2018 RESEARCH DAY
08.30-16.00 | Lister Centre, Maple Leaf Room | University of Alberta

TUESDAY OCTOBER 2

KEYNOTE SPEAKER
RICHARD DIMARCHI, PhD
Sandiford H. Cox Distinguished Professor of Chemistry,
Linda & Jack Gill Chair in Biomolecular Sciences,
Indiana University, USA
Program

2018 ADI RESEARCH DAY
Tuesday October 2
LISTER CENTRE, Maple Leaf Room, University of Alberta

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Thank you to our generous event sponsors MERCK and Eli Lilly and to the Alberta Diabetes Foundation for providing door prizes.

Leading the World in the Prevention, Treatment and Cure of Diabetes
Welcome to the 2018 Alberta Diabetes Institute Research Day. Activities at the ADI range from the study of immunology, basic cell/molecular biology and bioengineering to clinical research, nutrition and exercise, population health and the development of public policy in diabetes care. We also continue to grow – we have 59 ADI principal investigators and >200 trainees/staff, making us one of the largest and most active diabetes centres worldwide.

This annual event is intended to provide a forum to showcase the research efforts of our ADI Trainees – this year our trainees will present 15 oral presentations and 32 poster presentations. We made a few changes to the day, for example, the oral presentation session is now 3 sessions of 5 speakers each (rather than 4 sessions). This change provided extra time for the “Trainee Lunch with the Speaker” event – organized by the ADI Trainee Working Group – all ADI Trainees presenting (podium / poster) and the ADI TWG members are invited to attend.

After lunch the poster presentation is from 1:00-2:30 pm please stop by each poster to see what exciting research our trainees are doing! Remember, for some of our trainees it will be the first time presenting their research in front of an audience of their peers, supervisors and principal investigators. Today is about giving you, as the next generation of diabetes researchers, an opportunity to present your most recent exciting results and ideas.

Research at the Alberta Diabetes Institute is made possible by your dedication and excellence. Through your efforts, we are ideally positioned to continue to make major advances in the prevention and treatment of diabetes, and ultimately to find a cure. We hope that you will be inspired by your peers to continue to excel in your scientific endeavours and I encourage you to ask questions during both the talks and poster sessions.

Thank you to our volunteer judges, session chairs, and a/v support. Also, thank you to the Alberta Diabetes Foundation, our long-standing funding partner for their continued efforts in raising money to support our research projects and trainees. Finally, I would also like to take this opportunity to thank our sponsors Merck Canada and Eli Lilly Canada for their generous and continued support of this research day and for sponsoring the visit of our esteemed guest speaker, Dr. Richard DiMarchi.

Best Regards,

Peter Light, PhD
Director, Alberta Diabetes Institute
Dr. Charles A. Allard Chair in Diabetes Research
Professor of Pharmacology
# 2018 ADI Research Day

**Tuesday October 2**  
Lister Centre, Maple Leaf Room, University of Alberta

## Morning Session

### Welcome

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<tr>
<td>0830-0844</td>
<td>Dr Peter Light</td>
<td>Welcome &amp; Overview</td>
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### Keynote Speaker

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<tr>
<td>0845-0945</td>
<td>Dr Richard DiMarchi</td>
<td>Chemical evolution of metabolic hormones.</td>
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<td>Indiana University</td>
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<td>0946-0954</td>
<td>Refreshment Break</td>
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<td>PRAIRIE ROOM</td>
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<tr>
<td>0955-1005</td>
<td>Bradi LORENZ</td>
<td>Metformin restores $\alpha/\beta$ cell ratio in 6 month-old prediabetic Nile rats</td>
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<td></td>
<td>Summer Student Supervisor: C Chan</td>
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<td>1006-1016</td>
<td>Mazzen BLACK</td>
<td>Evaluation of the role of epithelial (E)-cadherin in the postnatal development of pig islets</td>
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<td>Summer Student Supervisor: G Rayat</td>
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<td>1017-1027</td>
<td>Chen YANG</td>
<td>Assessment of gastrointestinal tolerance of three novel type 4 resistant starches in a human intervention study</td>
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<td>MSc Student Supervisor: J Walter</td>
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<tr>
<td>1028-1038</td>
<td>Koenraad PHILIPPAERT</td>
<td>Dual action of glimepiride on TRPM5 and KATP channels stimulates glucose-induced insulin secretion while preventing hypoglycemic events.</td>
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<td>1039-1049</td>
<td>Jacqueline KRYSA</td>
<td>APOB-remnant dyslipidemia and high-fat meal intolerance enhances metabolic syndrome risk clustering in overweight-obese children</td>
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<td>PhD Student Supervisor: S Proctor</td>
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<tr>
<td>1101-1111</td>
<td>Jamie BOISVENUE</td>
<td>Evaluating gestational diabetes education through a deliberative priority setting</td>
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<td>1112-1122</td>
<td>Malak ALMUTAIRI</td>
<td>The GLP-1R agonist liraglutide improves myocardial glucose oxidation rates via indirect mechanisms and mitigates diabetic cardiomyopathy</td>
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<td>MSc Student Supervisor: J Ussher</td>
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<tr>
<td>1123-1133</td>
<td>Kristin HARMS</td>
<td>Low diet diversity is associated with an increased expression of cardio-metabolic dysregulation and frailty in a cohort of adults with diabetes mellitus and chronic kidney disease</td>
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<td>Research Associate Supervisor: D Mager</td>
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<td>1134-1144</td>
<td>Jessy AZARCOYA BARRERA</td>
<td>Feeding a maternal diet containing buttermilk improves the ex vivo immune response to a T cell mitogen in lactating dams</td>
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<td></td>
<td>PhD Student Supervisors: C Richard / R Jacobs</td>
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<tr>
<td>1145-1155</td>
<td>Hayford AVEDZI</td>
<td>Healthy eating and active living for diabetes-glycemic index (HEALD-GI): A pragmatic randomized controlled trial</td>
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<td>PhD Student Supervisor: S Johnson</td>
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## AFTERNOON SESSION

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<td><strong>TRAINEE EVENT</strong></td>
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| 1200-1255 | Trainee LUNCH with Keynote Speaker Dr R DiMarchi  
AURORA ROOM  
• TRAINEES / Dr DiMarchi Round Table Discussion – organized by the ADI Trainee Working Group  
• INVITED PARTICIPANTS – ADI Trainees Presenting at Research Day & ADI TWG Members and Dr DiMarchi |
| **POSTER PRESENTATIONS**                                                                               |
| 1300-1430 | 32 Posters  
• Posters located at the back of Maple Leaf Room  
• 2 poster judges per category  
• Poster presenters have 5 minutes in total to present their poster (3 min presentation to the judges with 2 minutes for Q&A) |
| **SESSION 3**                                                                                           |
| 1435-1445 | Janyne JOHNSON  
Summer Student  
Supervisor: P Light  
HUMAN ISLETS EXPRESS A SUBPOPULATION OF GLP-1 SECRETING ALPHA CELLS THAT IS UPREGULATED AND SUPPORTS INSULIN SECRETION IN TYPE 2 DIABETES. |
| 1446-1456 | Shaelyn HOULDER  
Summer Student  
Supervisor: J Yardley  
MORNING VS AFTERNOON PERFORMANCE OF RESISTANCE EXERCISE IN TYPE 1 DIABETES: INTERSTITIAL GLUCOSE RESPONSES |
| 1457-1507 | Camila ORSSO  
MSc Student  
Supervisor: A Haqq  
DEVELOPMENTAL REGULATION OF OBESTATIN AND ADROPIN IN PRADER-WILLI SYNDROME AND NON-SYNDROMIC OBESITY: ASSOCIATIONS WITH WEIGHT, BMI-Z, HOMA-IR, AND LIPID PROFILE |
| 1508-1518 | Jiaxin LIN  
PhD Student  
Supervisor: C Anderson  
A REDUCED INTENSITY CONDITIONING PROTOCOL INDUCES CHIMERISM AND TRANSPLANT TOLERANCE TO FULLY ALLOGENEIC ISLETS IN AUTOIMMUNE DIABETIC NOD MICE |
| 1519-1529 | Megan JARMAN  
Postdoc Fellow  
Supervisor: R Bell  
DESCRIPTION OF INFANT FEEDING PRACTICES AT 3 MONTHS POSTPARTUM IN WOMEN WHO EXPERIENCED DIABETES IN PREGNANCY |
| **WRAP UP & PRIZES**                                                                                     |
| 1545-1600 | WRAP UP, AWARDS, AND PRIZES  
Facilitated by Dr Peter Light |
KEYNOTE SPEAKER

Richard DiMarchi, PhD

Dr. DiMarchi’s contributions in peptide & protein sciences consists of three decades of work in academia, the pharmaceutical industry and biotechnology companies. He is the Cox Distinguished Professor of Biochemistry and Gill Chair in Biomolecular Sciences at Indiana University. He is a co-founder of Ambrx, Inc., Marcadia Biotech, Assembly, Calibrum and MB2 Biotech. He has served as a scientific advisor to multiple pharmaceutical companies and venture funds. He is currently Chairman of the Peptide Therapeutics Foundation and external board member at Assembly Biosciences.

Dr. DiMarchi is a Vice President at Novo Nordisk Research Laboratories and a retired Group Vice President at Eli Lilly & Company where for more than two decades he provided leadership in biotechnology, endocrine research and product development. He is readily recognized for discovery and development of rDNA-derived Humalog® (LisPro-human insulin). As scientist and executive, Dr. DiMarchi also significantly contributed to the commercial development of Humulin®, Humatrope®, rGlucagon®, Evista®, and Forteo®. His current research is focused on developing macromolecules with enhanced therapeutic properties through biochemical and chemical optimization, an approach he has termed chemical-biotechnology. His academic research has broadened the understanding of glucagon physiology while championing the discovery of single molecule mixed agonists for the treatment of diabetes and obesity. He is identified as a top-five translation researcher by Nature Biotechnology for the years 2014 and 2015.

Dr. DiMarchi is the recipient of numerous awards including the 2005 AAPS Career Research Achievement Award in Biotechnology, the 2006 ACS Barnes Award for Leadership in Chemical Research Management, the 2006 ACS Esselen Award for Chemistry in the Service of Public Interest, the 2007 Carothers Award for Excellence in Polymer Sciences, the 2009 Watanabe Award for Life Sciences Research, the 2011 Merrifield Award for Career Contributions in Peptide Sciences, the 2014 German National Erwin Schrödinger-Preis, the 2015 Meienhofer Prize, 2015 Max Bergmann Medal and the 2016 ACS Alfred Burger Career Award in Medicinal Chemistry. He was inducted into the National Inventors Hall of Fame in 2014 and the National Academy of Medicine in 2015.
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PRIZES

Prize announcements at 15:45-16:00

ORAL PRESENTATION AWARDS

- 1 Best Award :: SUMMER STUDENT
- 1 Best Award :: MSC STUDENT
- 1 Best Award :: PHD STUDENT
- 1 Best Award :: POSTDOCS / RESEARCH ASSOCIATES

POSTER PRESENTATION AWARDS

- 1 Best Award :: SUMMER STUDENT
- 1 Best Award :: MSC STUDENT
- 1 Best Award :: PHD STUDENT
- 1 Best Award :: POSTDOCS / RESEARCH ASSOCIATES

DOOR PRIZES

- Door prize draws at end of ADI Research Day (courtesy of Alberta Diabetes Foundation)
- Must be in attendance to collect a prize
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## Abstracts

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<td>LOW DIET DIVERSITY IS ASSOCIATED WITH AN INCREASED EXPRESSION OF CARBOHYDRATE-METABOLIC DYSREGULATION AND FRAILTY IN A COHORT OF ADULTS WITH DIABETES MELLITUS AND CHRONIC KIDNEY DISEASE</td>
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<td>C Anderson</td>
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<td>THE EFFECTS OF BRAIN GLUCAGON SIGNALLING ON LIVER LIPID SECRETION</td>
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<td>P Senior</td>
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METFORMIN RESTORES THE α/β CELL RATIO IN SIX-MONTH-OLD PREDIABETIC NILE RATS
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Background: The Nile rat (NR) is a novel model of spontaneous type 2 diabetes (T2D) that develops T2D when fed a standard laboratory chow diet. It has previously been reported that the NR undergoes progression through five stages of T2D similar to that of humans. These stages of T2D progression can be characterized by morphological changes in pancreatic islet structure. Although loss of β-cell mass does not necessarily bring on T2D, β-cell dysfunction plays a role in disease progression. This dysfunction can then lead to changes in β-cell area and alter the α/β cell ratio which may further T2D progression. Metformin (Met) is a drug that has previously been shown to improve glucose tolerance in pre-diabetic Nile rats. However, the mechanism by which this occurs is still unknown. We hypothesize that intervention with Metformin on young, prediabetic NRs may prevent the early onset of islet morphological changes.

Methods: After weaning, NRs were randomized into two groups: fed a standard laboratory chow diet (Chow) or a high-fibre diet (HF). Chow animals were further randomized into two groups: Chow or Chow-Met, without/with Metformin. Animals were euthanized at either three or six months and their pancreases were collected. Pancreatic tissue was then mounted onto slides and used in immunohistochemical peroxidase staining to determine α- and β-cell area. Immunofluorescent staining was also performed to determine the presence of Ki67, a cellular marker for proliferation. Cell proliferation rate was calculated by dividing the number of Ki67+/Insulin+ cell to the total number of Insulin+ cell.

Results: At three months, both Chow and Chow-Met NRs displayed significantly higher relative β-cell area and average islet size than HF-fed NRs. Increase in α-cell area was detected in Chow but not in Chow-Met, leading to a significantly lower α/β cell ratio in Chow-Met than HF at three months. At six months, Chow-fed NRs maintained significantly higher relative β-cell area than HF and there was no difference between Chow-Met and Chow or Chow-Met and HF. Chow-Met and HF NRs showed a significantly higher α/β cell ratio than Chow, thought the difference in α-cell area was not significant at six months. However, unlike the increase in β-cell area, the β-cell proliferation rate was actually decreased in Chow and Chow-Met compared with HF at 3 months. The proliferating cells marked by Ki67 in Chow and Chow-Met at 6 months was barely detectable.

Conclusion: Our findings suggest that Metformin does not prevent the increase in β-cell area, but it does restore α/β cell ratio in six-month-old Chow-fed NRs. These morphological changes observed is not due to cell proliferation. Further studies should be done to investigate apoptosis and neogenesis in islet, as well as β-cell function to determine the mechanism by which Metformin improves glucose tolerance in NRs.

Keywords: Nile rats, type 2 diabetes, Metformin, islet morphology

ADI Research Day, October 2, 2018
EVALUATION OF THE ROLE OF EPITHELIAL (E)-CADHERIN IN THE POSTNATAL DEVELOPMENT OF PIG ISLETS

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**Background:** Islet transplantation is being considered as an alternative treatment for Type 1 Diabetes Mellitus. The shortage of human donors limits this therapy, and therefore, our group is studying pig islets as a potential alternative source. More transgenic pigs are being created with the aim of preventing graft rejection; however, this strategy may compromise the biology and function of the islets. The overall aim of this project is to gain a better understanding of the basic biology of pig islets, so that transgenic pig islets are able to fulfil their intended use. The specific objective of this project is to investigate the role of E-cadherin, a type of cell adhesion molecule, in the development of pig islets.

**Methods:** Pancreatic tissues were harvested from 1-, 3-, 7-, and 10-day-old pigs (n=4 for each) and were fixed in a zinc-formaldehyde fixative for 24 hours. The tissues were then embedded in paraffin. Additionally, islets were isolated from pigs of the ages listed above (n=4) and cultured in Ham's F10 medium. Islets were collected at day 0, 1, 3, 5, and 7 of culture. The islets were fixed, as described above, and embedded in paraffin. Pancreas and islets were stained using immunohistochemistry to detect the expression of E-cadherin, insulin, glucagon, and cytokeratin-7 (CK-7), a marker for precursor islet cells. Images were taken and analyzed for expression of these molecules.

**Results:** In the pancreas, the protein expression of E-cadherin is less in 1- and 3-day-old pigs, compared to the pancreas from 7- and 10-day-old pigs. E-cadherin expression in pancreas from 7-day-old pigs is higher than that from 10-day-old pigs. While insulin expression is increased in pancreas from older pigs, glucagon and CK-7 expression is higher in pancreas of younger pigs. The stained islets from 1-day-old pigs display a higher expression of E-cadherin compared to the islets from 10-day-old pigs. Islets from 1-day-old pigs show lower expression of E-cadherin, insulin, and glucagon at days 0 and 1 of culture. At days 3 and 5 of culture, the E-cadherin, insulin, and glucagon expression is higher, and cells begin to form clusters. At day 7 of culture, E-cadherin is expressed around the islets, with intense and plentiful insulin as well as glucagon expression. Islets from 10-day-old pigs are already developed by day 0 of culture, expressing insulin and glucagon, and lower E cadherin. Higher expression of CK-7 is observed in 1-day-old pig islets at early days of culture, with little expression of CK-7 in 10-day-old pig islets.

**Conclusion:** Results suggest that E-cadherin plays a crucial role in the formation of the islets during early development. As the islets mature, E-cadherin appears to maintain the islet's outermost structure.

**Keywords:** Epithelial-cadherin, Cell Adhesion Molecule, Pig Islets, Xenotransplantationss
ASSESSMENT OF GASTROINTESTINAL TOLERANCE OF THREE NOVEL TYPE 4 RESISTANT STARCHES IN A HUMAN INTERVENTION STUDY

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Background: Dietary fibers offer potential health benefits, yet intake in Canada is half of that recommend. Resistant starches (RS) can replace digestible starch in flour-based foods and are typically being well tolerated offering potential physiological benefits to the consumer. Prior to utilizing novel RSs in the food supply, an assessment of gastrointestinal (GI) tolerance is essential. The objective of this study was to assess the GI tolerance of three novel RS type 4 (RS4) at an increasing dose of fiber from 10 to 50 g/day in healthy adults.

Method: Using a randomized, double blind, placebo-controlled four-arm human trial, 40 participants were assigned to consume one of three RS4s (derived from either hi-maize, potato, or tapioca) or a forth-digestible corn starch (control). During the 4 week dietary intervention, the dose of fiber provide as RS4 was increased weekly from 10 g to 50 g/day. A composite GI tolerability score (sum of individual GI symptoms), stool frequency, stool consistency, and perceived satiety were assessed at the end of each study week.

Results: Overall, the average supplementation compliance was high at 98.9%. The composite GI tolerability scores were affected by supplement dose when considering all treatments. However, the average composite GI score remained below 3 on the 12 point scale, consistent with only a “somewhat more than usual” or no increase in GI symptoms. Furthermore the RS4s were tolerated as well as the control, indicating that all RS4s were tolerate well at 50 g/day, with potato RS4 being tolerated the best. Supplementation with 50 g/day significantly increased bowel movement frequency and reduced fecal hardness, particularly in Potato RS4 group when compared to baseline. Perceived satiety at 4-hrs after a meal was significantly increased by each dose, especially for Maize RS4 and Potato RS4. However, due to the high inter-individual variation at baseline and low sample size, caution should be taken.

Conclusion: Enrichment of food products with around 10 g/serving of all three RS4 would be tolerated well, assuming 3-4 servings/day was consumed. Supplementing at least 50 g/day of these RS4 would be plausible in future research on the benefits of fiber supplementation, as only mildly increases in GI symptoms were observed, similar to the control group. RS4 supplementation may enhance perceived satiety but needs further investigation.

Keywords: Resistant Starch Type 4 (RS4); dietary fiber; gastrointestinal symptoms; bowel habits; perceived satiety

ADI Research Day, October 2, 2018
DUAL ACTION OF GLIMEPIRIDE ON TRPM5 AND KATP CHANNELS STIMULATES GLUCOSE-INDUCED INSULIN SECRETION WHILE PREVENTING HYPOGLYCEMIC EVENTS.

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Background: Glimepiride is a third generation sulfonylurea drug, used to stimulate insulin secretion in type II diabetic patients. Since the introduction of tolbutamide, decades of research have lead to the development of compounds like glimepiride that improve the pharmacological effects and largely limit the side effects as hypoglycemia. The interaction of glimepiride with KATP channels, the bona fide target of sulfonylureas, cannot fully explain the differences in observed effects between glimepiride and earlier sulfonylureas. While screening a large library of compounds, we observed that glimepiride potentiates the activity of TRPM5. TRPM5 is a calcium-activated monovalent cation channel that is expressed in the pancreatic beta-cells where it is involved in the regulation of glucose-induced insulin secretion.

Methods and results: We further examined the interaction between glimepiride and TRPM5 in a series of in vitro and in vivo experiments. We observe increased TRPM5-mediated currents upon perfusion of glimepiride in HEK cells. In isolated WT mouse pancreatic islets, we observe calcium activity in the presence of glimepiride, in a lower concentration range compared to Trpm5⁻/⁻ islets. Furthermore, in islets isolated from KATP pore-mutant mice, there is increased Ca²⁺ activity in the beta-cells upon glimepiride application. Ultimately in Trpm5⁻/⁻ mice, glimepiride has less antihyperglycemic effects after a glucose injection compared to WT mice, indicating TRPM5 has a role in the signal transduction of glimepiride in the beta-cells.

Conclusions: The action on TRPM5 is downstream of increases in [Ca²⁺]ᵢ, and as such glucose-dependent. Therefore, our data suggest an explanation for the reduced hypoglycemic effect of glimepiride. Taken together, the promiscuity of glimepiride leads to synergetic action on TRPM5 and KATP channels to stimulate insulin secretion from pancreatic beta-cells. This new information confirms the hypothesis that targeting TRPM5 is a valid approach to stimulate insulin secretion and in fact, is unknowingly already widely used.

Keywords: Sulfonylurea drugs, ion channels, insulin secretion

ADI Research Day, October 2, 2018
APOB-REMNANT DYSLIPIDEMIA AND HIGH-FAT MEAL INTOLEANCE ENHANCES METABOLIC SYNDROME RISK CLUSTERING IN OVERWEIGHT-OBESE CHILDREN

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Introduction: Cardiovascular disease (CVD) is the leading cause of death for patients with type 2 diabetes. Recently, plasma apolipoprotein (apo) B-remnant cholesterol lipoproteins have been causally associated with CVD and ischemic-events in adults. Fasting and non-fasting plasma apoB-remnant lipoproteins are elevated in obesity, insulin resistance as well as type 1 and type 2 diabetes and contribute to early CVD risk in these conditions. Non-fasting or postprandial lipemia (or dietary fat-intolerance following a high-fat meal) includes elevated plasma triglycerides (TG) and apoB48, and fasting plasma apoB48-remnants have been shown to predict elevated non-fasting TG and apoB48 following a high fat-meal in adults. We have shown obese pre-pubertal children and adolescents with the metabolic syndrome have elevated fasting apoB48-remnant lipoproteins compared to healthy-weight youth. The aim of this study is to determine if elevated fasting apoB48-remnant lipoproteins are able to predict postprandial lipemia in healthy-weight and overweight-obese children.

Methods: Fasting and non-fasting plasma concentrations of apoB48 and TG were determined by SDS-PAGE and colorimetric methods following a high-fat meal (62.5% fat, 30% carbohydrates, and 7.5% protein) in healthy-weight and overweight-obese children aged 8-14 years.

Results: Our preliminary data shows fasting and non-fasting apoB48-remnant lipoproteins following a high-fat meal are elevated in overweight-obese compared to healthy-weight youth (apoB48: 8.60 ± 0.99 vs 26.42 ± 3.31, p<0.0001, and apoB48AUC 68.48 ± 9.93 vs. 262.8 ± 27.05 p<0.001). In addition, fasting plasma apoB48-remnant lipoproteins are highly correlated with non-fasting or postprandial response in apoB48AUC (r=0.87, p<0.001).

Conclusion: Our results suggest fasting plasma apoB48-remnant lipoproteins are elevated in overweight-obese youth and can predict postprandial lipemia in response to a high-fat meal, and these appear to be early biomarkers of the metabolic syndrome in youth.

Key words: lipids, obesity, children

ADI Research Day, October 2, 2018
EVALUATING GESTATIONAL DIABETES EDUCATION THROUGH A DELIBERATIVE PRIORITY SETTING

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Objectives: Management of gestational diabetes mellitus (GDM) relies heavily on timely patient education. For many, pregnancy is enlightening however, this experience can be overwhelming when one is diagnosed with GDM. To adequately manage GDM, women are asked to closely monitor blood glucose and eating habits with good self-discipline to manage dysglycemia[1]. The guidance provided by a multidisciplinary health care team in delivering gestational diabetes education helps improve self-care behaviors and birth outcomes[1]. This study aims to explore GDM education and care experiences amongst women diagnosed with GDM who are attending publicly provided education classes at diabetes clinics in Edmonton, Alberta, Canada.

Methods: A deliberative priority-setting methodology was used as defined by the Canadian Institute of Health Research (CIHR)[2]. Using deliberative priority-setting, a dialogue was established through six working sessions with 5 women with GDM and 7 diabetes health care providers. The iterative working sessions identified perceptions of educational material provided in classes, feelings and emotions surrounding GDM, and how the healthcare system can improve to meet the needs of the participants better.

Results: Twelve priorities were identified by a combination of nurses, dietitians, and women with GDM. These include future impacts of GDM on mother and child, blood glucose number interpretation; insulin administration instruction; GDM pathophysiology; how to manage GDM when basic necessities and support are unavailable; language and culture-specific materials; mental health and emotional management and ensuring consistent communication and messaging from health care providers. Participants identified a website (www.diabetes-pregnancy.ca) used as a shared resource in this region as an effective way to provide supplementary information to women and was decided as the main priority to re-design. Participants were most interested in incorporating materials into the site that focused on capturing the patient narrative through text and video.

Conclusions: Women with GDM and health care providers identified the need for consistent, readily accessible information and determined a priority list of items that they would find most helpful. The iterative working sessions created a priority-setting partnership amongst study participants, which allowed for honest dialogue on issues relevant to women living with GDM and their health care providers. The use of an online resource that women can access before and after attending a GDM education class may help solidify learning and improve self-care behaviors.

Keywords: Gestational diabetes, education, deliberative priority-setting,
THE GLP-1R AGONIST LIRAGLUTIDE IMPROVES MYOCARDIAL GLUCOSE OXIDATION RATES VIA INDIRECT MECHANISMS AND MITIGATES DIABETIC CARDIOMYOPATHY

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Purpose: Type 2 diabetes (T2D) is associated with an increased risk for cardiovascular disease. Of interest, liraglutide, a therapy for T2D that activates the glucagon-like peptide-1 receptor (GLP-1R) to augment insulin secretion, reduces cardiovascular-related death in people with T2D. However, it remains enigmatic as to how liraglutide may reduce cardiovascular death in patients with T2D. Importantly, the GLP-1R is not expressed in ventricular cardiac myocytes, so it is likely that indirect actions independent of the myocardium are involved. We hypothesized that augmented insulin secretion is a key factor contributing to liraglutide-induced cardioprotection, which thereby increases myocardial glucose oxidation.

Method: C57BL/6J male mice were fed either a low-fat diet (lean) or were subjected to experimental T2D and treated with either saline or liraglutide (30 g/kg via subcutaneous injection) 3x over a 24-hr period. 2-hrs following the final injection, all mice were euthanized and had their hearts perfused in the working mode to assess myocardial energy metabolism. In a separate cohort of mice subjected to our experimental model of T2D, animals were randomized to receive either vehicle control or liraglutide treatment for 2-weeks, and cardiac function was assessed via ultrasound echocardiography prior to and upon completion of the study.

Results: Systemic treatment of lean mice with liraglutide increased myocardial glucose oxidation rates without affecting glycolysis rates. Conversely, direct treatment of the isolated working heart with liraglutide had no effect on glucose oxidation. These findings were recapitulated in mice with experimental T2D and associated with increased circulating insulin levels. Furthermore, Liraglutide treatment attenuated declining diastolic function in mice with experimental T2D.

Conclusion: Our data demonstrates that liraglutide augments myocardial glucose oxidation via indirect mechanisms, which may mechanistically explain how liraglutide improves cardiovascular outcomes in people with T2D.

Key words: GLP-1, Glucose Oxidation ,Diabetic Cardiomyopathy
LOW DIET DIVERSITY IS ASSOCIATED WITH AN INCREASED EXPRESSION OF CARDIO-METABOLIC DYSREGULATION AND FRAILTY IN A COHORT OF ADULTS WITH DIABETES MELLITUS AND CHRONIC KIDNEY DISEASE

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Background: Cardio-metabolic dysregulation (CMD) and Frailty are significant co-morbid conditions in adults with type 1 and type 2 diabetes mellitus (DM) with chronic kidney disease (CKD). Although, poor diet quality (DQ) has been shown to influence CMD and Frailty, no information is available regarding the influences of diet diversity (DD). DD reflects the variability in food intake between and within a food group and is an important factor that determines the overall health value (HV) of an individual's diet. The study objective was to evaluate the associations between DD with CMD and Frailty prevalence in adults with DM and CKD.

Methods: We prospectively studied DD in adults (n=16F/34M) with type 1 (n=2) and type 2 DM (n=48) and CKD (stages 2-5) using 3-day food intake records. Dietary data was analyzed using the Canadian Nutrient File. DD was measured using two validated methods: 1) Berry Index (BI) and the Healthy Food Diversity Index (HFD-I). Blood work indicative of CMD (TG, HDL-and-LDL cholesterol, total cholesterol (TC), C-reactive protein (CRP), glycemic control (hemoglobin A1C (A1C), glucose) and renal function (urea, creatinine, eGFR, PTH) was collected. Frailty was assessed using the Edmonton Frail Scale.

Results: Mean age, BMI, DM duration was 67.2 ± 8.6 yrs, 31.6 ± 5.9 and 19.1 ± 11.7 yrs, respectively. In comparison to healthy adults, BI (0.86 ± 0.04) and HFD-I (0.35 ± 0.16) was low (p<0.05). Dietary BI and HFD-I was positively correlated with plasma HDL-cholesterol (p=0.04) and inversely related to levels of TG (p=0.006) and TC (p=0.005), but not to plasma CRP, LDL-cholesterol, A1C, glucose, urea, creatinine, CKD stage or DM type (p>0.05). BI (frail: 0.74 ± 0.04 vs non-frail: 0.87 ± 0.03 p<0.001) and HFD-I (frail:0.39 ± 0.13 vs non-frail: 0.05 ± 0.2; p=0.02) were lower in frail participants.

Conclusion: Low DD was associated with Frailty and CMD prevalence. Dietary interventions aimed at improving DD may be important therapeutic targets to reduce the risk for long term complications such as CMD and Frailty in adults with DM and CKD.

Key words: Diet diversity, kidney disease, diabetes mellitus, cardio-metabolic dysregulation

ADI Research Day, October 2, 2018
FEEDING A MATERNAL DIET CONTAINING BUTTERMILK IMPROVES THE EX VIVO IMMUNE RESPONSE TO A T CELL MITOGEN IN LACTATING DAMS

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Background: Choline is an essential nutrient needed during pregnancy and lactation; currently 77-90% of Canadian women do not meet daily recommendations. Choline exists in different forms in the diet including water soluble (free choline (FC), glycerophosphocholine (GPC) and phosphocholine (Pcho)) and lipid soluble (phosphatidylcholine (PC) and sphingomyelin (SM)) forms. We have previously demonstrated in rodents that feeding lactating dams a mixture of choline forms (PC, GPC and FC) resulted in a more efficient maternal immune response when compared to FC, a form of choline mainly found in plant based foods. Buttermilk has a unique composition as it is not only rich in total choline but also contains high amounts of SM. It is currently unclear whether dietary SM has any influence on the immune system during pregnancy and lactation. The objective of this study was to determine the effect of buttermilk, as a main source of choline, on maternal immune function during lactation.

Methods: Sprague-Dawley dams were randomized to one of the three nutritionally adequate experimental diet: 1-Control (100% FC), 2-Buttermilk (37% PC, 34% SM, 17% GPC, 7% FC, 5% Pcho) and 3-Placebo (50% PC, 25% FC, 25% GPC). The placebo diet was design to match the composition of the buttermilk diet in term of dairy ingredients (i.e. dairy fat, casein, whey protein and calcium) except for the different choline moieties. Diets all contained the same amount of total choline (1.9 g/kg of diet), were matched for total macro- and micronutrients content and were fed to dams ad libitum from the second week of gestation and throughout the lactation period. At the end of the lactation period, immune cell phenotypes and ex vivo cytokine production by mitogens-stimulated (Concanavalin A (ConA), lipopolysaccharide (LPS)) splenocytes were measured by flow cytometry and ELISA, respectively.

Results: Despite no change in body and organs weight among groups, feeding buttermilk-enriched diet to dams led to a significantly higher production of IL-2, TNF-α and IFN-γ by splenocytes stimulated with ConA (a T cell mitogen) compared to both placebo and control diets (all p<0.05). Dams fed the buttermilk or the placebo diet had a higher production of the regulatory cytokine IL-10 by splenocytes stimulated with LPS (both p<0.05) compared with the control diet. No significant changes were observed in the proportion and activation of immune cell types among groups including helper T and cytotoxic T cells, B lymphocytes, dendritic and natural killer cells and monocytes.

Conclusion: In summary, our results suggest that feeding buttermilk-derived choline forms to lactating dams improves maternal immune responses to a T cell mitogen while having little effect of the proportion of immune cell types. Feeding a mixture of choline forms (both buttermilk and placebo) also improved the ability of splenocytes to produce the regulatory cytokine IL-10 in response to a bacterial an important role in the resolution of inflammation. These finding provide clear evidence that the forms of choline in the maternal diet should be considered for optimal maternal immune health.

Key words: choline forms, pregnancy, lactation period, immunology, spleen

ADI Research Day, October 2, 2018
HEALTHY EATING AND ACTIVE LIVING FOR DIABETES-GLYCEMIC INDEX (HEALD-GI): A PRAGMATIC RANDOMIZED CONTROLLED TRIAL

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Background: Rigorous evidence is needed to support uptake of Diabetes Canada’s evidence-based recommendations to include low glycemic index (GI) foods in daily meal planning as an effective dietary self-care strategy for glycemic control among people with type 2 diabetes (T2D). Objective: To present preliminary findings from the Healthy Eating and Active Living for Diabetes-Glycemic Index (HEALD-GI) trial, a 12-week lifestyle intervention designed to evaluate the effectiveness of a web-based GI-targeted nutrition education on dietary intake and GI-related knowledge among adults with T2D in Edmonton, Alberta.

Methods: Participants (N=67) were randomized to a control group that received standard printed copies of Canada’s Food Guide and Diabetes Canada’s GI resources OR to an intervention group that received those same materials, plus a customized online platform with six self-directed learning modules and supplementary print materials. Each module consisted of a customized video, links to reliable websites, chat rooms, and quizzes. Evidence-based GI concept information included GI values of foods and low-GI shopping, recipes, and cooking tips by a Registered Dietitian. Support through email, text messaging, phone calls, or postal mail to reinforce participants’ learning were also provided. The primary outcome, average dietary GI, was assessed using 3-day food records. Additional measures including GI knowledge and self-efficacy, glycated hemoglobin A1c, lipids, systolic blood pressure, weight and height (for body mass index), waist circumference, and computer proficiency were assessed at baseline and at three months post-intervention.

Results: Participants were 64% men; mean age 69.5 (9.3) years, with mean diabetes duration of 19.7 (14.4) years, BMI 29.9 (5.8) kg/m2, and HbA1c 7.1 (1.2)% at baseline. Final 3-month visits were completed in July 2018; dietary data are being processed now and final results will be made available during full presentation.

Conclusion: The GI concept is often difficult to teach. The HEALD-GI study aims to provide evidence to support the translation of the GI concept to adults with T2D. Findings from this study may help Registered Dietitians and other clinicians to better disseminate low-GI dietary recommendations.

Keywords: Type 2 diabetes, glycemic index, randomized control trial.

ADI Research Day, October 2, 2018
HUMAN ISLETS EXPRESS A SUBPOPULATION OF GLP-1 SECRETING ALPHA CELLS THAT IS UPREGULATED AND SUPPORTS INSULIN SECRETION IN TYPE 2 DIABETES.

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Background: Recent studies in genetic mouse models suggest that intra-islet GLP-1 is required for proper glucose homeostasis, highlighting the importance of paracrine GLP-1 signaling within the islet. However, information on intra-islet GLP-1 expression, secretion and action within human islets, both non-diabetic (ND) and type 2 diabetic (T2D), is lacking. We have identified a GLP-1 expressing alpha cell subpopulation within human islets and compared the difference in GLP-1 expression between ND and T2D human islets as well as characterize the insulin secretory phenotype.

Methods: Human islet sections were stained for glucagon, amidated GLP-1, and insulin. The resultant images were then analyzed, revealing the proportions of insulin+, glucagon+ or GLP-1+glucagon+ (double positive) cells. Human islets were also dispersed and subjected to flow cytometry for further GLP-1 and PC1/3 quantitative analysis. For perifusions, islets were incubated for 3 hours with 2.5mM glucose perfusate, followed by perfusion with 2.5mM glucose and then 11.1mM glucose at 20min. Exendin-9 (100nM), or vehicle control was present during pre-incubation and perfusion. Static GLP-1 secretion experiments were performed at 2.8mM and 11.1mM glucose. Stimulation Index (SI) for insulin secretion was performed at 2.8mM and 28mM glucose.

Results: Human islets in culture secrete ~50-fold more active GLP-1 than mouse islets. GLP-1+glucagon+ cells were identified in ND and T2D islet sections and GLP-1+ staining was restricted to glucagon+ cells. We quantified GLP-1 expression in human islets through flow cytometry (52% of glucagon+ cells) and demonstrated that PC1/3 expression is ~2-fold higher in GLP-1+ cells compared to GLP-1- cells). Image and flow cytometry analysis indicates that there is a significant ~30% increase in the proportion of GLP-1+glucagon+ cells in T2D islets compared to ND islets (42% to 59%, p<0.01). When perfused with Exendin-9, insulin secretion was decreased by 28% in ND islets and by 62% in T2D islets. Finally, active GLP-1 levels negatively correlated with the stimulation index for insulin secretion.

Conclusions: We have identified a novel alpha cell subpopulation in ND and T2D human islets that express and secrete large amounts of active GLP-1. Furthermore, this subpopulation is increased in T2D islets as compared to ND islets. Our results show that intra-islet derived GLP-1 signaling contributes to glucose stimulated insulin secretion (GSIS) in human ND islets, with the effect of intra-islet GLP-1 being even greater in T2D islets. These results suggest that intra-islet GLP-1 plays an important role in the physiology and pathophysiology of human islets.

Key Words: Alpha cell, Intra-islet, GLP-1, pc1/3, incretin hormone

ADI Research Day, October 2, 2018
MORNING VS AFTERNOON PERFORMANCE OF RESISTANCE EXERCISE IN TYPE 1 DIABETES: INTERSTITIAL GLUCOSE RESPONSES

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Background: One small study of resistance exercise (RE) found increases in blood glucose during exercise and recovery in individuals with type 1 diabetes. Conversely, another small study suggested that resistance exercise decreases plasma glucose and increases hypoglycemia during the night. The former involved fasting exercise in the morning, the latter involved exercise at 5pm. This study aimed to determine if the time of day of RE performance influenced interstitial glucose levels following exercise. Because insulin levels are lower in the morning and regulatory hormones such as cortisol and growth hormone may be higher, it is suspected that morning RE will result in higher BG levels.

Methods: Eleven individuals [sex: male n=3 and female n=8; age: 31.3 ± 8.9 years; HbA1c: 7.4 ± 0.8%; predicted VO2max : 39.18 ± 8.2 mL O2 kg−1] performed RE (three sets of eight repetitions of seven exercises) during morning/fasting (7 am) and afternoon (5 pm) trials with at least 48 hours between testing sessions. Interstitial glucose levels were recorded using continuous glucose monitoring.

Results: A significantly (p= 0.037) higher percentage of time was spent in hyperglycemia during the recovery period (0-6 hours after exercise) following morning (median = 61.95%; IQR = 58.54%) RE compared to afternoon RE (median = 11.64%; IQR = 52.13%). Mean absolute glucose change (MAG) in the 6 hours following exercise was also significantly higher after morning exercise (2.66 ± 0.05 mmol/L) compared to afternoon exercise (2.02 ± 0.74 mmol/L; p=0.02), indicating greater glucose variability. Percentage of time in hypoglycemia or euglycemia and mean blood glucose were not significantly different for this period. No significant differences in the percentage of time in hypoglycemia were found between morning and afternoon exercise during the 0-6 hours or overnight following exercise (11pm-6am).

Conclusion: Performance of RE in the morning is associated with higher interstitial glucose levels for 6 hours post-exercise compared to RE performed in the evening. If individuals struggle with low blood glucose levels following resistance exercise, it may be advised that they perform RE in the morning rather than the afternoon. If individuals find hyperglycemia to be an issue after RE, afternoon exercise may be advisable.

Keywords: type 1 diabetes, time of day, resistance exercise

ADI Research Day, October 2, 2018
DEVELOPMENTAL REGULATION OF OBESTATIN AND ADROPIN IN PRADER-WILLI SYNDROME AND NON-SYNDROMIC OBESITY: ASSOCIATIONS WITH WEIGHT, BMI-Z, HOMA-IR, AND LIPID PROFILE

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Background: The peptides obestatin and adropin are thought to regulate glucose and lipid metabolism, weight gain, and fluid intake in adults. The roles of obestatin and adropin in the regulation of weight and glucose and lipid metabolism in Prader-Willi syndrome (PWS) and non-syndromic pediatric obesity are poorly understood. This study compares the concentrations of obestatin and adropin in infants and children with PWS and age- and BMI-z matched controls, and explores the associations between these peptides and other energy-regulating hormones.

Methods: The cohort included 21 infants and 14 children with PWS and 31 controls of similar age, sex, and BMI-z-score. Fasting plasma obestatin and adropin were measured by ELISA. Fasting plasma ghrelin, leptin, and insulin were assayed by radioimmunoassay, and lipid panel and glucose by a Hitachi 911 autoanalyzer.

Results: Obestatin (median 2691.0 pg/mL) and adropin (3.50 ng/mL) levels were higher in infants with PWS than controls (obestatin, 2101.0 pg/mL, p=0.04; adropin, 2.57 ng/mL, p=0.05); adropin was also higher in older children with PWS (2.69 vs. controls, 1.93 ng/mL, p=0.04). Growth hormone (GH) treatment had no effects on obestatin or adropin in PWS and levels were comparable in insulin resistant and insulin sensitive subjects. The ratio of ghrelin to obestatin declined from infancy to childhood but was higher in older PWS than older controls (p< 0.01 and p<0.0005, respectively). Adropin correlated with fasting glucose in the PWS group only (rS=0.78, p<0.01). Analysis of the lipid profile of children with PWS revealed higher high-density lipoprotein (HDL, 49.10 mg/dL) and lower triglycerides (TG, 55.50 mg/dL) compared to controls (HDL, 32.35 mg/dL, p=0.03; TG, 80.00 mg/dL, p=0.03) but similar low-density lipoprotein (PWS, 78.50 vs. controls, 85.95 mg/dL, p=0.86) and total cholesterol (PWS, 132.00 vs. controls, 123.50 mg/dL, p=0.86). Obestatin was correlated with HDL (rS=-0.569, p=0.034) and TG (rS=0.541, p=0.046) in older controls only.

Conclusions: Higher levels of obestatin and adropin in PWS may have implications for glucose and lipid metabolism and water intake. Changes in the ratio of ghrelin to obestatin suggest changes in the processing of proghrelin to ghrelin and obestatin during development and preferential processing of proghrelin to mature ghrelin in children with PWS.

Keywords: Obestatin, Adropin, Prader-Willi syndrome, Obesity

ADI Research Day, October 2, 2018
A REDUCED INTENSITY CONDITIONING PROTOCOL INDUCES CHIMERISM AND TRANSPLANT TOLERANCE TO FULLY ALLOGENEIC ISLETS IN AUTOIMMUNE DIABETIC NOD MICE

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Background: Hematopoietic chimerism is a robust method for generating donor specific tolerance with the potential to allow islet transplant tolerance. However, its clinical application is prevented by the toxicity of current recipient conditioning regimens. We recently developed a T cell depletion based chimerism protocol in pre-diabetic, non-obese diabetic (NOD) mice. As generating chimerism in diabetic NOD mice is even more challenging compared to pre-diabetic recipients, we sought to test if we could induce chimerism and transplant tolerance to allogeneic islets in spontaneously diabetic NOD recipients.

Methods: We preconditioned spontaneously diabetic NOD mice with donor specific transfusion from fully mismatched FVB mice (d-10), cyclophosphamide (d-8), antibodies against CD4/8/90 (d-6, -1, 4, 9, 14), and busulfan (d-1). Donor islets and/or bone marrow transplantation (BMT) were done at d0. Blood glucose levels of recipients were assessed weekly. Flow cytometry was used to detect chimerism.

Results: We induced transient mixed chimerism in 10/13 diabetic NOD mice. The survival of donor islets was significantly prolonged in chimeric mice. In contrast, normoglycemia was not restored without islet transplant (3/3); donor islets were rejected in 4 weeks if BMT was not included (2/2). Recipient T cells in diabetic NOD mice were depleted as efficiently as in pre-diabetic NOD mice but rebounded quickly, starting at d14, which may explain the instability of chimerism. Levels of chimerism and donor T cells are lower in spontaneous diabetic recipients in early time points compared to young NOD mice. Similar results were observed in non-diabetic aged littermates (n=5), suggesting that aging contributes to the difficulties in chimerism induction in spontaneously diabetic NOD mice. In an attempt to generate stable chimerism base on our T cell depletion based protocol, purified donor CD8 T cells were given at d19. The delayed infusion of donor CD8 T cells facilitated the establishment of a high level and stable multilineage donor chimerism (n=5) and the acceptance of donor islets (n=4) without the presence of Graft versus Host Disease.

Conclusion: A T cell depletion based mixed chimerism protocol induces chimerism in diabetic NOD mice and promotes tolerance to fully allogeneic islets.

Key words: Hematopoietic chimerism, Transplantation tolerance, Bone marrow transplantation, Islet transplantation

ADI Research Day, October 2, 2018
DESCRIPTION OF INFANT FEEDING PRACTICES AT 3 MONTHS POSTPARTUM IN WOMEN WHO EXPERIENCED DIABETES IN PREGNANCY

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Background: Women who experience diabetes in pregnancy, either pre-existing or gestational diabetes, have been found less likely to breastfeed their baby. However, there is little research examining why this association exists. Therefore we established a study to address this gap in the literature. This abstract describes socio-demographics and infant feeding behaviours of the cohort.

Methods: This case-control study is nested within the Alberta Pregnancy Outcomes and Nutrition study - a prospective study of women during pregnancy and their offspring. Cases were participants who experienced either pre-existing diabetes (n=26) or gestational diabetes (n=50) during pregnancy. Cases were matched with controls 1:3 on pre-pregnancy BMI, mode of delivery, pre-term birth, and parity. Socio-demographics at recruitment, intentions to breastfeed (collected in the 3rd trimester) and infant feeding practices at 3 months postpartum were collected via questionnaires. Differences in socio-demographics and intention to breastfeed score between cases and controls were assessed using t-tests or Fisher's exact for continuous or categorical data, respectively.

Results: A total of 76 cases and 220 controls with complete data on infant feeding practices at 3 months postpartum were identified. There were no differences between cases and controls in terms of education, marital status or income. Cases tended to be slightly older (mean age: 32.5 years SD 4.7) compared to controls (mean age 31.3 years SD 4.4) (P=0.04) and a greater proportion of cases were non-Caucasian (32%) compared to controls (16%) (P=0.003). In the 3rd trimester there were no differences in women's intentions to breastfeed (P=0.247). At 3 months postpartum 29% of cases were exclusively breastfeeding, compared to 50% of controls. A third of cases reported mixed feeding (34%) compared to around a quarter of controls (26%). Furthermore 14% of cases had initiated but stopped any breastfeeding compared to only 8% of controls.

Conclusions: The cohort were well matched on socio-demographics, although a greater proportion of cases had a non-Caucasian ethnicity compared to controls. Despite similar intentions to breastfeed reported in the 3rd trimester of pregnancy, a lower proportion of women who had diabetes in pregnancy were exclusively breastfeeding at 3 months postpartum compared to controls. The next steps are to link participants data to their medical records and complete qualitative interviews to explore why these differences may exist so that supports can be better targeted in the future.

Key words: Infant feeding; Diabetes in pregnancy; Case-control

ADI Research Day, October 2, 2018
THE EFFECTS OF BRAIN GLUCAGON SIGNALLING ON LIVER LIPID SECRETION

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Background: The effects of glucagon to regulate glucose metabolism are well known, including its direct action on the liver to promote glycogenolysis and gluconeogenesis. Interestingly, circulating glucagon is also known to lower plasma triglycerides (TG) and cholesterol levels, and acute elevations in plasma glucagon levels lower liver secretion of TG and lipoproteins in mice and humans. The brain can sense circulating nutrients and hormones to regulate whole-body lipid metabolism. We hypothesized that glucagon can act in the mediobasal hypothalamus (MBH), via its receptors, to regulate lipid metabolism. We aimed to test glucagon action, via its receptors and PKA-mediated signalling in the hypothalamus, in altering triglyceride-rich very low-density lipoprotein (VLDL-TG) secretion from the liver in vivo. Here, we report an emerging role for glucagon signalling in the brain to lower liver VLDL-TG secretion in both regular chow and high-fat diet (HFD)-fed animals.

Methods: Nine-week-old male Sprague Dawley rats underwent stereotaxic MBH cannulation and vascular catheterization prior to experiments. For HFD groups, a 3-day regimen of lard oil enriched chow was given instead of regular chow prior to experiments. On the experiment day, in 10-hour fasted rats, MBH pre-infusions of saline (vehicle control), glucagon receptor antagonist, or PKA antagonist rp-cAMPS began at t = -60 min, and other treatments (glucagon or PKA activator sp-cAMPS) commencing at t = -10 min. Infusions were maintained until the end of the experiment at t = 300 min. Poloxamer was intravenously injected at t = 0 min to prevent circulating lipolytic action. Arterial blood samples were taken before and during pre-infusions, then every 30 mins starting at t = 0 min for 3 hours, and every 60 min until the end of the experiment. Plasma TG and glucose levels were assayed. Liver was collected for analysis of key lipogenic enzymes via Western blot.

Results: MBH glucagon lowers plasma TG levels and liver VLDL-TG secretion rates in regular chow-fed rats compared to saline controls. The action of glucagon is mediated via its receptors and PKA in the MBH since MBH co-infusion of glucagon receptor antagonist, or PKA inhibitor rp-cAMPS, with glucagon abolished the lipid-lowering effect of glucagon. The effect of glucagon to lower liver VLDL-TG secretion was mimicked by MBH infusion of PKA activator sp-cAMPS. Changes to VLDL-TG levels occurred independently of plasma blood glucose concentrations, food intake, and body weight. In HFD-fed rats, MBH glucagon, or PKA activation, similarly lowered liver VLDL-TG secretion rates.

Conclusion: MBH glucagon lowers hepatic VLDL-TG secretion rates and plasma concentrations in regular chow and 3-day HFD-fed rats. Thus, targeting central glucagon signalling may hold therapeutic potential to regulate circulating VLDL-TG levels in diabetes and obesity.

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Key Words: glucagon, mediobasal hypothalamus, very low-density lipoproteins, triglycerides

ADI Research Day, October 2, 2018
TOLERANCE TO A-ANTIGEN AFTER TREATMENT OF INFANT OR ADULT MICE WITH MHC-MATCHED A-EXPRESSING BLOOD CELLS

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Purpose: ABO-incompatible heart transplantation (ABOi HTx) is safe during infancy and allows increased donor access. Post-ABOi HTx B cell tolerance develops to donor blood group antigen(s) by mechanisms not fully defined. We developed A-transgenic mice (A-Tg) that express A-antigen on vascular endothelium and erythrocytes and demonstrated A-antigen specific tolerance induced by HTx into 4 wk-old, MHC-identical, wild-type (WT) mice. Herein, we explored intentional tolerance induction in infant and adult WT mice using A-Tg blood cells.

Methods: WT BALB/c mice were injected ip (weeklyx3) with intact A-Tg BALB/c blood cells (±40Gy irradiated), beginning at 7 days (neonates) or 5 months of age (adults). Two weeks after treatment, all mice were injected ip (weeklyx5) with human A-erythrocytes (‘A-sensitized’) in an attempt to elicit anti-A antibody (Ab) production. Serum anti-A and 3rd-party (non-A anti-human) Ab were assessed by hemagglutination assay.

Results: In response to A-sensitization, high levels of anti-A Ab were produced in untreated mice (median titre 1:256, n=11). In contrast, anti-A remained undetectable (≤1:2) in A-sensitized mice treated as neonates with irradiated (n=5) or non-irradiated A-Tg BC (n=6) (p<0.0001). Treatment of adult mice with A-Tg blood cells resulted in reduced anti-A production in response to A-sensitization compared with untreated mice (p<0.05). Adult mice with undetectable natural anti-A Ab prior to treatment produced less anti-A (≤1:2 to 1:4, n=5) vs those with pre-existing natural anti-A Ab (1:16 to 1:64, n=5) (p<0.05). Mice treated with enriched A-Tg RBC as neonates produced undetectable anti-A Ab (≤1:2, n=4) following A-sensitization, in contrast to those treated with enriched A-Tg PBMCs as neonates (≤1:2048, n=3) (p<0.0001). Third-party Ab responses were high for all groups (≥1:128).

Conclusions: Our results suggest that the erythrocyte component of A-Tg blood cells can induce robust A-antigen-specific tolerance in WT mice. Importantly, our findings suggest that tolerance to A-antigen is not limited to the neonatal period but can also be induced in adults, especially in mice without previously detectable natural anti-A Ab. Intentional induction of tolerance to A/B-antigen(s) may allow subsequent ABOi HTx.

Keywords: tolerance, ABO-incompatible transplantation, ABO antibody, mouse model
EFFECT OF EGG WHITE HYDROLYSATE ON INSULIN SIGNALLING IN WHITE ADIPOSE TISSUE

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Background: As the prevalence of type II diabetes increases worldwide, functional foods, which exert beneficial physiological effects beyond its nutritional value, may lead to an alternative method of diabetes management with minimal side-effects. Egg white hydrolysate has previously been shown to enhance insulin signaling (AKT phosphorylation) and potentially affect adipogenesis (enhanced PPAR-γ and decreased adipocyte size). This study seeks to investigate the effects of EWH on insulin signaling and adipogenesis upstream proteins, such as glucose transporter type 4 (GLUT4), insulin receptor β (IR-β) and extracellular signal regulated kinase 1/2 (ERK1/2) in white adipose tissue of rats fed with a high-fat diet (HFD). I hypothesize that the EWH treatment group will show increased GLUT4 abundance and IR-β phosphorylation, improving insulin sensitivity. Additionally, based on previous results involving greater PPAR-γ abundance, I expect the EWH group to have higher levels of ERK phosphorylation.

Methods: Previously, two groups of rats were fed HFD for six weeks to induce insulin resistance. Thereafter, one group (n=7) continued on the HFD while the other (n=8) was simultaneously fed with 4% EWH for another six weeks. From both HFD and EWH groups, a subgroup (n=4) was injected with insulin 10 minutes prior to the euthanization. Retroperitoneal and epididymal adipose tissues were then collected and used in western blotting to measure the abundance of GLUT4 and the phosphorylation of IR-β and ERK1/2.

Results: In white adipose tissue, insulin injection and EWH treatment had no effect on GLUT4 abundance or IR-β phosphorylation. Additionally, while insulin and EWH treatment resulted in no difference in ERK1/2 phosphorylation in retroperitoneal adipose tissue, insulin increased ERK1/2 phosphorylation in epididymal adipose tissue in both HFD and EWH groups. However, EWH ultimately demonstrated no significant effect on GLUT4 abundance, nor IR-β and ERK1/2 phosphorylation.

Conclusions: While EWH showed no change in GLUT4 abundance and IR-β phosphorylation, our samples contained whole cell lysate. Since previous studies showed an increase in AKT phosphorylation, a precursor to GLUT4 translocation into the plasma membrane, further studies are being conducted to explore changes in GLUT4 abundance and IR-β phosphorylation in the membrane. Additionally, although EWH had no effect on ERK1/2 phosphorylation, its ability to increase PPAR-γ abundance suggests that more research is needed to explore EWH's effect on adipogenesis cascade proteins.

Keywords: diabetes, egg white hydrolysate, bioactive peptides, insulin sensitivity
INTRA-INDIVIDUAL VARIABILITY OF THE BETA-2 SCORE IN CLINICAL ISLET TRANSPLANT RECIPIENTS

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Background: The BETA-2 score was developed as a practical alternative to the mixed meal tolerance test for assessing beta cell function. It is calculated from a fasting blood sample and integrates glycemic control, insulin use, and endogenous insulin production into an easily interpretable single score. The BETA-2 score therefore allows for frequent and comprehensive assessment of islet graft function in clinical practice. The aim of this study was to assess the intra-individual variability of the BETA-2 score and to establish the critical difference in sequential BETA-2 scores that represents a true change in graft function.

Methods: Weekly BETA-2 scores were calculated based on fasting c-peptide, fasting plasma glucose, HbA1C, and average insulin use per day in subjects transplanted between 2014-2016. A total of 26 subjects with stable graft function at 2-4 month post-transplant were included of whom 17 were insulin independent. The critical difference in BETA-2 score was calculated based on the coefficient of variation (CV) across BETA-2 scores with significant change defined as p-value <0.05.

Results: Intra-individual CV for the BETA-2 score was 11.2%, 95% CI [8.0, 14.4], compared to 22.2%, 95% CI [15.9, 28.6] for fasting C-peptide, and 62.6%, 95% CI [28.6, 96.6] for insulin dose (among insulin-dependent subjects). The CV for the BETA-2 score was not different between insulin-independent and insulin-dependent subjects (9.9% vs 13.3%, p=0.28). The critical difference for the BETA-2 score was 31.4% for all patients, 37.1% for insulin-dependent patients, and 27.8% insulin-independent patients.

Conclusions: The BETA-2 score appears stable with less intra-individual variation compared to fasting C-peptide or insulin dose in subjects with stable islet graft function and a threshold for significant change in BETA-2 score of 31% may be useful for clinical decision making when monitoring islet transplant recipients.

Keywords: BETA-2 score, Clinical islet transplantation, Intra-individual variability
EARLY LIFE AMoxicillin EXPOSURE EFFECTS ON PANCREATIC BETA-CELL DEVELOPMENT IN PIGLETS

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Background: Amoxicillin is a pediatric broad-spectrum antibiotic and its impact on the gut microbiota has been described by previous papers. In human infants, early life antibiotics treatments have been linked to higher weight gain in later childhood. Previously, we developed a piglet model to study the role of the gut microbiome in this phenotype and found disruptions in pancreatic islet function along with altered rates of proliferation and apoptosis at post-natal day (PND) 14 (unpublished), 21 and 49 (Ji et al. 2017). However, earlier developmental periods were not studied. Experiments from this study seek to assess beta-cell proliferation and apoptosis involved in pancreatic tissue development at PND 7 when microbiome changes induced by antibiotics are most profound, that could explain later life pancreatic beta-cell abnormalities.

Methods: Piglets were orally administered amoxicillin (30mg/kg/day) or a placebo twice a day from birth until they were euthanized at PND 7 for sample collection. Pancreatic tissue samples were fixed, dewaxed and rehydrated before immunostaining was carried out. Slides were stained either by using anti-KI67 antibodies to detect proliferation, or a TUNEL assay (In Situ Cell Death Detection Kit, Sigma-Aldrich) for apoptosis. The slides were then double stained with anti-insulin antibodies to detect beta-cells and mounted with ProLong Gold Antifade Mount with DAPI. Image analysis was used to determine total %beta-cell area (insulin stained area/total tissue area) and proliferation or apoptosis of pancreatic beta-cells (# of KI67 or TUNEL positive cells / beta-cell area). The results were then analyzed using a two-tailed unpaired T-test.

Results: The slides were analysed for either KI67 or TUNEL, in addition to insulin. No significant differences were seen in total beta-cell area (p = 0.21, n=9 per group), beta-cell proliferation (p = 0.55, n=5 per group), and beta-cell apoptosis (p = 0.51, n=4 per group) between the control and amoxicillin treatment groups in PND 7 piglets.

Conclusion: Early life administration of amoxicillin to piglets does not seem to cause detectable changes in beta-cell development and growth at PND 7. This suggests antibiotic manipulation of the gut microbiome leads to changes in beta-cell morphology that are not detected until PND 14.

Keywords: Antibiotics, pancreas, beta-cells


ADI Research Day, October 2, 2018
VALIDATION OF A TOOL TO ASSESS APPETITE IN CHILDREN

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Background: Understanding appetite, including sensations of hunger and satiety, allows further investigation of energy balance in children. Visual analogue scales (VAS), which are commonly used to measure appetite, have limited use in children because they require the ability to seriate (an ability to arrange conditions in a series which develops around 7.4 years of age). Therefore, we developed an appetite assessment tool to assess motivation to eat and level of hunger or fullness in younger children. Our objectives are to determine if the new tool is sensitive to expected changes in appetite, predictive of energy intake, and similar to results from a validated VAS appetite assessment.

Methods: Participants (n=10) included children 4-10 years of age with a healthy body mass index (BMI) percentile and normal development. At visit 1, we measured participants’ height and weight, determined their ability to seriate (> 7 years of age), and administered the appetite tool which also asked where they felt hungry/full. Participants who were able to seriate also completed a VAS appetite assessment. Snacks were consumed ad libitum, and the weight of foods was measured. The same questionnaires were administered five, thirty, and sixty-minutes post meal. The second visit followed the same procedures with participants provided 25% of the snacks consumed during their first visit.

Results: 10 children participated in the study (7.4± 2.7 years of age; mean BMI z-score of -0.15). Eighty percent of participants reported that they felt hunger in their stomach, and ninety percent felt fullness in their stomach. There was a significant difference in the satiety scores from baseline to 60 minutes post-snack (V1: F3,36=7.594, P<0.05). Satiety scores increased at 5 minutes post-snack and subsided at the 30 minute mark (V1 Baseline: 5.90± 2.23, 5m: 8.60± 1.58, 30m: 8.00± 1.89). There was an increase in satiety scores post-snack when compared to baseline (V1 5m: t=4.669, P<0.05; 30m: t=3.042, P<0.05; 60m: t=2.201, P=0.03). At V2, satiety scores decreased at 30 mins after the consumption of a lower energy meal (t=-3.743, P<0.05); 5 and 60 min post-meal reduction in satiety was not significant. For those who completed the VAS assessment, there was also a strong relationship between the satiety score from the new tool and hunger score from the VAS (n=6, r=-0.776).

Conclusion: Preliminary data demonstrates that the new appetite tool is sensitive to expected changes in appetite and the results obtained from the tool are similar to those obtained using validated VAS appetite assessment. Ultimately, a validated tool to assess appetite in young children can be used to better assess and target behavioral, dietetic and/or pharmacologic interventions in children with alterations in weight and energy balance.

Key words: Appetite, hunger, satiety, children, validation of tool
MIXED LYMPHOCYTE REACTION OPTIMIZATION USING MONOCYTE-DERIVED DENDRITIC CELLS: UTILITY IN STUDYING PEDIATRIC IMMUNE RESPONSES

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BACKGROUND: T cell proliferation assays are a commonly used tool to study immune responses in vitro. Our goal was to explore T cell responses in pediatric heart transplant recipients who develop de novo donor-specific antibody to human leukocyte antigen (HLA). We used mixed lymphocyte reaction (MLR) to investigate reactivity between recipient and donor cells. MLR experiments and flow cytometry phenotyping were previously performed using peripheral blood mononuclear cells and irradiated splenocytes; despite T cell proliferation responses in all positive controls, proliferation to donor cells was undetectable. Dendritic cells (DCs) are the most efficient antigen presenting cell (APC). To optimize MLR reactivity we compared the use of donor splenocytes vs donor monocyte-derived dendritic cells (moDC) as stimulators.

METHODS: From donor splenocytes, moDCs were generated by isolation of monocytes and incubation with GM-CSF and IL-4. T cell responses were measured using CellTrace™ proliferation dye combined with the Duraclone IM Basic flow cytometry panel. Proliferation controls included PHA, CD3/CD28, and CD2/3/28 tetramer. 5.0-10⁴ responder and irradiated donor cells were incubated at 37°C for 7 days. Proliferation was compared between moDC or splenocytes. Patient and control selection were performed by review of pre- and post-transplant antibody data from the clinical HLA laboratory.

RESULTS: Clear CD4 and CD8 T cell proliferation was detected to positive controls in all experiments however the moDC were more potent stimulators of T cell proliferation than splenocytes alone. The Duraclone panel provided a standardized staining of the MLR responses and differentiation of cell populations.

CONCLUSION: The moDC offer a clear advantage in these MLR conditions. Large blood draws are rarely possible in pediatric research. Using more potent APCs may be required in the setting of low responder cell numbers. We will use donor moDC as the MLR stimulator cells combined with the Duraclone panel for future experiments carried out with our selected patients and controls. This method of measuring allo and auto-immune responses may also be applicable in pediatric type 1 diabetes patients from whom only small samples sizes may be available.

KEYWORDS: APC, MLR, Immune responses, Pediatric

ADI Research Day, October 2, 2018
HYPOTHALAMIC ACTION OF GLUCOCORTICOIDS IN REGULATING LIPID METABOLISM

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Background: One common characteristic of obesity and diabetes is a disruption of lipid homeostasis, specifically hypertriglyceridemia and increased hepatic secretion and production of very low-density lipoprotein triglycerides (VLDL-TG). Excessive levels and/or actions of glucocorticoids (GCs) are associated with these symptoms and occur in diabetic humans and animal models of type 2 diabetes. Whereas the peripheral effect of GCs to stimulate lipid production is well known, less is known about the central brain effect of GCs to regulate lipid metabolism. Illuminating GC action in the brain in the regulation of hepatic VLDL production and plasma triglyceride (TG) levels is the first step to discovering novel therapeutic molecules to lower blood lipid levels in obesity and diabetes. We hypothesize that GCs act on GC receptors (GRs) in the mediobasal hypothalamus (MBH) to modulate lipid homeostasis through increased plasma TGs and hepatic VLDL-TG secretion.

Methods: Sprague Dawley rats with stereotaxic MBH cannulation and vascular catheterizations underwent a lipid regulatory experiment in response to brain treatment with direct MBH infusion of dexamethasone, a synthetic GC, with and without GR antagonism. Poloxamer was injected intravenously at t=0 to block lipoprotein lipase, thus preventing the breakdown of TG-rich lipoproteins. Plasma was collected to determine TG concentrations over 300 minutes. Tissues were collected for analyses of protein levels of key hepatic lipogenic enzymes and GRs in the MBH and the liver. These analyses will begin revealing the underlying biochemical and molecular mechanisms that underlie some of the metabolic effects of MBH GCs.

Results: As expected, rats that received an MBH infusion of GCs demonstrated higher levels of plasma TGs and VLDL TG-secretion compared to the vehicle rats. This effect is mediated by GRs because co-infusion of a GR-antagonist, mifepristone (MIF), or chronic inhibition of GRs in the MBH by GR shRNA, negates the increase in plasma TG and VLDL-TG secretion rate caused by MBH GCs. High-fat diet (HFD)-fed rats had elevated basal plasma GC levels and hepatic TG secretion compared to regular fed rats. Interestingly, however, acute GR-antagonism with MIF did not lower hepatic VLDL-TG secretion in HFD rats.

Conclusion: MBH GCs, via their receptors, increase hepatic VLDL-TG secretion independent of body weight and blood glucose. Follow-up studies will test whether targeted chronic inhibition of MBH GC action improves lipid regulation in obesity-related metabolic disease.

Acknowledgements: This work is supported by Diabetes Canada and NSERC. Undergraduates were supported by AIHS (MW & EJL) and NSERC (HJL) summer awards. EBB is supported by CIHR CGS-M. JTYY is supported by a Diabetes Canada Scholar Award.

Key words: Glucocorticoids, lipid homeostasis, MBH, liver

ADI Research Day, October 2, 2018
EMPAGLIFLOZIN IMPROVES THE CARDIAC FUNCTION OF RATS WITH HFPEF THROUGH THE INHIBITION OF THE NLRP3 INFLAMMASOME

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Background: Cardiovascular disease is currently the leading cause of death in North America and the number of individuals affected by cardiovascular disease continue to rise. Empagliflozin is a sodium/glucose cotransporter 2 (SGLT2) inhibitor which targets the kidneys to increase urinary excretion of glucose and has recently been found to improve cardiac outcomes in diabetic patients with heart failure (HF). Additionally, empagliflozin has been shown to blunt the decline in cardiovascular function of a non-diabetic mouse model with established HF with reduced ejection fraction (HFrEF), suggesting that the beneficial effects of empagliflozin and other SGLT2 inhibitors may occur in the absence of overt diabetes or hyperglycemia. Although beneficial in HFrEF, the cardiac effects of empagliflozin in HF with preserved ejection fraction (HFpEF) are unknown. Therefore, we utilized a rat model of HFpEF induced by a high-salt diet to determine the cardioprotective effect of empagliflozin.

Methods & Results: We show for the first time, in nondiabetic rats with HFpEF, that empagliflozin ameliorates diastolic dysfunction and attenuates detrimental cardiac remodeling. Empagliflozin treatment of rats with HFpEF is also associated with reduced cardiomyocyte cell size, and reduced myocardial fibrosis compared to vehicle-treated rats. Using qRT-PCR and immunoblotting, empagliflozin treatment is also with the inhibition of the inflammasome signaling pathway (caspase 1, IL-1β, NLRP3).

Conclusion: These data provide support that empagliflozin may be beneficial in treating HFpEF, even in the absence of diabetes, potentially via a pathway that involves inhibition of the NLRP3 inflammasome signaling.

Keywords: Empagliflozin, HFpEF, NLRP3 inflammasome

ADI Research Day, October 2, 2018
GUT MICROBIOME COMPOSITION AND FUNCTION IN NORTH-AMERICAN CHILDREN WITH AND WITHOUT PRADER-WILLI SYNDROME

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Background: Prader-Willi Syndrome (PWS) is the most common syndromic form of childhood obesity and is characterized by failure to thrive during infancy followed by abnormally increased appetite (hyperphagia) and progressive obesity. The pathogenesis of hyperphagia and weight gain in PWS is poorly understood and management strategies have been met with variable and limited success. An imbalance in gut microbial composition (gut dysbiosis) has been linked to the development and maintenance of non-syndromic obesity and metabolic dysfunction. Several studies support an etiological contribution of dysbiotic gut microbiota in the metabolic derangements of obesity; however, the specific role of the gut microbiome in energy balance and metabolic control in PWS and childhood obesity is not fully understood. This study aims to identify and characterize the bacterial composition present in children with and without PWS as this is an important first step to guide the design of effective therapies targeting the gut microbiome to achieve weight control and management of hyperphagia. This is especially pertinent as there is currently no established effective therapy for PWS-related hyperphagia and obesity.

Methods: Children with PWS (ages 3-17 years, n=25) and age-, sex- and body mass index (BMI) percentile matched controls (n=25) were recruited. Stool samples, a 3-day dietary record, a hyperphagia questionnaire (validated in PWS), physical activity data, and anthropometric measures (height, weight and waist circumference) were collected. Co-variate information, including gestational age; birth history; infant feeding (breast versus formula-feeding); use of probiotics, and medications was also collected. Analysis of partial 16S rRNA sequence reads obtained by MiSeq sequencing (Illumina) will be obtained to allow characterization of fecal microbiota composition at phylum, family, genus and OTU (proxy for bacterial species) level. α and β- diversity indices as well as short chain fatty acid (SCFA) profiles will be determined and contrasted between groups.

Preliminary Results: Recruitment is ongoing. We have enrolled 23/25 children with PWS (12F:11M; median age = 6.4 (3 to 17y); median BMI percentile = 75.35; 13 deletion: 10 uniparental disomy) and 25 healthy control children (9F:16M; median age = 8.8 (3 to 17y); median BMI percentile = 77.6). We expect to see functional and structural difference in the gut microbiota composition of children with and without PWS. In addition, we hope to gain further insight on the SCFA profiles of individuals with PWS, as a decreased relative abundance of SCFAs have been implemented in satiety and as a contributing factor to metabolic complications including Type 2 diabetes and obesity.

Conclusion/Future directions: Gaining a better understanding of the gut microbial profile of children with PWS has the potential to unveil more personalized approaches for effective treatment of excessive weight gain and hyperphagia associated with PWS to improve overall health and quality of life. The current study precedes a planned single-blind, placebo-controlled crossover study which will employ a high dietary fiber intervention with the goal to promote satiety, limit excessive weight gain and improve inflammatory and metabolic profiles and overall quality of life in children with PWS.

Key Words: Prader-Willi Syndrome (PWS), obesity, microbiome, hyperphagia

ADI Research Day, October 2, 2018
REGULATION OF GLUCOSE PRODUCTION BY GLUCOCORTICOID ACTION IN THE MEDIOBASAL HYPOTHALAMUS

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Background: Diabetes is characterized by dysregulated glucose homeostasis that leads to hyperglycemia, due in part to increased hepatic glucose production (GP) and insulin resistance. Excessive levels and/or action of glucocorticoids (GCs), are associated with obesity, insulin resistance, and hyperglycemia. Whereas the peripheral effect of GCs to elevate glycemia is well known, less is known about the brain effect of GCs to modulate metabolism. The brain senses nutrients and hormones to regulate glucose homeostasis. The aim of this study is to delineate a mechanism of GC action in the mediobasal hypothalamus (MBH) that modulates GP in normal and pre-obese rodents. We hypothesize that GC action in the brain alters glucose metabolism.

Methods: Male Sprague Dawley rats underwent stereotaxic MBH bilateral cannulation and intravenous (iv) and intraarterial catheterization to allow for simultaneous direct infusions into the MBH, iv infusions, and blood sampling, respectively. Pancreatic basal insulin euglycemic clamps with tracer dilution methodology combined with MBH GC infusion – GC receptor inhibition enables measurement of GP and utilization while assessing MBH GC binding with its MBH receptors independent of changes in plasma insulin and glucagon levels.

Results: MBH GC infusion potently stimulates GP and lowers the requirement for exogenous glucose infusion during clamp conditions without altering glucose utilization. This effect is mediated via GC receptors since co-infusion of GC receptor antagonist mifepristone negates the ability of GCs to increase GP. A separate group of rats were fed with high fat diet (HFD) for 3 days and presented altered glucose kinetics as well as increased basal plasma corticosterone, insulin, and blood glucose levels independent of changes in body weight. MBH mifepristone lowered GP compared to MBH vehicle HFD rats, suggesting that blocking MBH GC action attenuates GP to improve glucose homeostasis in a model of pre-obesity.

Conclusion: We demonstrate that MBH GC action modulates GP in health and pre-obesity. Targeted inhibition of MBH GC action may help improve glucose regulation in obesity-related metabolic disease.

Acknowledgements: This work is supported by Diabetes Canada and NSERC. EBB is supported by CIHR CGS-M. Undergraduates were supported by ADI (HK) and AIHS (SY) summer awards. JTYY is supported by a Diabetes Canada Scholar Award.

Key words: Metabolism, Diabetes, Glucocorticoids, Mediobasal hypothalamus

ADI Research Day, October 2, 2018
DIET DIVERSITY IN CHILDREN WITH NON-ALCOHOLIC FATTY LIVER DISEASE AND PRADER-WILLI SYNDROME: ASSOCIATION WITH CARDIO-METABOLIC RISK FACTORS.

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Background: Cardio-metabolic dysregulation (CMD) is a common feature in obese children with non-alcoholic fatty liver disease (NAFLD) and Prader Willi syndrome (PWS). Few studies have examined whether this is related to poor diet quality (DQ) and lack of dietary diversity (DD). The study purpose was to describe and compare DD, health value (HV) and overall healthy food diversity (HFD) in 1) youth with NAFLD and PWS and 2) between those with and without cardio-metabolic (CMD) risk factors.

Methods: Children with PWS (n=8), NAFLD (n=12) and lean controls with no CMD risk factors (n=16) between 7-18 years were recruited from the Stollery Children's Hospital GI and Endocrine clinics and the community. Anthropometrics (BMI, waist and hip circumference), fasting blood (AST, ALT, GGT, TG, HDL and LDL cholesterol, glucose, insulin, HOMA-IR), food intake records (diet diversity and health value using Healthy Food Diversity Index [HFD-I]) and blood pressure (systolic and diastolic) were measured.

Results: The prevalence of CMD characteristics was higher in NAFLD patients than PWS and controls (p< 0.001). DD, HV and HFD-I scores were significantly lower in youth with NAFLD than PWS (p=0.03, p<0.05 and p<0.001 respectively). Youth with NAFLD had also lower DD and HV than controls (p= 0.038). PWS children had the highest scores for DD, HV and HFD-I. However, the difference observed between PWS children and controls was not statistically significant except for HV (p<0.05). No child had elevated fasting glucose. Obese participants (BMI≥ 90th percentile), those with hyperinsulinemia (> 20 mU/L) or insulin resistance (HOMA≥ 3) had lower DD, HV and HFD-I scores (p< 0.05) than children with values within reference ranges. HV and HFD-I scores were significantly lower (p< 0.03) in youth with elevated blood pressure (≥ 90th percentile). Children with decreased HDL-C (< 1.16 mmol/L) had lower HFD-I scores (p< 0.05). No significant difference was seen between children with larger waist to hip ratios (≥ 0.5) or higher TG levels (>0.85 mmol/L < 9 years and > 1.02 for older children) with others in terms of DD, HV and HFD-I scores.

Conclusion: Diversity and health value of a diet might be linked to CMD risk factors and could be considered as a therapeutic target for lifestyle interventional approaches to reduce the risk for CMD in obese children with NAFLD or PWS.

Key Words: Diet diversity, Non-alcoholic fatty liver disease, Prader -Willi syndrome, Cardio-metabolic dysregulation, Children

ADI Research Day, October 2, 2018
ROLE OF INTESTINAL DE NOVO PHOSPHATIDYLCHOLINE SYNTHESIS IN HIGH FAT DIET INDUCED OBESITY

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Background: Phosphatidylcholine (PC) is vital for the structural integrity of mammalian membranes and is the primary phospholipid in bile, lung surfactant, and plasma lipoproteins. In intestinal cells, PC can be synthesized from dietary choline via the Kennedy pathway. The enzyme CTP:phosphocholine cytidylyltransferase (CT) regulates flux through this pathway, and the predominant isoform is CTα. Intestinal PC can be obtained from de novo synthesis, or from luminal supply (biliary and dietary sources). Luminal PC is digested by phospholipases to lysoPC before entry into enterocytes, where it is acylated back to PC. Our lab has created an intestinal-specific CTα gene knockout mouse (iCTα-) that has reduced de novo PC synthesis. Our initial findings show that iCTα- mice on a high fat diet (HFD) have a decreased intestinal PC/PE ratio, characteristic of impaired membrane function. These mice also present with impaired lipid absorption and delayed chylomicron secretion, leading to protection from diet induced obesity. We hypothesize that inducing the knockout in obese mice will lead to improved plasma lipid parameters for iCTα- mice compared to control mice due to weight loss. In a second study, the effects of a significant (9-fold) increase in circulating active GLP-1, observed in iCTα- mice following a meal, will be examined. The hormone GLP-1 is secreted from the distal intestine following a meal and serves to control glucose homeostasis, lipid metabolism and satiety. We hypothesize that inhibiting GLP-1 action will increase triacylglycerol (TG) absorption in iCTα- mice.

Methods: iCTα- mice are treated with tamoxifen for 5 days to induce Cre recombinase expression, and thus create an intestinal-specific CTα knockout mouse. Tamoxifen-treated CTαflox/flox are used as controls. In the first set of experiments, mice will be fed a 60% HFD for 10 weeks before inducing the knockout to monitor changes in weight gain and glucose tolerance in obese mice. In the second set of experiments, mice will receive daily I.P injections of a saline control or exendin-(9 -39) (Ex9), a GLP-1 receptor antagonist, to inhibit the physiological actions of GLP-1. Fluctuations in weight will be monitored and plasma glucose and TG levels will be compared for all groups.

Results: Knockout of iCTα in obese mice resulted in rapid weight loss due to severe malabsorption. As such, the feed trial had to be prematurely ended. The iCTα- obese mice also had significantly lowered plasma glucose and TG levels in the fed state. When iCTα- mice were fed a HFD and treated with Ex9 there were no changes in weight loss, plasma glucose levels or plasma TG levels compared to the iCTα- mice on a saline control.

Conclusion: For obese mice, reduction in PC synthesis in the small intestine leads to severe malabsorption and weight loss. In lean mice, blocking the physiological effects of increased active GLP-1 levels in iCTα- mice does not increase lipid absorption or prevent weight loss. Future studies will need to be conducted to fully understand the connection between high dietary fat feeding and lipid malabsorption in mice with reduced de novo PC synthesis.

Keywords: Phosphatidylcholine synthesis, High fat feeding, Obesity
EGG WHITE HYDROLYSATE (EWH) EFFECTS IN INSULIN-SENSITIVE ISSUES OF HIGH FAT DIET (HFD)- INDUCED INSULIN RESISTANT RATS

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Background: Type 2 diabetes and hypertension are chronic diseases that lead to complications when not treated properly. Approaches that can tackle both diseases and cause minimal side effects are desired. Bioactive peptides are short amino acid sequences that exert benefits beyond their nutritional value, improving health. Egg is nutrient dense and egg white is a rich source of bioactive peptides. Egg white peptides and hydrolysates have been shown to reduce blood pressure, inflammation and fat mass. Previously, we showed that feeding EWH for 6 weeks improved glucose and insulin tolerance in insulin resistant (IR) rats. Here, we aimed to identify EWH mechanism(s) of action. We hypothesized that EWH acts on peripheral tissues by reducing renin-angiotensin system (RAS) and activating insulin signalling pathways.

Methods: Sprague-Dawley rats were fed HFD for 6 weeks and then divided into two groups, HFD (n=7) and HFD+4% EWH (n=8) for another 6 weeks. Insulin signalling and RAS components in peripheral tissues were studied by western blot, white adipose tissue (WAT) inflammatory markers by ELISA, and adipocyte size by histological analysis.

Results: EWH enhanced Akt phosphorylation in muscle and WAT of EWH-treated animals. RAS components abundance presented minimal changes, but there was increased angiotensin type 2 receptor in liver and WAT after EWH supplementation. Liver gluconeogenesis enzymes did not change. EWH reduced adipocyte size in epidydimal and retroperitoneal WAT, despite no changes in tissue inflammatory cytokines, resistin nor adiponectin levels.

Conclusion: EWH has potential to affect insulin signaling and improve glucose tolerance. We have seen changes in WAT morphology and insulin signaling in both skeletal muscle and WAT after EWH supplementation. How EWH elicits these effects is still unknown. Our study showed the potential of EWH as a functional food/nutraceutical ingredient for the prevention of HFD induced IR.

Key words: Bioactive peptides, egg white, type 2 diabetes, metabolic syndrome, functional food.

ADI Research Day, October 2, 2018
Background: Autism Spectrum Disorder (ASD) is a developmental disorder characterized by difficulties in social, communication, and/or behavioral domains. Obesity, and its associated complications, are among the most common and severe health risks in children with ASD, and likely contribute to a reduced quality of life as compared to children without ASD. Current literature on the rates of obesity and overweight, in ASD, report a higher prevalence of obesity in children with ASD. Obesity and overweight are a key concern to parents, of children with ASD, due to the unique needs and behavioral challenges that can often accompany this disorder. Current research in the area has focused more on the behavioral aspects of ASD, and their contribution to weight gain and obesity, as compared to the possible influence of biological drivers. Research suggests there may be differences in specific satiety hormones in populations with ASD, in comparison to controls, such as decreases in ghrelin and an increases in leptin concentrations. Ghrelin and leptin are key appetite hormones which influence eating behaviors by increasing appetite and inhibiting food intake, respectively. Although research in this area is limited, it suggests the possibility of neuroendocrine influences on eating behaviors in children with ASD. The primary aim of this study will be to assess for differences in hormones (ghrelin, leptin, GLP-1, insulin) and glucose and compared to populations without ASD. And secondly, to assess for differences in feeding behaviors between populations with ASD and controls using the Food Related Problems Questionnaires (FRPQ).

Methods: Participants aged 5-12 years old will complete one study visit to the Clinical Research Unit at the University of Alberta. Anthropometric measurements (height, weight, and waist circumference) will be completed during the visit. Participants will be assigned to one of the four arms of the study: Obese/overweight and ASD, normal weight and ASD, obese/overweight and without ASD, and normal weight and without ASD. An 8 hour fasting blood draw will be taken and assessed for differences in hormones (ghrelin, leptin, GLP-1, insulin) and glucose and compared to populations without ASD. Participants will also complete a Food Related Problems Questionnaire (FRPQ) in order to better understand any differences in challenging eating behaviors between populations with and without ASD.

Expected Results: It is hypothesized that we are likely to find shifts in hormonal factors in children with ASD, when compared to populations without ASD. The different BMI groupings will allow for a better understanding of the independent effect of being obese/overweight and ASD on shifts in hormonal factors.

Conclusions: This study may provide further insight into specific biological drivers of increased weight gain in children with ASD. Findings may help develop targeted treatment measures and allow for a better understanding of the role of modifiable factors, such as diet, and how they relate to the development of obesity.

Key Words: Autism Spectrum Disorder (ASD), obesity, overweight, appetite hormones
ISOLATION AND EXPANSION OF HUMAN PERI-PANCREATIC ADIPOSE TISSUE-DERIVED MULTIPOTENT MESENCHYMAL STROMAL CELLS (PPAMSCS)

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Background: Multipotent Mesenchymal Stromal Cells (MSCs) are specialized cells that have self-renewal and differentiation characteristics. They have been shown to have immunomodulatory, pro-angiogenic and regenerative properties through secretion of various factors. We have previously demonstrated the cytoprotective effects of human bone-marrow derived and pancreatic derived MSCs on human islets in vitro. Furthermore, co-transplantation of neonatal porcine islets (NPIs) and human bone marrow MSCs into diabetic mouse model resulted in better functional outcomes than NPIs alone. In this study we isolated and characterized MSCs derived from human peri-pancreatic adipose tissue.

Methods: Human peri-pancreatic adipose tissue (~5 cm³) was digested in 0.15% collagenase for an hour at 37°C and cultured in α-MEM media (2.5 ng/ml FGF, 10% FBS 1 mM Na-pyruvate). Cells were seeded in tissue-treated T175 flasks and once the cells were confluent, they were counted and passaged four times.

Results: Morphological analysis revealed gradual adherence of ppaMSCs to the plastic and once attached they displayed characteristic spindle-shaped long protrusions. From the approximately 5 gm of tissue we recovered 40-80 million MSCs. Furthermore, FACS analysis showed ppaMSCs were positive for CD73, CD90, CD105, and negative for CD14, CD45, CD34. Differentiation study revealed the ability of ppaM

Conclusion: In this study we isolated, expanded and characterized MSCs from peri-pancreatic adipose tissue. In agreement with the International Society for Cellular Therapy 2006 position statement, our ppaMSCs adhered to the plastic, expressed high levels of MSC-specific surface antigens and were able to differentiate into mesoderm. This study is part of the bigger project where we will assess the effects of co-transplanted ppaMSCs on NPIs function.

Keywords: Diabetes, Islet Transplantation, Stem Cells, MSCs, NPIs

ADI Research Day, October 2, 2018
INVESTIGATING THE EFFECTS OF 2-AMINOADIPIC ACID ON HUMAN ISLET FUNCTION

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Background: 2-aminoadipic acid (2-AAA) is a breakdown product of lysine metabolism that has been found to be an accurate biomarker for future development of diabetes. Investigation of over 2000 patients from multiple cohorts, found that patients in the upper quartile of initial blood 2-AAA levels showed a 2-4x higher incidence of diabetes development over the next 12-13 years compared to the lowest quartile. The same study then investigated mouse models and in-vitro static murine and human islet cultures, which both suggested that 2-AAA increases basal insulin release at low glucose levels. Additionally, previous 2-AAA studies indicate 2-AAA's toxicity to glial cells by the inhibition of cystine uptake and glutathione production, leading to lowered antioxidant capacity. This toxicity inducing inhibition could also be taking place in β-cells, as the affected transporters and enzymes are present and required in both cell types. This, along with the metabolic stress of chronically high basal insulin production, could result in β-cell damage leading to a higher incidence of future diabetes.

Methods: Human islets isolated at the University of Alberta clinical and core facilities were cultured overnight, treated with buffer containing 2-AAA, and were perifused in first 2.5mM glucose and then 11.1μM glucose. Changes in insulin secretion were measured over time. The rat β-cell line INS-1 was cultured overnight in 96 well plates and subjected to either media or buffer containing 2-AAA along with H2O2. Cellular necrosis was measured 2 hours after H2O2 treatment.

Results: Our data, based on the perifusion of human islets in the presence of 2-AAA, suggests that 2-AAA decreases insulin secretion at high glucose levels. We did not observe any significant change in low glucose insulin release. Additional data, based on the treatment of INS-1 cells with 2-AAA under conditions of oxidative stress, suggests that 2-AAA can lead to an increased level of cellular necrosis during β-cell stress.

Conclusions: While no increase in low glucose insulin secretion was observed, a decrease in high glucose insulin secretion is also consistent with a diabetic profile of insulin secretion. Further experiments investigating 2-AAA's effect on β-cells undergoing oxidative stress will be completed by examining different markers of cell stress and death. With a better understanding of 2-AAA's effects on islets and diabetes we will be in a better position to determine the most optimal way to prevent the subset of non-diabetic patients with high blood 2-AAA levels from developing diabetes in the future.

Key words: 2-Aminoacidipic Acid, Perifusion, Necrosis, Diabetes
ACUTE AND CHRONIC EFFECTS OF EXERCISE ON 24-HOUR GLUCOSE PROFILES IN INDIVIDUALS WITH TYPE 2 DIABETES-A META ANALYSIS

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Introduction: Exercise has been shown to improve glycemic control in individuals with Type 2 Diabetes (T2D). The use of continuous glucose monitors (CGM) is growing rapidly in exercise studies. In 2013, members from our group published the first meta-analysis examining how exercise affects CGM outcomes in T2D. Many studies have been published since this review including longer term training studies. The purpose of this meta-analysis is to examine the acute and chronic effects of exercise on glucose outcomes as assessed by CGM in T2D.

Methods: A literature search of databases (PubMed, Medline and EMBASE) was performed up to May 2018. Eligible studies had participants with T2D complete standardized exercise interventions using CGM to measure glucose concentrations. A fixed effects model was used to calculate the weighted mean difference in 24-hour glucose concentrations following exercise and control conditions. The I² statistic was calculated to represent the percentage of the variability due to heterogeneity rather than sampling error (chance).

Results: A total of 31 studies were included. Of these, 26 studies (n=413) were short-term exercise interventions (<2 weeks), and 5 studies (n=149) were considered long-term interventions (>8 weeks). The short-term interventions typically included a single session of aerobic exercise whereas the duration of the long-term studies ranged from 8-16 weeks, including 3-5 sessions per week. Compared to the control condition, exercise significantly decreased 24-hour glucose concentrations in both short-term (-0.6mmol/L; 95% CI -0.79, -0.38; p<0.01, I² =33%) and long-term (-0.5mmol/L; 95% CI -0.93, 0.14; p<0.01, I² =0%) intervention group.

Conclusion: These data show that both short-term and long-term exercise interventions can be an effective tool to lower glucose in individuals with T2D. Although a direct comparison of short-term and longer-term studies can be affected by confounding variables, the magnitude of improvements appears similar among these types of studies.

Key Words: Type 2 Diabetes, Exercise, Meta-Analysis
ROLE OF T CELL CO-INHIBITORY RECEPTORS DURING EARLY LIFE

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Background: Co-inhibitory signals play a key role in T cell tolerance and homeostasis, preventing autoimmune diseases such as Type-1 diabetes (T1D). Conditions such as lymphopenia, which is physiological in the newborn or pathological in certain viremia, may contribute to loss of T cell tolerance when T cells undergo extensive clonal expansion in the setting of lymphopenia-induced proliferation (LiP). Deficiency or blockade of coinhibitory receptors like PD-1 accelerated autoimmune diabetes in non-obese diabetic (NOD) mice. We previously showed that recent thymic emigrants (RTEs) lacking PD-1 (with similar findings in BTLA deficient RTEs), from adult C57BL/6 (B6) mice, generate multi-organ autoimmunity in adult lymphopenic mice. Whereas PD-1 KO and BTLA KO mice develop late-life lupus-like and hepatitis-like autoimmune diseases respectively, they appear relatively healthy. We hypothesized that other co-inhibitory receptors may compensate for the lack of one in these mutant mice.

Method: Using thymocytes or splenocytes as a source of newly generated T cells or established T cells, respectively, we screened for coinhibitory receptors such as CD5, BTLA, LAG-3, and TIM-3 between PD-1 KO, BTLA KO, and wild-type (WT) mice by flow cytometry.

Result: Differential expression of coinhibitory receptors between the mutant mice and their WT counterparts was observed. The neonatal T cell repertoire in B6 mice expresses an elevated amount of the coinhibitory receptor CD5, which doubles as a marker of T cell signaling strength and self-reactivity.

Conclusion: Other co-inhibitory receptors may compensate for the lack of PD-1 or BTLA in B6 mice. Considering the physiological differences between the neonatal and adult T cell repertoire, the genetic differences between B6 mice and NOD mice, we plan to extend this study to the NOD background. We hypothesize that NOD mice may have a reduced ability to upregulate certain co-inhibitors during LiP. We will examine coinhibitory receptors expression, and Ki67 (a marker expressed in proliferating cells) in neonatal vs. control adult RTEs of NOD mice, comparing them to B6 controls.

Keywords: Lymphopenia-induced proliferation, Tolerance, Coinhibition, Recent thymic emigrants

Funding Source: CIHR, Alberta Diabetes Foundation, Blanch Graduate Award

ADI Research Day, October 2, 2018
THE IMPACT OF A HIGH-PROTEIN DIET ON DIET-INDUCED THERMOGENESIS AND SUBSTRATE OXIDATION IN PRADER-WILLI SYNDROME: PRELIMINARY FINDINGS

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Background: Meals of similar caloric content but differing in macronutrient composition may impact diet-induced thermogenesis (DIT), likely influencing total energy expenditure (TEE). Energy expended through digestion, absorption and storage of dietary protein is higher than for carbohydrate and fat. Therefore, a high-protein (HP) diet could have an influence on energy metabolism and weight control. Therefore, the aim of this study was to compare the impact of a HP diet versus a typical North American, high-carbohydrate diet on DIT and substrate oxidation in individuals with Prader-Willi syndrome (PWS).

Methods: Participants completed three separate study visits. Anthropometric measurements were completed at each study visit. In a randomized, crossover study design participants were allocated to two isocaloric arms: a) standard diet: 55% carbohydrate, 15% protein, and 30% fat; b) HP diet: 20% of carbohydrate, 50% protein, and 30% fat. Participants received the prescribed diets (three meals plus snacks per day accompanied by either a powder supplement (high protein diet test) or a snack (standard diet test) for one day prior to each study visit and a breakfast meal inside the whole-body calorimetry unit (WBCU). Diets were designed to ensure participants were in energy balance. Resting metabolic rate (RMR), diet-induced thermogenesis (DIT) and respiratory exchange ratio (RER) were assessed. Differences between diets were assessed by paired sample T-test or Wilcoxon matched pairs test, as appropriate, considering a critical significance value of p<0.05.

Results: Four individuals with PWS (3F/1M, age: 14.5±4 (11-20 years)), BMI percentile: (82.4±10 (70.2-91) and body mass index: 40.3 kg/m2) were assessed. No differences were observed in the DIT measurements between HP and standard diets (258±157 vs 231 ±119 kcal; p=0.66). However, the HP diet resulted in a lower RER in comparison to the standard diet (0.81±0.14 vs 0.86±0.19; p<0.038).

Conclusion: RER was lower in the HP diet compared to the standard diet in individuals with PWS; suggesting a shift towards fat rather than carbohydrate as a fuel source. However, due to the small sample size meaningful statistical considerations are not possible at this time. This preliminary data suggests a diet higher in protein may provide a metabolic advantage compared to a typical North American, high-carbohydrate diet. Future analysis of healthy children matched for age, sex and BMI percentile will confirm if individuals with PWS metabolize food differently as compared to healthy children.

Key words: Prader-Willi syndrome, High-protein diet, Energy metabolism

ADI Research Day, October 2, 2018
COMPUTER PROFICIENCY AND WEB-BASED LIFESTYLE INTERVENTION USE AMONG OLDER ADULTS WITH TYPE 2 DIABETES

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Background: Web-based information technologies can serve as an accessible and powerful medium for engaging, educating, and empowering individuals with chronic diseases such as type 2 diabetes (T2D). Participants, however, need to be proficient in certain domains of computer and Internet use in order to access and utilize web-based interventions for chronic disease management. Older adults are most likely to have chronic diseases, and may be less proficient with technology, thus limiting access to such educational technologies.

Objective: To assess baseline computer proficiencies of adults with T2D prior to participating in a web-based lifestyle intervention program.

Methods: A sample of older adult T2D patients participating in a lifestyle intervention (N=67) completed a validated Computer Proficiency Questionnaire (CPQ) for evaluating competencies in the domains of computer basics, printing, communication, Internet use, calendaring software and multimedia use. Average responses to items on a 5-point scale were summed to produce subscale and composite CPQ scores. Socio-demographic information was collected by questionnaire and use of email, website, chat room during a 12-week lifestyle intervention were assessed. Linear regression was used to determine relevant predictors of computer proficiency and t-tests were used to compare mean differences between CPQ scores by age and education.

Results: Participants were 64% men; mean age 69.5 (9.3) years, with mean diabetes duration of 19.7 (14.4) years. The CPQ subscales demonstrated excellent internal consistency reliability with subscales Cronbach’s alpha coefficients ranging from 0.89 to 0.91. Average subscale scores for basic computer skills (4.87±0.32), Internet use (4.3±1.0), and communication (4.3±0.7), while the overall composite CPQ score was 25.4±4.9 out of 30.0. Age and education were independently associated with the composite CPQ score (p<0.001).

Conclusion: Computer proficiency was very high among this sample of older adults with T2D, which helps to explain their use of the web-based intervention at baseline. Healthcare providers supporting this population might consider augmenting support services with web-based diabetes self-management but should consider the individual level of computer and technology proficiency.

Keywords: Computer proficiency, older adults, web-based interventions

ADI Research Day, October 2, 2018
EMPAGLIFLOZIN INCREASES CARDIAC ENERGY PRODUCTION IN DIABETES

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BACKGROUND: Empagliflozin treatment of diabetic patients at risk for cardiovascular disease results in a significant decrease in the risk of heart failure development and mortality. In this study, we determined whether empagliflozin's cardiovascular benefits are associated with an improvement in cardiac energy production.

METHODS AND RESULTS: 18 week-old diabetic (db/db) male mice were treated with empagliflozin or vehicle for 4 weeks (10/mg/kg/day via their food). Empagliflozin treatment prevented the development ex vivo cardiac dysfunction in db/db hearts. The rates of glucose, fatty acid and ketone oxidation were measured in isolated working hearts perfused with 0.8mM palmitate, 5 mM glucose, 0.5 mM B-hydroxybutyrate (B-OHB), and 500 µU/ml insulin. Compared to C57BL/6J mice treated with vehicle, db/db vehicle-treated mice exhibited a 61% decrease in glucose oxidation while db/db empagliflozin-treated mice had only a 43% decrease in glucose oxidation. Curiously, compared to control mice, myocardial ketone oxidation rates decreased by ~45% in db/db mice regardless of whether they were treated with vehicle or empagliflozin. Additionally, while db/db vehicle-treated hearts had decreased overall cardiac energy production compared to C57BL/6J hearts, db/db empagliflozin-treated hearts had a 31% increase in total energy production compared to the db/db vehicle-treated group. The empagliflozin-induced increase in total energy production was mainly attributed to a 61% increase in glucose oxidation's contribution to energy production. Despite an improvement in energy production, cardiac efficiency, while depressed in db/db vehicle-treated hearts compared to control hearts, was not improved with empagliflozin treatment in the db/db hearts. Lastly, since db/db hearts presented depressed myocardial ketone oxidation alongside impaired cardiac efficiency, we next determined whether the addition of 600 µM B-OHB to db/db hearts would improve cardiac efficiency. The addition of 600 µM B-OHB, while not affecting glucose or fatty acid oxidation rates, resulted in increased ketone oxidation rates and increased energy production in db/db hearts without any effect on cardiac efficiency.

CONCLUSION: Empagliflozin treatment is associated with improvements in myocardial energy production by increasing glucose oxidation in a diabetic mouse model of HFPEF. Although empagliflozin does not increase the capacity for oxidizing ketones, its in vivo effect of increasing circulating ketone levels may also contribute to an increase in cardiac energy production, independent of any changes in cardiac efficiency.

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KEY WORDS: empagliflozin, cardiovascular, diabetes, metabolism, ketones
METFORMIN REDUCES GLUCONEOGENESIS AND DELAYS BUT DOES NOT PREVENT THE CONVERSION OF PREDIABETES TO TYPE 2 DIABETES IN NILE RAT

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Background: Prediabetes is defined by an elevation of blood glucose above normal but below type 2 diabetes (T2D) thresholds, with impaired glucose tolerance (IGF) and impaired fasting glucose (IFG). Prediabetes is a high-risk stage and effective preventions are needed to prevent the conversion from prediabetes to T2D. Metformin has been the first-line drug for T2D for decades; it works as an insulin sensitizer to lower hepatic glucose output. It is also the most common drug approach in diabetes prevention, other than lifestyle intervention. Nile rat (NR), a model of T2D, develops diabetes when fed with standard chow diet. We have revealed staged progression of T2D in NR, similar to human diabetes, with early onset of insulin resistance and IGT and later onset of hyperglycemia. Here, we hypothesize that metformin treatment of NR with prediabetes will alleviate hepatic insulin resistance and thus prevent T2D development.

Methods: NR were fed standard chow diet or high-fiber diet (Hfib) after weaning. Chow animals were randomized into two groups: chow or chow+met, without/with metformin at 20 mg/kg body weight supplemented in drinking water starting at age 6 weeks. Intraperitoneal glucose tolerance (ipGTT), pyruvate (PTT) and insulin tolerance tests (ITT) were done at age 3 and 6 months. Tissues were collected from NR fasted overnight or after 4 hours of refeeding. Western blot was performed on liver samples to detect AMP-activated protein kinase (AMPK) and Akt signaling pathways. Data were analyzed by one-way or two-way ANOVA using PRISM.

Results: Chow NR presented impaired ipGTT and ITT compared to Hfib animals at 3 months (p<0.05). Metformin significantly improved ipGTT in chow+met, but didn't prevent the elevated insulin secretion during the ipGTT or impaired ITT seen in chow rats. Enhanced AMPK signaling was detected in liver from both fasted and refed chow+met animals compared to chow. The gluconeogenesis enzymes phosphoenolpyruvate carboxykinase (PEPCK) and glucose phosphatase (G6P) were reduced in liver from refed chow+met animals. The result of PTT confirmed significant reduction of gluconeogenesis in chow+met compared to chow. No change was observed in Akt phosphorylation. At 6 months, the ipGTT and ITT were worse in chow NR compared to Hfib. Chow+met animals exhibited slightly lower glucose and higher insulin in ipGTT compared to chow (p=0.06), but still significantly different from the healthy Hfib control.

Conclusion: Metformin ameliorated IGT occurring in NR fed on chow diet by reducing gluconeogenesis through AMPK activation at the earlier stage of T2D. However, metformin failed to reverse the elevated insulin secretion or block the conversion from IGT to diabetes over time.

Key words: Nile rats, impaired glucose tolerance, metformin, gluconeogenesis

ADI Research Day, October 2, 2018
**SENP1 IN COMPENSATION AND FAILURE OF INSULIN SECRETION WITH HIGH-FAT DIET**

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**Background:** Pancreatic β-cells adjust their ability to secrete insulin according to an individual's metabolic status. Whether hyperinsulinemia causes, or is an adaptive response to, obesity and insulin resistance may be debated. Functional up-regulation of β-cell insulin secretion may precede increases in islet mass in mice on a high fat diet (HFD), and at early time points β-cell functional changes likely outweigh structural change. Our recent studies identified the deSUMOylating enzyme SENP1 as a key factor to amplify insulin secretion. Interestingly, increasing SENP1 activity rescues insulin exocytosis in human β-cells from donors with type 2 diabetes (T2D). However, the involvement of SENP1 in the regulation of β-cell function in obesity and T2D conditions remains unclear.

**Methods:** We studied insulin secretion and exocytosis from human β-cells of donors that were lean or obese, and young or old. These measurements, along with single-cell measures of intracellular Ca\(^{2+}\), were also made in islets of wild type (WT) and islet SENP1 knockout (iSENP1-KO) mice fed HFD or chow diet (CD) for 2 days or 4 weeks.

**Results:** In humans, β-cells from young donors (<45) with high BMI (>25) have higher exocytotic capacity and insulin secretion compared to young donors with low BMI (<25). This difference appears lost in older donors (>55). In mice on 2-day and 4-week HFD, insulin secretion is higher at high glucose compared to mice on CD. This is not due to increased Ca\(^{2+}\) responses. Instead, the ability of depolarization induced Ca\(^{2+}\) entry to elicit an exocytotic response from HFD mice is up-regulated, even at low glucose, indicating that the 'amplifying pathway' of insulin secretion is up-regulated soon after starting the HFD. Infusion of SENP1 into β-cells can increase exocytotic response in 2-day HFD mice. However, the fold increase of response between SENP1 and GST is lower than that in mice on CD. In addition, SENP1 cannot further increase the exocytotic response in mice on 4-week HFD. When iSENP1-KO mice were fed with HFD for 2 days, in vivo insulin secretion was lower compared to control littermates.

**Conclusion:** Short-term high fat feeding increases insulin secretion by enhancing beta-cell exocytotic responses. This may involve the SUMO-protease SENP1 as a mediator of compensatory amplification of insulin secretion during HFD. Loss of SENP1 may lead to poorer glucose tolerance and diabetes.

**Keyword:** Compensation, SENP1, HFD

ADI Research Day, October 2, 2018
BLUE LIGHT REGULATES SUBCUTANEOUS WHITE ADIPOCYTE BIOLOGY VIA MELANOPsin/TRPC CHANNEL ACTIVATION

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Background: Our laboratory has discovered the presence of a blue light (470 nm)-sensitive inward current in human and murine white adipocytes. This effect is mediated by adipocyte-specific expression of melanopsin (OPN4 gene), a Gq protein coupled photoreceptor, originally discovered in the retina, that signals to open TRPC channels. Given the large human skin surface area exposed to sunlight, light stimuli may directly affect underlying subcutaneous white adipose tissue. The purpose of this study is to determine the biological importance and mechanism of this blue light-regulated effect.

Methods: PCR was used to determine expression of OPN4 and TRPC channel variants in human and murine adipocytes and adipose tissue. Whole cell patch clamp currents were recorded during stimulation with blue light and in the presence of opsinamide (melanopsin inhibitor), U73122 (phospholipase C inhibitor), or clemizole (TRPC channel inhibitor). Differentiated 3T3 L1 murine adipocytes and SGBS human adipocytes were exposed to chronic blue light stimulation (4h/day for 13 consecutive days) or dark control, and assessed for changes in lipid homeostasis determined by glycerol release and Oil Red O lipid staining. Changes in adipokine secretory profiles (leptin, adiponectin) were detected using electrochemiluminescent assays.

Results: Melanopsin and TRPC1, 3, 5 variants are expressed in human and murine adipocytes. The blue light-induced current is significantly reduced in the presence of opsinamide, U73122, and clemizole, confirming Gq-mediated activation of phospholipase C with subsequent activation of TRPC channels. Chronic blue light exposure causes an increase in glycerol release on day 11 and day 14, and a reduction in the median lipid droplet size and total number of lipid droplets in 3T3 L1 adipocytes. These changes are accompanied by significantly reduced leptin secretion (days 11 and 14) and reduced adiponectin secretion (days 5, 8, 11, 14) in the blue light-exposed cells. Interestingly, these phenotypic changes are observed homogenously across cells exposed to blue light, even though we observe a blue light-induced current in only 10-15% of the cells tested. Preliminary results suggest that treatment of naïve (non-light-treated) cells with conditioned media from blue light exposed cells mimics the latter's phenotype.

Conclusion: Dysfunctional adipose tissue is a hallmark of metabolic abnormalities linking obesity and diabetes. Our results suggest that regular sunlight exposure may directly regulate subcutaneous white adipocyte function through changes in lipid and adipokine homeostasis. Additionally, conditioned media results indicate that these effects may be mediated by an autocrine/paracrine factor, such as microRNA, secreted from a subpopulation of melanopsin-expressing cells. This research aims to shine light upon a novel regulatory mechanism of adipocyte biology that may in turn regulate whole body metabolism.

KEY WORDS Adipocyte, Melanopsin, Sunlight

ADI Research Day, October 2, 2018
SKELETAL MUSCLE-SPECIFIC CRE RECOMBINASE EXPRESSION CONTROLLED BY THE HUMAN α-SKELETAL ACTIN PROMOTER IMPROVES GLUCOSE TOLERANCE IN OBESE MICE

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Background: Cre-loxP systems are frequently used in mouse genetics as research tools for studying tissue-specific functions of numerous genes/proteins. However, the expression of Cre recombinase in a tissue-specific manner often produces undesirable changes in mouse biology that can confound data interpretation when using these tools to generate tissue-specific gene knockout mice. Our objective was to characterise the actions of Cre recombinase in skeletal muscle, and we anticipated that skeletal muscle-specific Cre recombinase expression driven by the human α-skeletal actin (HSA) promoter would influence glucose homeostasis.

Methods: Eight-week-old HSA-Cre expressing mice and their wild-type littermates were fed a low- or high-fat diet for 12 weeks. Glucose homeostasis (glucose/insulin tolerance testing) and whole-body energy metabolism (indirect calorimetry) were assessed. We also measured circulating insulin levels and the muscle expression of key regulators of energy metabolism.

Results: Whereas tamoxifen-treated HSA-Cre mice fed a low-fat diet exhibited no alterations in glucose homeostasis, we observed marked improvements in glucose tolerance in tamoxifen-treated, but not corn-oil-treated, HSA-Cre mice fed a high-fat diet vs their wild-type littermates. Moreover, Cre dissociation from heat shock protein 90 and translocation to the nucleus was only seen following tamoxifen treatment. These improvements in glucose tolerance were not due to improvements in insulin sensitivity/signalling or enhanced energy metabolism, but appeared to stem from increases in circulating insulin.

Conclusions: The intrinsic glycaemia phenotype in the HSA-Cre mouse necessitates the use of HSA-Cre controls, treated with tamoxifen, when using Cre-loxP models to investigate skeletal muscle-specific gene/protein function and glucose homeostasis.

Keywords: Cre recombinase, Glucose tolerance, Insulin, Skeletal muscle
ENGINEERING ISLET-SPECIFIC REGULATORY T CELLS AS A POTENTIAL CELLULAR THERAPY FOR T1D
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Background: Type 1 Diabetes (T1D) is an autoimmune disease characterized by the destruction of the insulin producing β-cells of the pancreatic islets. T1D occurs due to a breakdown of immune tolerance, resulting in the unchecked activities of numerous types of immune cells, including cells of the T cell lineage. Regulatory T cells (Treg) are a suppressive class of T cells characterized by expression of the transcription factor Foxp3 and inhibit immune responses through numerous mechanisms. Analysis of Treg isolated from T1D patients has shown that Treg activity is impaired relative to Treg from healthy donors. Given that impaired Treg activity is associated with immune dysfunction in T1D, the provision of exogenous functional Treg may serve as a viable strategy for the treatment of T1D. Furthermore, Treg cells can be engineered to express tissue-specific molecules, enhancing their ability to suppress autoimmunity in sites of interest. We aim to generate islet-specific Treg cells that express tissue homing and antigen-recognition molecules that will endow engineered Treg with the ability to migrate to the pancreas and respond efficiently to islet-specific antigens.

Methods: We have generated eGFP encoding lentiviral particles (eGFP-LV) to establish a protocol for generating functional engineered Treg cells using lentiviral transduction. Murine and human Treg were isolated through magnetic enrichment and stimulated through the T cell receptor (TCR) in vitro in the presence of IL-2. Following a 24 hour culture period, Treg were inoculated with eGFP–LV and eGFP+ Treg cells were FACS sorted after 7 days of culture. Purified eGFP+ Treg cells were expanded for an additional 7 days and transduced Treg were assessed for eGFP and Treg marker expression.

Results: FACS analysis of transduced murine and human Treg showed permissiveness of target cells to lentiviral transduction, with between ~10-50% of Treg being eGFP+. Following our Treg isolation, transduction, sorting and expansion protocol, we observed eGFP expression in ~90% of murine Treg and ~99% of human Treg. Furthermore, eGFP+ Treg were characterized by high levels of CD25 and Foxp3 expression, consistent with the expected phenotype of Treg cells.

Conclusions: Our results indicate that modification of murine and human Treg using lentiviral vectors is a feasible approach to generate islet-specific Treg. Future work will be geared towards using our transduction protocol to generate Treg cells expressing islet-specific homing and antigen-recognition complexes and testing the ability of engineered Treg to suppress disease in mouse models of T1D.

Keywords: Treg, autoimmunity, type 1 diabetes and cellular engineering

ADI Research Day, October 2, 2018
PHARMACOLOGICAL INHIBITION OF FORKHEAD BOX O1 ATTENUATES DIABETIC CARDIOMYOPATHY

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Background: Cardiovascular disease (CVD) represents the number 1 cause of death in people with type 2 diabetes (T2D). This includes diabetic cardiomyopathy (DC), of which there are no approved therapies. Previous studies have shown that myocardial glucose oxidation rates are markedly impaired during T2D due to reduced pyruvate dehydrogenase (PDH) activity. Furthermore, activity of the transcription factor, forkhead Box O1 (FoxO1), is enhanced in T2D and has been shown to increase expression of PDH kinase 4 (Pdk4), which phosphorylates and inhibits PDH activity. Our aim was to determine whether FoxO1 antagonism could mitigate experimental DC, and whether the potential mechanisms of benefit involve alterations in Pdk4 transcription and subsequent PDH activity.

Methods: 6-week old C57BL/6J male mice were fed with high-fat diet (HFD) for 10 weeks, injected 1x with Streptozotocin (75 mg/kg) at 4 weeks post-HFD and then treated for 2 weeks with the FoxO1 antagonist AS1842856 (100 mg/kg twice daily) via oral-gavage starting at 8-weeks post-HFD. In vivo cardiac function was assessed via ultrasound echocardiography. At study completion, mice were euthanized in response to either a 20-hr fast, or a 16-hr fast and 4-hr refeed, following which the heart and other peripheral tissues were extracted and evaluated for Pdk1/2/4 mRNA/protein expression, as well as PDH phosphorylation/activity.

Results: FoxO1 inhibition in mice with experimental T2D significantly alleviated diastolic dysfunction as assessed by the mitral E/A ratio (1.39±0.13 vs 2.02±0.12). Likewise, systolic function (ejection fraction; 57.4±2.4 vs 69.4±5.4, and fractional shortening; 29.9±1.7 vs 39.4±4.4) also showed signs of improvement following 2-weeks post-treatment with AS1842856. FoxO1 inhibition significantly decreased Pdk4 mRNA (~60%) and PDHK4 protein expression, which correlated with a decrease in PDH phosphorylation. Moreover, FoxO1 inhibition improved whole-body glucose homeostasis as determined by enhanced glucose clearance during glucose tolerance testing.

Conclusion: Our results suggest that FoxO1 inhibition mitigates the progression of cardiomyopathy in mice with experimental T2D, which may be due to reduced Pdk4 transcription in the heart and increased PDH activity/glucose oxidation.

Keywords: FoxO1, Pyruvate dehydrogenase, Diabetic cardiomyopathy, Glucose oxidation
TARGETING THE GLUCAGON RECEPTOR IMPROVES CARDIAC FUNCTION AND ENHANCES INSULIN SENSITIVITY FOLLOWING A MYOCARDIAL INFARCTION

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Introduction: Glucagon's action on cardiac glucose and lipid homeostasis counteract that of insulin's action. In heart failure, the myocardium becomes insulin resistant which influences cardiac metabolism and function.

Hypothesis: Antagonising myocardial glucagon action, using a human monoclonal antibody (mAb A) against the G coupled glucagon receptor, enhances insulin sensitivity and improves cardiac energy metabolism and function post myocardial infarction (MI).

Methods and Results: Male C57BL/6 mice were subjected to a permanent left anterior descending artery ligation, and were treated for 3 weeks with mAb A (4 mg/kg/day), which resulted in an improved ejection fraction (30.7 ± 1.8 (n=31) to 39.7 ± 2.3 (n=28) in vehicle vs mAb A treated mice) and limited adverse remodelling (i.e. decreased dilation and cardiac hypertrophy). mAb A mediated cardioprotection post-MI was associated with an activation of the IRS-1/Akt/GSK-3β pathway and increased GLUT4 expression. Enhanced insulin signalling along with a reduction in pyruvate dehydrogenase (PDH) phosphorylation resulted in a marked increase in insulin-stimulated glucose oxidation rates in the post-MI hearts. Furthermore, glucose oxidation contribution toward tricarboxylic acid (TCA) cycle acetyl CoA production, measured in isolated working hearts, was also significantly increased. Intriguingly, there was a significant reduction in cardiac ketone oxidation rates in the post-MI hearts which were further decreased by mAb A treatment. The decreased cardiac remodelling by mAb A treatment was also associated with inhibition of cardiac mTOR/P70S6K signalling compared to the vehicle-treated post-MI mice.

Conclusions: Antagonising the cardiac glucagon receptor with mAb A improves cardiac contractility and prevents adverse remodelling post-MI. mAb A-induced cardioprotection is associated with improving insulin sensitivity and a selective enhancement of glucose oxidation contribution to TCA acetyl CoA production in the infarcted hearts. Antagonizing glucagon action represents a novel and effective intervention to alleviate cardiac dysfunction and adverse remodelling post-MI.

Keywords: Glucagon, insulin sensitivity, glucose oxidation, ketone oxidation, myocardial infarction

ADI Research Day, October 2, 2018
VITAMIN D IS A PARTIAL AGONIST OF TRPV1 CHANNELS

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Background: Vitamin D deficiency is a risk factor for inflammatory diseases and metabolic disorders, like Type I diabetes. Supplementation of Vitamin D is also known to suppress the overreactive immune system possibly by dampening naïve T-cell activation and/or the inflammatory response. However, the exact mechanisms of how Vitamin D regulates the immune system have not been discovered. Traditional pharmacology suggests that Vitamin D acts almost exclusively on the Vitamin D receptor (VDR). However, naïve T-cells possess very low or absent VDR expression, therefore any effects of Vitamin D on naïve T-cell activation may be VDR-independent. In this regard, it has been shown that TRPV1 channels activation is necessary for naïve T-cell activation.

Hypothesis: We hypothesize that vitamin D is a partial agonist of TRPV1, through direct binding to TRPV1, and modulate naïve T-cell activation.

Results: Our calcium imaging results show that 25-OHD can partially activate TRPV1. In addition, our electrophysiological data demonstrate that both the 25-OHD and 1,25-OHD can inhibit capsaicin, but not pH, stimulated TRPV1 activities at physiologically relevant concentrations (~100 nM). This suggests that the lipophilic 25- and 1,25-OHD interact with TRPV1 in the same binding sites as capsaicin. Previous studies show that phosphorylation of TRPV1 through PKC augments capsaicin-mediated TRPV1 activation. Our experiments reveal that 25-OHD opposes this PKC effect. Moreover, 25OHD inhibition of TRPV1 increases in the presence staurosporine, a PKC inhibitor. In silico modeling and docking of 25-OHD to the TRPV1 structure indicates that 25-OHD binds to TRPV1 in the same region as capsaicin and previously documented PKC phosphor-acceptor residues. With respect to naïve T-cells, our flow cytometry studies confirm that both 100 nM 25-OHD and 100 nM 1,25-OHD significantly reduce TNF alpha / INF gamma and IL2 / IL4 production after 24 hours activation by anti CD3/CD28 on enriched mouse CD4+ naïve T-cells.

Summary: Our results support that the concept that vitamin D binds directly to TRPV1 channels and competes the same binding site(s) as known TRPV1 activators. Moreover, naïve T-cell activation can be dampened by vitamin D in a VDR-independent manner. These novel findings provide evidence of an additional site of action for vitamin D and advances our knowledge of the underlying cellular mechanism by which vitamin D may beneficially dampen naïve T-cell activation in autoimmune diseases such as T1D.

Key words: Vitamin D, TRPV1, Type 1 Diabetes, Autoimmune diseases

ADI Research Day, October 2, 2018
STRUCTURAL DETERMINANTS OF POTASSIUM CHANNEL MODULATION BY THE AMINO ACID TRANSPORTER SLC7A5

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Background: Branched-chain amino acids (BCAA) have been well established as an important regulator of glucose homeostasis. BCAA can influence insulin secretion and sensitivity via activation of mammalian target of rapamycin complex 1 (mTORC1). Knockdown of BCAA transporter LAT1 (SLC7A5) inhibits mTORC1 signalling, insulin secretion and islet cell proliferation. We have recently identified the BCAA transporter Slc7a5 as a powerful regulator of Kv1.2, a voltage dependent potassium channel. Co-expression of Slc7a5 with Kv1.2 reduces expression and alters the voltage-dependence of channel gating. Despite 80% sequence identity with Kv1.2, Kv1.1 channels exhibit a distinct response to Slc7a5, while Kv1.5 channels are completely insensitive. We used these subtype specific differences to investigate structural features that regulate the interaction between Kv1 channels and Slc7a5.

Methods: Chimeric channel constructs substituting segments of Kv1.2 with either Kv1.1 or Kv1.5 sequence were generated using overlapping PCR approaches. Mouse ltk- fibroblast cells were transiently transfected with chimeric channel constructs in the presence and absence of Slc7a5. Successfully transfected cells were used to measure membrane currents using whole-cell patch technique.

Results: Chimeric combinations of Kv1.2 and Kv1.5 revealed a strong influence of amino acids in the S1 transmembrane segment on channel sensitivity to Slc7a5. We identified Kv1.2 I164 as an important determinant of Slc7a5 sensitivity. In addition, Kv1.1 and Kv1.2 exhibit marked differences in the effects of Slc7a5 on voltage-dependent activation, and we mapped these differences to I257 and S3-S4 linker. Further point mutations will be introduced in Kv1.2 and Kv1.1 channels to confirm the site of interaction and regulation of Kv1.2 by Slc7a5.

Conclusion: The role of BCAA transports in regulating mTORC1 activity is largely unexplored. However, growing evidence suggest that BCAA-dependent activation of mTORC1 may influence electrical properties of excitable cells. Our study identifies structural determinants of a previously unrecognized interaction between potassium channels and a BCAA transporter Slc7a5. The results of this study will also help to better understand the unique role of Slc7a5 in disease pathogenesis in patients with Kv1.2, Slc7a5 mutations.

Key Words: Amino acid transporter, Slc7a5, Potassium channel, Kv1.2.

ADI Research Day, October 2, 2018
THE ROLE OF LYN IN BETA-CELL FUNCTION, SURVIVAL, AND PROLIFERATION

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Background: The loss of beta-cell mass is a defining characteristic of diabetes. Our research group focuses on the investigation of the determinants of beta-cell mass reduction. In our past investigation of GLP-1 signaling in beta-cells, we identified a critical role for a member of the Src family of proteins in the regulation of beta-cell mass. We herein identify this key regulator to be the Src family member Lyn, and investigate its role in beta-cell mass both in vitro and in vivo.

Methods: The expression and activity of Lyn was measured in INS cells and in human islets. We performed gain-of-function experiments using virus-mediated Lyn overexpression and loss-of-function experiments using siRNA-mediated Lyn knockdown. We also used a beta-cell-specific Lyn knockout (bLynKO) mouse model to investigate the effects of loss of Lyn function on islet morphology and glucose homeostasis.

Results: We show that pancreatic beta-cells express Lyn, as well as 3 other Src family members: c-Src, Fyn, and Yes. Of these members, only c-Src and Lyn were activated by the beta-cell growth factor GLP-1. Through overexpression and down-regulation of Lyn in INS cells and human islets, we demonstrate the key regulatory effect of Lyn on beta-cell proliferation and survival. Specifically, we show that Lyn gain-of-function significantly increases beta-cell proliferation, and markedly reduces beta-cell apoptosis in both INS cells and human islets when exposed to glucolipotoxicity. In contrast, Lyn loss-of-function elicits a decrease in beta-cell proliferation and an increase of beta-cell apoptosis. Additional experiments using a pharmacological Lyn activator, MLR1023, re-iterated the effects of Lyn gain-of-function. In our in vivo bLynKO model, over a 4-week period we witness an increase in the incidence of diabetes compared to normal control mice. Interestingly, this effect is seen only in males under high-fat diet (HFD) conditions. These mice also exhibited lower beta-cell mass than normal controls. We also observe that the proliferative effect of GLP-1 on beta-cells in normal control mice is negated in bLynKO mice.

Conclusion: Our study identifies and characterizes Lyn as a novel regulator of beta-cell mass with key roles in beta-cell proliferation and survival. As such, Lyn represents a promising novel molecular target for diabetes treatment.

Keywords: Lyn, c-Src, tyrosine protein kinases, beta-cells, proliferation, apoptosis.

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