

Curriculum Vitae of Simon A. Hinke, Ph.D.

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Personal Information

Date of Birth: December 7th, 1974
Place of Birth: Delta, British Columbia

Nationality: Canadian
Civil status: Married to Christine Jeffrey

Education, Employment & Work Experience

- Senior Fellow (09/2008-present), UW Dept. of Pharmacology, Seattle, USA
(01/2006-09/2008), The Vollum Institute, OHSU, Portland, USA
Project: A-Kinase Anchoring Proteins (AKAPs) in Metabolic Function.
Supervisor: JD Scott
- Postdoctoral Fellow (03/2003-11/2005), VUB, Diabetes Research Center, Brussels, Belgium
Project 1: AMPK induced β -cell toxicity.
Supervisors: DG Pipeleers, M van de Casteele
Project 2: Incretin hormone signaling – synergy with glucose and phenotype of double incretin knockout mice.
Supervisor: FC Schuit
- Ph.D. Candidate (09/1997-03/2003), UBC Dept. of Physiology, Vancouver, Canada
Project: Modulation of peptide hormone signaling – receptor desensitization and enzymatic ligand degradation.
Supervisor: CHS McIntosh
- Academic Exchange (08/2000-12/2000), Probiobdrug, Halle, Germany
Project: Metformin inhibition of dipeptidyl peptidase IV & antidiabetic mechanism.
Supervisor: H-U. Demuth
- Teaching Assistant (09/1997-05/2000), UBC Dept. of Physiology, Vancouver, Canada
- B.Sc. (Hon.) (09/1993-05/1997), UBC Dept. of Physiology, Vancouver, Canada
- Student Research Project (05/1996-09/1996), UBC Dept. of Physiology, Vancouver, Canada

Research Interests

Doctoral training focused on potential mechanisms for ablated responsiveness to GIP (glucose-dependent insulinotropic polypeptide) in human type-II diabetes, and the therapeutic potential of superactive enzyme resistant analogs of GIP, GLP-1 (glucagon-like peptide-1) and glucagon. Postdoctoral training initially examined synergism between glucose metabolism and the cyclic AMP cascade in beta cells, and the phenotype of GIPR null/GLP-1R null mice. Further studies were conducted to elucidate the role of nutrient metabolism and intracellular signal transduction cascades in beta cell death, specifically examining reactive oxygen species and involvement of AMP-activated protein kinase. Current research focuses on A-kinase anchoring proteins in spatio-temporal regulation of cellular metabolism, cell survival and function of islet beta cells.

Fields of Research

Signal Transduction, Physiology, Endocrinology, Molecular and Cellular Biology, Metabolism and Metabolic Diseases, Molecular Medicine

Techniques

Cell culture (clonal and primary), cDNA and siRNA transfection (over-expression and knock-down), electroporation, metabolic phenotyping transgenic models (bioassay), primary tissue isolation (including pancreatic islet isolation), islet perfusion, radioimmunoassay, radioactive labelling of bioactive peptides (¹²⁵I), high performance liquid chromatography (HPLC), biochemical analysis, surface plasmon resonance (BIAcore), molecular biology: polymerase chain reaction (PCR; real time quantitative and conventional), Western and Southern blotting, DNA manipulation (including site directed mutagenesis), *et cetera*.

Fellowships, Honours, Grants, or Awards

Canadian Diabetes Association Postdoctoral Fellowship (2007-2009)
CIHR Postdoctoral Fellowship (2005-2007)
Belgian National Science Foundation (FWO Vlaanderen) Visiting Postdoctoral Fellowship (2003-2004)
MRC/CIHR Doctoral Research Fellowship (1999-2002)
Izaak Walton Killam Predoctoral Fellowship (1999-2001; Honourary)
Canadian Physiological Society Travel Award (2000; 2002)
DAAD Short Term Research Grant (2000)
UBC/Canadian Airlines Travel Award (2000)
UBC Graduate Fellowship (1997-1999)
UBC Science Scholar (1997)
Physiology Prize (1997)
Chan and Peggy Gunn Prize (1997)
Dean's Honour List (1994-1997)
UBC Faculty of Medicine Summer Studentship Research Project (1996)
University of BC Scholarship (1995)
J Fred Muir Memorial Scholarship in Science (1995)
BC Provincial Scholarship (1993)

Membership in Professional Societies & Scientific Activities

- American Diabetes Association (2008)
- European Association for the Study of Diabetes (2002-Present)
- Endocrine Society (1999-Present)
- Canadian Physiological Society (1997-Present)
- Canadian Federation of Biological Science (1997-Present)
- Peer-review of scientific articles: Diabetes, Endocrinology, Journal of Biological Chemistry, Journal of Physiology Lond., Diabetologia, American Journal of Physiology, ChemBioChem, Nature, Expert Opinion in Emerging Drugs.
- Peer-review of grants: Juvenile Diabetes Research Foundation (USA), National Science Foundation (USA), Free University of Brussels Research Fund (Belgium).
- Thesis examiner: Chen Yuhong, M.Sc. thesis "Effects of rapamycin on glycemic control in normal rats", Vrije Universiteit Brussel, Belgium, 2004
- Thesis examiner: Marcella Mori, Ph.D. thesis "Profiles of gene expression induced by ionizing radiation in different human cell types" Vrije Universiteit Brussel, Belgium, 2005.
- Official internal referee: Dominique Delmeire, Ph.D. thesis "Molecular and cellular analysis of incretin signalling in pancreatic beta cell function"; Vrije Universiteit Brussel, Belgium, 2004.
- Consultation for Probiodrug AG (Halle, Germany), invited speaker to the Probiodrug annual research conference (2003).
- Guest speaker: Diabetes Research Center, Brussels, Belgium (2002), Institute of Pharmacology and Toxicology, University of Lausanne, Switzerland (2002) (Topic: "Modulation of GIP Bioactivity").
- Guest Lecturer: Masters Program in Medical and Pharmaceutical Research, VUB, Belgium (2004) (Topic: "Cellular basis of current and future type 2 diabetic therapies acting as insulin releasers").
- Invited Plenary Speaker: 2nd International Conference on Dipeptidyl Amino Peptidases, Magdeburg, Germany (Topic: "Relative contribution of incretin hormones in the glucose lowering action of DP IV inhibitors in type 2 diabetes").

Peer Reviewed Publications

- Goehring, AS, Pedroja, BS, **Hinke, SA**, Langeberg, LK, and JD Scott. MyRIP anchors protein kinase A to the exocyst complex. *J. Biol. Chem.* In press, 2007.
- Hinke, SA**, Martens, GA, Cai, Y, Finsi, J, Heimberg, H, Pipeleers, D, and M Van de Castele. Methylsuccinate antagonises biguanide-induced AMPK-activation and death of pancreatic β -cells through restoration of mitochondrial electron transfer. *Brit. J. Pharmacol.* 150:1031-43, 2007.
- Cai, Y, Martens, G, **Hinke, S**, Heimberg, H, Pipeleers, D, and M Van de Castele. Increased oxygen radical formation and mitochondrial dysfunction mediate beta cell apoptosis in conditions of AMPK-stimulation. *Free Radic. Biol. Med.* 42: 64-78, 2006.
- Martens, G, Cai, Y, **Hinke, S**, Stangé, G, Van de Castele, M and D Pipeleers. Glucose suppresses superoxide generation in metabolically responsive pancreatic beta cells. *J. Biol. Chem.* 280:20389-20396, 2005.
- Hinke, SA**, Manhart, S, Speck, M, Pederson, RA, Demuth, H-U, and CHS McIntosh. In depth analysis of the N-terminal bioactive domain of gastric inhibitory polypeptide. *Life Sci.* 75:1857-1870, 2004.
- Delmeire, D, Flamez, D, Moens, K, **Hinke, SA**, Van Schravendijk, C, Pipeleers, D, and F Schuit. Prior *in vitro* exposure to GLP-1 with or without GIP can influence the subsequent beta cell responsiveness. *Biochem. Pharmacol.* 68:33-39, 2004.
- Hansotia, T, Baggio, LL, Delmeire, D, **Hinke, SA**, Yamada, Y, Tsukiyama, K, Seino, Y, Holst, JJ, Schuit, F, and DJ Drucker. Double incretin receptor knockout (DIRKO) mice reveal an essential role for the enteroinsular axis in transducing the glucoregulatory actions of DPP-IV inhibitors. *Diabetes* 53:1326-1335, 2004.
- Hinke, SA**, Manhart, S, Kühn-Wache, K, Nian, C, Demuth, H-U, Pederson, RA, and CHS McIntosh. [Ser²]- and [(P)Ser²]-Incretin Analogs: Comparison of dipeptidyl peptidase IV resistance and biological activities *in vitro* and *in vivo*. *J. Biol. Chem.* 279: 3998-4006, 2004.
- Delmeire, D, Flamez, D, **Hinke, SA**, Cali, JJ, Pipeleers, D, and F Schuit. Type VIII adenylyl cyclase in rat beta cells: coincidence signal detector/generator for glucose and GLP-1. *Diabetologia* 46:1383-1393, 2003.
- Hinke, SA**, Gelling, R, Manhart, S, Lynn, F, Pederson, RA, Kühn-Wache, K, Rosche, F, Demuth, H-U, and CHS McIntosh. Structure-activity relationships of glucose-dependent insulinotropic polypeptide (GIP). *Biol. Chem.* 384:403-407, 2003.
- Pamir, N, Lynn, FC, Buchan, AMJ, Ehses, J, **Hinke, SA**, Pospisilik, JA, Miyawaki, K, Yamada, Y, Seino, Y, McIntosh, CHS, and RA Pederson. Glucose-dependent insulinotropic polypeptide receptor null mice (GIPR^{-/-}) exhibit compensatory changes in the enteroinsular axis. *Am. J. Physiol. Endocrinol. Metab.* 284:E931-E939, 2003.
- Manhart, S, **Hinke, SA**, McIntosh, CHS, Pederson, RA, and H-U Demuth. Structure-function analysis of a series of novel GIP-analogs containing different helical length linkers. *Biochemistry* 42:3081-3088, 2003.
- Lynn, FC, Thomson, SA, Pospisilik, JA, Ehses, JA, **Hinke, SA**, Pamir, N, McIntosh, CHS, and RA Pederson. A novel pathway for regulation of glucose-dependent insulinotropic polypeptide (GIP) receptor expression in β -cells. *FASEB J.* 17:91-93, 2003.
- Demuth, H-U, **Hinke, SA**, Pederson, RA, and CHS McIntosh. Rebuttal to Deacon and Holst: "Metformin effects on dipeptidylpeptidase IV degradation of glucagon-like peptide-1" versus "Dipeptidyl peptidase inhibition as an approach to the treatment and prevention of type 2 diabetes: a historical perspective". *Biochem. Biophys. Res. Commun.* 296:229-232, 2002.
- Hinke, SA**, McIntosh, CHS, Hoffmann, T, Kühn-Wache, K, Wagner, L, Bär, J, Manhart, S, Wermann, M, Pederson, RA, and Demuth, H-U. On combination therapy of diabetes with metformin and DP IV inhibitors [letter]. *Diabetes Care.* 25:1491-1492, 2002.
- Hinke, SA**, Kühn-Wache, K, Hoffmann, T, Pederson, RA, McIntosh, CHS, and Demuth, H-U. Metformin effects on dipeptidylpeptidase IV degradation of glucagon-like peptide-1. *Biochem. Biophys. Res. Commun.* 291:1302-1308, 2002.
- Hinke, SA**, Gelling, RW, Pederson, RA, Manhart, S, Nian, C, Demuth, H-U, and CHS McIntosh. Dipeptidyl peptidase IV-resistant [D-Ala²]glucose-dependent insulinotropic polypeptide (GIP) improves glucose tolerance in normal and obese diabetic rats. *Diabetes* 51:652-661, 2002.

Hinke, SA, Manhart, S, Pamir, N, Demuth, H-U, Gelling, RW, Pederson, RA, and CHS McIntosh. Identification of a bioactive domain in the amino-terminus of glucose-dependent insulinotropic polypeptide (GIP). *Biochim. Biophys. Acta* 1547:143-155, 2001.

Pospisilik, JA*, **Hinke, SA***, Hoffmann, T, Rosche, F, Schlenzig, D, Heiser, U, Glund, K, McIntosh, CHS, Pederson, RA and H-U. Demuth. Metabolism of glucagon by dipeptidyl peptidase IV. *Regul. Pept.* 96:133-141, 2001. *Dual primary authorship.

Hinke, SA, Pauly, RP, Ehses, J, Kerridge, P, Demuth, H-U, McIntosh, CHS, and RA Pederson. Role of glucose in chronic desensitization of isolated rat islets and mouse insulinoma (β TC-3) cells to glucose-dependent insulinotropic polypeptide. *J. Endocrinol.* 165:281-291, 2000.

Hinke, SA, Pospisilik, JA, Demuth, H-U, Manhart, S, Kühn-Wache, K, Hoffmann, T, Nishimura, E, Pederson, RA and CHS McIntosh. Dipeptidyl peptidase IV degradation of glucagon: characterization of glucagon degradation products and DPIV resistant analogs. *J. Biol. Chem.* 275:3827-3834, 2000.

Wheeler, MB, Gelling, RW, **Hinke, SA**, Tu, B, Pederson, RA, Lynn, F, Ehses, J, and CHS McIntosh. Characterization of the carboxyl-terminal domain of the rat glucose-dependent insulinotropic polypeptide (GIP) receptor. A role for serines 426 and 427 in regulating the rate of internalization. *J. Biol. Chem.* 274:24593-24624, 1999.

McIntosh, CHS, Bremsak, I, Lynn, FC, Gill, R, **Hinke, SA**, Gelling, R, Nian, C, McKnight, G, Jaspers, S, and RA Pederson. Glucose-dependent insulinotropic polypeptide stimulation of adenylyl cyclase and lipolysis in differentiated 3T3-L1 cells: Wortmannin-sensitive inhibition of insulin. *Endocrinology.* 140:398-404, 1999.

Gelling, RW, Coy, DH, Pederson, RA, Wheeler, MB, **Hinke, S**, Kwan, T, and CHS McIntosh. GIP_{6-30amide} contains the high affinity binding region of GIP and is a potent inhibitor of GIP₁₋₄₂ action in vitro. *Regul. Pept.* 69:151-154, 1997.

Chapters, reviews and symposia

SA Hinke. Finding GAD: Early detection of β -cell injury. [News & Views] *Endocrinology* In press, 2007.

Hinke, SA, Pederson, RA and CHS McIntosh. Relative contribution of incretins to the glucose lowering effect of DP IV inhibitors in type 2 diabetes mellitus (T2DM). *in* Dipeptidyl Aminopeptidases: Basic Science and Clinical Applications. U. Lendeckel (ed). Kluwer Academic Publishers *Adv. Exp. Med. Biol.* 575:119-133, 2006.

Martens, G, Cai, Y, **Hinke, SA**, Stangé, G, Van de Castele, M and D Pipeleers. Nutrient sensing in pancreatic beta cells suppresses mitochondrial superoxide generation and its contribution to apoptosis. *Biochem. Soc. Trans.* 33:300-301, 2005.

Hinke, SA, Hellemans, K, and FC Schuit. Plasticity of the beta cell insulin secretory competence: preparing the pancreatic beta cell for a next meal. *J. Physiol. (Lond.)* 558:369-380, 2004.

Hinke, SA, Lynn, F, Ehses, J, Pamir, N, Manhart, S, Kühn-Wache, K, Rosche, F, Demuth, H-U, RA Pederson and CHS McIntosh. Glucose-dependent insulinotropic polypeptide (GIP): development of DPIV-resistant analogues with therapeutic potential. *in* Dipeptidyl Aminopeptidases in Health and Disease. M. Hildebrandt, B. Klapp, T. Hoffmann, and H-U. Demuth (eds). Kluwer Academic Publishers *Adv. Exp. Med. Biol.* 524:293-301, 2003.

Kühn-Wache, K, Manhart, S, Hoffmann, T, **Hinke, SA**, Gelling, R, Pederson, RA, McIntosh, CHS and H-U Demuth. Analogs of glucose-dependent insulinotropic polypeptide (GIP) with increased dipeptidyl peptidase IV (DP IV) resistance. *in* Cellular Peptidases in Immune Functions and Diseases Vol.2. J Langner and S. Ansoerge (eds). Kluwer Academic/Plenum Publishers *Adv. Exp. Med. Biol.* 477:187-195, 2000.

Patents

Hinke, SA, Ehses, JA, Pederson, RA, McIntosh, CHS, Manhart, S, Demuth, H-U. Novel analogues of glucose-dependent insulinotropic polypeptide. Patent WO03/082898 PCT/EP03/03307 (Application date: March 28th, 2003).

Doctoral Dissertation

Hinke, SA. Modulation of Insulinotropic Hormone Bioactivity with a Focus on Glucose-dependent Insulinotropic Polypeptide and Its Receptor. CHS McIntosh (supervisor), S Katz (chair), RA Pederson, YN Kwok, B Rodriguez, R Brownsey, PR Flatt (examiners). Department of Physiology, Faculty of Medicine, University of British Columbia, Vancouver, Canada. **pp.** 244, January 2003.