BIOGRAPHICAL SKETCH

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NAME: Sherwin, Robert S.

eRA COMMONS USER NAME (credential, e.g., agency login): rsherwin

POSITION TITLE: C.N.H. Long Professor of Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Union College, Schenectady, NY	B.S.	5/63	Biology (Honors)
Albert Einstein College of Medicine, Bronx, NY	M.D.	5/67	Medicine (AOA)
The Mount Sinai Hospital, New York, NY	Internship	6/68	Internal Medicine
The Mount Sinai Hospital, New York, NY	Residency	6/72	Internal Medicine
National Institute of Aging, Baltimore, MD	Postdoctoral	6/71	Metabolism
Yale School of Medicine. New Haven, CT	Postdoctoral	6/74	Endocrinology

A. Personal Statement

My research program over the past 25 years has focused on: 1) the mechanisms used by the ventromedial hypothalamus (VMH) to sense glucose and activate counter-regulatory responses to hypoglycemia; 2) how this response to hypoglycemia is altered by type 1 diabetes (T1DM) and intensive insulin treatment; 3) the adaptive response of brain glucose and alternative fuel metabolism to recurrent insulin-induced hypoglycemia in T1DM (using fMRI, MRSpectroscopy) so that brain function and fuel supply can be maintained; 4) the influence of insulin on brain glucose sensing; 5) the effect of oral glucose and fructose as well as food images on brain activation and desire for high-calorie foods; and 6) the immune mechanisms driving beta cell destruction in T1DM. This research spans both clinical and basic research in metabolism, neuroscience, immunology, and imaging and has been recognized by receipt of the Banting Medal for Lifetime Scientific Achievement and the Renold Award to Mentoring from the American Diabetes Association. I also serve as the Principal Investigator of the NIDDK Yale Diabetes Center and the CTSA-funded Yale Center for Clinical Investigation.

a. Sherwin RS, Kramer KJ, Tobin JD, Insel PA, Liljenquist JE, Berman M, Andres R (1974). A model of the kinetics of insulin in man. J Clin Invest 53:1481-1492.
b. Amiel SA, Tamborlane WV, Simonson DC, Sherwin RS. (1987) Defective glucose counterregulation after strict control of insulin-dependent diabetes mellitus. N Engl J Med 316:1376-1383.
c. Wen L, Wong FS, Burkly L, Altieri M, Mamalaki C, Kloussis D, Flavell RA, and Sherwin RS (1998) Induction of insulitis by glutamic acid decarboxylase peptide-specific and HLA-DQ8-restricted $CD4^+$ T cells from human DQ transgenic mice. J Clin Invest 102:947-957.
d. Page KA, Chan O, Arora J, Belfort-Deaguiar R, Dzuira J, Roehmholdt B, Cline GW, Naik S, Sinha R, Constable RT, Sherwin RS. (2013) Effects of fructose vs. glucose on regional cerebral blood flow in brain regions involved with appetite and reward pathways. JAMA. 309: 63-70.

B. Positions and Honors

Positions and Employment

1974-78 Assistant Professor of Medicine, Yale University School of Medicine
1978-86 Associate Professor of Medicine, Yale University School of Medicine (tenured 1983),
1986-95 Professor of Medicine, Yale University School of Medicine
1980-2003 Associate Director, Clinical Research Center, Yale University School of Medicine
1983-present Director, Endocrine Training Program, Yale University School of Medicine, New Haven, CT

1984-92 Director, Diabetes Unit, Yale University School of Medicine, New Haven, CT
1993-present Director, Diabetes Research Center, Yale University School of Medicine
1995-present C.N.H. Long Professor of Medicine, Yale University School of Medicine, New Haven, CT
2003-2006 Director, General Clinical Research Center, Yale University School of Medicine
2005-present Section Chief (Endocrinology), Dept. of Medicine, Yale School of Medicine, New Haven, CT
2006-present Director, Yale Center for Clinical Investigation (CTSA), Yale School of Medicine

Other Experience and Professional Memberships

1977-1981 Ad Hoc Member NIH Metabolism Study Section
1981-1985 Member, NIH Metabolism Study Section, NIH
1989-1992 Chairman, Medical Science Review Committee and Medical Science Advisory Board, JDRF
1995-2000 Member and Chair, FDA Advisory Committee, Endocrinologic & Metabolic Drugs
1997-1998 Chairman, ADA Grant Review Committee
1998-2000 Vice-President & President-Elect, American Diabetes Association
2000-2001 President, American Diabetes Association

Honors

1977-82 Recipient of NIH Research Career Development Award; the first ever awarded by NIH
1993 David Rumbough Award for Diabetes Research, Juvenile Diabetes Research Foundation
1995 & 2003 MERIT Award, NIDDK
2002 Distinguished Alumnus Award, Albert Einstein College of Medicine
2004 Novartis Award for Lifetime Scientific Achievement in Diabetes
2007 Banting Medal for Lifetime Scientific Achievement, American Diabetes Association
2011 Albert Renold Award for Diabetes Research Mentoring, American Diabetes Association
2004-present Chairman, DSMB for Islet Transplantation, NIDDK
2005-2013 Member, NIDDK T1DM Strategic Planning Committee
Elected to the ASCI, AAP, and as a Honorary Member the Royal College of Physicians

C. Contribution to Science

1. My first research project has had an enormous impact on diabetes research. While serving as a research fellow in Dr. Reubin Andres' lab at the NIH, I was given the project to design and develop the euglycemic hyperinsulinemic clamp, which I used in conjunction with glucose tracers to model insulin kinetics and its relationship to glucose metabolism in liver and periphery. These seminal studies showed that insulin-stimulated glucose uptake was not mirrored by its rapid changes in the circulation, but rather by its build up and decay in a slowly equilibrating insulin compartment in peripheral tissues and predicted this reflected insulin binding to muscle tissue, a novel concept at the time. This paper is the first peer-reviewed publication using the clamp procedure, now the most widely accepted method for quantifying insulin sensitivity. A decade later, I modified the clamp technique to create a standardized hypoglycemic stimulus, now the gold standard for assessing glucose counterregulation. Other early work focused on the mechanisms used by hormones that oppose insulin. It showed that glucagon's capacity to promote hyperglycemia is, to a large extent, dependent on the degree of insulin deficiency and that fasting hyperglycemia can occur despite glucagon suppression. This work stimulated debate, but ultimately helped place the relative contribution of insulin and glucagon in human diabetes in proper perspective. Other studies in my lab helped define the mechanisms driving stress-induced diabetes, showing that glucagon, epinephrine and cortisol act synergistically to produce severe hyperglycemia.

a. Sherwin RS, Kramer KJ, Tobin JD, Insel PA, Liljenquist JE, Berman M, Andres R (1974). A model of the kinetics of insulin in man. J Clin Invest 53:1481-1492.
b. Simonson DC, Tamborlane WV, DeFronzo RA, Sherwin RS. (1985) Intensive insulin therapy reduces counterregulatory hormone responses to hypoglycemia in patients with Type I diabetes. Ann Intern Med 103:184-190.
c. Sherwin RS, Fisher M, Hendler R, Felig P (1976). Hyperglucagonemia and blood glucose regulation in normal, obese and diabetic subjects. N Engl J Med 294:455-561.
d. Eigler N, Sacca L, Sherwin RS. (1979). Synergistic interactions of physiologic increments of glucagon, epinephrine and cortisol in the dog: a model for stress-induced hyperglycemia. J Clin Invest 63:114-123.

2. My most important direct contribution to patient care derives from my role in developing insulin pump therapy (CSII) and the planning of the DCCT. Based on studies I conducted with my fellow Dr. Luigi Sacca showing the beneficial effect of continuous overnight basal insulin delivery on glucose's capacity to suppress hepatic glucose production and in turn minimize hyperglycemia, I recognized that continuous subcutaneous infusion of small amounts of insulin via a small pump would provide a more physiological and relatively safe method of insulin delivery in diabetes. When my fellow Dr. William Tamborlane, uncovered such a pump, we rapidly translated the concept clinically. A series of studies followed showing that most of the metabolic abnormalities of diabetes were reversed by CSII served to initiate the intensive insulin therapy era. Moreover, this work prompted Dr. Harry Keen and I to organize and co-direct the KROC multicenter trial, which established the feasibility of conducting a large long-term trial on the effect of glycemic control on diabetic complications, leading NIDDK to initiate the DCCT, which was, to a large extent, based on the KROC protocol.

a. Saccà L, Hendler R, Sherwin RS. (1978) Hyperglycemia inhibits glucose production in man independent of changes in glucoregulatory hormones. J Clin Endocrinol Metab 47:1160-1163.
b. Tamborlane WV, Sherwin RS, Genel M, Felig P (1979) Reduction to normal of plasma glucose in juvenile diabetes by subcutaneous administration of insulin with a portable infusion pump. N Engl J Med 300:573-578.
c. Sherwin RS, Tamborlane WV, Genel M, Felig P. (1980) Treatment of juvenile-onset diabetes by subcutaneous infusion of insulin with a portable pump. Diabetes Care 3:301-308.
d. Tamborlane WV, Hintz R, Bergman M, Genel M, Felig P, Sherwin RS: (1981) Insulin infusion pump treatment of diabetes. Influence of improved metabolic control on plasma somatomedin levels. N Engl J Med 305:303-307.

3. Many CSII treated type 1 diabetic (T1D) patients report the loss of hypoglycemic symptoms, which prompted us to test if this was due to suppression of counterregulatory responses. We found this was indeed caused by a downward setting of the glucose level triggering epinephrine (and other hormone) release. A key patient safety issue is whether the downward shift of glycemic thresholds is mirrored by a similar downward shift in the glucose level at which brain function becomes impaired. To address this issue, we showed that a greater decrease in plasma glucose was required to impair cognitive function in T1D patients on intensified insulin therapy, helping to explain the phenomenon of hypoglycemia unawareness. To define the impact of intensive insulin treatment on brain function in greater detail I conducted microdialysis studies to measure, for the first time, glucose levels in brain interstitial fluid of conscious humans. We discovered that the brain is exposed to a metabolic milieu very different from the circulation. Glucose levels in brain interstitial fluid were only ~25% of those in plasma; this disparity persisted during hypoglycemia, resulting a more profound reduction in brain glucose than is commonly appreciated. Thus, contrary to the prevailing view, glucose is rate limiting during moderate hypoglycemia when the brain is activated. We also developed an awake rat model and showed antecedent hypoglycemia makes the brain more energy efficient, helping to explain hypo unawareness.

a. Simonson DC, Tamborlane WV, DeFronzo RA, Sherwin RS. (1985). Intensive insulin therapy reduces counterregulatory hormone responses to hypoglycemia in patients with Type I diabetes. Ann Intern Med 103:184-190.
b. Amiel SA, Tamborlane WV, Simonson DC, Sherwin RS. (1987) Defective glucose counterregulation after strict control of insulin-dependent diabetes mellitus. N Engl J Med 316:1376-1383.
c. McNay EC, WilliamsonA, McCrimmon RJ, Sherwin RS. (2006) Cognitive and neural hippocampal effects of long-term moderate recurrent hypoglycemia. Diabetes 55: 1080-1087.

4. Reversal of defective defenses against hypoglycemia requires a better understanding of the tissues and molecular mechanisms used to sense hypoglycemia and trigger counterregulation. My lab thus employed rodent models to establish the key role played by the ventromedial hypothalamus (VMH) in glucose sensing. Rats exposed to recurrent hypoglycemia developed impaired counterregulation due to a failure of the VMH to detect hypoglycemia. We next tested the hypothesis that the VMH senses glucose via mechanisms similar to those used by beta cells. Indeed, local VMH delivery of the K_{ATP} channel openers and closers were found to modulate hypoglycemic counterregulation. Moreover, inhibition of VMH GABA tone stimulated hormonal release during acute hypoglycemic, a response we showed was impaired by antecedent hypoglycemia or T1D. We also generated data showing AMP-kinase was expressed in the VMH glucose-inhibited neurons that

regulated the magnitude of the response of hepatic glucose production during hypoglycemia. Corticotrophin releasing factor (CRF) release and its activation of specific hypothalamic CRH inhibitory and stimulatory receptors also was found to regulate hypoglycemia-induced counterrregulatory hormone secretion.

a. During MJ, Leone P, Davis KE, Kerr D, Sherwin RS. (1995) Glucose modulates rat substantia nigra GABA release in vivo via ATP-sensitive potassium channels. J Clin Invest 95:2403-2408.
b. Borg M, Sherwin RS, Borg W, Tamborlane WV, Shulman GI (1997). Local ventromedial hypothalamus glucose perfusion blocks counterregulation during systemic hypoglycemia in awake rats. J Clin. Invest 99: 361-365.
c. McCrimmon RJ, Song Z, Cheng H, McNay E, Weikart-Yeckel C, Fan X, Routh VH, Sherwin, RS. (2006). Corticotrophin releasing factor (CRF) receptors within the ventromedial hypothalamus (VMH) regulate hypoglycemia-induced hormonal counterregulation. J Clin Invest 116: 1723-1730.
d. Chan O, Paranjape S, Czyzyk D, Horblitt A, Zhu W, Ding Y, Fan X, Seashore M, Sherwin R. (2011) Increased GABAergic output in the ventromedial hypothalamus contributes to impaired hypoglycemic counterregulation in diabetic rats. Diabetes 60: 1582-1589.

5. While rodent models are valuable tools for dissecting molecular mechanisms, the unique size and metabolic demands of the human brain mean that data gleaned from rodents may not always apply to humans. Thus, my work is increasingly focused on human brain imaging studies to identify specific regions regulating counterregulation and eating behavior. We measured cerebral blood flow (CBF) using fMRI as glucose fell in healthy human subjects. Hypothalamic CBF increased when glucose fell to only 77 mg/dl, demonstrating the hypothalamus is exquisitely sensitive to small decrements in glucose, preceding any rise in counterregulatory hormones. We next examined the effects of mild hypoglycemia on brain responses to visual food cues in lean and obese humans during a eu- & mild hypoglycemic (68mg/dl). In lean subjects food cues activated executive control, e.g. prefrontal cortex (PFC) at euglycemia, whereas mild hypoglycemia activated subcortical regions (dorsal/ventral striatum, insula, hypothalamus and thalamus), suppressed the PFC, and increased hunger. The food cue effect was markedly different in obesity; much greater activation of limbic-striatal brain regions occurred and greater 'wanting' for high-calorie foods. Remarkably, PFC activation seen lean subjects at euglycemia did not occur in obesity. Thus, while circulating glucose modulates neural stimulatory and inhibitory control over motivation for food, glucose's restraining effect is lost in obesity. We also studied whether T1DM patients with hypoglycemia unawareness exhibit altered brain fuel metabolism, accounting for their inability to detect decrements in glucose. T1DM unaware patients, T1DM aware controls, and non-diabetics underwent ^{13}C MR Spectroscopy. Unaware T1DM showed increased blood brain barrier transport and metabolism of acetate vs. both control groups, much like our rodent data. Acetate transport/metabolism was inversely correlated with epinephrine responses to hypoglycemia, suggesting that brain metabolic adaptations may cause both impaired hypothalamic function and unawareness in intensively treated T1D patients.

a. Page KA, Arora J, Qiu M, Relwani R, Constable RT, Sherwin RS. (2009) Small decrements in systemic glucose provoke increases in hypothalamic blood flow prior to the release of counterregulatory hormones. Diabetes 58, 448-452.
b. Page K, Seo D, Aguiar R, Lacadie C, Dziura J, Naik S, Amarnath S, Constable RT, Sherwin RS, Sinha R. (2011) Circulating glucose modulates neural control of motivation for high-calorie foods in humans. J. Clin. Invest, 121(10): 4161-9.
c. Page KA, Chan O, Arora J, Belfort-Deaguiar R, Dzuira J, Roehmholdt B, Cline GW, Naik S, Sinha R, Constable RT, Sherwin RS. (2013) Effects of fructose vs glucose on regional cerebral blood flow in brain regions involved with appetite and reward pathways. JAMA. 309: 63-70.
d. Gulanski BI, De Feyter HM, Page KA, de Aguiar RB, Mason GF, Rothman DL, Sherwin RS. (2013) Increased Brain Transport & Metabolism of Acetate in Hypoglycemia Unawareness. JCEM 98:381-20.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/robert.sherwin.1/bibliography/40315855/public/?sort=date&direction=ascending

D. Research Support

2 R01 DK20495 Sherwin (PI) 9/9/13 – 8/31/18

NIH/NIDDK
"Glucoregulatory Hormone Interactions in Diabetes".
The major goals of this project are to evaluate the influence of insulin-dependent diabetes on the CNS, metabolic, and hormonal response to changes in circulating glucose.

5 P30 DK 45735 Sherwin (PI) 3/15/13 – 1/31/18
Diabetes Research Center
NIH/NIDDK
This is a multidisciplinary program to support common services that are being used by a number of diabetes/endocrine investigators at Yale.

UL1, KL2,T32 RR 024139 Sherwin (PI) 9/30/06 – 6/30/21
NIH/NCATS: CTSA
This is a University resource for clinical and translational investigation.

R01 DK092882 Wen (PI) 4/25/12-3/31/17
NIH/NIDDK
"Role of TLR9 in beta cell function and diabetes"
The aims of this project are to test preclinically the efficacy of a TLR9 antagonist in prevention and/or treatment of T1D and T2D using different mouse models of both types of diabetes and to better understand the basic mechanisms of how TLR9 regulate immune and beta cell function with or without TLR9 expression.
Role: Co-PI

JDRF 2-SRA-2014-271-M-R Sherwin (PI) 10/1/14 – 9/30/17
"Development of Agents to Diminish the Risk of Hypoglycemia-Induced Brain Injury in Diabetes"
The goal of this project is to develop novel and cost saving oral therapeutic strategies that could protect the brain from hypoglycemia-induced injury and sustain normal brain metabolism under hypoglycemia.

American Diabetes Association Wen (PI) 1/1/14-12/31/16
"Innate immunity and obesity in animal model and man"

Merck Sherwin (PI) 10/8/14-10/8/16
Establishment of the dose of Compound A required for amplification of the glucagon response to hypoglycemia in normal rats. The aim is to test a novel drug to promote defense mechanisms against hypoglycemia in T1DM.

R01 DK100500 Wen (PI) 08/15/14-05/31/18
NIH/NIDDK
"Dendritic Cells in Immune-Metabolic Disorder in Mouse and Man"

R01 HL122822 Mani (PI) 11/19/14-10/31/18
NIH/NHLBI
"Hepatic Wnt/LRP6 Regulation of Plasma Lipids"
The major goal of this project is to study the mechanism of hyperlipidemia in a mouse model of the mutation in a gene called LRP6 in order to identify novel drug targets.

Completed Research in Last 3 years Support:

JDRF 4-2007-1059 Flavell (PI) 3/1/08 – 2/28/13
A humanized mouse model of Type 1 diabetes
Role: PI for Project 3 "Role of Reg, a new beta cell autoantigen, in human T1DM"

NIDDK 1R21DK090764 Ding/Sherwin (PI) 9/1/11-2/28/14
The Norepinephrine Transporter: A Novel Target for Imaging Brown Adipose Tissue

JDRF 4-2010-433 Sherwin (PI) 9/1/10-8/31/14
R&D Grant "The neuroprotective effects of medium chain triglycerides in hypoglycemia unawareness"