Casual Friday Series

Functional Blood Chemistry Series
Pt. VII: Glucose (4)

A Biogenetix Clinical Presentation

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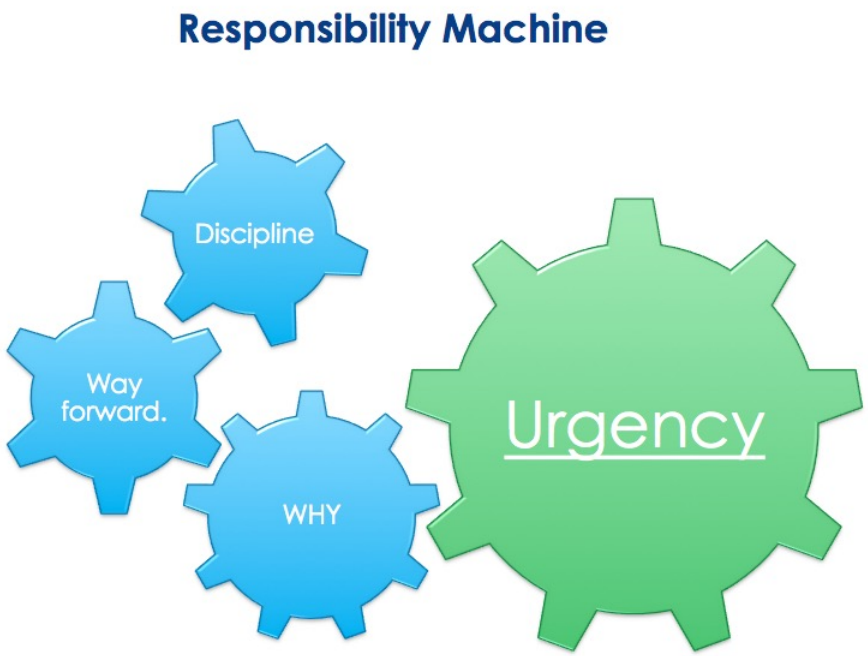
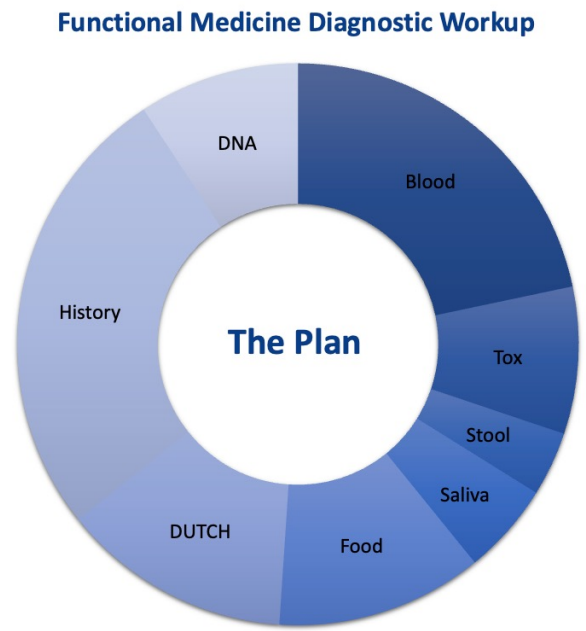
- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*

Applied FM

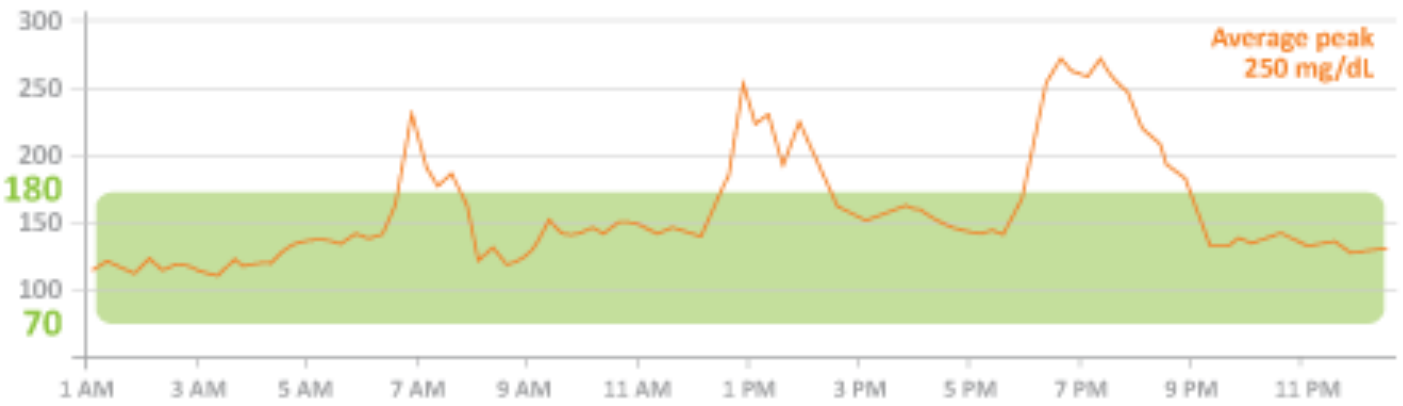




Progress.

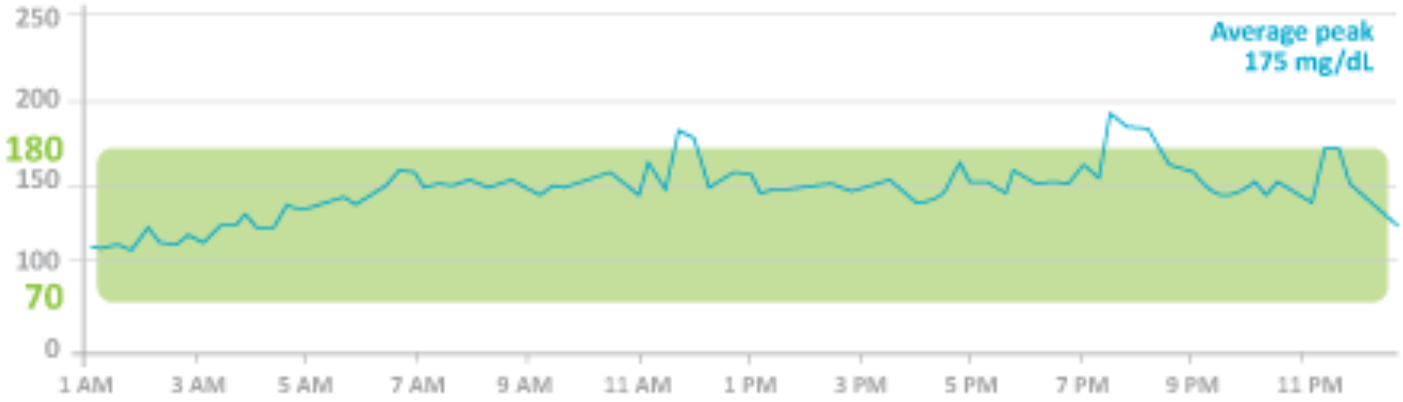
Glycemic Variability

GlycoMark Value 3.0 µg/mL | **A1C 7.4%** | **Mary**



Extreme frequent glucose peaks

GlycoMark Value 15.1 µg/mL | **A1C 7.4%** | **William**



High baseline glucose overall

Glycomark

- Hyperglycemia and glycemic variability have been linked to diabetes-related health complications including:
- vascular damage (reduced flow-mediated dilation and coronary lumen diameter; increased carotid artery stiffness and carotid intima-media thickness)
- oxidative stress (plasma 3-nitrotyrosine and 24-h urinary excretion rates of free 8-iso PGF2)
- increased inflammatory markers (C-Reactive Protein, Interleukin 6)
- poor cardiovascular outcomes (repeat MI, acute heart failure)
- stroke
- dementia
- increased risk of death from cardiovascular causes

Homeostatic Model Assessment (HOMA)

- HOMA2 estimates steady state beta cell function (%B) and insulin sensitivity (%S), as percentages of a normal reference population. These measures correspond well, but are not necessarily equivalent, to non-steady state estimates of beta cell function and insulin sensitivity derived from stimulatory models and the intravenous glucose tolerance test, and the oral glucose tolerance test.

Homeostatic Model Assessment (HOMA)

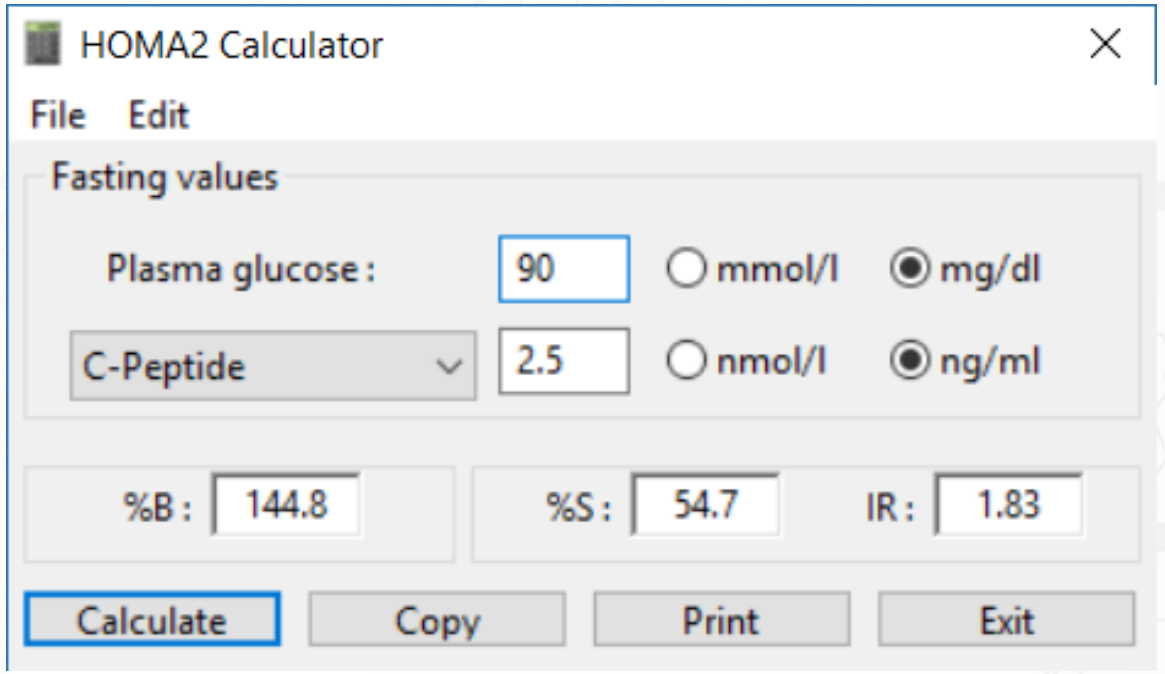
- Traditionally used serum insulin, but has been validated to use C-peptide as well
  - Homa-IR (CP) = 1.5 + fasting blood glucose x fasting C-peptide/2800
  - Homa-islet (CP-Normal) = 0.27 x fasting C-peptide /(fasting blood glucose - 3.5) + 50
  - https://www.dtu.ox.ac.uk/homacalculator/

Homeostatic Model Assessment (HOMA)

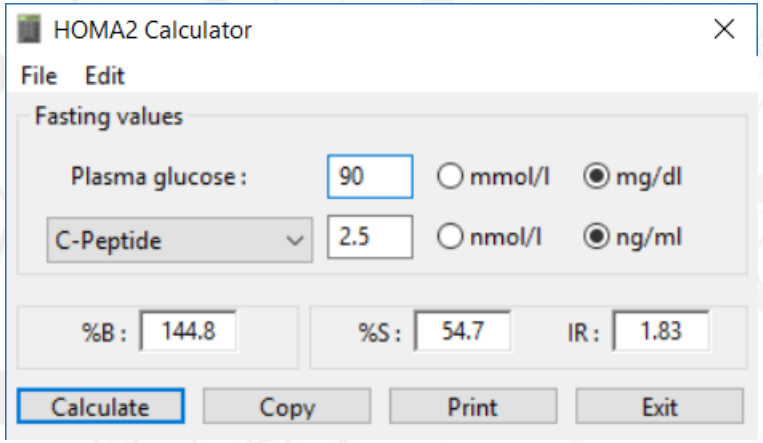
Insulin resistance = <1.8

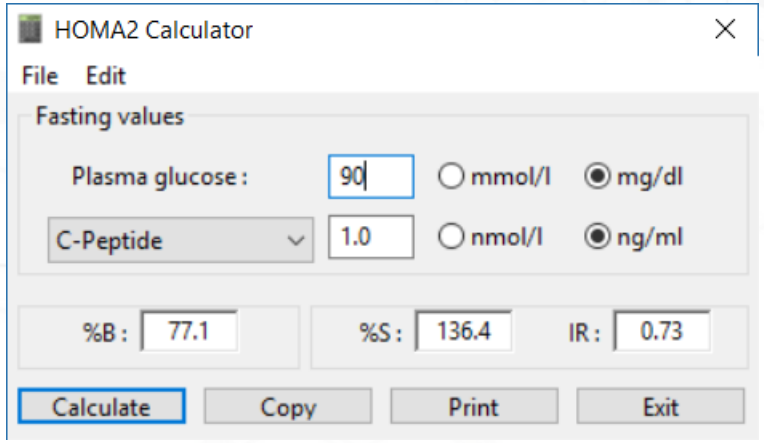
Beta cell (%B) = <145

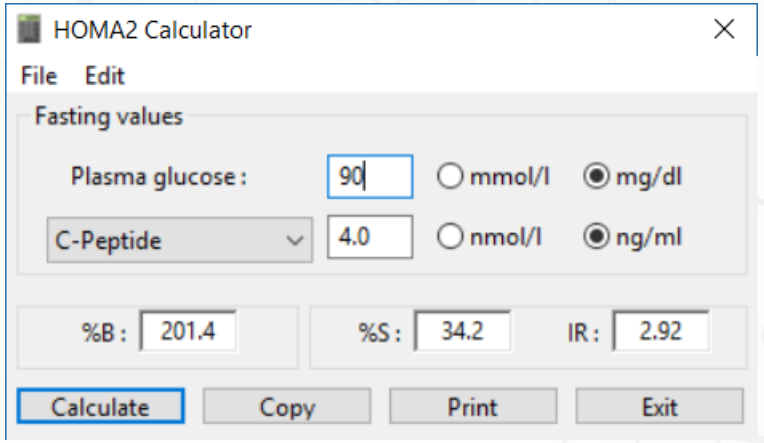
Insulin Sensitivity (%S) = > 55



Homeostatic Model Assessment (HOMA)







STEP 1 - Glycomark

If Glycomark is <15 µg/mL:

1. Focus on diet – quality of food (macronutrient ratio) and quantity of food
2. GLP-1 stimulators (pre-meal)
    1. Fish oil
    2. Pea protein, glutamine (Metaboclear, CI ResQ)
    3. Quercitin
    4. Bile acid support (ProBile +)
    5. Chew food thoroughly
    6. Olive leaf extract

Diabetes Care 1

Glucose Variability in a 26-Week Randomized Comparison of Mealtime Treatment With Rapid-Acting Insulin Versus GLP-1 Agonist in Participants With Type 2 Diabetes at High Cardiovascular Risk

DOI: 10.2337/dc15-2782

The FLAT-SUGAR Trial Investigators*

CLIN CARE/EDUCATION/NUTRITION/PSYCHOSOCIAL

OBJECTIVE

A1C is associated with diabetes complications but does not reflect glycemic variability (GV), which may worsen outcomes by inducing inflammation, oxidative stress, and cardiac arrhythmias. We tested whether a glucagon-like peptide 1 agonist-based regimen can reduce GV and cardiometabolic risk markers while maintaining similar A1C levels in people with insulin-requiring type 2 diabetes and high cardiovascular risk.

RESEARCH DESIGN AND METHODS

After run-in on metformin and basal-bolus insulin (BBI), 102 participants continued metformin and basal insulin and were randomized to exenatide dosing before the two largest meals glucacon-like peptide-1 receptor agonist and insulin (GLIPULIN group) or continuation of rapid-acting insulin analogs (BBI group). Indices of GV by continuous glucose monitoring (CGM), hypoglycemia, weight, risk markers, and cardiac arrhythmias were assessed. The primary end point was change in glucose coefficients of variation (CV) by CGM from baseline to 26 weeks.

RESULTS

At randomization, the median A1C was 7.3% (57 mmol/mol) for GLIPULIN and 7.4% (56.3 mmol/mol) for BBI, and glucose CVs were 30.3 for BBI and 31.9 for GLIPULIN. At 26 weeks, A1C levels were similar (7.1% [54 mmol/mol] vs. 7.2% [55 mmol/mol]), whereas mean CV improved with GLIPULIN (−2.4 vs. 0.4, P = 0.047). Other GV indices followed similar nonsignificant patterns of improvement with GLIPULIN. There were no differences in hypoglycemic events during CGM or arrhythmias during electrocardiographic monitoring. On-trial changes in body weight (−4.8 kg vs. +0.7 kg, P < 0.001), alanine aminotransferase (P = 0.0002), and serum amyloid A (P = 0.023) favored GLIPULIN.

CONCLUSIONS

GLIPULIN reduced GV, weight, and some cardiometabolic risk markers while maintaining equivalent A1C levels versus BBI and might improve clinical outcomes in a larger trial.

Corresponding author: Jeffrey L. Probstfield, jeffprob@uw.edu.

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*The members of the Writing Committee of the FLAT-SUGAR Trial are listed in the APPENDIX.

STEP 2 – Hemoglobin A1C

If HbA1C is above 5.6%:

1. Exercise – skeletal muscle contraction + steady state cardio (Zone 2)
2. Diet – macronutrient ratio, quantity of food

   Paleo-Mediterranean
3. Supplementation - Same supplements as Glycomark protocol +:

   Effecsulin

   Glucostatic Balance

   Super G Antioxidant

   NAD+

STEP 3 – C-Peptide

If C-peptide is above 2.5:

1. Mitochondrial support
   Glutathione (BioGmax GSH)
   NAC (Pure NAC)
   NAD+ (Biogmax NAD+)
   Carnitine

If C-peptide is below 1.1 + elevated A1C:

1. GABA (BioGmax GABA) NOTE

Intra-islet insulin suppresses glucagon release via GABA-$GABA_A$ receptor system

Elaine Xu,[1,2,7] Mohan Kumar,[1,2,7] Yi Zhang,[1,2] William Ju,[1,2] Toshiyuki Obata,[3] Nina Zhang,[2] Shiying Liu,[2] Anna Wendt,[4] Shaoping Deng,[5] Yousuke Ebina,[3] Michael B. Wheeler,[1] Matthias Braun,[4,6] and Qinghua Wang[1,2,*]

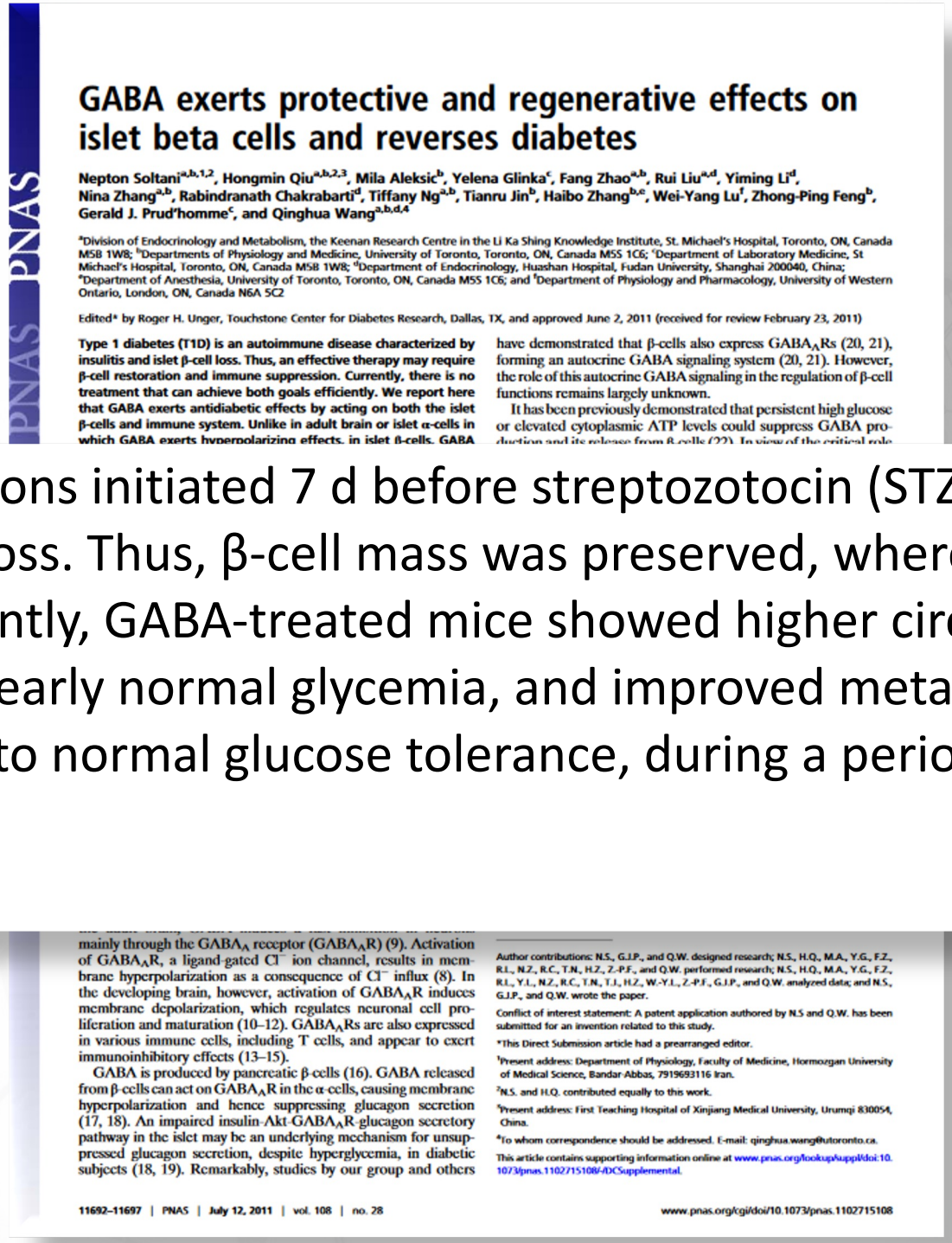
[1]Departments of Medicine and Physiology, University of Toronto, Ontario, Canada

The intra-islet action of insulin is essential to exert the effect of glucose on the alpha cells since, in the absence of insulin, glucose is not able to suppress glucagon release in vivo. However, the precise mechanism by which insulin suppresses glucagon secretion from alpha cells is unknown.

In this study, we show that insulin induces activation of GABAA receptors in the alpha cells by receptor translocation via an Akt kinase-dependent pathway. This leads to membrane hyperpolarization in the alpha cells and, ultimately, suppression of glucagon secretion. We propose that defects in this pathway(s) contribute to diabetic hyperglycemia.

quate understanding of the mechanisms underlying suppression of glucagon by insulin in response to hyperglycemia.

Secretion of glucagon from α cells is regulated by various factors, including glucose, zinc, and the chemical transmitter γ-aminobutyric acid (GABA) (Pipeleers et al., 1985; Ishihara (Rorsman et al., 1989). The failure to detect an increase in GABA release does not exclude the possibility that there is an increase in the responsiveness of $GABA_A$Rs on α cells upon hyperglycemia; however a clear-cut mechanism has not been delineated.



GABA exerts protective and regenerative effects on islet beta cells and reverses diabetes

Nepton Soltani[a,b,1,2], Hongmin Qiu[a,b,2,3], Mila Aleksic[b], Yelena Glinka[c], Fang Zhao[a,b], Rui Liu[a,d], Yiming Li[d], Nina Zhang[a,b], Rabindranath Chakrabarti[d], Tiffany Ng[a,b], Tianru Jin[b], Haibo Zhang[b,e], Wei-Yang Lu[f], Zhong-Ping Feng[b], Gerald J. Prud'homme[c], and Qinghua Wang[a,b,d,4]

[a]Division of Endocrinology and Metabolism, the Keenan Research Centre in the Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada M5B 1W8; [b]Departments of Physiology and Medicine, University of Toronto, Toronto, ON, Canada M5S 1C6; [c]Department of Laboratory Medicine, St Michael's Hospital, Toronto, ON, Canada M5B 1W8; [d]Department of Endocrinology, Huashan Hospital, Fudan University, Shanghai 200040, China; [e]Department of Anesthesia, University of Toronto, Toronto, ON, Canada M5S 1C6; and [f]Department of Physiology and Pharmacology, University of Western Ontario, London, ON, Canada N6A 5C2

Edited* by Roger H. Unger, Touchstone Center for Diabetes Research, Dallas, TX, and approved June 2, 2011 (received for review February 23, 2011)

Type 1 diabetes (T1D) is an autoimmune disease characterized by insulitis and islet β-cell loss. Thus, an effective therapy may require β-cell restoration and immune suppression. Currently, there is no treatment that can achieve both goals efficiently. We report here that GABA exerts antidiabetic effects by acting on both the islet β-cells and immune system. Unlike in adult brain or islet α-cells in which GABA exerts hyperpolarizing effects, in islet β-cells, GABA

have demonstrated that β-cells also express $GABA_AR$s (20, 21), forming an autocrine GABA signaling system (20, 21). However, the role of this autocrine GABA signaling in the regulation of β-cell functions remains largely unknown.

It has been previously demonstrated that persistent high glucose or elevated cytoplasmic ATP levels could suppress GABA pro-

Daily GABA injections initiated 7 d before streptozotocin (STZ) treatment prevented β-cell loss. Thus, β-cell mass was preserved, whereas α-cell mass was reduced. Consistently, GABA-treated mice showed higher circulating insulin, lower glucagon, nearly normal glycemia, and improved metabolic conditions, and maintained close to normal glucose tolerance, during a period of 53 d after STZ injections.

mainly through the $GABA_A$ receptor ($GABA_AR$) (9). Activation of $GABA_AR$, a ligand-gated Cl^- ion channel, results in membrane hyperpolarization as a consequence of Cl^- influx (8). In the developing brain, however, activation of $GABA_AR$ induces membrane depolarization, which regulates neuronal cell proliferation and maturation (10–12). $GABA_AR$s are also expressed in various immune cells, including T cells, and appear to exert immunoinhibitory effects (13–15).

GABA is produced by pancreatic β-cells (16). GABA released from β-cells can act on $GABA_AR$ in the α-cells, causing membrane hyperpolarization and hence suppressing glucagon secretion (17, 18). An impaired insulin-Akt-$GABA_AR$-glucagon secretory pathway in the islet may be an underlying mechanism for unsuppressed glucagon secretion, despite hyperglycemia, in diabetic subjects (18, 19). Remarkably, studies by our group and others

Author contributions: N.S., G.J.P., and Q.W. designed research; N.S., H.Q., M.A., Y.G., F.Z., R.L., N.Z., R.C., T.N., H.Z., Z.-P.F., and Q.W. performed research; N.S., H.Q., M.A., Y.G., F.Z., R.L., Y.L., N.Z., R.C., T.N., T.J., H.Z., W.-Y.L., Z.-P.F., G.J.P., and Q.W. analyzed data; and N.S., G.J.P., and Q.W. wrote the paper.

Conflict of interest statement: A patent application authored by N.S and Q.W. has been submitted for an invention related to this study.

*This Direct Submission article had a prearranged editor.

[1]Present address: Department of Physiology, Faculty of Medicine, Hormozgan University of Medical Science, Bandar-Abbas, 7919693116 Iran.

[2]N.S. and H.Q. contributed equally to this work.

[3]Present address: First Teaching Hospital of Xinjiang Medical University, Urumqi 830054, China.

[4]To whom correspondence should be addressed. E-mail: qinghua.wang@utoronto.ca.

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Indri Purwana,[1,2] Juan Zheng,[1,2] Xiaoming Li,[1,2] Marielle Deurloo,[2] Dong Ok Son,[1,2] Zhaoyun Zhang,[3] Christie Liang,[1,2] Eddie Shen,[1,2] Akshaya Tadkase,[1] Zhong-Ping Feng,[2] Yiming Li,[3] Craig Hasilo,[4] Steven Paraskevas,[4] Rita Bortell,[5] Dale L. Greiner,[5] Mark Atkinson,[6] Gerald J. Prud'homme,[7] and Qinghua Wang[1,2,3]

GABA Promotes Human β-Cell Proliferation and Modulates Glucose Homeostasis

Diabetes 2014;63:4197–4205 | DOI: 10.2337/db14-0153

GABA treatment increased grafted β-cell proliferation, while decreasing apoptosis, leading to enhanced β-cell mass. This was associated with increased circulating human insulin and reduced glucagon levels. Importantly, GABA administration lowered blood glucose levels and improved glucose excursion rates.

nals responsible for β-cell proliferation and survival. Our findings suggest that GABA regulates human β-cell mass and may be beneficial for the treatment of diabetes or improvement of islet transplantation.

Expanding β-cell mass by promoting β-cell regeneration is a major goal of diabetes therapy. β-Cell proliferation has

In the β-cells, GABA induces membrane depolarization and increases insulin secretion (9), while in the α-cells it induces membrane hyperpolarization and suppresses glucagon secretion (10). In mice, we previously observed that it enhanced β-cell proliferation and reduced β-cell death, which reversed T1D (9). Indeed, in various disease models, GABA exerts trophic effects on β-cells and

[1]Division of Endocrinology and Metabolism, Keenan Research Centre for Biomedical Science of St. Michael's Hospital, Toronto, Ontario, Canada
[2]Departments of Physiology and Medicine, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
[3]Department of Endocrinology, Huashan Hospital, Fudan University, Shanghai, China
[4]Department of Surgery, McGill University, and Human Islet Transplantation Laboratory, McGill University Health Centre, Montreal, Quebec, Canada
[5]Department of Molecular Medicine, University of Massachusetts Medical School, Worcester, MA
[6]Department of Pathology, Immunology and Laboratory Medicine, University of Florida Health Science Center, Gainesville, FL
[7]Department of Laboratory Medicine and Pathobiology, University of Toronto, Keenan Research Centre for Biomedical Science of St. Michael's Hospital

Corresponding author: Qinghua Wang, qinghua.wang@utoronto.ca.

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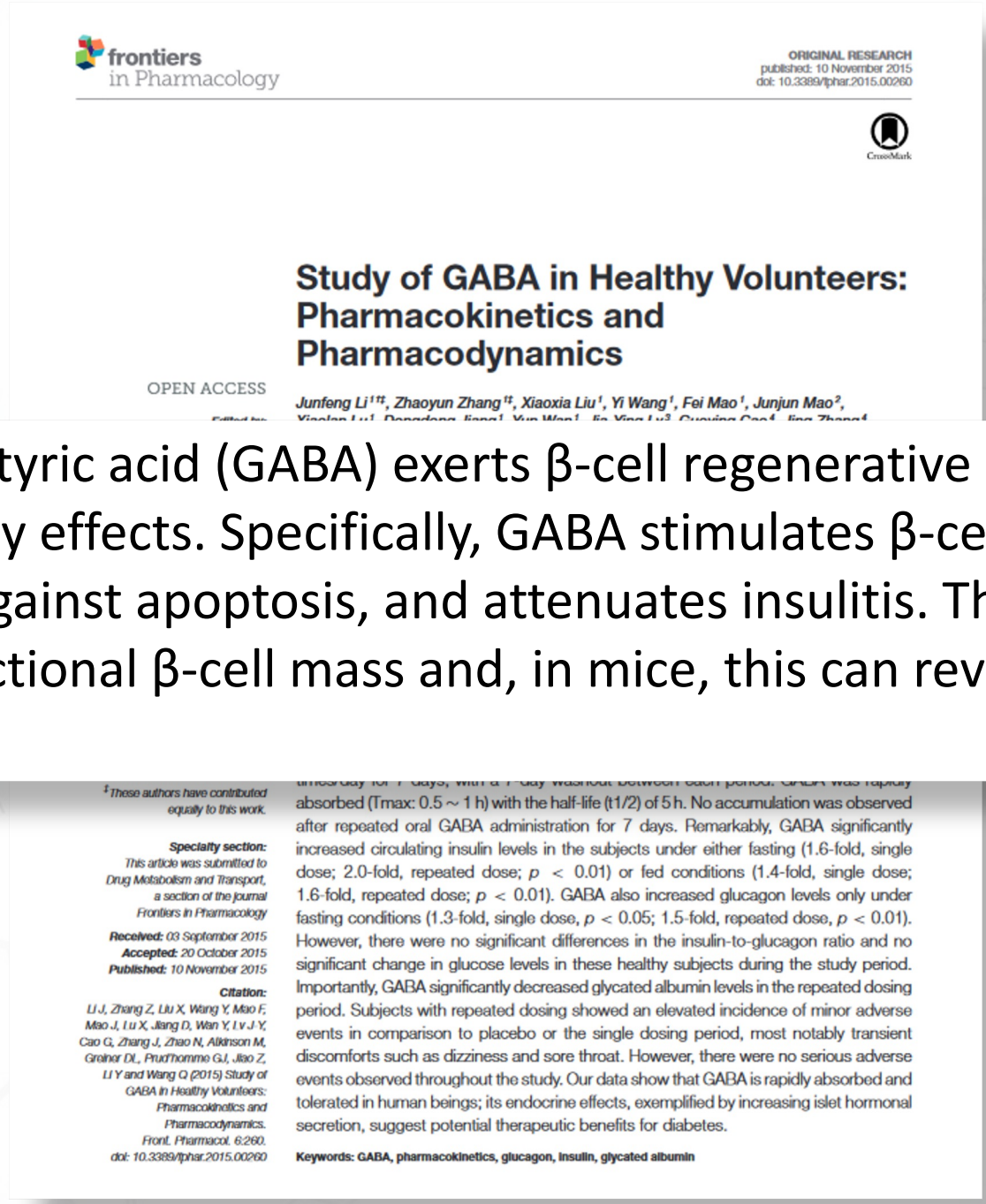
I.P., J.Z., and X.L. contributed equally to this study.

J.Z. is currently affiliated with the Department of Endocrinology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.



frontiers in Pharmacology

ORIGINAL RESEARCH
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Study of GABA in Healthy Volunteers: Pharmacokinetics and Pharmacodynamics

OPEN ACCESS

Junfeng Li[1†‡], Zhaoyun Zhang[1†‡], Xiaoxia Liu[1], Yi Wang[1], Fei Mao[1], Junjun Mao[2],

Gamma aminobutyric acid (GABA) exerts β-cell regenerative and immunoregulatory effects. Specifically, GABA stimulates β-cell replication, protects β-cells against apoptosis, and attenuates insulitis. These effects result in an enhanced functional β-cell mass and, in mice, this can reverse disease

absorbed (Tmax: 0.5 ~ 1 h) with the half-life (t1/2) of 5 h. No accumulation was observed after repeated oral GABA administration for 7 days. Remarkably, GABA significantly increased circulating insulin levels in the subjects under either fasting (1.6-fold, single dose; 2.0-fold, repeated dose; $p < 0.01$) or fed conditions (1.4-fold, single dose; 1.6-fold, repeated dose; $p < 0.01$). GABA also increased glucagon levels only under fasting conditions (1.3-fold, single dose, $p < 0.05$; 1.5-fold, repeated dose, $p < 0.01$). However, there were no significant differences in the insulin-to-glucagon ratio and no significant change in glucose levels in these healthy subjects during the study period. Importantly, GABA significantly decreased glycated albumin levels in the repeated dosing period. Subjects with repeated dosing showed an elevated incidence of minor adverse events in comparison to placebo or the single dosing period, most notably transient discomforts such as dizziness and sore throat. However, there were no serious adverse events observed throughout the study. Our data show that GABA is rapidly absorbed and tolerated in human beings; its endocrine effects, exemplified by increasing islet hormonal secretion, suggest potential therapeutic benefits for diabetes.

Keywords: GABA, pharmacokinetics, glucagon, insulin, glycated albumin

‡These authors have contributed equally to this work.

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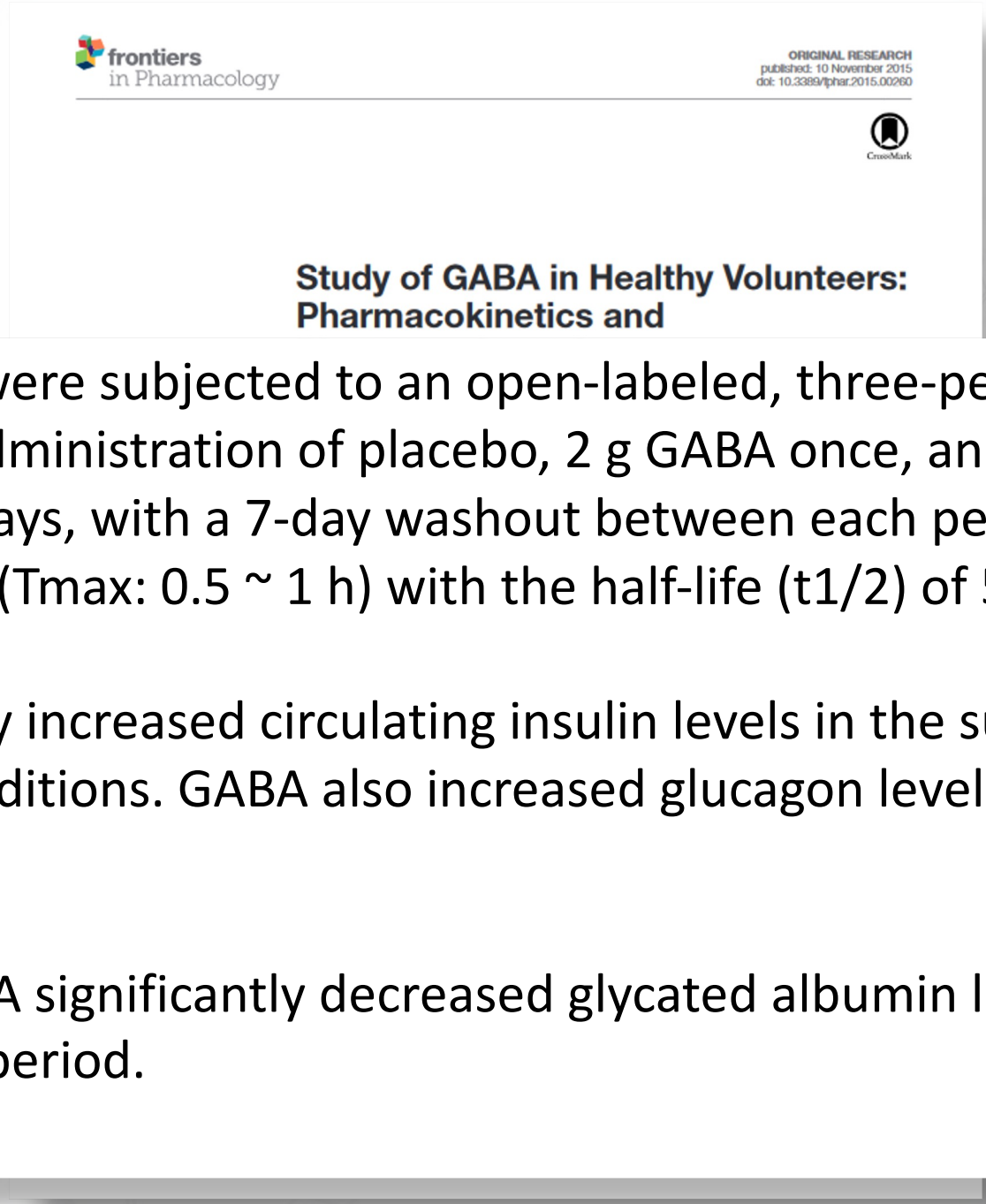

Twelve subjects were subjected to an open-labeled, three-period trial involving sequential oral administration of placebo, 2 g GABA once, and 2 g GABA three times/day for 7 days, with a 7-day washout between each period. GABA was rapidly absorbed (Tmax: 0.5 ~ 1 h) with the half-life (t1/2) of 5 h.

GABA significantly increased circulating insulin levels in the subjects under either fasting or fed conditions. GABA also increased glucagon levels only under fasting conditions.

Importantly, GABA significantly decreased glycated albumin levels in the repeated dosing period.

PNAS

Insulin resistance is a cellular antioxidant defense mechanism

Kyle L. Hoehn[a,1,2,3], Adam B. Salmon[b,1], Cordula Hohnen-Behrens[a], Nigel Turner[a], Andrew J. Hoy[a], Ghassan J. Maghzal[c], Roland Stocker[c], Holly Van Remmen[b], Edward W. Kraegen[a], Greg J. Cooney[a], Arlan R. Richardson[b], and David E. James[a,2]

[a]Diabetes and Obesity Program, Garvan Institute of Medical Research, 384 Victoria Street, Darlinghurst, NSW 2010, Australia; [b]Department of Cellular and Structural Biology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229-3900; and [c]Centre for Vascular Research, School of Medical Sciences (Pathology) and Bosch Institute, University of Sydney, 94 Parramatta Road, Camperdown, NSW 2036, Australia

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In the present study, we took a comprehensive approach to identify factor(s) that might unify multiple models of IR. Initially, we compared four diverse models of IR including chronic treatment with insulin, corticosteroids, proinflammatory cytokines, or lipid in both muscle and adipose cell lines.

We have now identified a direct correlation between mitochondrial oxidative stress in all models.

intermediate in the insulin action pathway or does IR represent a collection of distinct cellular disorders? For example, endoplasmic reticulum (ER) stress, proinflammatory responses, oxidative stress, intracellular ceramide accumulation, or the activation of JNK, IKK, or PKC are all currently implicated in the development of IR in overnourished or obese rodents (2, 3). In such models, correcting any one of these intracellular stresses is sufficient to improve IR leading to the possibility that these factors are somehow interconnected. One view is that insulin receptor substrate 1 (IRS1) represents a common convergence point for many defects contributing to IR (4). However, this view has been challenged in that the ability of IRS1-independent receptor tyrosine kinases to activate

Author contributions: K.L.H., A.B.S., and D.E.J. designed research; K.L.H., A.B.S., C.H.-B., N.T., A.J.H., and G.J.M. performed research; K.L.H., A.B.S., R.S., H.V.R., E.W.K., G.J.C., and A.R.R. contributed new reagents/analytic tools; K.L.H., A.B.S., and C.H.-B. analyzed data; and K.L.H. and D.E.J. wrote the paper.

The authors declare no conflict of interest.

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[1]K.L.H. and A.B.S. contributed equal data

[2]To whom correspondence may be addressed. E-mail: d.james@garvan.org.au or klh8st@virginia.edu.

[3]Present address: Department of Pharmacology, University of Virginia, Charlottesville, VA 22908.

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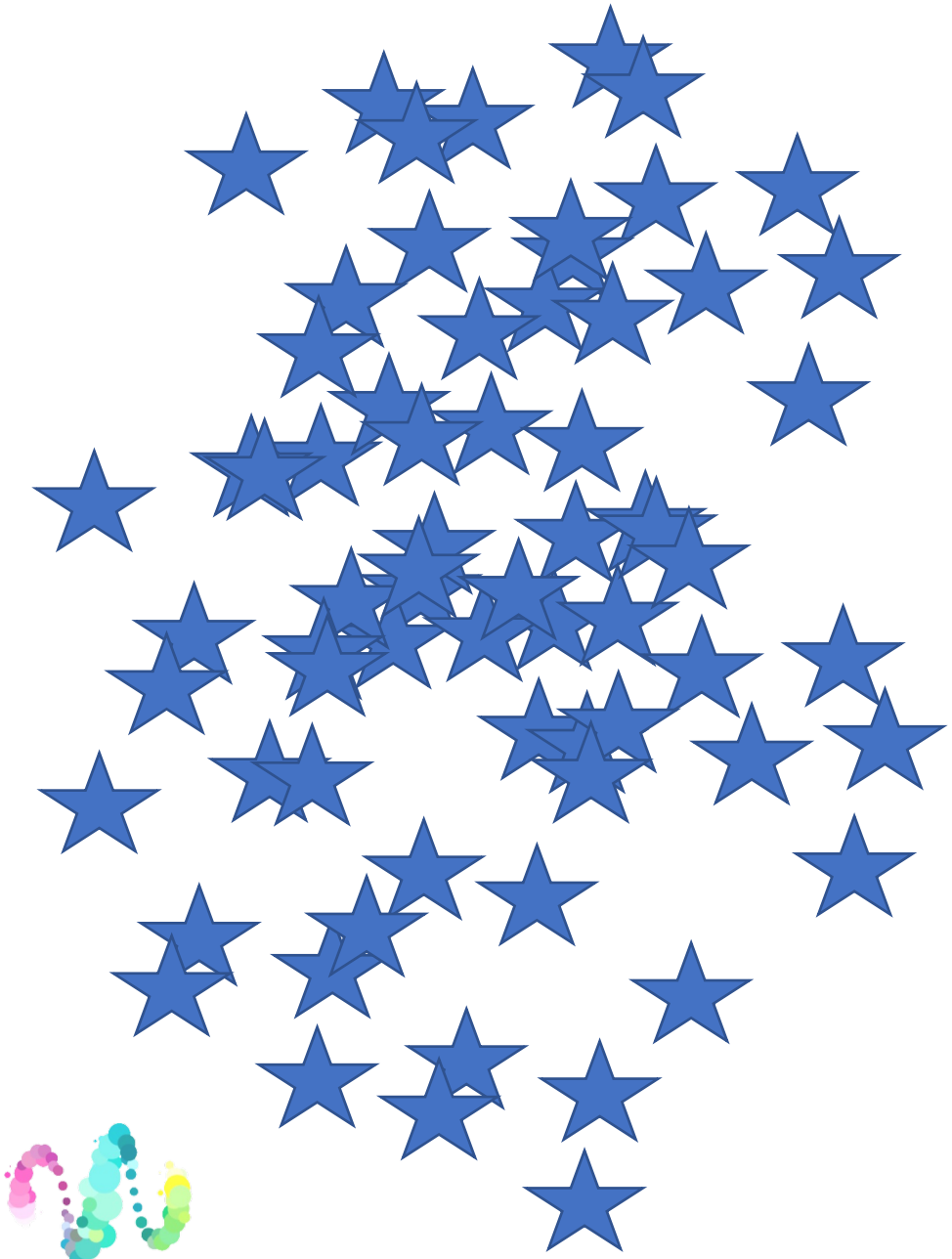
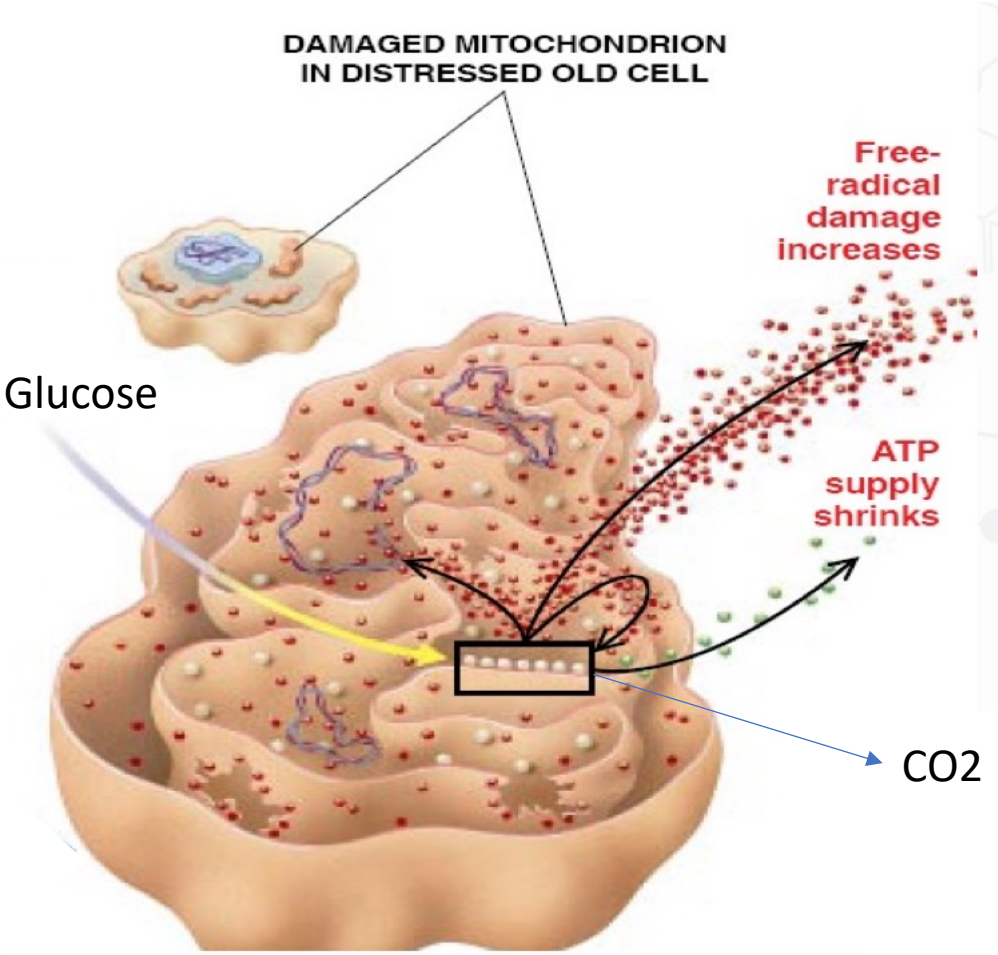


O2, Glucose



CO2

Insulin resistance is a cellular antioxidant defense mechanism

Kyle L. Hoehn[a,1,2,3], Adam B. Salmon[b,1], Cordula Hohnen-Behrens[a], Nigel Turner[a], Andrew J. Hoy[a], Ghassan J. Maghzal[c], Roland Stocker[c], Holly Van Remmen[b], Edward W. Kraegen[a], Greg J. Cooney[a], Arlan R. Richardson[b], and David E. James[a,2]

[a]Diabetes and Obesity Program, Garvan Institute of Medical Research, 384 Victoria Street, Darlinghurst, NSW 2010, Australia; [b]Department of Cellular and Structural Biology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229-3900; and [c]Centre for Vascular Research, School of Medical Sciences (Pathology) and Bosch Institute, University of Sydney, 94 Parramatta Road, Camperdown, NSW 2036, Australia

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Mitochondrial $O_2^{\bullet-}$ has previously been linked to hyperglycemia-induced metabolic dysfunction in endothelial cell systems and in inflammation in adipocytes.

A major advance of the present study is the observation that mitochondrial $O_2^{\bullet-}$ is upstream of IR in skeletal muscle and adipose tissue.

The origin of IR has been difficult to elucidate in part due to the diverse set of risk factors linked to this condition including overnutrition, physical inactivity, pregnancy, Hepatitis C, polycystic ovarian syndrome, HIV protease inhibitor therapy, and antiinflammatory corticosteroids. Do such factors converge at a common intermediate in the insulin action pathway or does IR represent a collection of distinct cellular disorders? For example, endoplasmic reticulum (ER) stress, proinflammatory responses, oxidative stress, intracellular ceramide accumulation, or the activation of JNK, IKK, or PKC are all currently implicated in the development of IR in overnourished or obese rodents (2, 3). In such models, correcting any one of these intracellular stresses is sufficient to improve IR leading to the possibility that these factors are somehow interconnected. One view is that insulin receptor substrate 1 (IRS1) represents a common convergence point for many defects contributing to IR (4). However, this view has been challenged in that the ability of IRS1-independent receptor tyrosine kinases to activate

described a reproducible system for studying IR in myotubes and adipocytes in culture relying on the translocation of the facilitative glucose transporter GLUT4 to the plasma membrane (5). This

Author contributions: K.L.H., A.B.S., and D.E.J. designed research; K.L.H., A.B.S., C.H.-B., N.T., A.J.H., and G.J.M. performed research; K.L.H., A.B.S., R.S., H.V.R., E.W.K., G.J.C., and A.R.R. contributed new reagents/analytic tools; K.L.H., A.B.S., and C.H.-B. analyzed data; and K.L.H. and D.E.J. wrote the paper.

The authors declare no conflict of interest.

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[1]K.L.H. and A.B.S. contributed equal data

[2]To whom correspondence may be addressed. E-mail: d.james@garvan.org.au or klh8st@virginia.edu.

[3]Present address: Department of Pharmacology, University of Virginia, Charlottesville, VA 22908.

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CELL BIOLOGY

Insulin resistance is a cellular antioxidant defense mechanism

Kyle L. Hoehn[a,1,2,3], Adam B. Salmon[b,1], Cordula Hohnen-Behrens[a], Nigel Turner[a], Andrew J. Hoy[a], Ghassan J. Maghzal[c], Roland Stocker[c], Holly Van Remmen[b], Edward W. Kraegen[a], Greg J. Cooney[a], Arlan R. Richardson[b], and David E. James[a,2]

[a]Diabetes and Obesity Program, Garvan Institute of Medical Research, 384 Victoria Street, Darlinghurst, NSW 2010, Australia; [b]Department of Cellular and Structural Biology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229-3900; and [c]Centre for Vascular Research, School of Medical Sciences (Pathology) and Bosch Institute, University of Sydney, 94 Parramatta Road, Camperdown, NSW 2036, Australia

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This hypothesis is exciting for a number of reasons. For example, it suggests that IR may be a protective mechanism, in which case we should perhaps reconsider using therapeutic strategies to overcome unless they also eliminate the primary defect. Moreover, it suggests that cells have evolved sophisticated mechanisms to not only guard against nutrient lack, such as the AMPK pathway, but also nutrient excess.

The origin of IR has been difficult to elucidate in part due to the diverse set of risk factors linked to this condition including overnutrition, physical inactivity, pregnancy, Hepatitis C, polycystic ovarian syndrome, HIV protease inhibitor therapy, and antiinflammatory corticosteroids. Do such factors converge at a common intermediate in the insulin action pathway or does IR represent a collection of distinct cellular disorders? For example, endoplasmic reticulum (ER) stress, proinflammatory responses, oxidative stress, intracellular ceramide accumulation, or the activation of JNK, IKK, or PKC are all currently implicated in the development of IR in overnourished or obese rodents (2, 3). In such models, correcting any one of these intracellular stresses is sufficient to improve IR leading to the possibility that these factors are somehow interconnected. One view is that insulin receptor substrate 1 (IRS1) represents a common convergence point for many defects contributing to IR (4). However, this view has been challenged in that the ability of IRS1-independent receptor tyrosine kinases to activate

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[2]To whom correspondence may be addressed. E-mail: d.james@garvan.org.au or klh8st@virginia.edu.

[3]Present address: Department of Pharmacology, University of Virginia, Charlottesville, VA 22908.

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Diabetes Volume 64, March 2015 673

Christopher J. Nolan,[1] Neil B. Ruderman,[2] Steven E. Kahn,[3] Oluf Pedersen,[4] and Marc Prentki[5]

Insulin Resistance as a Physiological Defense Against Metabolic Stress: Implications for the Management of Subsets of Type 2 Diabetes

The β-cell is particularly vulnerable to glucolipotoxicity. Other tissues, such as heart and skeletal muscle, that express the insulin-regulated glucose transporter GLUT4 have the capacity to protect themselves from glucolipotoxicity by developing IR, which restrains glucose entry into cells and therefore the glucose arm of this potentially damaging process.

T2D. Potential molecular mechanisms underlying these concepts; their clinical implications for stratification of T2D management, particularly in overweight and obese patients with difficult glycemic control; and future research requirements are discussed.

high-dose insulin therapy) will cause them harm. We believe that the concept of "insulin-induced metabolic stress" provides a plausible explanation for many of the unexpected outcomes of major T2D clinical trials. The important implications of this concept for ongoing

[1]Department of Endocrinology at Canberra Hospital and the Australian National University Medical School, Canberra, Australia
[2]Diabetes Research Unit, Boston University Medical Center, Boston, MA
[3]Division of Metabolism, Endocrinology and Nutrition, VA Puget Sound Health Care System, and University of Washington, Seattle, WA
[4]Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[5]CRCHUM and Montreal Diabetes Research Center and Departments of Nutrition and Biochemistry and Molecular Medicine, University of Montreal, Quebec, Canada

Corresponding author: Christopher J. Nolan, christopher.nolan@anu.edu.au.

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Christopher J. Nolan,[1] Neil B. Ruderman,[2] Steven E. Kahn,[3] Oluf Pedersen,[4] and Marc Prentki[5]

Insulin Resistance as a Physiological Defense Against

The combination of high levels of glucose and FFA entry into cells will overload the electron transfer chain with reducing equivalents resulting in mitochondrial dysfunction and increased reactive oxygen species (ROS) production. The increased glucose entry will also alter the malonyl-CoA/AMPK metabolic network to favor the partitioning of the FFA toward synthesis of complex lipids, including cholesterol and ceramide, and glucolipotoxicity, contributing to both mitochondrial dysfunction and endoplasmic reticulum stress. The increased FFA levels will also impede glucose oxidation, particularly at the level of pyruvate dehydrogenase, such that glucose flux into pathways above this step, including glycogen synthesis, the polyol and hexosamine pathways, and the production of advanced glycation end product (AGE) precursors, are likely to be increased.

[5]CRCHUM and Montreal Diabetes Research Center and Departments of Nutrition and Biochemistry and Molecular Medicine, University of Montreal, Quebec, Canada

Review

Patient A

- Low Glycomark
- Elevated C-peptide
- Normal A1C

Patient B

- Normal Glycomark
- Elevated C-peptide
- Elevated A1C (5.8%)

Patient C

- Normal Glycomark
- Low C-peptide
- Elevated A1C (5.8%)

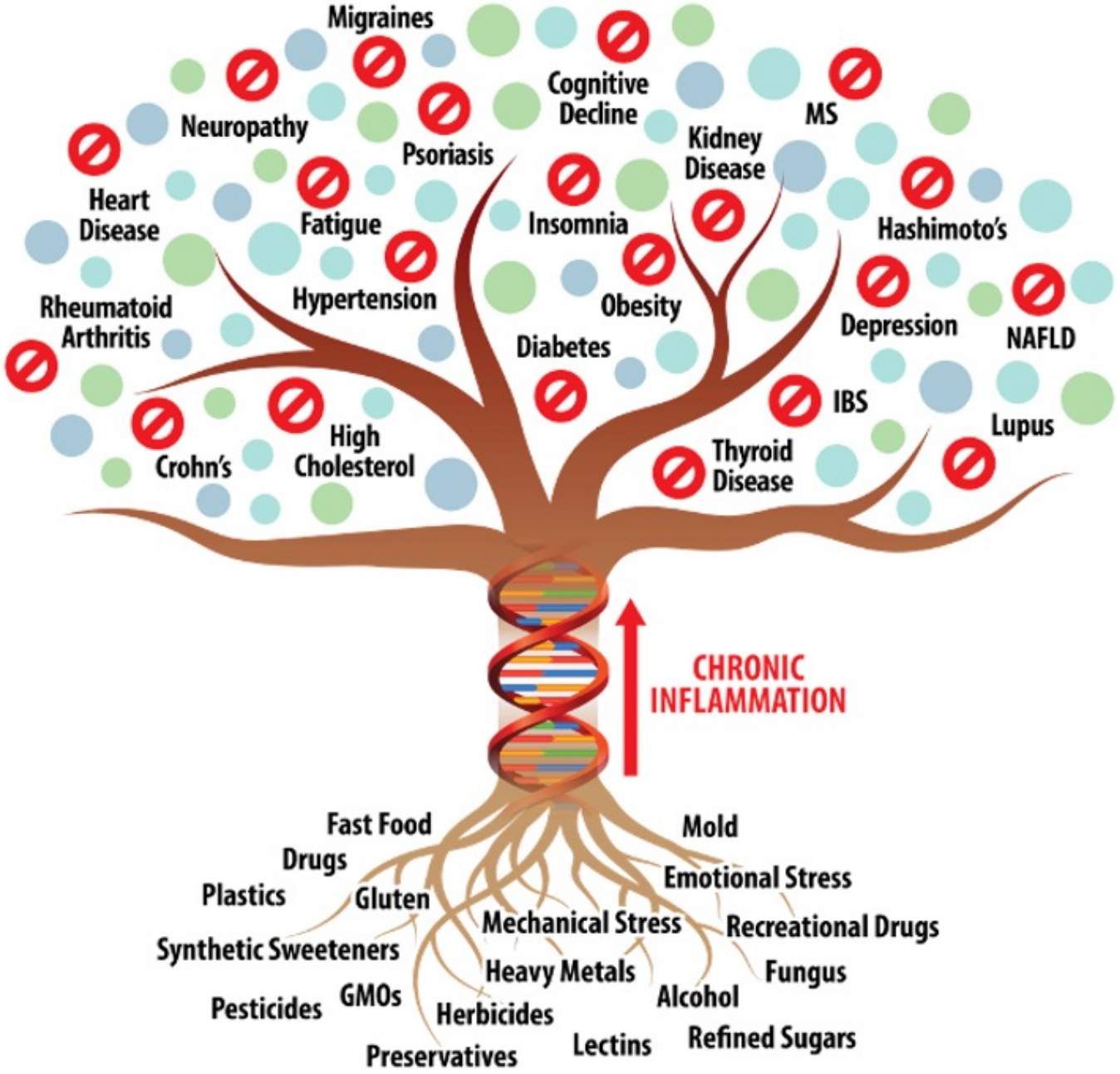
Patient D

- Low Glycomark
- Elevated C-peptide
- Elevated A1C (5.3%)

Review

	Hypoglycemia	Early IR	Insulin Resistance	Late IR	Type II Diabetes
Glucose	↓	Normal	↑	↑↑	↑↑↑
C-Peptide	↑/N	↑	↑↑	Normal	↓
HA1C	Normal/Low	Normal	↑	↑↑	↑↑↑
Cholesterol/ Triglyceride	Normal	Normal	Less than 2:1	Less than 2:1	Less than 2:1
LDH	↓	?	?	?	?

What have we learned so far?


Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Hashimoto's
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten
Mechanical Stress
Recreational Drugs
Synthetic Sweeteners
Heavy Metals
Fungus
Pesticides
GMOs
Herbicides
Alcohol
Preservatives
Lectins
Refined Sugars

The Wedge Protocol