST JJ, NIELSEN JH, RORSMAN P
Glucagon-Like Peptide 1 (7-36) Amide Stimulates Exocytosis in Human Pancreatic β -Cells by Both Proximal and Distal Regulatory Steps in Stimulus-Secretion Coupling.
Diabetes 1998; 47: 57-65
- [27] CATALAND S, CROCKETT SE, BROWN JC, MAZZAFERRI EL
Gastric Inhibitory Polypeptide (GIP) Stimulation by Oral Glucose in Man.
J. Clin. Endocrinol. Metab. 1974; 39: 223-228
- [28] CLEATOR IGM, GORLAY RH
Release of Immunoreactive Gastric Inhibitory Polypeptide (IR-GIP) by Oral Ingestion of Food Substances.
Am. J. Surg. 1975; 130: 128-135
- [29] HIGASHIMOTO Y, OPARA EC, LIDDLE RA
Dietary regulation of glucose-induced insulinotropic peptide (GIP) gene expression in rat small intestine.
Comp. Biochem. Physiol. 1995; 110C: 207-214

-
- [30] POLAK JM, BLOOM SR, KUZIO M, BROWN JC, PEARSE AGE
Cellular localization of gastric inhibitory polypeptide in the duodenum and jejunum. *Gut* 1973; 14: 284-288
- [31] SJÖLUND K, SANDÉN G, HÅKANSON R, SUNDLER F
Endocrine Cells in Human Intestine: An Immunocytochemical Study
Gastroenterology 1983; 85: 1120-1130
- [32] RÖNNBLUM A, DANIELSSON Å, EL-SALHY M
Intestinal endocrine cells in myotonic dystrophy: an immunocytochemical and computed image analytical study.
J. Int. Med. 1999; 245: 91-97
- [33] GESPACH C, BATAILLE D, JARROUSSE C, ROSSELIN G
Ontogeny and distribution of immunoreactive gastric inhibitory polypeptide (IR-GIP) in rat small intestine
Acta Endocrinol. 1979; 90: 307-316
- [34] BUCHAN AMJ, INGMAN-BAKER J, LEVY J, BROWN JC
A Comparison of the Ability of Serum and Monoclonal Antibodies to Gastric Inhibitory Polypeptide to Detect Immunoreactive Cells in the Gastroenteropancreatic System of Mammals and Reptiles.
Histochemistry 1982; 76: 341-349
- [35] SHULKES A, CAUSSIGNAC Y, LAMERS CB, SOLOMON TE, YAMADA T, WALSH JH
Starvation in the rat: effect on peptides of the gut and brain.
Aust. J. Exp. Biol. Med. Sci. 1983; 61: 581-587
- [36] SMITH PH
Immunocytochemical Localization of Glucagonlike and Gastric Inhibitory Polypeptidelike Peptides in the Pancreatic Islets and Gastrointestinal Tract.
Am. J. Anat. 1983; 168: 109-118
- [37] PEDERSON RA
Gastric Inhibitory Peptide. In WALSH JH, DOCKRAY GJ: *Gut Peptides-Biochemistry and Physiology*. Raven Press, New York, 1994 : 217-259
- [38] MORGAN LM
The metabolic role of GIP: physiology and pathology.
Biochem. Soc. Transactions 1996; 24:585-591
- [39] SCHMIDT WE, SIEGEL EG, CREUTZFELDT W
Glucagon-like peptide-1 but not glucagon-like peptide-2 stimulates insulin release from isolated rat pancreatic islets.
Diabetologia 1985; 28: 704-707

-
- [40] SIEGEL EG, CREUTZFELDT W
Stimulation of insulin release in isolated rat islets by GIP in physiological concentrations and its relation to islet cyclic AMP content.
Diabetologia 1985; 28: 857-861
- [41] ELAHI D, ANDERSEN DK, BROWN, JC, DEBAS HAT, HERSHCOPF RJ, RAIZES GS, TOBIN JD, ANDRES R
Pancreatic α - and β -cell responses to GIP infusion in normal man.
Am. J. Physiol. 1979; 237: E185-E191
- [42] PEDERSON RA, BROWN JC
The Insulinotropic Action of Gastric Inhibitory Polypeptide in the Perfused Isolated Rat Pancreas.
Endocrinology 1976; 99: 780-785
- [43] DING WG, GROMADA J
Protein Kinase A-Dependent Stimulation of Exocytosis in Mouse Pancreatic β -Cells by Glucose-Dependent Insulinotropic Polypeptide.
Diabetes 1997; 46: 615-621
- [44] DUPRÉ J, ROSS SA, WATSON D, BROWN, JC
Stimulation of Insulin Secretion by Gastric Inhibitory Polypeptide in man.
J. Clin. Endocrinol. Metab. 1973; 37: 826-828
- [45] SCHÄFER R, SCHATZ H
Stimulation of (pro-)insulin biosynthesis and release by gastric inhibitory polypeptide in isolated islets of rat pancreas.
Acta Endocrinol. 1979; 91: 493-500
- [46] ROBERGE JN, BRUBAKER PL
Regulation of Intestinal Proglucagon-Derived Peptide Secretion by Glucose-Dependent Insulinotropic Peptide in a Novel Enteroendocrine Loop.
Endocrinology 1993; 133: 233-240
- [47] PLAISANCIE P, BERNARD C, CHAYVIALLE JA, CUBER JC
Regulation of Glucagon-Like Peptide-1-(7-36) Amide Secretion by Intestinal Neurotransmitters and Hormones in the Isolated Vascularly Perfused Rat Colon.
Endocrinology 1994; 135: 2398-2403
- [48] ØRSKOV C, HOLST JJ, POULSEN SS, KIRKEGAARD P
Pancreatic and intestinal processing of proglucagon in man.
Diabetologia 1987; 30: 874-881
- [49] GRIMELIUS L, CAPELLA C, BUFFA R, POLAK JM, PEARSE AGE, SOLCIA E
Cytochemical and Ultrastructural Differentiation of Enteroglucagon and Pancreatic-Type Glucagon Cells of the Gastrointestinal Tract.
Virchows Arch. B Cell Path. 1976; 20: 217-228

-
- [50] EISSELE R, GÖKE R, WILLEMER S, HARTHUS HP, VERMEER H, ARNOLD R, GÖKE B
Glucagon-like peptide-1 cells in the gastrointestinal tract and pancreas of rat, pig and man.
Eur. J. Clin. Invest. 1992; 22: 283-291
- [51] BELL GI, SANCHEZ-PESCADOR R, LAYBOURN PJ, NAJARIAN RC
Exon duplication and divergence in the human preglucagon gene.
Nature 1983; 304: 368-371
- [52] HEINRICH G, GROS P, HABENER JF
Glucagon Gene Sequence.
J. Biol. Chem. 1984; 259: 14082-14087
- [53] MOJISOV S, HEINRICH G, WILSON IB, RAVAZZOLA M, ORCI L, HABENER JF
Preproglucagon Gene Expression in Pancreas and Intestine Diversifies at the Level of Post-translational Processing.
J. Biol. Chem. 1986; 261: 11880-11889
- [54] MOJISOV S, WEIR GC, HABENER JF
Insulintropin: Glucagon-like Peptide I (7-37) Co-encoded in the Glucagon Gene Is a Potent Stimulator of Insulin release in the Perfused Rat Pancreas.
J. Clin. Invest. 1987; 79: 616-619
- [55] ØRSKOV C, WETTERGREN A, HOLST JJ
Biological Effects and Metabolic Rates of Glucagonlike Peptide-1 7-36 Amide and Glucagonlike Peptide-1 7-37 in Healthy Subjects Are Indistinguishable.
Diabetes 1993; 42: 658-661
- [56] ØRSKOV C, BERSANI M, JOHNSON AH, HØJRUP P, HOLST JJ
Complete Sequences of Glucagon-like Peptide-1 from Human and Pig Small Intestine.
J. Biol. Chem. 1989; 264: 12826-12829
- [57] ROBERGE JN, BRUBAKER PL
Secretion of Proglucagon-Derived Peptides in Response to Intestinal Luminal Nutrients.
Endocrinology 1991; 128: 3169-3174
- [58] BRUBAKER PL
Regulation of Intestinal Proglucagon-Derived Peptide Secretion by Intestinal Regulatory Peptides.
Endocrinology 1991; 128: 3175-3182

-
- [59] DAMHOLT AB, BUCHAN AMJ, KOFOOD H
Glucagon-Like-Peptide-1 Secretion from Canine L-Cells Is Increased by Glucose Dependent-Insulinotropic Peptide but unaffected by Glucose.
Endocrinology 1998; 139: 2085-2091
- [60] BRUBAKER PL, SCHLOOS J, DRUCKER DJ
Regulation of Glucagon-Like Peptide-1 Synthesis and Secretion in the GLUTag Enteroendocrine Cell Line
Endocrinology 1998; 139: 4108-4114
- [61] BRUBAKER PL
Control of Glucagon-Like Immunoreactive Peptide Secretion from Fetal Rat Intestinal Cultures.
Endocrinology 1988; 123: 220-226
- [62] SAIFIA S, CHEVRIER AM, BOSSHARD A, CUBER JC, CHAYVIALLE JA, ABELLO J
Galanin inhibits glucagon-like peptide-1 secretion through pertussis toxin-sensitive G Protein and ATP-dependent channels in rat ileal L-cells.
J. Endocrinol. 1998; 157: 33-41
- [63] GÖKE B, FEHMANN HC, SCHIRRA J, HARETER A, GÖKE R
Das Darmhormon Glucagon-like peptide-1 (GLP-1): aus dem Experiment in die Klinik.
Z. Gastroenterol. 1997; 35: 285-294
- [64] AHRÉN B
Glucagon-like peptide-1 (GLP-1): a gut hormone of potential interest in the treatment of diabetes.
BioEssays 1998; 20: 642-651
- [65] NAUCK MA
Glucagon-like peptide 1 (GLP-1): a potent gut hormone with a possible therapeutic perspective.
Acta Diabetol. 1998; 35: 117-129
- [66] WETTERGREN A, SCHJOLDAGER B, MORTENSEN PE, MYHRE J, CHRISTIANSEN J, HOLST JJ
Truncated GLP-1 (Proglucagon 78-107-Amide) Inhibits Gastric and Pancreatic Functions in Man.
Dig. Dis. Sci. 1993; 38: 665-673
- [67] GIRALT M, VERGARA P
Sympathetic pathways mediate GLP-1 actions in the gastrointestinal tract of the rat.
Reg. Peptides 1998; 74: 19-25

-
- [68] TURTON MD, O'SHEA D, GUNN I, BEAK SA, EDWARDS CMB, MEERAN K, CHOI SJ, TAYLOR GM, HEATH MM, LAMBERT PD, WILDING JPH, SMITH DM, GHATEI, MA, HERBERT J, BLOOM SR
A role for glucagon-like peptide-1 in the central regulation of feeding.
Nature 1996; 379: 69-72
- [69] GUTZWILLER JP, GÖKE B, DREWE J, HILDEBRAND P, KETTERER S, HANDSCHIN D, WINTERHALDER R, CONEN D BEGLINGER C
Glucagon-like peptide-1: a potent regulator of food intake in humans.
Gut 1999; 44: 81-86
- [70] ØRSKOV C, POULSEN SS
Glucagonlike Peptide-I-(7-36)-Amide Receptors Only in Islets of Langerhans - Autoradiographic Survey of Extracerebral Tissues in Rats.
Diabetes 1991; 40: 1292-1296
- [71] WEIR GC, MOJSOV S, HENDRICK K, HABENER JF
Glucagonlike Peptide I (7-37) Actions on Endocrine Pancreas.
Diabetes 1989; 38: 338-342
- [72] YAJIMA H, KOMATSU M, SCHERMERHORN T, AIZAWA, T, KANEKO T, NAGAI M, SHARP GWG, HASHIZUME K
cAMP Enhances Insulin Secretion by an Action on the ATP-Sensitive K⁺ Channel-Independent Pathway of Glucose Signaling in Rat Pancreatic Islets.
Diabetes 1999; 48: 1006-1012
- [73] WHEELER MB, LU M, DILLON JS, LENG XH, CHEN C, BOYD III AE
Functional Expression of the Rat Glucagon-Like Peptide-I Receptor, Evidence for Coupling to both Adenylyl Cyclase and Phospholipase-C.
Endocrinology 1993; 133: 57-62
- [74] KREYMANN B, GHATEI MA, WILLIAMS G, BLOOM, SR
Glucagon-like Peptide-1 7-36: a physiological incretin in man.
Lancet 1987; II: 1300-1304
- [75] ENSINCK JW, D'ALESSIO DA
The Enteroinsular Axis Revisited
New Engl J. Med. 1992; 326: 1352-1353
- [76] PENMAN E, WASS JAH, MEDBAK S, MORGAN L, LEWIS JM, BESSER GM, REES LH
Response of Circulating Immunoreactive Somatostatin to Nutritional Stimuli in Normal Subjects.
Gastroenterology 1981; 81:692-699
- [77] PETERSON B, CHRISTIANSEN J, HOLST JJ
A Glucose-Dependent Mechanism in Jejunum Inhibits Gastric Acid Secretion: A Response Mediated through Enteroglucagon?
Scand. J. Gastroenterol. 1985; 20: 193-197

-
- [78] WÓJCIKOWSKI C, MAIER V, FUSSGÄNGER R, PFEIFFER EF
Release of Glucagon-Like Immunoreactive Material (GLI) from the Isolated Perfused Jejunum of Normal and Diabetic Rats.
Horm. Metabol. Res. 1985; 17: 105-106
- [79] READ NW, McFARLANE A, KINSMAN RI, BATES TE, BLACKHALL NW, FARRAR GBJ, HALL JG, MOSS G, MORRIS AP, O'NEILL B, WELCH I, LEE Y, BLOOM SR
Effect of Infusion of Nutrient Solutions Into the Ileum on Gastrointestinal Transit and Plasma Levels of Neurotensin and Enteroglucagon.
Gastroenterology 1984; 86: 274-280
- [80] HERRMANN C, GÖKE R, RICHTER G, FEHMANN HC, ARNOLD R, GÖKE B
Glucagon-Like Peptide-1 and Glucose-Dependent Insulin-Releasing Polypeptide Plasma Levels in Response to Nutrients.
Digestion 1995; 56:117-126
- [81] JETTON TL, LIANG Y, PETTEPHER CC, ZIMMERMAN EC, COX, FG, HORVATH K, MATSCHINSKY FM, MAGNUSON MA
Analysis of Upstream Glucokinase Promoter Activity in Transgenic Mice and Identification of Glucokinase in Rare Neuroendocrine Cells in the Brain and Gut.
J. Biol. Chem. 1994; 269: 3641-3654
- [82] SCOPSI L, GULLO M, RILKE F, MARTIN S, STEINER DF
Proprotein Convertases (PC1/PC3 and PC2) in Normal and Neoplastic Human Tissues: Their Use as Markers of Neuroendocrine Differentiation.
J. Clin. Endocrinol. Metab. 1995; 80: 294-301
- [83] DHANVANTARI S, SEIDAH, NG, BRUBAKER, PL
Role of Prohormone Convertases in the Tissue-Specific Processing of Proglucagon.
Mol. Endocrinol. 1996; 10: 342-355
- [84] EBERT R, FRERICHS H, CREUTZFELDT W
Serum Gastric Inhibitory Polypeptide (GIP) Response in Patients with Maturity Onset Diabetes and in Juvenile Diabetics.
Diabetologia 1976; 12: 388
- [85] NAUCK M, STÖCKMANN F, EBERT R, CREUTZFELDT W
Reduced incretin effect in Type 2 (non-insulin-dependent) diabetes.
Diabetologia 1986; 29: 46-52
- [86] ROVIRA A, GARROTE FJ, PASCUAL JM, SALVADOR MG, HERRERA POMBO JL, VALVERDE I
Plasma glucagon and glucagon-like immunoreactive components in Type 1 (insulin-dependent) diabetic patients and normal subjects before and after an oral glucose load.
Diabetologia 1985; 28: 80-86

-
- [87] NAUCK MA, HEIMESAAT MM, ØRSKOV C, HOLST JJ, EBERT R, CREUTZFELDT W
Preserved Incretin Activity of Glucagon-like Peptide 1 [7-36 Amide] but Not of Synthetic Human Gastric Inhibitory Polypeptide in Patients with Type-2 Diabetes Mellitus.
J. Clin. Invest. 1993; 91: 301-307
- [88] PERRET V, LEV R, PIGMAN W
Simple method for the preparation of single cell suspensions from normal and tumorous rat colonic mucosa.
Gut 1977; 18: 382-385
- [89] EVANS GS, FLINT N, SOMERS AS, EYDEN B, POTTEN CS
The development of a method for the preparation of rat intestinal epithelial cell primary cultures.
J. Cell Sci. 1992; 101: 219-231
- [90] WEISER MM
Intestinal Epithelial Cell Surface Membrane Glycoprotein Synthesis.
J. Biol. Chem. 1973; 248: 2536-2543
- [91] FLINT N, COVE FL, EVANS GS
A low-temperature method for the isolation of small-intestinal epithelium along the crypt-villus axis.
Biochem. J. 1991; 280: 331-334
- [92] SOLL AH, Yamada T, Park J, THOMAS LP
Release of somatostatinlike immunoreactivity from canine fundic mucosal cells in primary culture.
Am. J. Physiol. 1984; 247: G558-G566
- [93] POITRAS P, DUMONT A, CUBER JC, TRUDEL L
Cholinergic Regulation of Motilin Release From Isolated Canine Intestinal Cells.
Peptides 1993; 14:207-213
- [94] EADE OE, ANDRE-UKENA SS, BEEKEN WL
Comparative Viabilities of Rat Intestinal Epithelial Cells Prepared by Mechanical, Enzymatic and Chelating Methods.
Digestion 1981; 21: 25-31
- [95] SOLL AH
The Actions of Secretagogues on Oxygen Uptake by Isolated Mammalian Parietal Cells.
J. Clin. Invest. 1978; 61: 370-380
- [96] BUCHAN AMJ, BARBER DL, GREGOR M, SOLL AH
Morphologic and Physiologic Studies of Canine Ileal Enteroglucagon-Containing Cells in Short-Term Culture.
Gastroenterology 1987; 93: 791-800

-
- [97] KOOP I, BUCHAN AMJ
Cholecystokinin Release From Isolated Canine Epithelial Cells in Short-Term Culture.
Gastroenterology 1992; 102: 28-34
- [98] XUE W, CHEY WY, SUN Q, CHANG TM
Characterization of Secretin Release in Secretin Cell-Enriched Preparation Isolated from Canine Duodenal Mucosa.
Dig. Dis. Sci. 1993; 38: 344-352
- [99] MILTENYI BIOTEC GmbH
Magnetic Cell Sorting and Separation of Biomolecules. Katalog 1999
- [100] DYNAL
Cell Separation and Protein Purification. Technical Handbook. 2. Auflage.
Dynal A.S, Oslo, 1996
- [101] NAVONE F, JAHN R, DI GIOIA G, STUKENBROK H, GREENGARD P, DE CAMILLI P
Protein p38: An Integral Membrane Protein Specific for Small Vesicles of Neurons and Neuroendocrine Cells.
J. Cell Biol. 1986; 103: 2511-2527
- [102] WIEDENMANN B, HUTTNER WB
Synaptophysin and chromogranins/secretogranins- widespread constituents of distinct types of neuroendocrine vesicles and new tools in tumor diagnosis.
Virchows Archiv B Cell Pathol. 1989; 58: 95-121
- [103] CIRULLI V, BAETENS D, RUTISHAUSER U, HALBAN PA, ORCI L, ROUILLER DG
Expression of neural cell adhesion molecule (N-CAM) in rat islets and its role in islets cell type segregation.
J. Cell Sci. 1994; 107: 1429-1436
- [104] ROSE ML
HLA antigens in tissues. In DYER P, MIDDLETON D: Histocompatibility Testing - A practical Approach. IRL Press, Oxford, 1993: 191-210
- [105] KLARESKOG L, FORSUM U
Tissue Distribution of Class II Transplantation Antigens: Presence on Normal Cells. In: SOLHEIM BG, MØLLER E, FERRONE S: HLA Class II Antigens - A comprehensive Review of Structure and Function. Springer-Verlag, Heidelberg, 1986: 339-355
- [106] DIANOVA
Rhodamine Red-X und Carbocyanin gekoppelte Sekundärantikörper. Produkt- und Preisliste inklusive allgemeiner Produktinformationen zu Sekundärantikörpern von Jackson ImmunoResearch. Dianova, Hamburg, 1998

-
- [107] PENINSULA LABORATORIES
General Protocol for Immunofluorescence Kit. Peninsula Laboratories Inc., San Carlos.
- [108] LOWRY OH, ROSEBROUGH NJ, FARR AL, RANDALL RJ
Protein measurement with the folin phenol reagent.
J. Biol. Chem. 1951; 193: 265-275
- [109] KOMMISSION FÜR ENZYMDIAGNOSTIK UND STANDARDISIERUNG.
Standard Method for Determination of Alkaline Phosphatase (AP) Activity.
Z. Klin. Chem. Klein. Biochem. 1972; 10: 290
- [110] BOEHRINGER MANNHEIM
Cell Biology: Enzymes for Tissue Dissociation. Seite 13
- [111] DYNAL
Bioscience Product Katalogue 1999. Dynal A.S, Oslo, 1999
- [112] MILTENYI BIOTECH GmbH
Datenblatt: CD16 Microbeads for isolation of eosinophils. Appendix
- [113] DYNAL
Dynabeads Biomagnetic Separation, Cells & Proteins, Nucleic Acids, Microorganisms. Product Catalogue 1998. Dynal A.S, Oslo, 1998
- [114] DIENER M, HUG F, STRABEL D, SCHARRER E
Cyclic AMP-dependent regulation of K⁺ transport in the rat distal colon.
Br. J. Pharmacol. 1996; 118: 1477-1487
- [115] EBERL T, SCHMID T, HENGSTER P, WÖDLINGER R, OBERHUBER G, WEISS H, HEROLD M, WALDENBERGER F, MARGREITER R
Protective Effect of Various Preservation Solutions on Cultured Endothelial Cells.
Ann. Thorac. Surg. 1994; 58: 489-495
- [116] FRESENIUS
Euro-Collins-Lösung, Multiorgan-Perfusionssystem. Fresenius AG, Bad Homburg
- [117] PEDERSON RA, BUCHAN AMJ, ZAHEDI-ASL S, CHAN CB, BROWN JC
Effect of jejunoileal bypass in the rat on the enteroinsular axis.
Reg. Peptides 1982; 5: 53-63
- [118] ROTH KA, HERTZ JM, GORDON JI,
Mapping Enteroendocrine Cell Populations in transgenic Mice Reveals an Unexpected Degree of Complexity in Cellular Differentiation within the Gastrointestinal Tract.
J. Cell Biol. 1990; 110: 1791-1801

-
- [119] SHARMA R, SCHUMACHER U
The diet and gut microflora influence the distribution of enteroendocrine cells in the rat intestine.
Experientia 1996; 52: 664-670
- [120] URIBE A, ALAM M, MIDVEDT T, SMEDFORS B, THEODORSSON E
Endogenous Prostaglandins and Microflora Modulate DNA Synthesis and Neuroendocrine Peptides in the rat Gastrointestinal Tract.
Scand. J. Gastroenterol. 1997; 32: 691-699
- [121] HARTMANN F, OWEN R, BISSELL DM
Characterization of isolated epithelial cells from rat small intestine.
Am. J. Physiol. 1982; 242: G147-G155
- [122] EVANS EM, WRIGGLESWORTH JM, BURDETT K, POVER WFR
Studies on epithelial cells isolated from guinea pig small intestine.
J. Cell Biol. 1971; 51: 452-464
- [123] SOUBA WW, SMITH RJ, WILMORE DW
Glutamine Metabolism by the Intestinal Tract.
J. Parent. Ent. Nutr. 1985; 9: 608-617
- [124] WILMORE DW
Metabolic Support of the gastrointestinal Tract. Potential Gut Protection during Intensive Cytotoxic Therapy.
Cancer 1997; 79: 1794-1803
- [125] WATFORD M, LUND P, KREBS HA
Isolation and Metabolic Characteristics of Rat and Chicken Enterocytes.
Biochem. J. 1979; 178: 589-596
- [126] PORTELA-GOMES GM, STRIDSBERG M, JOHANSSON H, GRIMELIUS L
Co-localization of synaptophysin with different neuroendocrine hormones in the human gastrointestinal tract.
Histochem. Cell Biol. 1999; 111: 49-54
- [127] WYNICK D, BLOOM SR
Magnetic Bead Separation of Anterior Pituitary Cells.
Neuroendocrinology 1990; 52: 560-565
- [128] LEA T, VARTDAL F, DAVIES C, UGELSTAD J
Magnetic monosized polymer particles for fast and specific fractionation of human mononuclear cells.
Scand. J. Immunol. 1985; 22: 207-216
- [129] FALKO JM, CROCKETT SE, CATALAND S, O'DORISIO TM, KRAMER W, MAZZAFERRI EL
The effect of increasing doses of ingested glucose on insulin and gastric inhibitory polypeptide (GIP) concentrations in man.
Clin. Endocrinol. 1980; 13:587-593

-
- [130] EVANS GS, FLINT N, POTTEN CS
Primary cultures for studies of cell regulation and physiology in intestinal epithelium.
Ann. Rev. Physiol. 1994; 56: 399-417
- [131] BENYA RV, SCHMIDT LN, JASMINDER S, LAYDEN TJ, RAO MC
Isolation, characterization and attachment of rabbit distal colon epithelial cells.
Gastroenterology 1991; 101: 692-702
- [132] BOUDREAU N, SYMPSON CJ, WERB Z, BISSELL MJ
Suppression of ICE and Apoptosis in Mammary Epithelial Cells by Extracellular Matrix.
Science 1995; 267: 891-893
- [133] HAGUE A, HICKS DJ, BRACEY TS, PARASKEVA C
Cell-cell contact and specific cytokines inhibit apoptosis of colonic epithelial cells: growth factors protect against c-myc-independent apoptosis.
Br. J. Cancer 1997; 75: 960-968
- [134] KLEINMAN HK, MCGARVEY ML, HASSELL JR, STAR VL, CANNON FB, LAURIE GW, MARTIN GR
Basement Membrane Complexes with Biological Activity.
Biochemistry 1986; 25: 312-318
- [135] NAGLE WA, SOLOFF BL, MOSS AJ, HENLE KJ
Cultured Chinese Hamster Cells Undergo Apoptosis after Exposure to Cold but Nonfreezing Temperatures.
Cryobiology 1990; 27: 439-451
- [136] KRUMAN II, GUKOVSKAYA AS, PETRUNYAKA VV, BELETSKY IP, TREPAKOVA ES
Apoptosis of Murine BW 5147 Thymoma Cells Induced by Cold Shock.
J. Cell. Physiol. 1992; 153: 112-117
- [137] MUELLER AR, NALESNIK MA, LANGREHR JM, RAO PN, SNYDER JT, HOFFMAN RA, SCHRAUT WH
Evidence that small bowel preservation causes primarily basement membrane and endothelial rather than epithelial cell injury.
Transplantation 1993; 56: 1499-1504
- [138] SHAH KA, SHUREY S, GREEN, CJ
Characterization of apoptosis in intestinal ischaemia-reperfusion injury - a light and electron microscopic study.
Int. J. Exp. Path. 1997; 78: 355-363

-
- [139] PETERS SMA, RAUEN U, TIJSEN MJH, BINDELS RJM, VAN OS CH, DE GROOT H, WETZELS JFM
Cold preservation of isolated rabbit proximal tubules induces radical-mediated cell injury.
Transplantation 1998; 65: 625-632
- [140] POITOUT V, OLSON LK, ROBERTSON RP
Insulin-secreting cell lines: Classification, characteristics and potential applications.
Diabetes & Metabolism 1996; 22: 7-14
- [141] HERRMANN-RINKE C, VÖGE A, HESS M, GÖKE B
Regulation of glucagon-like peptide-1 secretion from rat ileum by neurotransmitters and peptides.
J. Endocrinol. 1995; 147: 25-31
- [142] DUMOULIN V, DAKKA T, PLAICANCIE P, CHAYVIALLE JA, CUBER JC
Regulation of Glucagon-Like Peptide-1-(7-36) Amide, Peptide YY, and Neurotensin Secretion by Neurotransmitters and Gut Hormones in the Isolated Vascularly Perfused Rat Ileum.
Endocrinology 1995; 136: 5182-5188
- [143] ROBERGE JN, GRONAU KA, BRUBAKER PL
Gastrin-Releasing Peptide Is a Novel Mediator of Proximal Nutrient-Induced Proglucagon-Derived Peptide Secretion from the Distal Gut.
Endocrinology 1996; 137: 2383-2388
- [144] MOGHIMZADEH E, EKMAN R, HÅKANSON R, YANAIHARA N, SUNDLER F
Neuronal gastrin-releasing peptide in the mammalian gut and pancreas.
Neuroscience 1983; 10: 553-563
- [145] NAUCK MA, BARTELS E, ØRSKOV C, EBERT R, CREUTZFELDT W
Additive Insulinotropic Effects of Exogenous Synthetic Human Gastric Inhibitory Polypeptide and Glucagon-Like Peptide-1-(7-36) Amide Infused at Near-Physiological Insulinotropic Hormone and Glucose Concentrations.
J. Clin. Endocrinol. Metab. 1993; 76: 912-917
- [146] ROCCA AS, BRUBAKER PL
Role of the Vagus Nerve in Mediating Proximal Nutrient-Induced Glucagon-Like Peptide-1 Secretion.
Endocrinology 1999; 140: 1687-1694
- [147] TOFT-NIELSEN M, MADSBAD S, HOLST JJ
Exaggerated secretion of glucagon-like peptide-1 (GLP-1) could cause reactive hypoglycaemia.
Diabetologia 1998; 41: 1180-1186
- [148] DEETJEN P, SPECKMANN EJ (EDS.)
Physiologie. 2. Auflage. Urban & Schwarzenberg, München, 1994: 443

-
- [149] LÖFFLER, G, PETRIDES PE
Biochemie und Pathobiochemie. 5. Auflage. Springer Verlag, Berlin, Heidelberg, 1997: 1010
- [150] DUMOULIN V, MORO F, BARCELO A, DAKKA T, CUBER JC
Peptide YY, Glucagon-Like Peptide-1, and Neurotensin Responses to Luminal Factors in the Isolated Vascularly Perfused Rat Ileum.
Endocrinology 1998; 139: 3780-3786
- [151] HOYT EC, LUND PK, WINESETT DE, FULLER CR, GHATEI MA, BLOOM, SR, ULSHEN MH
Effects of Fasting, Refeeding, and Intraluminal Triglyceride on Proglucagon Expression in Jejunum and Ileum.
Diabetes 1996; 45: 434-439
- [152] NAUCK MA
Is glucagon-like peptide 1 an incretin hormone?
Diabetologia 1999; 42: 373-379
- [153] RAWDON BB, ANDREW A
Origin and Differentiation of Gut Endocrine Cells.
Histol. Histopath. 1993; 8: 567-580
- [154] McCLENAGHAN NH, FLATT PR
Engineering cultured insulin-secreting pancreatic B-cell lines.
J. Mol. Med. 1999; 77: 235-243
- [155] VAN SCHILFGAARDE R, DE VOS P
Factors influencing the properties and performance of microcapsules for immunoprotection of pancreatic islets.
J. Mol. Med. 1999; 77: 199-205
- [156] OGAWA Y, NOMA Y, DAVILLI AM, WU YJ, THORENS B, BONNER-WEIR S, WEIR GC
Loss of glucose-induced insulin secretion and GLUT2 expression in transplanted β -cells.
Diabetes 1995; 44: 75-79
- [157] GUTNIAK M, ØRSKOV C, HOLST JJ, AHRÉN B, EFENDIC S
Antidiabetogenic effect of glucagon-like peptide-1 (7-36)amide in normal subjects and patients with diabetes mellitus.
N Engl. J. Med 1992; 326: 1316-1322
- [158] CREUTZFELDT WOC, KLEINE N, WILLMS B, ØRSKOV C, HOLST JJ, NAUCK MA
Glucagonostatic Actions and Reduction of Fasting Hyperglycemia by Exogenous Glucagon-Like Peptide I (7-36) Amide in Type I Diabetic Patients.
Diabetes Care 1996; 19: 580-586

-
- [159] FREYSE EJ, KNOSPE S, BECHER T, EL HAG O, GÖKE B, FISCHER U
Glucagon-Like Peptide-1 has No Insulin-Like Effects in Insulin-Dependent Diabetic Dogs Maintained Normoglycemic and Normoinsulinemic.
Metabolism 1999; 48: 134-137
- [160] HOLZ IV GG, KÜHTREIBER WM, HABENER JF
Pancreatic beta-cells are rendered glucose-competent by the insulintropic hormone glucagon-like peptide-1(7-37).
Nature 1993; 361: 362-365
- [161] DACHICOURT N, SERRADAS P, BAILBÉ D, KERGOAT M, DOARÉ L
Glucagon-like peptide-1(7-36)-amide confers glucose sensitivity to previously glucose-incompetent β -cells in diabetic rats: *in vivo* and *in vitro* studies.
J. Endocrinol. 1997; 155: 369-376
- [162] SHEN HQ, ROTH MD, PETERSON RG
The Effect of Glucose and Glucagon-Like Peptide-1 Stimulation on Insulin Release in the Perfused Pancreas in a Non-Insulin-Dependent Diabetes Mellitus Animal Model.
Metabolism 1998; 47: 1042-1047
- [163] BYRNE MM, GLIEM K, WANK U, ARNOLD R, KATSCHINSKI M, POLONSKY KS, GÖKE B
Glucagon-Like Peptide 1 Improves the Ability of the β -Cell to Sense and Respond to Glucose in Subjects With Impaired Glucose Tolerance.
Diabetes 1998; 47: 1259-1265
- [164] GUTNIAK MK, LARSSON H, HEIBER SJ, JUNESKANS OT, HOLST JJ, ÅHRÉN B
Potential therapeutic levels of glucagon-like peptide 1 achieved in humans by a buccal tablet.
Diabetes Care 1996; 19: 843-848
- [165] TODD JF, EDWARDS CMB, GHATEI MA, MATHER HM, BLOOM SR
Subcutaneous glucagon-like peptide-I improves postprandial glycaemic control over a 3-week period in patients with early Type 2 diabetes.
Clin. Sci. 1998; 96: 325-329
- [166] EDWARDS CMB, TODD JF, GHATEI MA, BLOOM SR
Subcutaneous glucagon-like peptide-1 (7-36)amide is insulintropic and can cause hypoglycaemia in fasted healthy subjects.
Clin. Sci. 1998; 96: 719-724
- [167] MENTLEIN R, GALLWITZ B, SCHMIDT WE
Dipeptidyl-peptidase IV hydrolyses gastric inhibitory polypeptide, glucagon-like peptide-1(7-36)amide, peptide histidine methionine and is responsible for their degradation in human serum.
Eur. J. Biochem. 1993; 214: 829-835

-
- [168] PEDERSON RA, WHITE HA, SCHLENZIG D, PAULY RP, McINTOSH CHS, DEMUTH HU
Improved Glucose Tolerance in Zucker Fatty Rats by Oral Administration of the Dipeptidyl Peptidase IV Inhibitor Isoleucine Thiazolidide.
Diabetes 1998; 47: 1253-1258
- [169] HOLST JJ, DEACON CF
Inhibition of the Activity of Dipeptidyl-Peptidase IV as a Treatment for Type 2 Diabetes.
Diabetes 1998; 47: 1663-1670
- [170] GREIG NH, HOLLOWAY HW, DE ORE KA, JANI D, WANG Y, ZHOU J, GARANT MJ, EGAN JM
Once daily injection of exendin-4 to diabetic mice achieves long-term beneficial effects on blood glucose concentrations.
Diabetologia 1999; 42: 45-50
- [171] BURCELIN R, DOLCI W, THORENS B
Long-Lasting Antidiabetic Effect of a Dipeptidyl Peptidase IV-Resistant Analog of Glucagon-Like Peptide-1.
Metabolism 1999; 48: 252-258