



Alberta Diabetes
INSTITUTE

2021 RESEARCH DAY

November 1 and 2

Monday (**Day 1**) 0900-1230 | Tuesday (**Day 2**) 0900-1230

Held Virtually

University of Alberta

KEYNOTE SPEAKER

Jenny Bruin, PhD

Associate Professor, Department of Biology & Institute of Biochemistry,
Carleton University, Ottawa



2021 ADI RESEARCH DAY

Monday, November 1 and Tuesday, November 2

PROGRAM

Note From the Director	Page i
Dr. Jenny Bruin - Bio	Page ii
Day 1 (November 1) schedule	Page iii-iv
Day 2 (November 2) schedule	Pages v-vi
Prizes	Page vii

ABSTRACTS (in order of presentation)

Session 1 (Junior Trainees) Abstracts	Pages 1-10
Session 2 (Junior Trainees) Abstracts	Pages 11-19
Session 3 (Senior Trainees) Abstracts	Pages 20-27
Session 4 (Senior Trainees) Abstracts	Pages 28-35



*Leading the World in the Prevention, Treatment
and Cure of Diabetes*

2021 ADI RESEARCH DAY

Monday, November 1 and Tuesday, November 2

NOTE FROM THE DIRECTOR

Welcome to the 2021 Alberta Diabetes Institute Research Day. This annual event, hosted by ADI since 2005, provides ADI Trainees - from first year undergraduate summer students to seasoned postdoctoral fellows - the opportunity to showcase their research efforts. This is the second year we are hosting our event virtually. With the help of our dedicated ADI Trainee Working Group and ADI Members, Trainees, and administration we have organized an exciting couple of mornings of talks and discussions that will provide an enriching experience for everyone attending.

We are excited to host keynote speaker Dr. Jenny Bruin, Associate Professor, Department of Biology & Institute of Biochemistry, Carleton University, Ottawa. She will be speaking on *The link between environmental contaminants and diabetes pathogenesis*. She is an old friend of the ADI's and we are delighted to welcome her back to Western Canada, albeit via Zoom!

Our Research Day is intended to provide a forum to showcase the research efforts of our **ADI Trainees**. With respect to this research day all abstracts submitted were selected for oral presentation. There are four sessions held over two days. On Day 1 our junior trainees will be presenting (summer students / MSc students) with our senior trainees presenting on Day 2 (PhD students / postdoctoral fellows). Junior trainees have 5 minutes in total (including Q&A) and senior trainees have 10 minutes in total (including Q&A) to present their research.

Earlier this year we marked the 100th anniversary of the discovery of insulin, and the huge contributions made by Canadian researchers. I am extremely excited by this year's program highlighting the work of the next generation of Canadian researchers. The mission is still the same - to Defeat Diabetes (watch for a special event hosted by the Faculty of Medicine & Dentistry, University of Alberta, to be held November 17).

The contributions of the Alberta Diabetes Foundation, DRIFCan, and many other partners is deeply appreciated for their vital and sustained contributions to the work of the ADI.

I am indebted to our ADI Trainee Working Group (supported by Colleen Ruptash) for their help in organizing and running this year's ADI Research Day. I would also like to thank our volunteer judges, session chairs, and zoom support. Huge thanks, finally, to Eli Lilly for their ongoing support of our Research Day.

We hope today will provide an opportunity to interact with and learn from your peers by listening and asking questions, further inspire your curiosity and encourage us all to pursue excellence in our scientific endeavors.

Best Regards,



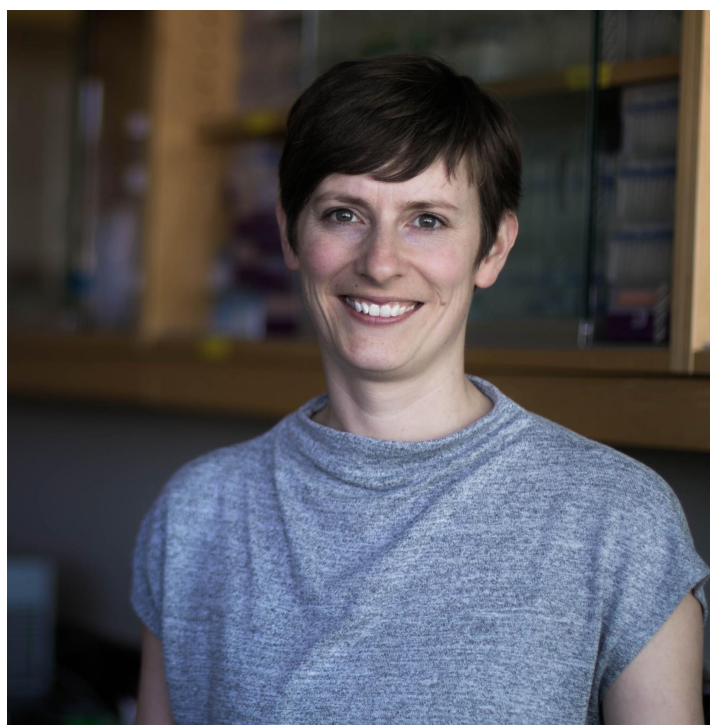
Dr. Peter Senior
Director, Alberta Diabetes Institute
Dr. Charles A. Allard Chair in Diabetes Research
Professor of Medicine, Division of Endocrinology and Metabolism

2021 ADI RESEARCH DAY

Monday, November 1

KEYNOTE SPEAKER

Jenny Bruin, PhD



Dr. Jenny Bruin is an Associate Professor in the Department of Biology and Institute of Biochemistry at Carleton University. She completed her BSc in Biomedical Toxicology at the University of Guelph in 2005 and her PhD in Medical Sciences at McMaster University with Dr. Alison Holloway in 2009. Her doctoral thesis investigated the effects of fetal and neonatal nicotine exposure on pancreas development and long-term metabolic outcomes in a rat model. From 2010 to 2016, Dr. Bruin was a postdoctoral fellow in Dr Tim Kieffer's laboratory at UBC, where she studied the development of human embryonic stem cells into pancreatic insulin-producing beta cells as a potential cell therapy for patients with diabetes. She started her independent position in 2016 at Carleton, where her lab studies the pathogenesis of diabetes with a focus on islet biology, pancreas development, and toxicology. The Bruin Lab has received funding from CIHR, NSERC, JDRF, and the

Ontario Institute of Regenerative Medicine. Dr Bruin has also been recognized at Carleton University with a New Faculty Excellence in Teaching Award and a Faculty Graduate Mentoring Award.

On November 1, from 0910-1010, Dr. Bruin will be talking about *The link between environmental contaminants and diabetes pathogenesis*. We would also like to thank Dr. Bruin for serving on the trainee presentation judge panel.

A special note of thanks to Eli Lilly for their ongoing support of our ADI Research Day, this support provides us the opportunity to invite keynote speakers from across Canada.

Welcome Dr. Bruin!

2021 ADI RESEARCH DAY

Monday, November 1

DAY 1

WELCOME Day 1

0900-0905	Opening Remarks & Welcome to Day 1 2021 ADI Research Day	Dr. Peter Senior, ADI Director
0906-0909	Introduction to Keynote Speaker	Theodore Dos Santos, ADI Trainee Working Group Chair

KEYNOTE SPEAKER

0910-1010	Dr. Jenny Bruin Associate Professor Department of Biology & Institute of Biochemistry Carleton University, Ottawa	THE LINK BETWEEN ENVIRONMENTAL CONTAMINANTS AND DIABETES PATHOGENESIS
-----------	--	--

SESSION 1 Chair: Dr. Caroline Richard

1025-1030	Ly-Anh REID Davenport Lab	MSc Student	Page 1	OPTIMIZING BLOOD GLUCOSE CONTROL THROUGH TIMING OF EXERCISE IN PREGNANT INDIVIDUALS WITH GESTATIONAL DIABETES MELLITUS
1031-1036	Adnan BLACK Rayat Lab	Summer Student	Page 2	PROTEIN EXPRESSION OF PGP9.5, CD31, AND vWF ON DEVELOPING PORCINE ISLETS IN VITRO AND IN VIVO
1037-1042	Hellen DA SILVA Yue Lab	MSc Student	Page 3	GLUCOCORTICOID ACTIONS IN THE DORSAL VAGAL COMPLEX STIMULATE GLUCOSE PRODUCTION
1043-1048	Saloni AGGARWAL Pepper Lab	MSc Student	Page 4	THE ROLE OF NECROPTOSIS IN B-CELL LOSS FOLLOWING ISLET CELL TRANSPLANTATION
1049-1054	Lucy LEE Tsai Lab	Summer Student	Page 5	THE IMPACT OF INSULIN RESISTANCE ON CD8+ T CELL- MEDIATED ANTI-TUMOR IMMUNITY
1055-1100	Megan LEE Tsai Lab	MSc Student	Page 6	YAP/TAZ SIGNALING IN DENDRITIC CELL-MEDIATED PATHOGENESIS OF INSULIN RESISTANCE AND NON-ALCOHOLIC FATTY LIVER DISEASE
1101-1106	Salma MOFTAH Chan Lab	MSc Student	Page 7	COMPARISON OF CHEESE, YOGURT, AND MILK EFFECTS ON HEPATIC LIPID METABOLISM IN MICE FED HIGH-FAT DIET
1107-1112	Omar MOUHAMMED Shapiro Lab	Summer Student	Page 8	ACQUIRING MACHINE LEARNING APPROACH TO IDENTIFY AND SELECT HUMAN PLURIPOTENT STEM CELLS DURING REPROGRAMMING
1113-1118	Mantash GREWAL Yue Lab	MSc Student	Page 9	HINDBRAIN GLUCAGON SIGNALLING REGULATES HEPATIC LIPID SECRETION
1119-1124	Bergen VETSCH Jacobs Lab	Summer Student	Page 10	DIETARY TRIMETHYLAMINE N-OXIDE SUPPLEMENTATION REDUCES OBESITY, GLUCOSE INTOLERANCE AND FATTY LIVER IN HIGH FAT DIET MICE.

BREAK

2021 ADI RESEARCH DAY

Monday, November 1

DAY 1

SESSION 2 Chair: Dr. Jane Yardley

1136-1141	Tianna RUSNAK Richard Lab	MSc Student	Page 11	A DOSE OF 50% EGG-PHOSPHATIDYLCHOLINE IS SUFFICIENT TO IMPROVE INTESTINAL BARRIER AND T CELL FUNCTION IN THE CONTEXT OF A HIGH-FAT DIET IN MALE WISTAR RATS
1142-1147	Sandhya SAPKOTA Shapiro Lab	Summer Student	Page 12	REPLICATION FORK STALLING IN HUMAN AUTOLOGOUS IPSC-DERIVED B-CELLS ENHANCE MATURATION BUT CHANGE MITOCHONDRIAL RESPIRATION AND FUNCTION
1148-1153	Shiva SHARMA Ussher Lab	Summer Student	Page 13	THE IMPACT OF OBESITY ON THE PROTEIN EXPRESSION OF ENZYMES REGULATING KETONE BODY METABOLISM
1154-1159	Boyan VASILEV Yue Lab	Summer Student	Page 14	EFFECTS OF GLUCAGON INFUSION IN THE DORSAL VAGAL COMPLEX ON HEPATIC LEVELS OF ENZYMES INVOLVED IN LIPID METABOLISM
1200-1205	Kevin VERHOEFF Shapiro Lab	MSc Student	Page 15	COMPARATIVE EVALUATION OF EARLY AND LONG-TERM OUTCOMES FOR PATIENTS TREATED WITH EXTRAHEPATIC AND INTRAPORTAL PANCREATIC ISLET TRANSPLANT
1206-1211	Yashvi PATEL Tsai Lab	Summer Student	Page 16	IGA MEDIATED IMMUNITY IN TYPE 1 DIABETES MELLITUS (T1D)
1212-1217	Kun WANG Proctor Lab & Richard Lab	MSc Student	Page 17	CONSUMPTION OF DAIRY PRODUCTS IN THE CONTEXT OF A HIGH FAT DIET INCREASES MYRISTIC ACID AND MARGARIC ACID IN A SWINE MODEL OF LOW BIRTH WEIGHT AND EARLY INSULIN RESISTANCE
1218-1223	Olivia WEAVER Eurich Lab & Proctor Lab	MSc Student	Page 18	ELEVATED NON-FASTING REMNANT CHOLESTEROL ASSOCIATED WITH CARDIOVASCULAR DISEASE RISK IN THE ALBERTA TOMORROW PROJECT
1224-1229	Reid MCCLURE Yardley Lab	MSc Student	Page 19	META-ANALYSIS OF BLOOD GLUCOSE RESPONSE TO HIGH INTENSITY EXERCISE

ADJOURNED UNTIL November 2 (Day 2)

2021 ADI RESEARCH DAY

Tuesday, November 2

DAY 2

WELCOME Day 2

0900-0903	Welcome to Day 2 2021 ADI Research Day	Dr. Peter Senior ADI Director
-----------	---	----------------------------------

SESSION 3 Chair: Dr. Andrew Pepper

0905-0915	Zeinab MOMENI Yardley Lab	Postdoc	Page 20	THE EFFECT OF STARTING CAPILLARY GLUCOSE LEVELS ON SERUM ELECTROLYTES DURING AND AFTER EXERCISE IN TYPE 1 DIABETES
0916-0926	Hui HUANG Buteau Lab	Postdoc	Page 21	A NOVEL SMALL MOLECULE FOR THE TREATMENT OF TYPE 1 DIABETES
0927-0937	Theodore DOS SANTOS MacDonald Lab	PhD 1st year	Page 22	MODELLING OF ELECTRICAL FINGERPRINTS REVEALS TRANSCRIPTOMIC PROFILES LINKED TO ALPHA-CELL DYSFUNCTION IN TYPE 2 DIABETES
0938-0948	Lina LAU Bello Lab	PhD 3rd year	Page 23	THE INTERSECTION OF DIABETES AND ESTRADIOL IN MORTALITY AND OTHER ADVERSE HEALTH OUTCOMES AMONG WOMEN UNDERGOING HEMODIALYSIS – A PROSPECTIVE STUDY
BREAK				
0953-1003	Jamie BOISVENUE with co-presenter Heather HINZ Yeung Lab	PhD 3rd year	Page 24	RESHAPET1D: UTILIZING THE STRENGTHS OF QUANTITATIVE ETHNOGRAPHY AND PATIENT AND CLINICIAN LED RESEARCH TO UNDERSTAND TYPE 1 DIABETES LIVED EXPERIENCES IN ALBERTA
1004-1014	Braulio MARFIL-GARZA Shapiro Lab	PhD 4th year	Page 25	PANCREATIC ISLET TRANSPLANTATION: 20-YEAR OUTCOMES AT THE UNIVERSITY OF ALBERTA
1015-1025	Ila JASRA Shapiro Lab	Postdoc	Page 26	MODELLING HUMAN PLURIPOTENT STEM CELLS PHYSIOLOGICAL BENEFITS IN 3D SCALE-UP MICROENVIRONMENT VS. 2D PLANAR PLATFORM
1026-1036	Julia MONTENEGRO Prado Lab	PhD 1st year	Page 27	ACCURACY OF RESTING ENERGY EXPENDITURE PREDICTIVE EQUATIONS IN INDIVIDUALS WITH EXCESS BODY WEIGHT

BREAK

Note: Session 3 & 4 updated Oct 22/21

2021 ADI RESEARCH DAY

Tuesday, November 2

DAY 2

SESSION 4 Chair: Dr. Jessica Yue

1041-1051	Amanda SCHUKARUCHA GOMES MacDonald Lab	PhD 2nd year	Page 28	GLYCINE RECEPTOR SIGNALLING IN BETA CELLS IS DOWNREGULATED IN TYPE 2 DIABETES AND AFTER HIGH GLUCOSE CULTURE
1052-1102	Jenneffer Rayane BRAGA TIBAES Richard Lab	PhD 3rd year	Page 29	SEX DIFFERENCES ON IMMUNE CELL PHENOTYPES IN OBESITY AND TYPE 2 DIABETES: PRELIMINARY ANALYSIS OF THE NUTRITION AND IMMUNITY STUDY
1103-1113	Haopeng LIN MacDonald Lab	PhD 6th year	Page 30	UPREGULATION OF CYTOSOLIC REDUCING SIGNALING THROUGH SENP1 IS REQUIRED FOR BETA-CELL FUNCTIONAL COMPENSATION TO SHORT-TERM HIGH FAT DIET
1114-1124	Nerea CUESTA GOMEZ Shapiro Lab	Postdoc	Page 31	METHOD OPTIMIZATION TO MANUFACTURE OFF-TARGET CELL FREE HUMAN IPSC-DERIVED ISLETS
BREAK				
1129-1139	Jessy AZARCOYA BARRERA Richard Lab & Jacobs Lab	PhD 4th year	Page 32	THE LIPID SOLUBLE FORMS OF CHOLINE INFLUENCE THE DEVELOPMENT OF THE GUT-ASSOCIATED IMMUNE SYSTEM IN SPRAGUE-DAWLEY RATS.
1140-1150	Kholoud ELMIH Jacobs Lab	PhD 2nd year	Page 33	UNDERSTANDING THE PHYSIOLOGICAL ROLE OF ETHANOLAMINE PHOSPHATE PHOSPHOLYASE IN MICE
1151-1201	Yongbo SHE Proctor Lab & Richard Lab	PhD 3rd year	Page 34	LOW-FAT DAIRY CONSUMPTION FAVORABLY MODULATES IMMUNE FUNCTION MORE THAN HIGH FAT DAIRY IN A LOW BIRTHWEIGHT SWINE MODEL OF INSULIN RESISTANCE
1202-1212	Emad YUZHASHIAN Chan Lab	PhD 1st Year	Page 35	ASSOCIATION OF DAIRY CONSUMPTION PATTERNS WITH THE INCIDENCE OF TYPE 2 DIABETES: FINDINGS FROM ALBERTA'S TOMORROW PROJECT

CLOSING REMARKS

1213-1218	Dr. Peter Senior	Wrap Up & Closing Remarks	Awards & Prizes to be announced the next day
-----------	------------------	---------------------------	--

Note: Session 3 & 4 updated Oct 22/21

2021 ADI RESEARCH DAY

Monday, November 1 and Tuesday, November 2

PRIZES

Prize winners will be notified by email on November 3 and announced via ADI Update and social media.

Session 1 (Junior Trainees)

- 1 Best Award & 1 Honourable Mention

Session 2 (Junior Trainees)

- 1 Best Award & 1 Honourable Mention

Session 3 (Senior Trainees)

- 1 Best Award & 1 Honourable Mention

Session 4 (Senior Trainees)

- 1 Best Award & 1 Honourable Mention

2021 ADI RESEARCH DAY

Monday, November 1 and Tuesday, November 2

ABSTRACTS

Session 1

OPTIMIZING BLOOD GLUCOSE CONTROL THROUGH TIMING OF EXERCISE IN PREGNANT INDIVIDUALS WITH GESTATIONAL DIABETES MELLITUS

Ly-Anh Reid, Aine Brislaine, Rshmi Khurana, Margie Davenport

Program for Pregnancy and Postpartum Health; Faculty of Kinesiology, Sport, and Recreation; University of Alberta

Background: Postprandial blood glucose control is key to improving maternal/fetal health outcomes. Exercise is a frontline therapy to manage postprandial blood glucose; however, the optimal timing of exercise around meals is not known. This study investigated the optimal timing of light-to-moderate intensity exercise on postprandial and 24h blood glucose values in pregnant individuals with and without GDM.

Methods: Ten pregnant individuals (n=5 with GDM) wore a flash glucose monitoring system for 14 days. They each completed two exercise interventions in random order. The first intervention required participants to walk for 10 minutes immediately following meals three times per day (SHORT), while the complementary condition required participants to go for one 30-minute walk each day at any time other than within the hour immediately following their meals (LONG). Both conditions occurred for a duration of 5 days with a two day washout in between, for a total of 150 mins of light to moderate intensity physical activity per week.

Results: Fasting, 24h mean, peak, nadir glucose values and time > 7.8 mmol/L were higher in the women with GDM compared to the normoglycemic group pre-intervention. There was a significant effect of group by condition whereby the GDM group had significantly higher 1 hour postprandial blood glucose values after lunch and dinner in the NORMAL and LONG condition, but not in the SHORT. Fasting, 24h mean, and nadir glucose values were not influenced by exercise. Both exercise conditions were effective at reducing peak glucose values and time spent > 7.8 mmol/L in women with GDM to be comparable with that of the healthy pregnant population. Dietary intake and physical activity were not different between groups prior to the intervention.

Conclusion: Shorter, more frequent bouts of physical activity compared to one longer bout of physical activity more effectively normalize GDM 1h post-lunch and dinner glucose values to be comparable with that of a normoglycemic pregnant group.

Key words: gestational diabetes mellitus, glycemic control, pregnancy, blood glucose

PROTEIN EXPRESSION OF PGP9.5, CD31, AND vWF ON DEVELOPING PORCINE ISLETS IN VITRO AND IN VIVO

Adnan Black, Kieran Purich, Gina R. Rayat

Alberta Diabetes Institute, Alberta Transplant Institute, Ray Rajotte Surgical-Medical Research Institute, Department of Surgery, Faculty of Medicine and Dentistry, University of Alberta

Background: Transplantation of pig islets is a potential treatment for those with Type 1 diabetes; however, studies on innervation and vascularization of pig islets during development are limited. To better understand pig islet biology and maturation, we investigated the protein expression of protein gene product 9.5 (PGP9.5) as well as cluster of differentiation 31 (CD31) and von Willebrand factor (vWF) to examine innervation and vascularization, respectively.

Methods: Pancreases from three day-old pigs (n=13) were surgically removed. Each pancreas underwent mechanical (mincing) and enzymatic (collagenase) digestion. Islets were then placed in culture, and samples (n=4) were collected on day 0, 1, 3, 5, 8 of culture as islets developed in vitro. Islets cultured for 7 days were transplanted under the kidney capsule of diabetic immune-deficient mice (n=9) and the islet grafts were procured at 1 day (n=3), 30 days (n=3), and 50 days (n=3) post-transplantation. The protein expression of endocrine hormones, PGP9.5, CD31, and vWF was determined by immunofluorescence staining in islets and islet grafts.

Results: For islets in culture, the endocrine cells were localized both peripherally and centrally within the islets. Cells that were stained positive for insulin and glucagon increased steadily throughout the days in culture. Somatostatin expression varied throughout the days of culture, but overall increased from day 0 to day 8. PGP9.5 protein was detected peripherally and centrally within the islets and increased steadily throughout the days in culture. CD31 protein increased from day 0 to day 1 but decreased on day 3 to day 8 of culture. vWF protein remained constant throughout the culture period. For islet grafts, insulin, glucagon, somatostatin, and PGP9.5 proteins increased steadily until the end of the study (50 days post-transplant). CD31 and VWF had low expression on 1 day post-transplant but each increased from 30 days to 50 days post-transplant.

Conclusion: These results provide a better understanding of the trends of innervation and vascularization of pig islets as they developed in culture and after transplantation. The biggest difference we observed was the opposing trends of CD31 protein expression as islets develop in vitro and in vivo.

Key words: islet transplantation, innervation, vascularization, protein expression

GLUCOCORTICOID ACTIONS IN THE DORSAL VAGAL COMPLEX STIMULATE GLUCOSE PRODUCTION

Hellen da Silva, Shuling Yang, Boyan Vasilev, Jessica T.Y. Yue

Department of Physiology, Faculty of Medicine and Dentistry; University of Alberta

Background: Type 2 diabetes is characterized by insulin resistance and increased glucose production (GP), which leads to chronic hyperglycemia. Excessive glucocorticoid (GCs) levels are associated with hyperglycemia and insulin resistance; however, the central mechanisms responsible for these effects remain unclear. The dorsal vagal complex (DVC) plays an important role in integrating nutritional and hormonal cues and regulating GP. We hypothesize that it is a potential target for GC actions. Here, we aim to identify the role of GC actions in the DVC on the regulation of glucose metabolism.

Methods: Sprague Dawley rats were subjected to stereotaxic brain DVC cannulation to enable direct infusions into this hindbrain region. These animals underwent jugular vein and carotid artery catheterizations, allowing for intravenous infusions and blood sampling. A hyperinsulinemic-euglycemic clamp, a gold-standard methodology to assess insulin sensitivity and glucose turnover, was performed to assess glucose production and utilization in response to concomitant DVC infusions with GC receptor (GR) agonist (dexamethasone), GR inhibitor, GR agonist + inhibitor, or saline as a control. To alternatively assess the requirement of DVC GR, a subset of rats received DVC GR shRNA or mismatch (MM) as a control on the day of stereotaxic surgery and received DVC saline or GR agonist on the day of the clamp experiment. Glucose kinetics were measured using tracer dilution methodology.

Results: DVC GC infusion stimulated GP and decreased exogenous glucose requirement, with no change in glucose utilization. Pharmacological inhibition of DVC GC signalling reversed GCs effects on GP, showing that these effects are mediated by GRs. In addition, genetic inhibition of DVC GR with shRNA into the DVC prevented the GC-induced increase in GP and increased the exogenous glucose requirement compared to MM control, supporting that GR signalling acts within the DVC to modulate glucose kinetics and hepatic insulin resistance.

Conclusion: Here we demonstrate that DVC GC modulates glucose production and hepatic insulin sensitivity and provide novel evidence suggesting that blocking GC effects in the DVC could be an approach to treat insulin resistance.

Keywords: glucose production, glucocorticoids, dorsal vagal complex, insulin resistance

THE ROLE OF NECROPTOSIS IN B-CELL LOSS FOLLOWING ISLET CELL TRANSPLANTATION

Saloni Aggarwal, Sandra Kelly, Joy Paramor, Karen Seeberger, Mandy Rosko, Chelsea Castro, Jessica Worton, Kateryna Polyshevska, Purushothaman Kuppan, Gregory S. Korbitt, Andrew R. Pepper

Department of Surgery, Faculty of Medicine and Dentistry, University of Alberta

Background: Intrahepatic islet transplantation requires islets isolated from multiple donors, and results in an estimated 70% loss of transplanted β -cell mass acutely post-transplant. Necroptosis, a programmed and regulated form of necrotic cell death, occurs following cell damage or inflammation. The signaling cascade requires the involvement of receptor interacting protein kinase 1 and 3 (RIPK1 and RIPK3, respectively), which form the necrosome. Herein, we hypothesize that inhibition of RIPK1 and RIPK3 in islets, and subsequently, inhibition of the necrosome formation, will prevent necroptosis from occurring following transplant.

Methods: Necrostatin-1s is an inhibitor of RIPK1 and necrostatin-1 is an inhibitor of both RIPK1 and RIPK3. Human islets were also co-cultured in $\pm$ Z-VAD-FMK, a pan-caspase inhibitor. Following culture with inhibitors, in-vitro islet function was assessed by oxygen consumption rate, glucose stimulated insulin secretion, and cell membrane integrity. In-vivo islet function was assessed through human islet marginal mass transplantation (500 islet equivalents) under the kidney capsule of diabetic immunodeficient Rag-/- mice, following 24 hours culture in 100 μ M necrostatin-1s or necrostatin-1. Graft function was assessed via measurement of non-fasting blood glucose, and intraperitoneal glucose tolerance testing (IPGTT).

Results: When paired with a pan-caspase inhibitor, at 48 hours, cell membrane integrity of cells treated with necrostatin-1 is significantly increased, as compared with controls ($p < 0.001$). Furthermore, post-transplant non-fasting blood glucose means and blood glucose area under the curve (AUC) calculated following IPGTT are lowest in mice transplanted with subtherapeutic doses of human islets treated with necrostatin-1 + ZVAD ($p < 0.05$), and ZVAD alone ($p < 0.01$), and are highest in mice transplanted with subtherapeutic doses of untreated human islets.

Conclusions: The present results indicate the therapeutic potential of administration of combination therapy of an apoptosis and necroptosis inhibition in improving islet survival, which may improve human marginal islet engraftment, leading to an increased rate of cell survival and improved rates of single donor success rates. Furthermore, pre-treatment of islets alone, as opposed to systemic delivery of inhibitors, provides a safer translational pathway to clinical therapeutic use.

Keywords: islet cell transplantation, necroptosis, regulated necrosis

THE IMPACT OF INSULIN RESISTANCE ON CD8+ T CELL-MEDIATED ANTI-TUMOR IMMUNITY

Lucy Lee, Masoud Akbari, Sue Tsai

Department of Medical Microbiology and Immunology, Faculty of Medicine and Dentistry, University of Alberta

Background: Obesity and associated insulin resistance can contribute to an increased risk in various cancers and chronic immunological disorders. In cancer specifically, anti-tumor immunity is crucial in tumor surveillance and elimination in which CD8+ T cells play a key role in tumor elimination. However, previous research has shown that diet-induced obesity led to T cells becoming less responsive to insulin receptor (InsR) signaling, resulting in metabolic dysfunction. This begs the question of how obesity-related insulin resistance in CD8+ T cells dampens anti-tumor immunity.

Methods: High-fat diet (HFD)-induced obese mice develop whole body and T cell insulin resistance compared to normal-chow diet (NCD)-fed lean mice. Using a subcutaneous MC38 tumor implant model, we compared the tumor growth between the two groups and characterized tumor-specific immune responses through flow cytometry. Specifically, we measured the activation and function of CD8+ T cells through activation markers, cytokine and granzyme B expression.

Results: We observed similar tumor growth and tumor-specific immune responses between the obese and lean mice. The number of tumor-specific CD8+ T cells and naïve vs activated T cells showed no significant difference. In addition, the cytokine and granzyme B (GzmB) expression were similar between the two groups.

Conclusion: Nutrient excess and its complex effects on the immune environment in diet-induced obese mice may have tumor-promoting vs immune-promoting effects. Further studies will need to be done to tease out how obesity and insulin resistance may differentially affect anti-tumor immune responses.

Key words: Obesity, Insulin Resistance, Anti-tumor Immunity

YAP/TAZ SIGNALING IN DENDRITIC CELL-MEDIATED PATHOGENESIS OF INSULIN RESISTANCE AND NON-ALCOHOLIC FATTY LIVER DISEASE

Megan Lee, Sue Tsai, Xavier Clemente-Casares

Department of Medical Microbiology and Immunology, Faculty of Medicine and Dentistry, University of Alberta

Background: Obesity and associated insulin resistance (IR) predispose individuals to develop chronic metabolic diseases, such as type 2 diabetes and non-alcoholic fatty liver disease (NAFLD). These disorders affect a significant proportion of the global population; however, their underlying mechanisms remain incompletely understood. We have previously identified two key molecules involved in the HIPPO pathway, Yes-associated protein (YAP) and Transcriptional co-activator with PDZ-binding motif (TAZ), as potential sensors of mechanical and nutrient cues in dendritic cells (DCs). Since the HIPPO pathway positively regulates inflammatory responses, we hypothesized that YAP/TAZ in DCs may perpetuate obesity-linked inflammation in a feed-forward manner, contributing to the pathogenesis of IR and NAFLD.

Methods: CD11cCre YAP^{fl/fl} and/or TAZ^{fl/fl} mouse models were used, which have DC-specific deficiency of YAP and/or TAZ, respectively. These mice were fed a high fat diet (HFD) consisting of 60%kcal fat for 25 weeks, followed by assessment of IR using insulin tolerance tests (ITT) and intraperitoneal glucose tolerance tests (IPGTT). Subsequently, liver and visceral adipose tissue (VAT) were dissected, digested and stained with antibodies to quantify memory T cell populations. The liver and VAT were also processed and stimulated with PMA/ionomycin, then stained with anti-interferon gamma (IFN γ), anti-tumor necrosis factor- α (TNF- α), and anti-interleukin 17 (IL-17) antibodies to evaluate cytokine production by T cells.

Results: HFD-fed CD11cCre⁺ TAZ^{fl/fl} mice and CD11cCre⁻ TAZ^{fl/fl} mice demonstrated no difference in insulin tolerance, but the CD11cCre⁺ TAZ^{fl/fl} mice demonstrated increased glucose tolerance. Decreased proportion of memory T cell subsets, and decreased IFN γ , TNF- α , and IL-17 production by T cells was also observed in the liver and VAT of the HFD-fed CD11cCre⁺ TAZ^{fl/fl} mice compared to our CD11cCre⁻ TAZ^{fl/fl} mice.

Conclusion: TAZ deficiency in DCs appear to improve glucose tolerance in HFD-fed mice. This is concomitant with a reduction in VAT and liver inflammation, as seen with decreased memory T cell subsets and pro-inflammatory cytokine production by T cells.

Key words: Insulin resistance, Obesity, YAP/TAZ signaling, Dendritic cells

ADI Research Day 2021

COMPARISON OF CHEESE, YOGURT, AND MILK EFFECTS ON HEPATIC LIPID METABOLISM IN MICE FED HIGH-FAT DIET

Salma Mofteh, Xiaoying Wu and Catherine B. Chan

Department of Physiology, Faculty of Medicine and Dentistry, University of Alberta

Background: Recently, overweight and obesity have significantly increased worldwide, and both are major risk factors for cardiovascular disease and type 2 diabetes. Hepatic lipid metabolism is affected due to insulin resistance (IR), which can lead to liver injury and non-alcoholic fatty liver disease. Previous studies have shown that low-fat dairy intake can improve liver function and reduce steatosis. This study evaluates the effect of regular fat dairy milk, yogurt, and cheese on hepatic lipid accumulation in IR mice.

Methods: An 8-week feeding intervention of a dairy diet (high-fat yogurt, milk, and cheese) was performed in high-fat diet-fed (HFD) insulin-resistant male C57Bl6/J mice (N=60 with n=12/group). A low-fat diet (LFD) control group was included (n=12). Mice were weighed weekly and body fat mass was measured in week 6. Serum at the time of euthanasia was used to measure alanine transferase (ALT), triglyceride (TG), and non-esterified fatty acids (NEFA). Frozen liver tissue was used to measure liver TG. Liver histology was done to quantify the accumulation of fat droplets following dairy consumption.

Results: All mice on HFD had significantly more body fat % than the LFD group, independent of dairy consumption. Milk diet (P=0.049) significantly lowered whereas Yogurt elevated (P=0.036) serum TG compared to the LFD group. Dairy had no significant effect on serum NEFA. Yogurt also elicited higher liver TG (P=0.007) compared to the LFD group, with no significant impact on ALT. Liver histology showed improvement in hepatic lipid storage in the Milk group; this improvement was evidenced by decreased macrovesicle area (P= 0.039) and increased microvesicle area (P=0.038) compared to the HFD group.

Conclusion: Our results support that milk consumption, even in a small amount (equivalent to half a serving) was beneficial in reducing serum TG and improving hepatic lipid metabolism.

Key words: Dairy, Milk, Yogurt, Cheese, steatosis, Microvesicle, Macrovesicle.

ACQUIRING MACHINE LEARNING APPROACH TO IDENTIFY AND SELECT HUMAN PLURIPOTENT STEM CELLS DURING REPROGRAMMING

Omar Mouhammed, Nidheesh Dadheech, Ila Tewari Jasra, Abhineet Singh, Nilanjan Ray, and James Shapiro

Department of Surgery, Faculty of Medicine and Dentistry, University of Alberta

Background: Human-induced pluripotent stem cells (iPSC) generation is a complex, time-consuming, and labour-intensive process. Four “Yamanaka” transcription factors rewind somatic cells in time and make more malleable cells that can be driven forward to generate any desired cell types, such as pancreatic β -cells. Generating fast and consistent iPSC lines without intra- and inter-patient variability remains a challenge.

Using a machine learning approach, iPSC reprogramming clones can be predicted early and help to eliminate subjectivity. Artificial intelligence (AI) with supervised learning with subtle pattern recognition may provide an optimal resource to train AI models for early and consistent iPSC generation for cell therapy manufacturing. We aim to develop an AI model to recognize iPSC colony growth patterns and precisely discriminate between iPSC vs pseudo vs spontaneously differentiating colonies during line establishment.

Methodology: Patient-derived blood PBMCs were reprogrammed using the Sendai virus. Throughout the iPSC reprogramming process, time-lapse images were captured with fixed time interval duration. Images were collected and tracked utilizing custom- built in-house tracking software. Utilizing the tracking information, we attempted training an AI model for pattern and early prediction of iPS cell colony identification.

Results: Sendai virus was efficient in reprogramming human iPSC within 20 days post- viral transduction. Clone generation was observed within 12-18 days that were morphologically confirmed with tightly packed cells within colonies pattern and displayed highly condensed nucleus and minimal cytoplasm. Further, pluripotency induction in isolated clones was confirmed using flow cytometry that confirmed the presence of >90% Oct4+, Sox2+, Nanog+, Tra1-60+ and Tra181+ cells. Preliminary results after assigning user-encoded colony ID and morphology marking demonstrated pattern identification and cell migrating tracking capability in the trained model. The tracking software showed automated clone prediction with simple iPSC morphology.

Conclusion: Our early effort in machine learning confirmed that the developed AI model was able to modestly trace cell migration and colony pattern identification in small and uniform iPSC clonal structures. More robust data-driven training and in-depth supervised learning are required to train the AI model for complex and heterogeneous colony pattern identification.

Keywords: Machine Learning, Artificial Intelligence, iPSC Reprogramming, Diabetes.

HINDBRAIN GLUCAGON SIGNALING REGULATES HEPATIC LIPID SECRETION

Mantash Grewal, Neel Phaterpekar, Christy Chan, Boyan Vasilev, Hellen Da Silva, Jessica T.Y. Yue

Department of Physiology, FoMD; MCBL Group; University of Alberta

Background: Diabetes and obesity are metabolic disorders characterized by dyslipidemia and elevated very low-density lipoprotein rich in triglycerides (VLDL-TG). Some hyperlipidemic individuals exhibit hyperglucagonemia and glucagon resistance in the periphery where normally glucagon acts at the liver to regulate glucose and lipid metabolism via PKA activation. However, the role of glucagon in the brain is not widely known. Glucagon can cross the blood brain barrier in specific brain regions, such as the dorsal vagal complex (DVC). The DVC responds to various hormones to regulate metabolism. Hence, we examined if glucagon infusion into the DVC regulates hepatic lipid secretion and if PKA activation in the DVC is required for glucagon to mediate its liporegulatory effects.

Methods: DVC cannulations and carotid and jugular catheterizations allowed for direct DVC infusions, arterial blood sampling, and intravenous injections in Sprague Dawley rats. To assess the requirement of PKA for DVC glucagon action, a subset of rats received either a DVC injection of GFP (control) or PKA shRNA. On the experimental day, hepatic VLDL-TG secretion in 10-hour fasted rats was assessed following intravenous poloxamer injection. Plasma TG concentration in response to DVC infusions were measured for 4 hours following poloxamer administration.

Results: DVC glucagon infusion lowered VLDL-TG secretion compared to infusions of DVC vehicle, glucagon receptor antagonist alone, or glucagon + glucagon receptor antagonist. This demonstrated that DVC glucagon receptors are required for DVC glucagon to lower VLDL-TG. Additionally, concomitant DVC infusion of PKA inhibitor Rp-cAMPs with DVC glucagon blunts the ability of glucagon to lower VLDL-TG. Similarly, DVC glucagon infusion lowered VLDL-TG secretion in DVC GFP rats, but not in DVC PKA knockdown rats. Notably, DVC PKA activation with DVC Sp-cAMPs infusion lowered hepatic VLDL-TG secretion.

Conclusion: We propose that glucagon acts within the DVC via glucagon receptors and requires DVC PKA activation to lower VLDL-TG secretion from the liver. Additionally, DVC PKA activation alone is sufficient to lower hepatic VLDL-TG secretion.

Keywords: Glucagon, Hindbrain, Hepatic Lipid Secretion, PKA

ADI Research Day 2021

DIETARY TRIMETHYLAMINE N-OXIDE SUPPLEMENTATION REDUCES OBESITY, GLUCOSE INTOLERANCE AND FATTY LIVER IN HIGH FAT DIET MICE.

Bergen Vetsch., Kelly-Ann Leonard., Randal Nelson., Robin Clugston René Jacobs.

Department of Agricultural, Food & Nutritional Science, University of Alberta

Introduction: Choline is an essential nutrient involved in lipid transport, methyl group donation and the synthesis of membrane phospholipids. The consumption of excess dietary choline may be metabolized by the gut microbiota to generate trimethylamine, is absorbed into the body and converted to trimethylamine-oxide (TMAO) by the liver. While much of the TMAO generated by the liver is excreted into the urine within 24 hrs, recent reports have suggested a biological role for TMAO in regulating lipid metabolism, hormonal homeostasis, and immune function. It is possible that TMAO influences cellular function through varying mechanisms. For example, TMAO may act as a stabilizer of protein folding, an osmolyte, a chemical chaperone, or as a signaling molecule. The action of TMAO is likely concentration- and cell-type dependent. In this study, we investigate the effects of dietary TMAO supplementation on liver health, lipid metabolism and insulin signaling in mice fed a high fat diet.

Methods: 10 male and 10 female C57BL/6 mice were fed a high fat (42%) diet for 8 weeks; half of the mice received diets that was supplemented with TMAO (0.2%). Glucose tolerance tests were performed at week 7. Samples (plasma, liver and white adipose tissue) were collected after a 12 hour fast. Histological analysis was performed on the tissues. Liver samples were homogenized for lipid analysis (HPLC) and assessment of various ER stress markers. Plasma TG, cholesterol, NEFA and ALT were measured in plasma samples.

Results: TMAO supplementation reduced weight gain and improved glucose tolerance in both in both male and female mice. Histology showed noticeably less fat accumulation in the liver of the TMAO group. Western blot results showed an acute ER stress response in the control group, with a higher quantity of P-PERK as compared to the TMAO supplemented mice.

Conclusion: Dietary TMAO supplementation appears to reduce the development of the metabolic syndrome in mice fed a HFD. Preliminary Western Blot data suggests that a potential mechanism for this is the reduction of ER stress. While elevated plasma TMAO has been associated increased cardiovascular disease, dietary TMAO supplementation may also have beneficial consequences related to lipid metabolism. Work is ongoing to understand our understanding of the impact TMAO metabolism plays in metabolic health.

Key Words: Choline, Trimethylamine N-oxide, Lipid Metabolism, Liver Health

2021 ADI RESEARCH DAY

Monday, November 1 and Tuesday, November 2

ABSTRACTS

Session 2

A DOSE OF 50% EGG-PHOSPHATIDYLCHOLINE IS SUFFICIENT TO IMPROVE INTESTINAL BARRIER AND T CELL FUNCTION IN THE CONTEXT OF A HIGH-FAT DIET IN MALE WISTAR RATS

Tianna Rusnak, Jessy Azarcoya-Barrera, Bethany Wollin, Anna Thomsen, Alexander Makarowski, René Jacobs, Caroline Richard.

Department of Agricultural Food and Nutritional Science, University of Alberta

Background: Phosphatidylcholine (PC) and phosphatidylethanolamine (PE) are the main phospholipids in mammalian cell membranes. Both an abnormally high or low PC to PE ratio has been linked to disease progression. PC, a form of choline mainly found in eggs, is thought to support immune function through maintaining immune cell membrane and intestinal barrier integrity. Therefore, the objective of this study was to determine how varying proportions of choline in the form of egg-PC affect intestinal barrier and T cell function.

Methods: Male Wistar rats were randomized to consume one of 6 diets (n=10/group), all containing 1.9g of total choline/kg of diet differing in choline forms: 1- Control Low Fat (CLF, 20% fat, 100% free choline (FC)); 2- Control High Fat (CHF, 50% fat, 100% FC); 3- 100% PC (100PC, 50% fat, 100% PC); 4- 75% PC (75PC, 50% fat, 75% PC+25% FC); 5- 50% PC (50PC, 50% fat, 50% PC+50% FC); 6- 25% PC (25PC; 50% fat, 25% PC+75% FC). Intestinal permeability was measured in plasma 2h after administering FITC dextran. T cell proliferation by splenocytes stimulated with anti-CD3 and anti-CD28 was measured by colorimetric assay. PC and PE were quantified in splenocytes using high performance liquid chromatography.

Results: CLF had the lowest concentration of FITC dextran which was significantly increased in the CHF ($p < 0.05$). Feeding 100PC, 75PC and 50PC lowered plasma FITC dextran concentrations to levels similar to the CLF diet ($p > 0.05$). T cell proliferation was lower in CHF compared with CLF ($P < 0.01$). The 50PC and 25PC showed an increase in T cell proliferation compared with CHF ($p < 0.05$). In splenocytes, the PC to PE ratio was significantly increased in CHF compared to CLF ($p < 0.01$). Feeding 100PC, 75PC and 50PC significantly reduced the PC to PE ratio compared with CHF ($p < 0.05$) to proportions that were similar to CLF ($p > 0.05$).

Conclusion: Our results suggest that providing a physiologically relevant dose of egg-PC (i.e. 50%) is sufficient to improve intestinal barrier function in the context of a high-fat diet. This could partly explain the enhanced T cell proliferation observed in this group. The increase in the PC to PE ratio in splenocytes following a high-fat diet could be a potential marker of obesity-related immune dysfunction in this model.

Key words: Nutritional immunology, phosphatidylcholine, intestinal permeability

REPLICATION FORK STALLING IN HUMAN AUTOLOGOUS iPSC-DERIVED β -CELLS ENHANCE MATURATION BUT CHANGE MITOCHONDRIAL RESPIRATION AND FUNCTION

Sandhya Sapkota, Ila Jasra, Nidheesh Dadheech, A.M. James Shapiro

Department of Surgery, Faculty of Medicine and Dentistry, University of Alberta

Background: Presence of contaminating off-target rousé cells within the induced pluripotent stem cell (iPSC)-differentiated β -cell product, is a challenge. Selective elimination of such cells has been tested using DNA replication repressor, like Aphidicolin (APH) treatment during endocrine stage (S) 5-7 differentiation. These show enhanced endocrine differentiation with controlled graft size. Our preliminary observation confers profound APH effect on endocrine cell maturation with graft size control, enhancing endocrine differentiation, but adversely affected β -cell mass and *in-vivo* maturation. Long-term APH exposure reduces replication fork speed and alters mitochondrial respiration, under hypoxic environment post transplantation. APH removal at the end of differentiation may help restore mitochondrial respiration potential.

Methods: We measured APH exerted changes in cell metabolism based on cellular oxygen consumption rates (OCR) in predicting β -cell maturation and islet transplantation outcome using human autologous SC-derived β -cells compared with human donor islets and iPSCs. We exposed cell clusters to APH for 2,4, and 6 days, with following 4 days washout period without APH. Cellular OCR was measured using oxygen electrode measurement normalized to DNA (OCR/DNA), islet equivalent (IE) and APH-treated cell transplantation to characterize islet differentiation and maturation while correlating APH effect on β -cell survival and function.

Results: Similar IEQ dose cell preparations with and without APH treatment resulted in reduced OCR within 24 hours. SC-islet characterization compared with human islets displayed identical APH action with reduced OCR/DNA that recovered after the washout period at day 8 and 10, respectively. Glycaemia data from APH-treated S5 and donor islets transplanted mice did correlate with reduced β -cell survival and function

Conclusion: This study shows some utility in predicting β -cell function. Clinical islets requires high quality and pure cell population before transplantation for high sensitivity and specificity. While APH dose reduces graft growth, it doesn't maintain islet cell quality and *in-vivo* function. OCR dose may allow accurate β -cell evaluation if greater recovery time is given.

Key Words: Aphidicolin, Mitochondrial respiration, iPSC-derived β -cells, Islet-transplantation

ADI Research Day 2021

The Impact of Obesity on the Protein Expression of Enzymes Regulating Ketone Body Metabolism

Shiva Sharma², Seyed Amirhossein Tabatabaei Dakhili^{1,2}, Farah Eaton^{1,2}, Jared Scharff¹, John R. Ussher^{1,2}

¹Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB Canada

²Alberta Diabetes Institute, University of Alberta, Edmonton, AB Canada

Background: During periods of prolonged fasting, the liver produces ketone bodies through the oxidation of fatty acids, a process referred to as ketogenesis; which produces an alternative fuel source for the body in times of low carbohydrate availability. The enzyme succinyl-CoA:3-ketoacid-CoA transferase (SCOT, encoded by the gene *Oxct1*) is the rate-limiting enzyme in ketone body oxidation, and we have previously demonstrated that obesity increases the expression of SCOT (as well as other enzymes involved in ketone body oxidation) in mouse skeletal muscle. Moreover, inhibition of SCOT activity promotes glucose-lowering, suggesting that decreasing ketone body oxidation may be a novel strategy for the treatment of type 2 diabetes (T2D). Our objective was to determine whether the protein expression of the enzymes of ketone body oxidation (e.g. SCOT) was also elevated in other peripheral tissues of obese mice

Methods: Male and female C57BL/6J mice were fed either a low-fat diet or a high-fat diet for 8 weeks, following which mice were euthanized after either a 20-hr fast, or a 16-hr fast and 4-hr refeed. Tissues (skeletal muscles, heart, liver, adipose tissue, brain, etc.) were isolated and extracted in protein lysis buffer in order to quantify protein expression of SCOT and other ketone body oxidation enzymes via western blotting

Results: Although we have previously demonstrated that experimental obesity increases the expression of SCOT and other enzymes of ketone body oxidation in mouse skeletal muscle, this was not observed in other body tissues such as the brain and heart.

Conclusions: The obesity mediated increase in SCOT expression appears specific to the skeletal muscle, and may thus suggest that the beneficial actions of decreasing SCOT activity in T2D are primarily attributed to decreases in muscle ketone body oxidation.

Keyword: Succinyl CoA:3-ketoacid CoA Transferase, Ketone Body Oxidation, Obesity, Type 2 Diabetes

ADI Research Day 2021

EFFECTS OF GLUCAGON INFUSION IN THE DORSAL VAGAL COMPLEX ON HEPATIC LEVELS OF ENZYMES INVOLVED IN LIPID METABOLISM

Boyan Vasilev, Mantash Grewal, Miguel Cardoso, Christy Chan, Hellen da Silva, Jessica T.Y. Yue

Department of Physiology, Faculty of Medicine and Dentistry, University of Alberta

Background: The brain has an imperative role in regulating whole-body metabolism. It performs this function by integrating various signals (e.g. nutrient status in the blood, afferent signals etc.) from the body, and initiating responses to maintain homeostasis. In particular, the dorsal vagal complex (DVC), a group of three distinct nuclei in the brainstem, is one of the key metabolic regulatory sites in the brain. One of the signals that the DVC was shown to sense is the peptide hormone, glucagon. This pancreatic hormone is commonly associated with glucose homeostasis, given its actions on triggering increased hepatic glucose production. However, recent research reports that glucagon's role extends much further than glucose metabolism alone. For instance, lipid metabolism is also dependent on glucagon signaling. As an example of this, we demonstrated that direct infusion of glucagon into the DVC lowers hepatic release of triglyceride-rich very low density lipoproteins in comparison with DVC saline infusions in rats. Following these observations, we wanted to better understand some of the mechanisms underlying these changes in hepatic lipid metabolism. We hypothesized that this phenotype was due to a change in liporegulatory enzyme levels in the liver.

Methods: Following *in vivo* experiments in Sprague-Dawley rats, liver samples were stored at -80C, before subsequent Western blot analyses. Liver (20 mg) total protein lysates determined by BCA protein assays underwent SDS-PAGE with 5% or 8% gels. Proteins were transferred to nitrocellulose membranes. Membranes were probed with five different primary antibodies: MTP, FAS, alpha-tubulin, ACC, and pACC. Protein levels were detected using HRP-linked secondary antibodies (GAM or GAR) and subsequently ECL substrate. Immunoblots were imaged using a ChemiDoc Imaging System and quantified using ImageJ software. One-Way ANOVA tests were performed using Microsoft Excel for statistical analysis.

Results: Protein levels between four treatment groups (DVC control, DVC glucagon, DVC glucagon receptor antagonist (gcgrA), and DVC gcgrA+glucagon combined) were compared for each of our proteins of interest. MTP and FAS were normalized to alpha-tubulin. There were no differences in hepatic MTP, FAS, or pACC:ACC protein levels between groups.

Conclusion: DVC glucagon infusion in the DVC lowers hepatic lipoprotein release. Our recent data suggests that this hypolipidemic effect of DVC glucagon is not due to a change in MTP, FAS, ACC, or pACC protein levels in the liver. Further investigation is required to elucidate hepatic mechanisms underlying the liporegulatory effects of brain glucagon action.

Key words: lipid homeostasis, dorsal vagal complex (DVC), glucagon, liver.

COMPARATIVE EVALUATION OF OUTCOMES FOLLOWING EXTRAHEPATIC AND INTRAPORTAL PANCREATIC ISLET TRANSPLANTATION

*Kevin Verhoeff, *Braulio A. Marfil-Garza, Gurpal Sandha, Peter A. Senior, A.M. James Shapiro.

* Denotes Co-Primary Authors

AMJ Shapiro Lab, Department of Surgery, Faculty of Medicine and Dentistry University of Alberta

Background: Work to optimize pancreatic islet cell transplantation (ITx) is ongoing with preliminary studies suggesting promising outcomes from novel transplant sites including the gastric submucosa, prevascularized subcutaneous space, and omentum. However, no current in-human study has reported outcomes from extrahepatic compared to intraportal ITx.

Methods: This is a single-center retrospective cohort study of prospectively collected data comparing patients receiving extrahepatic to intraportal ITx at the University of Alberta between January 1999 and October 2018. Primary outcome was graft survival measured by fasting serum C-peptide levels. Secondary outcomes included stimulated C-peptide, BETA-2 scores, SUITO indices, fasting plasma glucose (FPG), and insulin independence.

Results: After querying the Alberta ITx database, 265 patients were included in this study with 9 (3.5%) receiving extrahepatic ITx (gastric submucosal = 2, prevascularized subcutaneous = 3, omental = 4). Cohorts were similar with regards to age, BMI, duration of T1D, and diabetes measures. Patients receiving extrahepatic transplant had significantly lower C-peptide (0.04 nmol/L vs 0.54 nmol/L, $p < 0.001$), stimulated C-peptide (0.05 nmol/L vs 1.2 nmol/L, $p < 0.001$), BETA 2 scores (0 vs 11.6, $p < 0.001$), SUITO indices (1.5 vs 39.6, $p < 0.001$), and higher FPG (9.3 mmol/L vs 7.3 mmol/L, $p < 0.001$) 1-month after first infusion compared to patients receiving intraportal implantation. No patients receiving extrahepatic grafts produced substantial C-peptide in the first 60-days after transplant (median < 0.1 nmol/L). Following subsequent intraportal transplant in patients who initially received extrahepatic implants, similar C-peptide, stimulated C-peptide, FPG, HbA1c, and insulin independence rates were achieved compared to patients initially receiving intraportal transplant.

Conclusions: Clinically, intraportal ITx remains the gold-standard implantation site with substantially better graft survival and diabetes outcomes compared to extrahepatic sites. While promising preliminary data exists supporting extrahepatic ITx, further work is needed prior to routine implementation of these experimental techniques.

IGA MEDIATED IMMUNITY IN TYPE 1 DIABETES MELLITUS (T1D)

Department of Medical Microbiology & Immunology, Faculty of Medicine and Dentistry,
University of Alberta

Yashvi Patel, Erin Strachan, Lucy Lee, Sue Tsai

Introduction

T1D is an autoimmune disease characterized by the destruction of insulin-producing beta islet cells. T1D is associated with increased gut permeability and dysbiosis that can trigger an autoimmune response against the beta cells. Secretory IgA in the intestinal lumen prevents microbes from crossing the intestinal barrier. We aim to determine if IgA plays a role in T1D.

Hypothesis

We hypothesize IgA is protective against T1D by reducing gut permeability and dysbiosis.

Methods

We tracked the incidence of diabetes in non-obese diabetic (NOD) mice that were IgA +/-, +/-, or -/-. The pancreas, small and large intestine, spleen, pancreatic and mesenteric lymph nodes, serum, and feces were processed and subjected to flow cytometric analyses to see if IgA deficiency affects the levels of B and T cells and their activation markers.

Results

Preliminary data shows IgA +/- mice have a greater diabetes incidence than the IgA -/- and IgA +/+. IgA +/- have increased production of both IgA and lipocalin 2 (LCN2), an inflammatory marker around 10-15 weeks of age, before they develop diabetes. Diabetic IgA KO mice have fewer B cells in their bowels and an increased number of B cells in both the lymph nodes.

Conclusion

The mechanisms by which IgA heterozygosity exacerbates diabetes or how IgA deficiency differentially affects B cell numbers in tissues are not known yet. The correlation between a peak in IgA production and LCN2 before mice become diabetic is significant because it shows us that we should look at gut changes in this time window and their potential impact on disease induction.

Keywords Type 1 diabetes, IgA, dysbiosis

CONSUMPTION OF DAIRY PRODUCTS IN THE CONTEXT OF A HIGH FAT DIET INCREASES MYRISTIC ACID AND MARGARIC ACID IN A SWINE MODEL OF LOW BIRTH WEIGHT AND EARLY INSULIN RESISTANCE

Kun Wang, Yongbo She, Rabban Mangat, Alexander Makarowski, Bimol C. Roy, Heather L. Bruce, Michael K. Dyck, Caroline Richard, Spencer D. Proctor

Department of Agricultural, Food and Nutritional Science, University of Alberta

Background: The metabolic complications of early insulin resistance often underpin the development of type II diabetes. Specifically, the physiological adaptations of intestinal lipid metabolism and muscle lipid deposition during insulin resistance are still under-appreciated. We have established a low birth weight (LBW) swine model of insulin resistance (IR) which exhibits increased intestinal triglyceride (TG) absorption and skeletal muscle steatosis (pork marbling) when fed a high fat (HF) diet. The literature implicates the role of CD36 as a potential fatty acid transporter in both small intestine and muscles. Dairy derived fatty acids such as odd-chain fatty acids (C15:0 & C17:0) will potentially be deposited in muscle tissues (pork) when dairy products are introduced in the feed.

Objectives: 1. To investigate candidate mechanistic pathways responsible for increased intestinal lipid absorption and muscle lipid deposition in LBW swine. 2. To explore the extent to which different fatty acids from the diet get incorporated into muscles in LBW swine.

Method: At 6-week of age, normal birth weights (NBW) and LBWs were randomly assigned to consume 1. control chow, 2. HF diet or 3. isocaloric HF diet supplemented with full-fat dairy products for a period of 6 weeks. Five to eight piglets were allocated to each group. Animals were euthanized at 12-week of age, and fasting blood and tissue samples were collected.

Results: Muscle TG contents in LBW-HF tended to be greater than NBW-HF ($p=0.087$). CD36 (but not FABP2 nor VAMP7) protein levels were significantly higher in both mucosal scrapings and muscles ($p<0.05$) in LBW-HF compared with NBW-HF and NBW-C. Dairy products did not significantly change muscle TG contents or CD36 expressions in LBW swine fed a HF diet. Interestingly, dairy products significantly increased myristic acid (C14:0) ($p<0.05$) in muscles in HF-fed LBW swine. Margaric acid (C17:0) contents were also significantly higher in plasma ($p<0.05$) and tended to be higher in muscle ($p=0.093$) in LBW-HF+Dairy compared with LBW-HF group.

Conclusions: Increased lipid absorption and muscle steatosis in response to a HF diet are partially due to increased expressions of CD36 in the small intestine and muscle of LBW swine. These metabolic alterations lead to an increased proportion of dairy-derived fatty acids in plasma and muscle of LBW swine. This study provides mechanistic evidence that fatty acid compositions of marbled pork cuts can be modulated by the diet, which potentially is of benefit to the pork industry.

Key words: intestinal lipid absorption, muscle lipid deposition, swine model

ADI Research Day 2021

ELEVATED NON-FASTING REMNANT CHOLESTEROL ASSOCIATED WITH CARDIOVASCULAR DISEASE RISK IN THE ALBERTA TOMORROW PROJECT

Olivia Weaver, Jacqueline Krysa, Ming Ye, Jennifer Vena, Dean Eurich, Spencer Proctor

School of Public Health, University of Alberta

Background: Individuals with type 2 diabetes (T2D) often have atherogenic dyslipidemia and are at increased risk of cardiovascular disease (CVD). Fasting low-density lipoprotein cholesterol (LDL-C) is the traditional lipid marker for CVD risk. However, after reducing fasting LDL-C to recommended levels, residual CVD risk remains. Non-fasting remnant cholesterol (RC) is a novel lipid marker that may predict CVD risk better than LDL-C. However, Canadian data does not exist to support clinical use of non-fasting RC in CVD risk screening. Therefore, the current analysis aimed to determine the relationship between non-fasting RC (vs LDL-C) and CVD incidence in a Canadian population, prior to an analysis of this relationship in those with T2D.

Methods: n=16,251 participants of the Alberta Tomorrow Project/Canadian Partnership for Tomorrow Project (a prospective cohort study of chronic disease) were selected for the current analysis if they had a complete non-fasting lipid panel with lipid values >0. Data linkage with Alberta Health administrative databases was used to obtain individual-level data on CVD outcomes, statin use and comorbidities. Multiple logistic regression was used to analyze the relationship between non-fasting lipids (RC, LDL-C) and a composite variable of incident CVD events, while adjusting for age, sex, Elixhauser comorbidity index, statin use and LDL-C/RC).

Results: Mean RC was significantly higher in participants with incident CVD events compared to those without (0.88 ± 0.41 mmol/L vs 0.79 ± 0.38 mmol/L, $p < 0.0001$), while mean LDL-C was significantly *lower* in those with incident CVD compared to those without (2.69 ± 0.93 mmol/L vs 2.84 ± 0.86 mmol/L, $p < 0.0001$). Odds of incident CVD events per mmol/L increase in RC were significantly increased (adjusted OR: 1.42, 95% CI: 1.23-1.65), whereas odds per mmol/L increase in LDL-C were significantly reduced (adjusted OR: 0.80, 95% CI: 0.75-0.86).

Conclusion: Increased odds of incident CVD events were associated with elevated non-fasting RC but not LDL-C in this Canadian sample. Further research in a wider Canadian population is warranted to investigate the RC/CVD relationship in the context of T2D and to develop sex-specific RC reference ranges which may help improve CVD risk screening for Canadians.

Keywords: Cardiovascular Disease, Type 2 Diabetes, Remnant Cholesterol

ADI Research Day 2021

META-ANALYSIS OF BLOOD GLUCOSE RESPONSE TO HIGH INTENSITY EXERCISE

Reid McClure^{1,2}, Emma Weseen^{1,3}, Francisco Cordero⁴, Miranda Maldaner^{1,2}, Sarah Hart^{1,2}, Normand Boulé^{1,2}, Jane Yardley¹⁻³

Physical Activity and Diabetes Laboratory¹; Faculty of Kinesiology, Sport, and Recreation (University of Alberta)², Augustana Faculty³ (University of Alberta), Universidad de Seville⁴

Background: High intensity exercise-induced hyperglycemia is recognized in clinical guidelines on the treatment of type 1 diabetes mellitus (T1D), but its occurrence after high intensity intermittent exercise (HIIE) in acute studies is inconsistent. The primary purpose of this meta-analysis was to compare and summarize the available evidence of blood glucose (BG) responses to HIIE. The secondary purpose was to examine the role of prandial status on BG outcomes. We hypothesized that there would be no consistent effect on BG from HIIE, unless examined in the context of participant prandial status.

Methods: We conducted a search of the literature through Scopus. Web of Knowledge. SportDiscuss (Ebsco-Host), Medline, Pubmed. CINHALL using keywords related to T1D and HIIE. Inclusion criteria required each study have a minimum of 6 participants with T1D aged 17 years or older, involving a HIIE intervention, and a pre- and post-exercise measure of BG. Data were analysed using a general inverse variance statistical method with a random effects model on RevMan5 statistical software.

Results: Seventeen interventions from thirteen studies were included in the final analysis (plasma glucose, n=6; capillary glucose, n=11). A mean overall difference of -1.4 mmol/L (CI:-3.0, 0.2) was found from pre- to post-exercise BG which should be interpreted with caution due to high heterogeneity (I²= 92%). Fasted exercise was associated with an increase in BG of +1.7 mmol/L (CI:-0.2, 3.6), while fed exercise was associated with an overall decrease of -2.6 mmol/L CI:(3.7, -1.5), with a statistically significant difference between groups. Heterogeneity within subgroups was (I²= 65%) and (I²=86%) for the fed and fasted groups respectively.

Conclusions: The effect of HIIE on BG is inconsistent, but partially explained by prandial status.

Keywords: High intensity interval exercise, type 1 diabetes, blood glucose, fasted exercise

2021 ADI RESEARCH DAY

Monday, November 1 and Tuesday, November 2

ABSTRACTS

Session 3

THE EFFECT OF STARTING CAPILLARY GLUCOSE LEVELS ON SERUM ELECTROLYTES DURING AND AFTER EXERCISE IN TYPE 1 DIABETES

Zeinab Momeni¹⁻³, Normand G Boulé^{1,3,4}, Carla M Prado^{3,4,5}, Jane E Yardley¹⁻⁴

¹ Physical Activity and Diabetes Laboratory, ² Augustana Faculty, ³ Alberta Diabetes Institute, ⁴ Faculty of Kinesiology Sport and Recreation, ⁵ Human Nutritional Research Unit, ⁶ Department of Agricultural, Food and Nutritional Sciences, University of Alberta

Background: Exercise is highly beneficial for people with type 1 diabetes (PWT1D), but fear of hypoglycemia is a major barrier to its practice. As a result, although guidelines recommend starting exercise with blood glucose concentration at 7-10 mmol/L, PWT1D often prefer a higher range. Prolonged hyperglycemia may affect kidney function and serum electrolyte balance, leading to changes in nerve signaling and muscle contraction. We examined serum electrolyte concentrations during aerobic exercise in PWT1D with two different starting levels of blood glucose: 8-10 mmol/l, to approximate exercise guidelines for T1D (moderate-MOD), and 12-14 mmol/l, a common starting point for PWT1D (high-HI).

Methods: Twelve PWT1D (10F/2M, mean $\pm$ SD: age 29 ± 7 years, A_{1C} $7.6 \pm 0.8\%$, VO_{2peak} 37.8 ± 7.6 mL/kg/min) completed exercise sessions (cycling 45 minutes at 60% VO_{2peak} on an ergometer) in random order with either MOD or HI blood glucose levels. Meal timing/composition and insulin dosage were kept as consistent as possible between sessions. Blood samples were taken at baseline (pre), at the end of exercise (post), as well as 60 minutes post-exercise (recovery) for the measurement of sodium, potassium, magnesium, and calcium, as well as glucose and insulin.

Results: Exercise intensity (respiratory exchange ratio, heart rate) was identical between sessions. Sodium, potassium, magnesium, and calcium all increased during exercise and decreased during recovery (effect of time $p < 0.0001$), with no difference between the conditions (effect of treatment $p > 0.05$). Conversely, serum glucose decreased during exercise and increased during recovery (effect of time $P = 0.0005$), with serum glucose being higher during the HI session (effect of treatment $p = 0.0008$).

Conclusion: Although there were significant changes in serum electrolytes during and after exercise in PWT1D, no differences between MOD and HI sessions were observed. However, this was a moderate intensity protocol, of relatively short duration. Longer, or potentially more intense exercise sessions could alter the impact of hyperglycemia on electrolyte balance.

Keywords: Type 1 diabetes, exercise, serum electrolytes, blood glucose

A NOVEL SMALL MOLECULE FOR THE TREATMENT OF TYPE 1 DIABETES

Hui Huang, Qian Wang, Jean Buteau

Department of Agricultural, Food and Nutritional Science (AFNS), University of Alberta

Background: MLR1023 is a small molecule activator of Lyn and a candidate anti-diabetes medication. Indeed, in phase 2 clinical trials, MLR1023 showed potent glucose-lowering activity in participants with type 2 diabetes. However, the exact mechanisms by which MLR1023 exerts its action remained unknown. Using genetically engineered mice, our lab has shown that Lyn is a critical regulator of beta-cell mass and function. Consistently, pharmacological activation of Lyn with MLR1023 induced β -cell proliferation and survival. Thus, we herein hypothesized that MLR1023 could improve glucose tolerance and β -cell proliferation and survival in type 1 diabetes.

Methods: We sought to test the effects of MLR1023 in two different models of T1D: non-obese diabetic (NOD) mice and streptozotocin-induced diabetic mice. In brief, NOD and streptozotocin (STZ, 100mg/kg, single-dose) injected C57BL/6J mice were treated with MLR1023 or vehicle at a dose of 30 mg/kg body weight daily for 7 consecutive days, followed by ipGTT and pancreases collection. The α - β -cell mass and cell proliferation were determined by immunohistochemistry staining. We explored the cytoprotective action of MLR1023 in INS1 cells exposed to cytokines and in the STZ-induced β -cell destruction mouse model. Lastly, islet insulinitis was analyzed by insulinitis score and immunofluorescent microscopy of CD4, CD8, B220, and CD68.

Results: Newly diabetic NOD mice treated with MLR1023 exhibited improved glucose tolerance and lower fasting blood glucose, consistent with previous results obtained in type 2 diabetic models. MLR1023, compared to vehicle, significantly increased β -cell mass in both NOD and STZ mice without changing α -cell mass. Increases in the number of large islets and the presence of PCNA-positive β -cells indicated a contribution of β -cell proliferation to the effects of MLR1023. Of note, the replication of α -cell and ductal cell was not elevated by MLR1023 treatment. In addition, MLR1023 protected β -cells from apoptosis induced by cytokines *in vitro* and STZ *in vivo* via its action on Lyn kinase. Finally, we showed that MLR1023 alleviated the insulinitis of NOD mice and reduced the occurrence of leukocytes surrounding the islets, suggesting a potential mechanism of MLR1023 in immune cells.

Conclusion: MLR1023 protects residual β -cell mass and promotes beta-cell regeneration in models of T1D, thereby delaying disease progression. Our study identifies Lyn as a promising target in T1D treatment.

Keywords: Lyn, MLR1023, β -cell mass, proliferation

MODELLING OF ELECTRICAL FINGERPRINTS REVEALS TRANSCRIPTOMIC PROFILES LINKED TO ALPHA-CELL DYSFUNCTION IN TYPE 2 DIABETES

Theodore dos Santos^I, Linford Briant^{II}, XiaoQing Dai^I, Joan Camunas-Soler^{III}, Austin Bautista^I, Patrik Rorsman^{III}, Patrick E. MacDonald^I

I. Alberta Diabetes Institute, University of Alberta, Edmonton, AB, CAN

II. Oxford Centre for Diabetes Endocrinology and Metabolism, University of Oxford, UK

III. Stanford University School of Medicine, Stanford, CA, USA

Background: The heterogeneity and dysfunction of β -cells receives more attention than pancreatic α -cells; however, the malfunction of α -cells is well documented in multiple forms of diabetes. We developed approaches to study the heterogeneity of human islet cell electrophysiological behaviour and applied these to α -cell phenotypes in type 2 diabetes (T2D).

Methodology: Machine learning methods were applied to patch-clamp electrophysiology to generate classifier models that empirically predict and score human α - and β -cell phenotypes. We then linked the model scores to single-cell RNA sequencing data (patch-seq) from non-diabetic (ND) and T2D human islet donors.

Results: As validation, the model's scoring, without *a priori* knowledge of cell type, intuitively correlates with the expression of relevant lineage and identity markers in ND donors. Applying the model to α - and β -cells of T2D donors, we find impaired α - and β -scores compared to ND, indicative of a loss of electrophysiological identity. To investigate the α -cell impairment our model revealed, we correlated the T2D α -cell scores with their respective single-cell transcriptomes. We find that pathways involved with the mitochondrial respiratory chain complex assembly were enriched in T2D α -cells with the most dramatically impaired scores. Further, we discover that T2D α -cell exocytosis is selectively impaired in α -cells enriched in lineage and maturity factors such as ISL1, NEUROD1, NKX2-2, and ARX.

Conclusions: We generated modelling approaches combined with electrophysiological patching and single-cell sequencing techniques to improve the understanding of human islet cell phenotypes. We advocate important links between α -cell mitochondrial function, lineage, maturation state, and susceptibility to dysfunction in human T2D.

Keywords: Machine Learning, Patch-Seq, Human Donors, Diabetes, α -cells

THE INTERSECTION OF DIABETES AND ESTRADIOL IN MORTALITY AND OTHER ADVERSE HEALTH OUTCOMES AMONG WOMEN UNDERGOING HEMODIALYSIS – A PROSPECTIVE STUDY

Lina Lau^{1,2}, Natasha Wiebe¹, Sharanya Ramesh³, Sofia Ahmed³, Marcello Tonelli³, Barbara Thorand², Aminu Bello¹

¹Department of Medicine, University of Alberta

²Institute of Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany

³Department of Medicine, University of Calgary

Introduction: Estradiol (E2) levels fall over time among female patients on hemodialysis (HD). Although low E2 is linked with increased risk of adverse clinical outcomes, it is still unclear whether the relationships are modified by diabetes status in female patients undergoing HD. We aimed to determine if endogenous E2 are associated with all-cause mortality, cardiovascular (CV) mortality, non-fatal CV events, functional status, and quality of life among female HD patients. Furthermore, we aimed to determine whether diabetes would modify any possible relationships.

Methods: A prospective study was conducted using data from the Canadian Kidney Disease Cohort Study. Participants included females (n = 319) not using exogenous sex hormones and did not undergo gynecological procedures. Cox proportional hazards models were used to examine the associations between E2, all-cause mortality, fatal and non-fatal CV events. Adjusted mixed models were used to fit the Health Utility Index Mark 3 (HUI3), and the KDQOL-12 physical and mental component score (KDQOL12-P/MCS), where participants were modelled as random effects and visit as a fixed effect. Effect modification of diabetes status as baseline was entered as a multiplicative term in models.

Results: Median age was 67 (61, 76) years. 55% had diabetes. Median E2 levels were not significantly different between female HD patients with or without diabetes (0.054 vs. 0.043 nmol/L). Over the study period of 14 years, 199 (62%) participants died, of which 62 (31%) were CV-related. E2 was associated with lower HUI3 scores (MD=-0.03, [-0.06; -0.01]), and no other significant associations with all-cause mortality, CV mortality, non-fatal CV events, KDQOL12-PCS, and KDQOL12-MCS were observed. Diabetes status did not significantly modify the associations between hormone levels and clinical outcomes.

Conclusions: Elevated E2 among female HD patients were associated with lower quality of life – a relationship that was not modified by diabetes status. High E2 in female HD patients could be a modifiable risk factor for quality of life. However, further studies are warranted to assess whether the observed associations were causal.

ReshapeT1D: Utilizing the strengths of quantitative ethnography and patient and clinician led research to understand type 1 diabetes lived experiences in Alberta

Jamie Boisvenue¹ Heather Hinz[†], Peter Senior², Roseanne Yeung^{1,2}

¹School of Public Health, College of Health Sciences, University of Alberta

²Division of Endocrinology & Metabolism, Department of Medicine, Faculty of Medicine & Dentistry, College of Health Sciences, University of Alberta

[†]Patient Partner

Background: Type 1 diabetes (T1D) requires intensive education, constant monitoring, and adjustment of blood glucose, which can lead to burnout and distress. Our research seeks to answer two main questions: (1) what is T1D healthcare like in Alberta? and (2) how can T1D lived experiences in Alberta support diabetes care quality improvement?

Methods: We will employ a narrative based inquiry with a sample of 30-40 people through non-proportional quota sampling based on the following strata: sex (male/female), geographic region (urban/rural), education (high school/college/university/professional). Participants must be an Alberta resident of >18 years of age and living with T1D for 3+ years. Recruitment will take place through social media, our research information site ReshapeT1D.com, and the T1D patient recruitment platform ConnecT1D.ca. Data will be generated through a patient and clinician co-designed questionnaire and semi-structured interview. Questionnaire demographics include sex, age (DOB), gender, ethnicity, urban vs rural setting, education, employment status, and health insurance status, as well as diabetes related questions. The semi-structured interview will ask questions around themes on appointments, barriers, adaptability and resilience, accessibility, and sex and gender, and will be transcribed verbatim and coded in two phases. First, the codes will be developed inductively using interpretive phenomenological analysis by two raters working autonomously in creating codes and then collaboratively in code structure, triangulation, and code tree development. Coding and segmentation will be performed with the Reproducible Open Coding Kit (ROCK) [2]. Following coding and segmentation, we will use Epistemic Network Analysis (ENA) [3] to model networks of code co-occurrences in discourse and explore sample-level characteristics to address our research questions.

Expected Findings & Contributions: This study will contribute new evidence on networking personal narratives related to diabetes in Alberta and demonstrates the advantages and disadvantages of using QE and ENA to better understand diabetes related healthcare.

Keywords: Type 1 Diabetes, Quantitative Ethnography, Partner-Oriented Research

PANCREATIC ISLET TRANSPLANTATION: 20-YEAR OUTCOMES AT THE UNIVERSITY OF ALBERTA

Marfil-Garza BA, Hefler J, Verhoeff K, Lam A, Dajani K, Anderson B, O’Gorman D, Kin T, Kneteman N, Bigam D, Ryan E, Senior PA, Shapiro AMJ.

Department of Surgery, University of Alberta.

Background

Islet transplantation (ITx) has become a robust option to treat patients with type 1 diabetes (T1DM) suffering from problematic hypoglycemia. Long-term outcomes, however, are lacking. Herein, we report 20-year outcomes from the largest single transplant center internationally.

Methods

Patients with T1DM undergoing ITx at the University of Alberta from January 1st, 1999 to October 1st 2018 were analyzed (n=256). Primary outcomes include patient and graft survival. Secondary outcomes include insulin independence rates and duration, graft function, glycemic control, and measures of hypoglycemia. A comparative analysis of patients with sustained graft survival (graft function $\geq 90\%$ of patient survival, n=177, 69.1%) vs those with unsustained graft survival (graft function $< 90\%$ of patient survival, n=79, 30.9%) were performed.

Results

Median (IQR) patient survival was 7.5 years (4.5 - 12.2), with a mortality rate of 9.8% (25/256). Median graft survival was 6.0 years (3.0 - 9.5), with a graft failure rate of 35.5% (91/256). At first transplant, patients with sustained graft survival were older ($p < 0.001$), had a longer duration of their disease ($p < 0.001$) and lower insulin requirements (units/kg/day) ($p < 0.05$). A higher number of infusions ($p = 0.009$) and total infused islet mass (islet equivalents/kg of body weight) were observed in this group ($p < 0.001$). Patients with sustained graft survival had higher rates of insulin independence, coupled with sustained decreases in insulin requirements during follow-up, and improvements in glycemic control and measures of hypoglycemia ($p < 0.001$ for all). A multivariable logistic regression model identified three factors associated with increased probability of sustained graft function: the use of anakinra plus etanercept (OR 9.4, 95%CI 2.6 - 34.0, $p = 0.001$), and both the Beta-2 score (OR 6.9, 95%CI 2.4 - 20.0, $p < 0.001$) and SUITO index (OR 4.3, 95%CI 2.0 - 9.1, $p = 0.001$) measured at 6-12 months post-first infusion.

Conclusion

This study documents long-term benefits following ITx and identifies factors associated with sustained graft function. Although more studies are needed, we provide comprehensive data to improve clinical practice in the field.

Keywords: diabetes, islet, transplant, graft failure

MODELLING HUMAN PLURIPOTENT STEM CELLS PHYSIOLOGICAL BENEFITS IN 3D SCALE-UP MICROENVIRONMENT Vs. 2D PLANAR PLATFORM

Ila Jasra, Nerea Cuesta Gomez, Kevin Verhoeff, Sandhya Sapkota, Perveen Anwar, Rena Pawlick, Nidheesh Dadheech, and James Shapiro

Department of Surgery, Faculty of Medicine and Dentistry, University of Alberta.

Background: Investigations on human induced pluripotent stem cells (iPSC) present ample evidence that 3D cell culture mimic better in-vivo conditions to maintain cellular physiology and metabolism than 2D planar adherent surfaces. Self-renewal and pluripotency are greatly impacted by epiblastic structure that promotes cell proliferation. We hypothesize that transitioning autologous iPSC from 2D to 3D using vertical-wheel (VW) bioreactors will scale-up yield while maintaining pluripotency, genomic integrity, and metabolism.

Methods: Sendai virus reprogrammed established human iPSC lines from blood cells were cultured, expanded, and compared for physiological parameters in 2D Vs 3D suspension microenvironment. Cells expanded in matrix-coated plates (2D planar) and VW-based bioreactor (3D) were evaluated for growth kinetics, viability, genetic/genomic integrity (RT-PCR), and pluripotency makers (FACS) to compare the scale-up efficacy and optimal utility of these methods. In addition, mitochondrial metabolic function based on oxygen consumption rates (OCR/DNA) was evaluated for aerobic or anaerobic respiration.

Results: Head-to-head comparison of 2D Vs 3D methods clearly highlighted the physiological benefit of 3D suspension method. Human iPSC expansion using 0.1L VW-based bioreactor was evaluated as favorable culture method for high-throughput scale-up production of stem cells. Nearly 100-fold cell amplification per week was measured with VW-bioreactors compared to 18-fold expansion with 2D planar method. In bioreactors, epiblast structure of iPSC promoted fast and high-fidelity cell proliferation, while maintaining maximum viability (~90%) compared to 2D plates. Longitudinal media rotation was beneficial in maintaining efficient gas, nutrient and growth factors exchange with minimal sheer-stress injury and 200ml batch-feed media requirement per week. Real-time PCR confirmed uncompromised genetic stability and genomic integrity in long-term (>20) passaged iPSC. Furthermore, 3D organization enhanced pluripotency nuclear transcription factors expression (70% Oct4+, 80% Nanog+, 90% Sox2+, and membrane markers >90% Tra1-60 and Tra1-81) compared to much abrogated in 2D cultured cells (<30% Oct4, Nanog, Sox2; and 60% Tra1-60, Tra 1-81). OCR measurements of 30nmol/min/mgDNA further characterized 3D cultured cells favoring anaerobic respiration.

Conclusion: Single batches of 200-million cells in 0.1L and over 1-billion cells in 0.5L bioreactors can be obtained per week using minimal media consumption. 3D cell expansion promotes higher yield, improved viability, stable genomic integrity, and enhanced cellular metabolism. Bioreactor-based scale-up of iPSCs prove most efficient means to translate cGMP manufacturing of autologous pluripotent stem cells for regenerative therapeutic application.

Keywords: Human iPSC, 2D cell culture, 3D cell culture, Suspension Bioreactors, Scale-up.

ACCURACY OF RESTING ENERGY EXPENDITURE PREDICTIVE EQUATIONS IN INDIVIDUALS WITH EXCESS BODY WEIGHT

Julia Montenegro¹, Camila L.P. Oliveira¹, Aloys Berg², Arya Sharma³, Laurie Mereu³, Jens Walter^{1,4}, Carla M Prado¹

¹Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, Canada.

²Faculty of Medicine, University of Freiburg, Freiburg, Germany

³Department of Medicine, University of Alberta, Edmonton, Alberta, Canada.

⁴Department of Medicine, University College Cork, National University of Ireland, Cork, Ireland.

Background: Assessing resting energy expenditure (REE) is important for determining energy requirements. Indirect calorimetry is usually not available in clinical settings and for this reason, predictive equations for estimating REE have been developed. Body composition compartments such as fat mass (FM) and fat-free mass (FFM) may improve accuracy of these equations. The aim of this study was to assess the accuracy of REE prediction equations that include body composition compared with measured REE in individuals with excess body weight.

Methods: Preliminary baseline data from a randomized controlled trial in healthy adults, 18 to 40 years of age, with a body mass index (BMI) between 25 and 35 kg/m² were included. A metabolic chamber was used to assess individual's REE. Dual-energy X-ray absorptiometry was used to assess FM and FFM. Seven REE equations using body composition parameters were used to calculate predicted REE (pREE). A two-way ANOVA was used to compare measured REE (mREE) versus pREE and agreement was assessed by Bland-Altman analysis; pREE values between 95% and 105% of mREE were considered accurate.

Results: Eighteen participants (66.7% females, age: 26 ± 5 years, BMI: 28.81 ± 2.51 kg/m², mREE: 1780 ± 360 kcal/day) were included. Age, FM, and FFM were not different between sexes (p>0.05). The pREE equation developed by Muller *et al.*, 2001 was accurate for both sexes combined, as well as for females and males separately (p>0.05, limits of agreement: -381 to 327 kcal/day; -413 to 247 kcal/day; -231 to 402 kcal/day, respectively). The pREE equation by Horie *et al.*, 2007 was accurate for both sexes combined and for females (p>0.05, limits of agreement: -376 to 490 kcal/day; and -376 to 296, kcal/day, respectively). All other equations underestimated mREE, including 5 equations for all participants and females and 6 for males.

Conclusions: One pREE equation was identified as the most appropriate for this cohort of individuals with excess body weight. In general, equations appear to be more accurate in females than in males.

Keywords: Resting energy expenditure, fat-free mass, fat mass, excess body weight.

2021 ADI RESEARCH DAY

Monday, November 1 and Tuesday, November 2

ABSTRACTS

Session 4

GLYCINE RECEPTOR SIGNALLING IN BETA CELLS IS DOWNREGULATED IN TYPE 2 DIABETES AND AFTER HIGH GLUCOSE CULTURE

Amanda Schukarucha Gomes, Patrick E. Macdonald

Macdonald Lab, Department of Pharmacology and Alberta Diabetes Institute, University of Alberta, Edmonton, AB., Canada.

Background: Previous work from our group demonstrated that glycine receptors (GlyRs) are present in human β cells, and mediate glycine-evoked currents that contribute to cell depolarization, increasing insulin secretion. However, in islets from type 2 diabetic donors, GlyR signalling is impaired, and the mechanisms that lead to this change are still unknown. We aimed to investigate if the GlyR dysfunction in type 2 diabetes (T2D) is caused by hyperglycemia. This work will contribute to the understanding of neurotransmitter signalling in pancreatic islets and how they are affected in T2D, and if/how they can be targeted as possible therapeutic targets.

Methodology: Human islets from donors with and without T2D were dispersed into single cells and cultured in 5.5 mM or 15 mM glucose for 2 days. Glycine currents were measured through the whole-cell patch-clamp technique, at the holding membrane potential of -70 mV, in the presence and absence of 300 μ M glycine and 300 μ M glycine with 10 μ M strychnine (a GlyR antagonist). The identity of the cells was later confirmed by insulin immunostaining. The RNA expression of the GlyR α 1, α 3 and β subunit splice variant genes was quantified and compared between islets from non-diabetic and type 2 diabetic donors.

Results: The glycine current measured in β cells from T2D donors ($-0.7690 \text{ pA/pF} \pm 0.5298$, $n=7$) had smaller amplitudes than those measured in non-diabetic cells ($-9.679 \text{ pA/pF} \pm 2.068$, $n=29$), and the cells that were cultured in 15 mM glucose for 2 days ($-6.121 \text{ pA/pF} \pm 2.055$, $n=10$) had smaller amplitude than those cultured in control media ($-13.16 \text{ pA/pF} \pm 3.746$, $n=11$). The genetic expression of the GlyR subunit α 1 variants 1, 2, 3 and 4, α 3 variant 1 (but not 2) and β variant 1 (but not 3) was decreased in islets from type 2 diabetic donors.

Conclusions: Glycine-evoked currents in β cells are diminished after 2 days culture with high glucose, in a similar way to what happens in cells from T2D donors, showing that hyperglycemia is capable of modulating glycine receptor signalling. Our findings also indicate a decrease in overall GlyR gene expression in T2D, but not a shift in subunit splice variant expression.

Keywords: Islets, β -cells, Glycine, Neurotransmitters, Hyperglycemia

SEX DIFFERENCES ON IMMUNE CELL PHENOTYPES IN OBESITY AND TYPE 2 DIABETES: PRELIMINARY ANALYSIS OF THE NUTRITION AND IMMUNITY STUDY

Jenneffer Rayane Braga Tibaes, Maria Ines Barreto Silva, Valerie Moore, Alexander Makarowski, Paulina Blanco, Donna Vine, Sue Tsai, Caroline Richard

Department of Agricultural, Food and Nutritional Science, Faculty of Agricultural, Life & Environmental Sciences, University of Alberta

Background: Immune function is altered during obesity. Moreover, males and females across different species demonstrate distinct susceptibility to several diseases and infections. However, less is known about how men and women differ in term of immune phenotype in the context of obesity. This study aimed to determine sex differences on cardiometabolic risk factors and immune cell phenotypes in individuals with obesity and with or without type 2 diabetes (T2D).

Methods: This is a cross-sectional analysis of the values at baseline of a four-arm parallel trial consisting of four groups of adults: lean-normoglycemic (lean-NG; n=17 (F:7, M:10)), obese-NG (n=13 (F: 9, M: 4)), obese-insulin resistant (obese-IR; n=11 (F:4, M:7)), and obese-T2D (n=7 (F:5, M: 2)). Cardiometabolic risk factors were measured in the fasting state along with the proportion of cytotoxic T cells (CD3+CD8+) and helper T cells (CD3+CD4+) expressing the IL-2 receptor (CD25). Two-way ANOVA was used to assess the main effect of sex, group and their interaction followed by the post hoc analysis using the DUNCAN adjustment for comparison among groups.

Results: As expected, overall women had higher concentrations of HDL-cholesterol (C) and total-C compared to men. There was no sex effect on TG, LDL-C, and non-HDL-C concentrations. No other sex differences on cardiometabolic risk factors were observed specifically within each group. Overall, women presented lower proportions of cytotoxic T cells and higher proportions of helper T cells compared to men. This difference was also observed specifically in the Obese-T2D group. Total cells expressing CD25 was also higher in women compared to men. Interestingly, regardless of sex, the obese-T2D group had the lowest proportion of cytotoxic T cells ($p=0.04$) compared to all other groups, whereas the proportion of helper T cells and CD4+CD25+ cells were also higher in this group (both $p<0.001$).

Conclusion: The higher proportion of cytotoxic T cells and helper T cells in men and women, respectively, has been previously reported in the general population. We confirmed that this sex difference is maintained in individuals with obesity and T2D. The lower proportion of cytotoxic T cells in individuals with T2D could explain at least in part the increased risk of viral infections in this population.

Keywords: sex differences, obesity, immune system, type 2 diabetes.

**UPREGULATION OF CYTOSOLIC REDUCING SIGNALING THROUGH SENP1 IS
REQUIRED FOR β -CELL FUNCTIONAL COMPENSATION TO SHORT-TERM
HIGH FAT DIET**

Haopeng Lin, Kunimasa Suzuki, Nancy Smith, Xi Li, Lisa Nalbach, Sonia Fuentes, Aliya F Spigelman, Xiaoqing Dai, Austin Bautista, Mourad Ferdaoussi, Saloni Aggarwal, Andrew R Pepper, Emmanuel Ampofo, Leticia P Roma, Wen-hong Li, Patrick E MacDonald

Department of Pharmacology, University of Alberta, Edmonton, AB T6G 2E1, Canada

Background: Pancreatic β -cells adjust insulin secretion according to an individual's metabolic status. The underlying mechanisms remain unclear.

Methods and Results: We find β -cells from young overweight humans, and mice fed high fat diet (HFD) for 2-days, show compensatory facilitation of insulin exocytosis that is unrelated to enhanced Ca^{2+} entry. RNA-seq suggests an upregulation of oxidative phosphorylation and downregulation of cholesterol biosynthesis linked to mitochondrial export of reducing equivalents. Oxygen consumption is increased and cytosolic redox is reduced in 2-day HFD islets from Cyto-roGFP2-Orp1 reporter mice. Compensatory β -cell exocytosis can be blocked by direct intracellular infusion of oxidizers, and re-capitulated either by infusion of reducing agents or SENP1. This deSUMOylating enzyme transduces redox signals to facilitate insulin exocytosis via a coordinated interaction between Zn^{2+} and cysteines 603 and 535 at its catalytic site. Binding of Zn^{2+} with C535 tunes the dynamic range of SENP1, allowing robust activation by glutathione and glutaredoxin. Loss of the C535 thiol abolishes redox-regulation of β -cell exocytosis. Finally, while wild-type littermates maintain glucose tolerance following 2-day HFD, β -cell specific SENP1 knockout mice show rapidly worsening glucose tolerance and a loss of compensatory insulin exocytosis.

Conclusion: Redox signaling and SENP1 are indispensable in β -cell functional compensation.

Keywords: Functional compensation, HFD, Redox signaling, SENP1

METHOD OPTIMIZATION TO MANUFACTURE OFF-TARGET CELL FREE HUMAN IPSC-DERIVED ISLETS

Nerea Cuesta-Gomez, Ila Tewari Jasra, Kevin Verhoeff, Perveen Anwar, Rena Pawlick, Nidheesh Dadheech, and James Shapiro

Department of Surgery, Faculty of Medicine and Dentistry, University of Alberta

Background: Human pluripotent stem cell (PSC)-based islet cell therapy shows clear advantages over islet transplantation for functional diabetes cure. Major limitation with this approach is the impure cell product that contains undifferentiated off-target cells producing uncontrolled noncarcinogenic cystic grafts or teratoma. Methods to selectively eliminate such rogue cells within the islet cells may allow rapid clinical translation of PSC-derived islets to treat diabetes.

Methods: We tested chemical and physical modifications in established 7-stage (S1-7) β -cell differentiation protocol to selectively eliminate unwanted iPSC while promoting maturation. Using flow cytometry, endocrine cell composition was assessed in head-to-head comparison during cell differentiation with replication fork inhibitor-Aphidicolin (APH), oleic acid synthesis inhibitor-PluriSln1 (PSln1) in parallel with S5 dispersed and reaggregated endocrine clusters.

Results: Reducing pancreatic progenitor cell proliferation with APH profoundly eliminated contaminating undifferentiated cells to $<0.1\%$ and promoted endocrine cell maturation with $\sim 90\%$ Pdx1+ containing 55% Pdx1+GP2+ and 84% ChrgA+ Nkx6.1+ cells, compared to untreated control cells with $<20\%$ Pdx1+ChrgA+ Nkx6.1+. Moreover, early treatment of oleic acid pathway inhibitor PSln1 at S3-4 during differentiation showed a more pronounced effect for PSC removal but also adversely affected the proliferative endocrine cell population, including Pdx1+ pancreatic progenitors. In parallel, physically disaggregated and reaggregated endocrine clusters after S5 differentiation, modestly eliminated residual contaminating off-target cells to $>0.5\%$ while compromising endocrine cell yield. Cell imaging and histology show positive staining for endocrine cell markers: Insulin, C-peptide glucagon, Chromogranin-A, Pdx1, and Nkx6.1 with both chemical (APH) and physical approaches without much teratogenic Oct4+, Tra1-60+ cells. Furthermore, the enriched cell product with APH displayed improved glucose stimulated insulin release and higher exocytosis than other methods.

Conclusions: Current modifications to differentiation protocols for off-target cell removal holds great promise to produce mature β -cell products. Combining such chemical (APH) and physical (dis-reaggregation) approaches may deliver a newer potential method to manufacture safe, reliable and mature “self” iPSC-islets for GMP-grade cell manufacturing.

Keywords: Endocrine cell enrichment, iPSC- β Cell Generation, Islet Differentiation, Diabetes.

THE LIPID SOLUBLE FORMS OF CHOLINE INFLUENCE THE DEVELOPMENT OF THE GUT-ASSOCIATED IMMUNE SYSTEM IN SPRAGUE-DAWLEY RATS.

Jessy Azarcoya-Barrera, Erin D. Lewis, Catherine J. Field, Susan Goruk, Yves Pouliot, Jonathan M. Curtis, René L. Jacobs, Caroline Richard.

Department of Agricultural, Food and Nutritional Science, University of Alberta.

Background: Oral tolerance is an important T cell mediated process that occurs early in life. This process begins in the gut and can impact both peripheral and local immune responses. The lipid soluble forms of choline have shown to beneficially modulate development of the peripheral immune system, however, little is known about the impact of dietary choline on the development of the gut-associated lymphoid tissue (GALT), an important modulator of glucose homeostasis and obesity-related insulin resistant. Therefore, the objective of this study was to determine the effect of feeding different forms of choline on the development of the GALT.

Methods: Three previous studies from our group were included. The studies were as follow: 1) a diet containing 100% phosphatidylcholine (PC) vs. a control diet containing 100% free choline (FC); 2) a diet high in glycerophosphocholine (GPC; 75% GPC, 12.5% PC, 12.5% FC) vs. a control diet (100% FC); 3) a diet high in sphingomyelin (SM) and PC (SMPC; 34% SM, 34% PC, 17% GPC, 7% FC, 5% phosphocholine, 3% Lyso-PC), a diet containing 50% PC (25% FC, 25% GPC) vs. a control diet (100% FC). Diets were fed from weaning to 10-weeks of age. *Ex vivo* cytokine production by mesenteric lymph nodes (MLN) stimulated with Concanavalin A (ConA) and Ovalbumin (OVA) was measured.

Results: MLN from rats that consumed 100% PC diet had a higher production of interferon (IFN)- γ after ConA stimulation compared to its respective control. Rats on the GPC diet had a lower production of interleukin (IL)-2 and IFN- γ after ConA stimulation compared to its respective control. Rats that consume the SMPC and 50%PC diets had a higher production of IL-2 and TNF- α after ConA stimulation, a higher production of IL-10 after both ConA and OVA stimulation and a lower production of IL-2, TNF- α and IL-6 following OVA stimulation vs. the control diet. Rats from the SMPC diet had, in addition, a higher production of IFN- γ (vs. the control diet only).

Conclusion: Our results suggest that a diet containing 50% PC or a mixture of lipid soluble forms of choline (SM and PC) had a greater beneficial effect on the development of the GALT. Moreover, the lower cytokine response after OVA stimulation could be beneficial for the induction of oral tolerance. On the other hand, a diet high in water-soluble forms (GPC) does not appear to confer the same immune benefits as the lipid soluble forms of choline on the development of the GALT.

Key words: choline forms, immune system, GALT, early developmental period.

UNDERSTANDING THE PHYSIOLOGICAL ROLE OF ETHANOLAMINE PHOSPHATE PHOSPHOLYASE IN MICE

Kholoud Alaa El-Mihi^{1,3}, Kelly-Ann Leonard¹, Randal Nelson², Robin D. Clugston⁴, René L. Jacobs^{1,2}.

1 Agricultural, Food and Nutritional Sciences Department, University of Alberta, Edmonton, Alberta, Canada.

2 Department of Biochemistry, University of Alberta, Edmonton, Alberta, Canada

3 Biochemistry Department, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt.

4 Department of Physiology, University of Alberta, Edmonton, Alberta, Canada

Background: Phospholipid metabolism is linked to liver health, insulin signaling, and whole-body energy metabolism. Alterations in the hepatic ratio of phosphatidylcholine (PC) and phosphatidylethanolamine (PE) have been associated with the development of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis. We have identified a potential new regulator of PE synthesis, ethanolamine phosphate phospholyase (ETNPPL), that could impact the development and progression of NAFLD. Importantly, ETNPPL expression is reduced in humans who develop hepatocellular carcinoma. ETNPPL converts phospho-ethanolamine to acetaldehyde, ammonia, and phosphate, which we predict would reduce PE synthesis and potentially supply acetate to cellular processes. Thus, the purpose of this project is to understand the physiological role of ETNPPL in regulating lipid metabolism

Methods: 8- 10-week-old ETNPPL WT (*etnppl*^{+/+}) and ETNPPL KO (*etnppl*^{-/-}) mice (C57B6/N) were fed a standard chow or high fat diet (HFD) (D12451i, 45% fat) for 8 weeks. Glucose tolerance test (GTT) and metabolic profiling were performed on HFD-fed mice. At the end of the feeding trial, fasted samples (plasma, liver) were collected for histology and lipid analysis.

Results: Chow-fed female *etnppl*^{-/-} mice had increased hepatic triacylglycerol (TG) accumulation with little change in plasma lipids. However, *etnppl*^{-/-} female mice had reduced weight gain as compared to *etnppl*^{+/+} mice when fed a HFD for eight weeks, which was associated with lower fasting glucose and a slight improvement in GTT. The reduction in weight gain may be explained by increased energy expenditure in *etnppl*^{-/-} mice. To our surprise, HFD-fed *etnppl*^{-/-} mice had reduced hepatic lipid storage and no changes in hepatic PE or PC/PE ratio.

Conclusion: ETNPPL plays a previously unreported role in regulating hepatic lipid metabolism and whole-body energy expenditure. Future studies will attempt to understand the biological mechanism for these observations.

Key words: ETNPPL, fatty liver, high fat diet, triacylglycerol.

Low-fat dairy consumption favorably modulates immune function more than high fat dairy in a low birthweight swine model of insulin resistance

Yongbo She^{1,2}, Kun Wang^{1,2}, Ben Willing¹, Sue Tsai³, Spencer D. Proctor^{1,2}, Caroline Richard^{1,2}

¹Division of Human Nutrition, ²Metabolic and Cardiovascular Diseases Laboratory, and/or ³Department of Medical Microbiology and Immunology, University of Alberta, Edmonton, Alberta, Canada.

Background: Biomarkers of dairy consumption have been inversely associated with variables of diabetes, insulin resistance (IR) and immune dysfunction. To understand the effect of consuming dairy fat *per se* on cardiometabolic risk factors and immune function in the context of IR, we used an established low birthweight (LBW) swine model of high fat (HF) diet-induced IR to compare the effects of diet supplementation with regular fat dairy products or low-fat dairy products versus un-supplemented control HF diet (CHF).

Hypotheses/Aim: We hypothesized that consuming a diet rich in dairy fat will improve cardiometabolic perturbations and immune function in the context of early IR and diabetes risk.

Methodology: At 5 weeks of age, LBW piglets were randomized to consume one of the 3 experimental diets: 1) CHF, 2) High-fat (HF) diet supplemented with 3 servings of HF dairy (HFDairy) and 3) HF diet supplemented with 3 servings low-fat (LF) dairy (LFDairy). As comparison groups, normal birthweight (NBW) piglets were fed a CHF or standard pig grower diet (Chow). A total of 35 pigs (LBW-CHF n=8, LBW-HFDairy n=8, LBW-LFDairy n=8, NBW-CHF n=6, NBW-Chow n=5) were fed for 7 weeks. At 12 weeks of age, peripheral blood immune cell responses to mitogens were assessed and compared across the above groups.

Findings: As expected, myristic acid (C14:0) and pentadecanoic acid (C15:0) levels in liver tissue were found to be higher in LBW-HFDairy than in LBW-CHF and LBW-LFDairy. There were no differences in fasting concentrations of triglyceride, total cholesterol and low-density lipoprotein cholesterol in any HF diet fed groups. However, fasting glucose in LBW-HFDairy was lower than LBW-CHF. HF dairy consumption had minor effects on immune parameters measured, whereas IL-2 and IFN- γ levels in LBW-LFDairy were found to be higher than in LBW-CHF after mitogen stimulation. Similarly, TNF- α levels in LBW-LFDairy were also found to be higher than in LBW-CHF after mitogen stimulation.

Summary: Current findings suggest that consumption of 3 servings/day of HF dairy products significantly increased the incorporation of dairy-derived fatty acids in liver tissue; however, did not modulate fasting lipid profile despite lowering (improving) fasting glucose and HOMA-IR. HF dairy had little effect on immune function, whereas LF dairy consumption ameliorated immune function, particularly T cell function in the context of early IR and diabetes risk.

Founding sources: Agriculture Funding Consortium, NSERC Discovery Program, Dairy Farmers of Canada-Nutrition Research Program

ASSOCIATION OF DAIRY CONSUMPTION PATTERNS WITH THE INCIDENCE OF TYPE 2 DIABETES: FINDINGS FROM ALBERTA'S TOMORROW PROJECT

Emad Yuzbashian¹, Mohammadreza Pakseresht², Jennifer Vena³, Catherine B. Chan^{1,4}

¹Department of Agricultural, Food and Nutritional Science, ^{2,3}Alberta Health Services, Edmonton, Alberta; ⁴Department of Physiology, University of Alberta, Edmonton, Alberta

Background: Recent research on whether dairy consumption is linked to type 2 diabetes (T2D) has reached mixed results. Epidemiological studies of the health effects of dairy have focused on it as a food group or single food. However, people's behavior toward food is very complex, and individuals consume a variety of dairy foods. It is probable that higher intakes of combinations of dairy foods concurrently influence the risk of T2D. Thus, we aimed to extract dairy consumption patterns (DCP) of men and women from the Alberta's Tomorrow Project (ATP) cohort and then assess the association of each extracted dairy pattern with the risk of T2D.

Methods: This prospective study was conducted within the framework of ATP, a provincial cohort of middle-aged adults, in which 8615 men and 15016 women without diabetes provided baseline dietary (via valid and reliable semi-quantitative food-frequency questionnaire) and personal health (including chronic diseases) data at baseline and were followed up. We calculated DCP using Principal Component Analysis (PCA) in SPSS. Incident T2D at follow-up was self-reported via questionnaire. We used multivariable logistic regression models to calculate odds ratios (OR) and 95% confidence intervals (CI) to estimate the association between extracted DCP and T2D incidence. Models were adjusted for age, body mass index, total energy intake, physical activity, education level, smoking status, alcohol consumption, and stress index as well as intakes of fruit, vegetables, grains, meat (processed and red) and added sugar that are associated with dairy intake and are risk factors for T2D.

Results: Three major DCPs were identified using PCA: low-fat dairy DCP (characterized by consumption of non-fat milk and reduced- and non-fat cheese), 2% fat dairy DCP (2% milk in cereal and to drink), and high-fat dairy DCP (whole milk to drink and in cereal and coffee). The incidence of T2D among men and women was 3.8 and 3.2% over the follow-up period (average follow-up time: 5.7±2.7 years), respectively. After controlling for potential confounders, the OR for men in the highest compared with those in the lowest quartile of the high-fat dairy DCP was 0.64 (95% CI: 0.47 to 0.88, P-trend=0.001). Low-fat dairy DCP and 2% fat dairy DCP were not associated with incident T2D in men or women.

Conclusion: Adherence to a high-fat dairy DCP was associated with decreased risk of incident T2D in men only while following a low-fat dairy DCP and 2% fat dairy DCP had no association with T2D. Our results support current evidence that dairy fat might be favorable for health maintenance; however, the association only was seen among men.

Keywords: Dietary pattern, Principal component analysis, Type 2 diabetes

ADI Research Day 2021



Alberta Diabetes
INSTITUTE

2021 ADI Research Day

November 1 and 2, 2021

CELEBRATING
100
YEARS OF **INSULIN**