Alberta Diabetes INSTITUTE

2023 RESEARCH DAY

0815-1630 | 1-040 LKS (Oborowsky Degner Seminar Hall) & LKS Foyer

FRIDAY SEPTEMBER 15

KEYNOTE SPEAKER

Maria Cristina Nostro, PhD

Associate Professor, Department of Physiology,
University of Toronto

UNIVERSITY OF ALBERTA

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Program

Alberta Diabetes INSTITUTE

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

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Note from the Director

Welcome to the 2023 Alberta Diabetes Institute Research Day. This annual event, hosted by the ADI since 2005, provides ADI Trainees - from first year undergraduate summer students to seasoned postdoctoral fellows - the opportunity to showcase their research efforts. This year, we are excited to host our event fully in-person! With the help of our dedicated ADI Trainee Working Group, ADI Members, Trainees, and Administration, we have organized an exciting day of oral and poster presentations that will provide an enriching experience for everyone attending.

We are delighted to welcome Dr. Cristina Nostro, Associate Professor of Physiology from the University of Toronto as this year's keynote speaker and judge. Dr Nostro is an international expert in generating islet cells from stem cells. She is a good friend and trusted collaborator to several ADI members. We are honoured that Dr. Nostro accepted our ADI Trainee Working Group members' invitation and we look forward to welcoming her to Alberta, and to the ADI.

Our research day is intended to provide a forum to showcase the research efforts of our **ADI Trainees**. With respect to this, there are two **oral presentation** sessions (junior/senior trainees) and two poster **presentation sessions** (junior/senior trainees). During research day, our trainees have the opportunity for direct interaction with Dr. Nostro over lunch.

The ongoing support and contributions from the Faculty of Medicine and Dentistry, the Alberta Diabetes Foundation, DRIFCan, endowments supporting the Muttart Diabetes Research & Training Centre, and generous donors and other partners, is deeply appreciated for their vital and sustained contributions to the work of the ADI.

I am indebted to our ADI Trainee Working Group (supported by Dr. Vincent Rogers) for their help in organizing and running this year's ADI Research Day. I would also like to thank all of our volunteers, judges, session chairs, and A/V support.

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

Best Regards,

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

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Keynote Speaker

Dr. Maria Cristina Nostro, PhD

The ADI is excited to announce this year's keynote speaker, Dr. Maria Cristina Nostro.

Dr. Nostro is an associate professor in the Department of Physiology at the University of Toronto, and is part of the McEwen Stem Cell Institute as a principal investigator. She began her academic career in Florence, Italy, receiving both her Bachelors of Science and Masters of Science degree in Biology from the University of Florence. Following her MSc, she received her PhD from the University of Manchester, UK, studying and profiling blood stem cells under the supervision of Dr. Gerard Brady. After successfully completing her PhD, she continued on into a postdoctoral position at the Mount Sinai School of Medicine in New York, in Dr. Gordon Keller's lab. Here she focused on understanding the formation of blood cells utilizing embryonic stem cells. In 2007, she relocated to Toronto and in 2012, became a principal investigator focusing on pancreatic development, specifically the generation and purification of functional pancreatic beta cells from human embryonic and induced pluripotent stem cells. Dr. Nostro currently holds the Harry Rosen Chair in Diabetes Regenerative Medicine Research, which is awarded to an outstanding investigator focused on applying state-of-the-art stem cell biology and regenerative medicine approaches to develop treatments for this chronic disease. The Nostro Lab is focused on the molecular regulators that control pancreatic development and beta cell maturation.

On September 15, from 8:45-9:45 am, Dr. Nostro will be delivering her keynote speech in the Oborowsky Degner Seminar Hall. We would also like to thank Dr. Nostro for hosting the trainee lunch Q&A and joining us for the entire day filled with exceptional research.

Welcome Dr. Nostro!

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Morning & Afternoon Schedule

MORNING SESSION

WELCOME

08:15	Welcome to 2023 Research Day	Refreshments in the LKS Foyer
08:30	Opening Remarks	Dr. Peter Senior, ADI Director
08:40	Introduction to Keynote Speaker	Nerea Cuesta Gomez – ADI Trainee Working Group President

KEYNOTE SPEAKER

08:45	Dr. Cristina Nostro Associate Professor, Department of Physiology, University of Toronto	Keynote speech

POSTER PRESENTATION - JUNIOR

09:50	Dineli Fernando Chan Lab	Undergrad student	**Page 1**	DIFFERENTIAL EFFECTS OF DAIRY PRODUCTS ON HEPATIC LIPID METABOLISM IN A HIGH-FAT DIET-INDUCED NON-ALCOHOLIC FATTY LIVER DISEASE MOUSE MODEL
09:58	Aaron Getachew Chan Lab	Undergrad student	**Page 2**	THE EFFECTS OF IRW (ILE-ARG-TRP) ON ER STRESS PROTEINS IN THE LIVER OF OBESE AND GLUCOSE-INTOLERANT C57BL/6 MICE
10:06	Mackenzie Merriott Yue Lab	Undergrad student	**Page 3**	ASSESSING GLUCOSE METABOLISM IN RATS TREATED WITH A LEPTIN SENSITIZER USING HYPERINSULINEMIC-EUGLYCEMIC CLAMPS
10:14	Elisa Molstad Ferdaoussi Lab	Undergrad student	**Page 4**	ROLE OF FERROPTOSIS IN GLUCOCORTICOIDS-INDUCED β CELL FAILURE
10:22	Anne Rinna Kouassi-Djan Ferdaoussi Lab	Undergrad student	**Page 5**	ROLE OF FERROPTOSIS IN GLUCOLIPOTOXICITY-INDUCED β CELL DYSFUNCTION AND DEATH
10:30	ZhiDi Deng Haqq Lab	Undergrad student	**Page 6**	EFFECTS OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS ISOLATED OR IN COMBINATION WITH OTHER DRUGS ON ENERGY EXPENDITURE: A SCOPING REVIEW PROTOCOL
10:38	Boshra Mandour Richard Lab	MSc student	**Page 7**	HYPERGLYCAEMIA IN OBESITY IS ASSOCIATED WITH IMPAIRED EX VIVO T CELL FUNCTION: AN INTERIM ANALYSIS OF THE NUTRITION AND IMMUNITY (NUTRIMM) STUDY
10:46	Gala Araujo Proctor Lab	MSc student	**Page 8**	IMMUNOGENICITY OF NOVEL VARIANTS OF THE CHIMERIC CHP3R99 ANTIATHEROGENIC ANTIBODY IN INSULIN-RESISTANT RATS
10:54	Kunyan Yang Ussher Lab	MSc student	**Page 9**	EXOGENOUS KETONE ESTER ADMINISTRATION IMPROVES GLUCOSE HOMEOSTASIS IN OBESE MALE MICE

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Morning & Afternoon Schedule

ORAL PRESENTATION - SENIOR

SESSION CHAIR: ADI Trainee Working Group Executives

11:15	Alice Carr Senior Lab	Postdoctoral Fellow	**Page 10**	BETA-2 SCORES OVERESTIMATE GRAFT FUNCTION IN PANCREATIC ISLET TRANSPLANT RECIPIENTS WITH AN ESTIMATED GLOMERULAR FILTRATION RATE OF < 30 ML/MIN/1.73M2
11:30	Jasmine Maghera MacDonald Lab	PhD student	**Page 11**	ELECTROPHYSIOLOGICAL CHARACTERIZATION OF STEM-CELL DERIVED β-CELLS TO HELP PRODUCE CLINICALLY RELEVANT CELLS FOR TRANSPLANTATION
11:45	Xiaoying Wu Vine Lab	PhD student	**Page 12**	PRE-DIABETES AND APO-B PREDICT EARLY CARDIOVASCULAR DISEASE IN YOUNG WOMEN WITH AND WITHOUT POLYCYSTIC OVARY SYNDROME
12:00	Christina Saed Ussher Lab	PhD student	**Page 13**	THE ANTIPSYCHOTIC AGENT PIMOZIDE ALLEVIATES NON-ALCOHOLIC FATTY LIVER DISEASE IN EXPERIMENTAL TYPE 2 DIABETES
12:15	Jordan Chan Ussher Lab	PhD student	**Page 14**	THE GLP-1 RECEPTOR AGONIST LIRAGLUTIDE ALLEVIATES TYPE 2 DIABETES-RELATED DIASTOLIC DYSFUNCTION IN A PYRUVATE DEHYDROGENASE-DEPENDENT MANNER

TRAINEE LUNCH WITH THE SPEAKER

12:30-13:30	LKS Foyer By invitation: ADI Trainee Research Day Presenters/ ADI Research Day Trainee Volunteers	Guest Dr. Cristina Nostro / Hosts ADI Trainees LUNCH PROVIDED

AFTERNOON SESSION

POSTER PRESENTATION - SENIOR

13:35	Zofia Czarnecka Shapiro Lab	MSc student	**Page 15**	COMPARING THE FUNCTION AND EFFICACY OF STAGE 6 AND STAGE 7 IPSC-DERIVED ISLET-LIKE CELLS
13:43	MohammadAli Maleki Bigdeli Stroberg Lab	PhD student	**Page 16**	MULTI-SCALE MODELING OF *GLAD*-FABRICATED ELECTROCHEMICAL BIOSENSORS FOR DIABETES MONITORING
13:51	Kholoud Elmihi Jacobs Lab	PhD student	**Page 17**	ETNPPL INFLUENCES LIPOPROTEIN METABOLISM BUT DOES NOT INDUCE FATTY LIVER DISEASE IN MICE
13:59	Amanda Schukarucha Gomes MacDonald Lab	PhD student	**Page 18**	GLYCINE RECEPTOR ACTIVITY IN β CELLS IS DOWNREGULATED IN TYPE 2 DIABETES AND AFTER HIGH GLUCOSE CULTURE
14:07	Danielle Nagy Simpson Lab	PhD student	**Page 19**	RURAL RESIDENCE IS ASSOCIATED WITH LIMITED GUIDELINE CONCORDANT CHOLESTEROL MANAGEMENT IN NEWLY TREATED TYPE 2 DIABETES

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POSTER PRESENTATION - SENIOR

14:15	Hui Huang Buteau Lab	Postdoctoral Fellow	**Page 20**	EXTRA-PANCREATIC ACTIONS OF MLR-1023, A NOVEL ANTIDIABETES DRUG CANDIDATE
14:23	Janyne Johnson Light Lab	PhD student	**Page 21**	CHARACTERIZING GLUCAGON-LIKE PEPTIDE-1 PRODUCTION IN ALPHA-CELLS
14:31	Julia Montenegro Prado Lab	PhD student	**Page 22**	METABOLIC PROFILE OF INDIVIDUALS WITH EXCESS BODY WEIGHT: BASELINE FINDINGS FROM THE *PREMIUM* STUDY
14:39	Reihane Taheri Proctor Lab	PhD student	**Page 23**	EATING INDEX SCORE IS ASSOCIATED WITH REDUCED INCIDENCE OF CARDIOVASCULAR DISEASE AS WELL AS A LOWER LEVEL OF NON-FASTING REMNANT CHOLESTEROL IN THE *ALBERTA TOMORROW PROJECT*
14:47	Alice Carr Senior Lab	Postdoctoral Fellow	**Page 24**	COMPOSITE SCORES USING FASTING AND STIMULATED C-PEPTIDE ARE EQUIVALENT AND CAN TRACK BETA CELL FUNCTION IN NEW ONSET TYPE 1 DIABETES

ORAL PRESENTATION - JUNIOR

SESSION CHAIR: ADI Trainee Working Group Executives

15:00	Courtney Holdaway Jacobs Lab	MSc student	**Page 25**	UNDERSTANDING THE IMPACT OF ALTERED PHOSPHATIDYLETHANOLAMINE (PE) METABOLISM IN HEPATOCYTE DERIVED CELLS
15:15	Tianna Rusnak Richard Lab	MSc student	**Page 26**	EGG-DERIVED PC ENHANCES T CELL RESPONSES TO A GREATER EXTENT THAN SOY-PC UNDER THE CONTEXT OF OBESITY
15:30	Claire Douglas Field Lab	MSc student	**Page 27**	THE ASSOCIATIONS BETWEEN DOCOSAHEXAENOIC ACID (DHA) AND CAROTENOIDS, EXERCISE PATTERNS, AND QUALITY OF LIFE IN WOMEN UNDERGOING NEOADJUVANT CHEMOTHERAPY IN THE DHA-WIN RCT
15:45	Nandini Basuray Haqq Lab	MSc student	**Page 28**	METFORMIN AND FIBER COMBINED THERAPY IN ADOLESCENTS WITH OBESITY AND INSULIN RESISTANCE (METFIBER TRIAL): PRELIMINARY BASELINE FINDINGS
16:00	Boyan Vasilev Yue Lab	MSc student	**Page 29**	AGONISM OF GLUCOCORTICOID RECEPTOR IN THE NUCLEUS OF THE SOLITARY TRACT STIMULATES VLDL-TG SECRETION FROM THE LIVER

CLOSING REMARKS

16:15-16:20	Dr. Peter Senior, ADI Director	Awards announced on Monday, September 18.

Awards

Prize winners will be notified by email on September 18 and announced via ADI Update and social media.

ORAL PRESENTATION SESSION (Junior Trainees)

- 1 Best Award & 1 Honourable Mention

ORAL PRESENTATION SESSION (Senior Trainees)

- 1 Best Award & 1 Honourable Mention

POSTER SESSION (Junior Trainees)

- 1 Best Award & 1 Honourable Mention

POSTER SESSION (Senior Trainees)

- 1 Best Award & 1 Honourable Mention

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Alberta Diabetes INSTITUTE

ABSTRACTS

Morning Session

Poster Presentation

JUNIOR

Pages 1-10

UNIVERSITY OF ALBERTA

Abstracts

DIFFERENTIAL EFFECTS OF DAIRY PRODUCTS ON HEPATIC LIPID METABOLISM IN A HIGH-FAT DIET-INDUCED NON-ALCOHOLIC FATTY LIVER DISEASE MOUSE MODEL

Dineli N. Fernando1, Emad Yuzbashian1, Catherine B. Chan1,2

1Department of Agricultural, Food and Nutritional Science, Faculty of Agricultural, Life & Environmental Sciences, University of Alberta; 2Department of Physiology, Faculty of Medicine & Dentistry, University of Alberta

BACKGROUND: Visceral adiposity, type 2 diabetes (T2D), and metabolic syndrome are pathological risk factors for non-alcoholic fatty liver disease (NAFLD). NAFLD is characterized by excess hepatic lipid accumulation. Left unmanaged, NAFLD progresses to non-alcoholic steatohepatitis and hepatocellular carcinoma. There remain no approved pharmacological treatments for NAFLD; thus, adherence to a healthy diet remains the only approach for NAFLD prevention. Dairy products, milk (M), cheese (C), and yogurt (Y), can reduce hepatic lipid accumulation though the exact mechanism by which dairy products improve liver lipid metabolism remain unknown. This study aims to elucidate the mechanisms by which dairy products affect hepatic lipid metabolism in a mouse model.

METHODS: 8-week male C57BL/6 mice (N=30) were randomly assigned to a 10% fat diet (LFD, n=6), and the remainder of the mice were assigned to a 45% fat HFD (n=24) for 1 week. Then, mice from the HFD group were randomly assigned 6/group: HFD, HFD+M, HFD+Y, and HFD+C. Mice were euthanized after 8 weeks, and liver tissues were harvested. Immunoblotting was used to quantify proteins involved in hepatic lipid metabolism. Histological analysis was performed on liver tissues and lipid droplet (LD) count and area was obtained via ImageJ.

RESULTS: Results showed a significant reduction of LD counts in the HFD+Y group compared to the HFD group. The average area of LDs observed in the HFD+M, HFD+C, HFD+Y, and LFD groups was significantly lower compared to the HFD group. Protein levels of cluster of differentiation (CD) 36 (involved in fatty acid uptake in the liver) were lower in HFD+C-fed mice compared to HFD-fed mice in re-fed and fasting conditions. The protein levels of long-chain acyl-coenzyme A synthetase 1 (ACSL1), an enzyme involved in the process of β-oxidation, were higher in HFD+M, HFD+Y, and HFD+C-fed mice compared to HFD-fed mice in re-fed and fasting conditions. Protein levels of fatty acid synthase (FAS), an enzyme involved in de novo lipogenesis, were higher in HFD+M, HFD+Y, and HFD+C-fed mice compared to the HFD-fed mice in the fasted state and were lower in HFD+M and HFD+C-fed mice compared to HFD-fed mice in the re-fed state. The protein abundance of acetyl-CoA synthetase (AceCS1), an enzyme involved in de novo lipogenesis, was higher in HFD+M, HFD+Y, and HFD+C-fed mice compared to HFD-fed mice in both re-fed and fasting conditions. Levels of microsomal triglyceride transfer protein (MTP), an enzyme involved in lipid export, were higher in HFD+M, and HFD+C-fed mice compared to HFD-fed mice in the fasted state and higher in HFD+M and HFD+Y-fed mice compared to HFD-fed mice in the re-fed state.

CONCLUSION: We demonstrate that the inclusion of dairy products in diets high in fat, similar to westernized diets, can have differential impacts on hepatic lipid accumulation in a high-fat diet-induced non-alcoholic fatty liver mouse model.

Abstracts

THE EFFECTS OF IRW (ILE-ARG-TRP) ON ER STRESS PROTEINS IN THE LIVER OF OBESE AND GLUCOSE-INTOLERANT C57BL/6 MICE

Aaron Getachew1, Stepheny C. de Campos Zani1,2, Jianping Wu3, and Catherine B. Chan1,2,3

1Department of Physiology, Faculty of Medicine and Dentistry, University of Alberta
2Alberta Diabetes Institute, University of Alberta
3Department of Agricultural Food & Nutritional Science, Faculty of Agricultural Life & Environmental Sciences, University of Alberta

Background: Non-alcoholic fatty liver disease (NAFLD) is a metabolic disorder characterized by the accumulation of fat in the liver, commonly accompanied by visceral obesity and type 2 diabetes (T2D). Despite its high prevalence in the global population, there are currently no pharmacological treatments available. Furthermore, the initiation of NAFLD and its progression into chronic conditions such as non-alcoholic steatohepatitis (NASH) is not fully elucidated. There is a potential role of endoplasmic reticulum (ER) stress in NAFLD development. ER stress occurs when the ER becomes overwhelmed by misfolded proteins, which can be due to a disruption in cellular function and metabolism triggered by excess fat in the liver. NAFLD is associated with improper protein folding which leads to ER stress and the unfolded protein response (UPR), a stress-signaling response to misfolded proteins, mediated by ER protein chaperones. IRW (Isoleucine-Arginine-Tryptophan) is a bioactive peptide derived from egg white that has previously shown to reduce hepatic steatosis and improve insulin resistance in mice. Therefore, I hypothesize that IRW supplementation will improve NAFLD by alleviating ER stress through the reduction of the UPR and ER stress-associated chaperone proteins.

Methods: 5-week-old male C57BL/6 mice were fed a high-fat diet (HFD) for 6 weeks to induce obesity and glucose intolerance. Mice were then divided into three groups (n=8): HFD control, HFD+IRW (45 mg/kg BW), and HFD+ROSI (rosiglitazone 2.5 µmol/kg BW) and received their diets for 8 weeks. Over the 14-week period, another group received a low-fat diet (LFD) (n=8). Liver was collected and liver proteins were extracted, then separated by SDS-PAGE 12% gels. Western blot was performed probing the membranes against the ER stress markers inositol-requiring enzyme 1 alpha (IRE1α), protein disulfide isomerase (PDI), and endoplasmic reticulum protein 72 (ERp72). Images were quantified using ImageJ.

Results: IRE1α and chaperone ERp72 protein abundance were increased in HFD mice, as compared to a LFD. However, no significant differences between HFD, HFD+ROSI, and HFD+IRW groups were observed. Similarly, PDI yielded no statistically significant differences among all groups.

Conclusion: IRW does not appear to play a regulatory role on the abundance of ER stress proteins analyzed. However, based on previous research, IRW improved hepatic steatosis while preserving mitochondria content thus more research is needed to elucidate the role of IRW on other ER stress markers and other branches of the UPR.

Abstracts

ASSESSING GLUCOSE METABOLISM IN RATS TREATED WITH A LEPTIN SENSITIZER USING HYPERINSULINEMIC-EUGLYCEMIC CLAMPS

Mackenzie Merriott1,2*, Jacques Zhang1,2*, D'arci Sutton1,2, Miriam Bernecker5, Bryan M. Lum1,2,3, Paul T. Pfluger5, Jessica T.Y. Yue1,2,3,4

1Department of Physiology, 2Alberta Diabetes Institute, 3Group on Molecular and Cell Biology of Lipids, 4Neuroscience and Mental Health Institute; University of Alberta, Edmonton, Canada. 5Helmholtz Diabetes Research Centre, Munich, Germany.

In addition to its potent effects on suppressing appetite, leptin regulates blood glucose levels. Leptin receptors are found in a variety of tissues, and thus leptin is thought to have both central and peripheral actions which mediate its beneficial effects on glucose metabolism. Obesity, and even acute high-fat diet (HFD)-feeding in rodents, can disrupt energy balance and glucose metabolism and contribute to leptin resistance. Thus, developing strategies to enhance endogenous leptin sensitivity may help to improve metabolic homeostasis. Celastrol is a plant-derived compound with leptin-sensitizing properties. The Pfluger lab has shown that peripheral administration of celastrol reduces body weight and improves glucose tolerance in diet-induced obese mice. However, less is known about the direct central effects of celastrol. Here, we aim to test whether celastrol acts centrally to confer metabolic benefits and hypothesize that hypothalamic infusion of celastrol improves whole-body glucose metabolism in HFD-fed rats.

Sprague-Dawley rats received a stereotaxically implanted cannula into the third ventricle (ICV3) and catheters into the right jugular vein and left carotid artery for hypothalamic infusions, intravenous infusions, and blood sampling, respectively. A subset of rats was fed with HFD (58% kcal fat) for 7 days. Rats underwent hyperinsulinemic-euglycemic clamp experiments ("insulin clamps") with tracer dilution methodology to assess glucose kinetics during basal and clamp periods with concomitant ICV3 infusion of celastrol or vehicle (0.9% DMSO in saline).

As expected, HFD rats exhibited mild hyperinsulinemia and modestly increased hepatic glucose production in the basal state compared to chow-fed controls. These differences occurred independent of changes in body weight. During insulin clamps, in which circulating insulin levels were elevated by ~40% from basal, insulin-induced glucose production was markedly less suppressed in HFD rats, indicating hepatic insulin resistance. Notably in HFD rats, ICV3 celastrol strikingly lowered glucose production and enhanced glucose utilization during insulin clamps compared to ICV3 vehicle controls, suggesting that celastrol in the hypothalamus increases insulin sensitivity in the liver to suppress glucose production and in adipose tissue and/or skeletal muscle to stimulate glucose uptake to improve whole-body glucose metabolism.

We provide evidence that hypothalamic celastrol enhances peripheral insulin sensitivity to improve whole-body glucose metabolism in an animal model of diet-induced insulin resistance. These findings may implicate stimulating endogenous leptin sensitivity as an approach to ameliorating glucose homeostasis in metabolic diseases like obesity and diabetes.

** Mackenzie Merriott and Jacques Zhang are considered co-first authors of this abstract.*
Mackenzie is supported by a FoMD Medicine Class of 1986 Research Scholarship. Jacques is supported by a NSERC Undergraduate Student Research Award.

Abstracts

ROLE OF FERROPTOSIS IN GLUCOCORTICOIDS-INDUCED SS CELL FAILURE

Elisa Molstad1,2, Sherilyne Ketsia Mvolo1,2, Zenab Gill2,3, Leah Isaac2, Meriem Baadi1,2, Anne Rinna Kouassi-Djan1,2, Mourad Ferdaoussi1,2

1- Alberta Diabetes Institute, University of Alberta. 2- Faculté Saint-Jean, University of Alberta. 3-McMaster University

Introduction: Glucocorticoids possess immunosuppressive and anti-inflammatory properties, making them effective drugs for treating various diseases and conditions. Dexamethasone and prednisone are the most commonly used corticosteroids. However, the chronic administration of these medications is often associated with the development of ß cell dysfunction and type 2 diabetes. Recent studies have shown in non-ß cells that glucocorticoids are potent activators of ferroptosis, a newly discovered programmed cell death mechanism. Herein, we aim to investigate whether ferroptosis mediates glucocorticoid-induced ß cell failure and death.

Methods and Results: Insulin secretion in mouse islets treated with 200 nM of dexamethasone was strongly reduced in response to 16.7 mM of glucose and 100 nM of GLP-1 receptor agonist Exendin-4 as measured by ELISA. Interestingly, our preliminary data showed that 24 hours of exposure of the insulin- secreting cell line INS832/13 to 200 nM of dexamethasone or 1 µM of prednisone, as well as 1 µM of ferroptosis activator RSL3, reduced the expression of glutathione peroxidase 4 (GPx4) and Islet Brain 1 (IB1) protein levels as assessed by western blot. While GPx4 is the hallmark of ferroptosis that uses glutathione to reduce the oxidized form of lipids (i.e., lipid peroxides), IB1 is a scaffold protein that regulates the transport of granules to exocytotic sites.

Discussion: Our data suggests that glucocorticoids activate the ferroptosis pathway in ß cells. We also suggest that ferroptosis could mediate its effects by reducing insulin granule trafficking by reducing IB1 expression. Together, these findings provide new perspectives on investigating the underlying mechanisms behind the diabetogenic effects of glucocorticoids.

Keywords: Ferroptosis, Glucocorticoids, ß cell.

Abstracts

ROLE OF FERROPTOSIS IN GLUCOLIPOTOXICITY-INDUCED SS CELL DYSFUNCTION AND DEATH

Anne Rinna Kouassi-Djan1,2, Meriem Baadi1,2, Leah Isaac1, Elisa Molstad1,2, Sherilyne Ketsia Mvolo1,2, Zenab Gill1,3, Mourad Ferdaoussi1,2

1- Alberta Diabetes Institute, University of Alberta. 2- Faculté Saint-Jean, University of Alberta. 3-McMaster University

Introduction: The mechanisms inducing pancreatic ß cell dysfunction and death in response to glucolipotoxicity are not yet fully understood. Ferroptosis, a newly uncovered programmed cell death mechanism, involves antioxidant glutathione depletion, concomitant with glutathione peroxidase 4 (GPx4) protein level reduction, ROS accumulation, and iron-dependent phospholipid peroxidation. These events result in substantial mitochondrial damage and inhibition of its turnover. Herein we investigate the potential of ferroptosis to mediate the glucolipotoxic effects on ß cells.

Methods & Results: Exposure of the insulin-secreting cell line INS832/13 to 400 mM palmitate (complexed to BSA at a ratio 1:5) and 25 mM glucose substantially reduces GPx4 protein levels within 2 hours as assessed by western blot. Preliminary data indicates a similar reduction of Gpx4 in human pancreatic islets after 24 hours of incubation. Interestingly, neither palmitate and glucose nor the pharmacological ferroptosis inducer, Erastin, alter the expression of Gpx4 mRNA levels measured by RT-PCR. However, Erastin reduced mitochondrial turnover markers as evidenced by the decrease of the expression levels of mitochondrial proteins Mitofusin 1 (MFN1) and Optic Atrophy Protein 1 (OPA1), which coordinate the fusion of the inner and outer mitochondrial membranes. Erastin also alters the phosphorylation pattern of the Dynamin Related Protein 1 (DRP1) that mediates mitochondrial fission.

Discussion: Our data suggests that the ferroptosis pathway is activated in response to glucolipotoxicity in ß cells. This alteration might impair mitochondrial turnover and contribute to an imbalance between oxidative stress and the capacity of antioxidants to defend ß cells from dysfunction and, ultimately, death.

Keywords: Ferroptosis, Glucolipotoxicity, Mitochondrial turnover.

Abstracts

EFFECTS OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS ISOLATED OR IN COMBINATION WITH OTHER DRUGS ON ENERGY EXPENDITURE: A SCOPING REVIEW PROTOCOL

ZhiDi Denga, Flavio T. Vieiraa, and Andrea M. Haqqa

aDepartment of Pediatrics, University of Alberta, Edmonton, AB T6G 2R3, Canada

Background: Obesity is a chronic condition that affects approximately 27% of Canadian adults.1 Established weight management strategies include nutrition and physical activity, psychological therapy, pharmacological therapy, and surgery. However, despite employment of these strategies, weight loss and maintenance of the lost weight are challenging. Weight loss is associated with metabolic adaptations, such as declines in energy expenditure (EE) and changes in circulating levels of orexigenic and anorexigenic hormones, that favor weight regain.2-4 There has been ongoing exploration of therapies that can mitigate this metabolic adaptation. In recent years, the discovery and application of Glucagon-Like Peptide-1 Receptor (GLP-1R) agonists in weight management, alone or in combination with hormones such as glucagon and glucose-dependent insulinotropic polypeptide, has attracted much attention for its efficacy. GLP-1R agonists act by reducing food cravings and increasing satiety. Certain combinations of the product have been shown to achieve weight loss of around 20%, on par with bariatric surgery. Yet the impact of these agents on EE is unclear and conflicting findings have been reported, varying according to drug formulation, dose, intervention duration, and assessment methods.

Objective: The objective of this scoping review is to explore the effects of GLP-1R agonists, isolated or in combination with other drugs, on energy expenditure.

Methods: We searched on MEDLINE, EMBASE, CINAHL, Web of Science, ProQuest, and Cochrane Library from their respective inception dates to June 2023 for studies that investigated the effects of GLP-1R agonists in combination with other drugs on EE in animals and humans. Additionally, to update a previous systematic review that focused on GLP-1R agonist monotherapy, we conducted additional searches in the aforementioned databases from 2018 to June 2023. Eligible study designs were controlled experimental trials with quantitative results. Any controls were accepted, including baseline status, placebo, or other anti-obesity pharmacotherapies. In vitro studies, studies without comparators, case reports, case series, reviews, letters to editor, book chapters, abstracts, and conference proceedings were excluded. One experienced reviewer in pharmacology and systematic reviews will perform the screening of titles, abstracts, and full texts, and extract the data (i.e., study and intervention characteristics, effects on EE, etc.). A second reviewer will be consulted about uncertainties. Disagreements will be resolved through discussion between the reviewers or in consultation with a third reviewer. A total of 6445 citations were identified in our search. After removing duplicates, 3420 unique citations remained. To date, titles and abstract screening have been completed and 257 studies have progressed to full-text review. The study is anticipated to be completed by August 31, 2023.

Discussion: We anticipate that the combination therapy of GLP-1R agonist, especially with glucagon, may significantly increase EE and shift substrate oxidation to fat. Obesity is a lifelong complex disease that negatively impacts the health of individuals and increases their risk of medical complications. Improved knowledge of pharmacotherapies may help to inform precision medicine for obesity. For instance, knowledge of the effects of various GLP-1R agonists on EE can help clinicians to better target different obesity phenotypes (i.e., decreased metabolic rate vs. abnormal satiety)5 and help patients achieve greater weight reductions going forward.

Abstracts

HYPERGLYCAEMIA IN OBESITY IS ASSOCIATED WITH IMPAIRED EX VIVO T CELL FUNCTION: AN INTERIM ANALYSIS OF THE NUTRITION AND IMMUNITY (NUTRIMM) STUDY

Boshra Mandour1, Jenneffer Rayane Braga Tibaes1, Jessy Azarcoya-Barrera1, Maria Ines Barreto Silva1, Dineli N. Fernando1, Paulina Blanco1, Alexander Makarowski1, Caroline Richard1

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

Introduction: Obesity and its related metabolic complications are associated with immune dysfunction. Little is known regarding the independent contribution of adiposity, hyperglycemia, and dietary patterns in altering immune responses. The aim of this study was to assess the immunophenotype of helper T (Th) cells and T cell function in lean individuals (lean-NG) and individuals with obesity and normoglycemia (OB-NG), glucose intolerance (OB-GI), and type 2 diabetes (OB-T2D).

Methods: Participants were stratified to one of four groups: 1) lean-NG (n=31), 2) OB-NG, (n=17), 3) OB-GI, (n=21) and 4) OB-T2D (n=13). All participants consumed an isocaloric standardized North American type diet (35% fat, 48% carbohydrate, 17% protein) for 4 weeks to dissect out the contribution of diet to that of glycemia on the immune system. Fasting blood samples were collected before and after the intervention. Immunophenotypic characterization was performed in whole blood using flow cytometry to identify the proportion of the following cell populations relative to the T helper (Th) population (CD3+CD4+): Th1 (CCR10-CD183+CD185+CD194-CD196-) and Th2 (CCR10-CD183-CD185-CD194+CD196-). Peripheral blood mononuclear cells (PBMC) were isolated and stimulated with anti-CD3 and anti-CD28 to assess T cell proliferation using the Alamar Blue assay. PBMC were stimulated with phytohaemagglutinin (PHA) to assess T cell function by measuring ex vivo interleukin-2 (IL-2) secretion (a T cell proliferation marker), TNF-alpha (Th1 cytokine), and IL-10 (Th2 cytokine).

Results: There were no differences between groups in the immune phenotype of Th cells both at baseline and post-intervention. At baseline, T cell proliferation and IL-2 secretion were higher in lean compared to OB-GI and OB-T2D, which was no longer significant after the intervention. There were no differences between groups in the secretion of IL-10, a Th2 cytokine. However, TNF-alpha secretion at baseline was higher in lean compared to OB-GI and OB-T2D, leading to a higher Th1/Th2 ratio in the lean compared to all other groups with obesity.

Discussion: Obesity and hyperglycemia lead to functional impairment of Th cells without alterations in phenotype. We have previously demonstrated that individuals OB-T2D had additional T cell dysfunction compared to OB-NG. In the current study, individuals with NG, independent of obesity, maintained adequate secretion of cytokines and cell proliferation compared to individuals with hyperglycemia. During activation, T cells depend on their ability of glucose uptake to maintain their effector function which can help explain lower cytokine secretion and proliferation in OB-GI and OB-T2D individuals.

Conclusions: Our interim analysis suggests that hyperglycemia impair the function of Th1 cells, which is in line with the reported increased risk of infection in this population.

Abstracts

IMMUNOGENICITY OF NOVEL VARIANTS OF THE CHIMERIC CHP3R99 ANTIATHEROGENIC ANTIBODY IN INSULIN-RESISTANT RATS

Gala Araujo1, Agata Martin-Ozimek1, Leidy Valencia1, Yosdel Soto1,2, Spencer Proctor1

1Metabolic and Cardiovascular Diseases Laboratory, Division of Nutrition, University of Alberta, 2Centre for Molecular Immunology, Havana, Cuba.

Background: Atherosclerosis is a pervasive form of cardiovascular disease (CVD) characterized by the accumulation of cholesterol-rich lipoproteins within the innermost arterial wall. Diabetes is a major comorbidity and contributor to atherosclerosis due to its inflammatory, hyperglycemic, and hypertensive effects. Therapeutic approaches for the treatment of atherosclerosis have been largely limited to the management of risk factors rather than disease prevention per se. However, a novel atheroprotective therapy has emerged in the form of a chimeric monoclonal antibody (mAb) produced in a murine myeloma (NS0) cell line known as chP3R99 mAb. chP3R99 has been shown to directly inhibit lipoprotein-proteoglycan binding by blocking chondroitin sulfate on sugar side chains of proteoglycans. Importantly, the variable regions of chP3R99 (crucial for antigen recognition) are highly immunogenic, inducing an idiotypic cascade of antibodies (Ab2, Ab3) within the host upon immunization with the chP3R99 (Ab1). However, production inefficiencies of chP3R99 in NS0 cells have led to the development of two novel chP3R99 variants produced from more efficacious cell lines: Chinese Hamster Ovary (CHO) and Human Embryonic Kidney (HEK). Thus, the aim of this study was to assess the immunogenic effects of variant chP3R99 immunizations in healthy and pro-atherogenic rodent models.

Methods/Results: We assessed the immunogenicity of the three chP3R99 mAb variants, HEK-R99, NSO-R99, and CHO-R99 in healthy and insulin resistant rat models. Two experimental conditions were conducted. (i) Immunization of healthy 9-month-old male lean rats (n=5 per group) (4 weekly doses each of 200µg, SC) (ii) Immunization of obese 9-month-old male JCR: LA-cp (insulin resistant) rats given 4 weekly doses of 200µg followed by two biweekly doses of 200µg (SC). ELISA was then employed to assess the presence of Ab2 (anti-chP3R99) antibodies in the pre-immune and post-immune (final dose) sera samples. For both models' immunizations with CHO-R99 and HEK-R99 produced an immunogenic cascade of similar strength to NSO-R99 regardless of their physiological status, (p<0.05, CI 0.95% Mann Whitney). Administration of R99 variants also produced significant levels of Ab2 antibodies compared to their respective pre-immune sera. Moreover, as expected, for all immunizations of the negative control hR3 did not produce significant levels of Ab2 antibodies.

Discussion: The results suggest that the new production variants of chP3R99 mAb, CHO-R99 and HEK-R99 induce an immunogenic response similar to that of the original NS0-R99 variant in rodent models. The outcomes from these validation studies are critical for the evaluation and efficacy of large scale-up protocols to move to human trials.

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Abstracts

EFFECTS OF MATERNAL DYSBIOSIS ON TYPE 1 DIABETES INCIDENCE IN OFFSPRING

Erin Strachan*, Tingting Ju#, Paulo José Basso*, Ben Willing#, Xavier Clemente Casares*, Sue Tsai*

*Dept. of Medical Microbiology & Immunology, University of Alberta
#Dept. of Agricultural, Food & Nutritional Science, University of Alberta

There is a growing appreciation for the role of gastrointestinal (GI) health in promoting whole body wellbeing. Key features of a healthy gut include a balanced microbiota and their interaction with host immune defense mechanisms such as the production of Immunoglobulin A (IgA). Synergistically, the microbiota and IgA work to preserve the integrity of the gut barrier and regulate immune responses both locally and systemically. During infancy, both the microbiota and immune system undergo rapid development and are strongly influenced by maternal factors, conveyed largely via events in the neonatal GI tract. When these events fail to occur at appropriate times, the long term detrimental effects resulting from suboptimal immune development can contribute to subsequent development of pathologies such as Type 1 Diabetes (T1D), where the erroneous activation of autoreactive lymphocytes leads to the destruction of the pancreatic beta cells. Interestingly, despite the well-documented importance of maternal factors on infant immune development, whether maternal immune dysregulation and dysbiosis can perpetuate the same in offspring remains largely unknown. To gain an understanding of how these maternal factors impact infant disease development, we use IgA-deficiency induced maternal dysbiosis in Non-Obese Diabetic (NOD) dams to study T1D development in their offspring. We found that maternal dysbiosis arising from IgA deficiency results in numerous neonatal changes in IgA-sufficient offspring, including increased GI immune cell numbers and cytokine production, increased gut inflammation, altered gut microbiome composition and a modified GI metabolomic profile. In adulthood, IgA-sufficient offspring born to IgA-deficient dams show lessened insulitis and a lower incidence of T1D overall as compared to those reared by IgA-sufficient dams. Cross-fostering experiments indicate this protective effect is mediated post-natally, leading us to hypothesize that maternal microbiome transfer plays a significant role. We are currently exploring various characteristics of breast milk from IgA-deficient dams as well as conducting fecal microbiota transfer experiments to explore how this protective effect may be mediated.

Abstracts

EXOGENOUS KETONE ESTER ADMINISTRATION IMPROVES GLUCOSE HOMEOSTASIS IN OBESE MALE MICE

Kunyan Yang1,2, Seyed Amirhossein Tabatabaei Dakhili1,2, Cassandra A. A. Locatelli3,4, Christina T. Saed1,2, Amanda A. Greenwell1,2, Jordan S. F. Chan1,2, Jadin J. Chahade1,2, Jared Scharff1,2, Shahad Al-Imarah1,2, Farah Eaton1,2, Keshav Gopal1,2, Erin E. Mulvihill3,4 , John R. Ussher1,2

1Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada. 2Alberta Diabetes Institute, University of Alberta, Edmonton, Alberta, Canada. 3Department of Biochemistry, Microbiology, and Immunology, University of Ottawa, Ottawa, Ontario, Canada. 4University Ottawa Heart Institute, Ottawa, Ontario, Canada.

During starvation the liver produces ketone bodies (β-hydroxybutyrate [βOHB] and acetoacetate; herein referred to as ketones), which serve as an alternative energy source for extrahepatic organs (primarily the brain) in times of low carbohydrate (i.e. glucose) availability. In addition to serving as an important fuel source, ketones play an essential role in regulating cell signaling, as they serve as ligands for G-protein coupled receptors (i.e. GPR109A) and inhibit class I histone deacetylases. Recent studies have also demonstrated that increased skeletal muscle ketone oxidation may contribute to the pathology of obesity-related hyperglycemia, since inhibition of succinyl CoA:3-ketoacid CoA transferase, the rate-limiting enzyme of ketone oxidation, alleviated obesity-related hyperglycemia in mice. Accordingly, our aim was to examine whether increasing circulating ketone levels may worsen glucose homeostasis in mice, due to increasing ketone supply to the muscle for subsequent oxidation. 8-week-old male C57BL/6J mice were subjected to experimental obesity or type 2 diabetes via provision of a high-fat, high-sucrose diet for 8-weeks, with the latter also receiving an injection of low-dose streptozotocin (75 mg/kg) at 4-weeks, whereas their lean controls received a low-fat, low-sucrose diet for an equivalent duration. Following 8-weeks of dietary provision, all mice were administered either a ketone ester (1719 mg/kg; https://hvmn.com) or placebo via oral gavage and underwent an intraperitoneal glucose tolerance test. In a separate cohort of lean and obese mice, islets were isolated for perifusion studies to quantify insulin secretion. Exogenous ketone ester administration increased circulating βOHB levels for at least 2-hrs (peak increase at ~15 min), which improved glucose tolerance in obese but not lean mice when compared to placebo treatment. Conversely, no improvement in glucose tolerance was observed in diabetic mice that received acute administration of the ketone ester. Moreover, isolated perifused islets from obese mice treated with the D- but not L-isomer of βOHB increased insulin secretion, whereas treatment with the ketone ester itself had no effect. Taken together, acute elevations in circulating ketones promote glucose-lowering in obesity, which may be due to increases in insulin secretion. As the D-isomer of βOHB can both regulate cell signalling and be oxidized, whereas the L-isomer only impacts signalling, it would seem prudent to understand how islet β-cell ketone oxidation may augment insulin secretion.

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BETA-2 SCORES OVERESTIMATE GRAFT FUNCTION IN PANCREATIC ISLET TRANSPLANT RECIPIENTS WITH AN ESTIMATED GLOMERULAR FILTRATION RATE OF <30 ML/MIN/1.73M2

Alice L. J. Carr*, Braulio A. Marfil-Garza* Meiying Zhuang, Anna Lam, Khaled Dajani, Blaire Anderson, Doug O'Gorman, Tatsuya Kin, David Bigam, James Shapiro, Peter A. Senior

Introduction: The BETA-2 score is a clinical composite score used to assess graft function after islet transplantation (ITx). This score incorporates C-peptide, fasting plasma glucose, hemoglobin A1c, and insulin requirements. However, C-peptide undergoes renal clearance and may accumulate in people with renal impairment. We sought to examine the effect of renal impairment on the BETA-2 score in ITx recipients.

Methods: This was a cross-sectional study of ITx recipients at the University of Alberta. Most recent BETA-2 scores (pre-graft failure), and its components (insulin requirements, fasting plasma glucose, HbA1c and serum C-peptide), as well as eGFR (CKD-EPI) during BETA-2 assessment were obtained. Analyses were stratified by insulin dependence status and eGFR groups (KDIGO stages of CKD). Segmented regression was used to identify inflection points where the BETA-2 score was disproportionally affected by changes in eGFR.

Results: We include 178 recipients (42% male, median (IQR) age at first transplant of 52.3 (44.8-58.6) years) who received a median of 2 (2-3) islet infusions and 15,312 (11,705-20,278) islet equivalents/kg. Median BETA-2 scores were 11.1 (6.0-19.4), with a median time from first transplant to BETA-2 score calculation of 8.0 (4.2-11.9) years. A total of 37% of recipients were insulin independent, with similar rates observed between eGFR groups (p=0.631). Overall, BETA-2 scores were higher in ITx recipients with stage 4 CKD (<30 ml/min/1.73m2) compared to stage 1-2 CKD (≥60 ml/min/1.73m2) for those being insulin dependent (p=0.03) and insulin independent (p=0.0032). These differences were driven by C-peptide levels, which are more pronounced in insulin independent recipients, with significantly increased levels in insulin independent recipients with stage 4 CKD compared to stage 1-2 CKD (p=0.00036), with this increase also demonstrated, although to a lesser extent, in those insulin dependent (0.075). All other BETA-2 score components were similar between groups. Segmented linear regression of the BETA-2 score with eGFR demonstrated an inflection point of eGFR 27 ml/min/1.73m2 for recipients being insulin dependent and 24 ml/min/1.73m2 for those being insulin independent.

Conclusions: This study shows that BETA-2 scores increase as eGFR declines, driven by the C-peptide component of the score, a phenomenon that is most notable in insulin independent recipients. These higher C-peptide levels (and BETA-2 scores) do not reflect better graft function, as they are not associated with better glycemic control or higher insulin independence rates. Our data suggests that in recipients with eGFR<30 ml/min/1.73m2 , BETA-2 scores and C-peptide levels should be cautiously interpreted.

Abstracts

ELECTROPHYSIOLOGICAL CHARACTERIZATION OF STEM-CELL DERIVED β-CELLS TO HELP PRODUCE CLINICALLY RELEVANT CELLS FOR TRANSPLANTATION

Jasmine Maghera1, Kevin Salim2, Shugo Sasaki2, Francis C. Lynn2, Patrick E. MacDonald1*

Department of Pharmacology1, University of Alberta, Edmonton, AB., Canada.
Department of Surgery and School of Biomedical Engineering2, University of British Columbia, Vancouver, BC., Canada

Background: Although significant progress has been made in treating type 1 diabetes with islet transplantation, new cell sources are needed since organ donors remains limited. Human embryonic Stem cell-derived β-cells (hESCβs) offer a promising alternative for cell replacement therapy; however, key characteristics displayed by mature primary human β-cells, such as glucose-regulated excitability and insulin secretion via the exocytosis of secretory granules, remain blunted in hESCβs, reflecting immaturity after cellular differentiation.

Methods: We seek to characterize the electrical and secretory machinery responsible for regulation of insulin secretion, comparing hESCβs and primary human β-cells, and assess the function of the cells as they are aged further in-vitro. Single-cell patch-clamp electrophysiology was used to assess the cell size, the activity of ion channels involved in action potential firing, and the fusion of secretory vesicles with the plasma membrane. We then used EM imaging to visualize mitochondrial and granule morphology. Finally, we assessed the metabolic function using the Seahorse XFe24 Analyzer, these data will later be connected to scRNA sequencing results to understand the differences between cells using a larger view approach. Results: We found that that younger (D23-40) hESCβs (N=13) and older (D48-54) hESCβs are significantly ($p<0.0001$) larger in cell size than primary β-cells (N=10), having a 1.37 and 1.55-fold larger initial cell initial membrane capacitance. The both young and aged hESCβs also display a 7.60 and 4.68-fold larger ($p<0.0001$ and $p =0.0015$) exocytosis compared with primary β-cells, even when normalized to cell size. This increased exocytosis is paralleled by increased voltage-activated Na+ and Ca2+ currents in young cells (2.25-fold increased, $p=.0004$) and (4.07-fold increased, $p<0.0001$), the latter being mediated mostly by L-type channels. However, when the cells are aged this difference disappears indicating changes in ionic currents. Despite these ionic changes in older hESCβs that precede insulin secretion, both cell types still do not show glucose responsiveness or changes in exocytosis in 1, 5 and 16.7 mM glucose. Using the Seahorse XFe24 assay, it was found that both older and younger hESCβs have a higher oxygen consumption rate (OCR) than compared to human primary β-cells, showing a notably larger non-mitochondrial, basal and proton leak OCR indicating mitochondrial differences when compared to human β-cells. Further research into the gene expression changes between the hESCβs will be used to elucidate what transcriptional changes occur in the cells as they age.

Conclusions: These findings suggest that, although hESCβs act differently compared with primary β-cells, the mechanical machinery responsible for excitability and exocytosis is intact and functional by stage 6 of differentiation. Future studies will examine the expression differences between hESCβs and primary β-cells that reduce glucose sensing and insulin release upstream of this secretory machinery.

Abstracts

PRE-DIABETES AND APO-B PREDICT EARLY CARDIOVASCULAR DISEASE IN YOUNG WOMEN WITH AND WITHOUT POLYCYSTIC OVARY SYNDROME

Xiaoying Wu1, Mich Wilke1, Mahua Ghosh2, Paolo Raggi3, Harald Becher3, Donna Vine1

Metabolic and Cardiovascular Disease Laboratory 1, Faculty ALES; Division Endocrinology and Metabolism2, Division Cardiology3, Faculty Medicine Dentistry, University of Alberta

Introduction: Polycystic ovary syndrome (PCOS) is a common reproductive-endocrine disorder that affects 10%of women, and is associated with a 2-fold increased risk for Type-2 diabetes and cardiovascular disease (CVD). Early screening of pre-diabetes risk factors and early atherosclerotic CVD (ACVD) is important in the management and prevention of diabetes and CVD in this high-risk population. The aim of this study was to assess pre-diabetes, atherogenic dyslipidemia and early atherosclerotic CVD in high-risk patients with and without PCOS, and healthy-weight controls.

Methods: A case-control study was conducted in PCOS and age-BMI matched controls and healthy-weight controls including assessment of fasting plasma lipids, apoB-lipoproteins and insulin-glucose indices. Ultrasound-speckled echocardiography was used to determine early ACVD (carotid plaque height (CPH) and intimal medial thickness (cIMT)) and cardiac function.

Results: PCOS (129.0±12.66 pmol/l) and BMI-matched controls (106.8±12.28 pmol/l) had 3-fold higher fasting plasma insulin compared to healthy-weight controls (39.89 pmol/l), as well as 3-fold higher HOMA-IR (5.17±0.54, 4.04±0.53, 1.38±0.12, respectively, p<0.05). Plasma triglycerides, remnant cholesterol, non-HDL-C, total apoB and apoB48 were 30-60% higher in PCOS and BMI-matched controls compared to healthy-weight controls, and these were exacerbated in those with PCOS. cIMT was 11-15% higher in PCOS (0.49±0.05mm) and BMI-matched controls (0.51±0.06) compared to healthy-weight controls (0.44±0.06, p<0.05). HOMA-IR and DBP predicted 40% of the variability in cIMT when adjusted for age and BMI. CPH was 30% higher in PCOS (0.4 ± 0.4mm) compared to BMI-matched (0.27±0.44) and healthy-weight controls (0.28±0.38). Total plasma ApoB predicted 16% of the variability in CPH when adjusted for age and BMI.

Discussion: Our results showed that high-risk women with and without PCOS have impaired insulin-glucose metabolism, an atherogenic lipid profile and early atherosclerotic CVD, and these are exacerbated in those with PCOS. These results highlight the different etiological risk factors for cIMT and CPH, and that early risk screening and management of pre-diabetes and CVD risk factors in high-risk women is important in the prevention of progression of CVD.

Abstracts

THE ANTIPSYCHOTIC AGENT PIMOZIDE ALLEVIATES NON-ALCOHOLIC FATTY LIVER DISEASE IN EXPERIMENTAL TYPE 2 DIABETES

Christina T. Saed1,2,3, Seyed Amirhossein Tabatabaei Dakhili1,2,3, Amanda A. Greenwell 1,2,3, Kunyan Yang1,2,3, Jordan S.F. Chan1,2,3, Kristil Almahfoud1,2,3, Farah Eaton1,2,3, Keshav Gopal1,2,3, John R. Ussher1,2,3

1Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Canada
2Alberta Diabetes Institute, University of Alberta, Edmonton, AB Canada
3Cardiovascular Research Centre, University of Alberta, Edmonton, AB Canada

Introduction: Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide, due to its strong association with obesity, and type 2 diabetes (T2D). Interstingly, we have recently demonstrated that an antipsychotic agent that canonically inhibits dopamine 2 receptors (D2R), pimozide, can lower blood glucose in experimental obesity/T2D. These observations were attributed to non-canonical actions of pimozide to inhibit succinyl-CoA:3-ketoacid CoA transferase (SCOT) in skeletal muscle. However, our follow-up studies have demonstrated that pimozide decreases hepatic steatosis in obese mice, despite liver not expressing SCOT. Our aim was to determine whether pimozide can mitigate obesity/T2D-related NAFLD, and to elucidate the mechanism of action.

Methods & Results: We subjected 12-week-old male C57BL/6J mice to experimental T2D model which encompasses supplementation with a high-fat diet (HFD) for 12-weeks, and a single injection of streptozotocin (STZ; 75 mg/kg) provided at 4-weeks of the dietary protocol. At 8-weeks into the protocol, all mice were randomized to receive treatment with either vehicle control or pimozide (10 mg/kg) once every other day via oral gavage. We assessed glucose homeostasis via glucose tolerance test. Hepatic triacylglycerol (TAG) content was assessed in frozen liver extracts via the Bligh and Dyer method. We also cultured HepaRg cells and randomized to treatment with either vehicle control (DMSO) or pimozide (12.5 µM). Pimozide treatment improved glucose tolerance in obese mice and reduced hepatic TAG content in obese/T2D mice. Of interest, treatment of obese mice with a structurally unrelated antipsychotic D2R antagonist, lurasidone, also alleviated obesity-related NAFLD. To identify pimozide's actions, HepaRg cells treated with pimozide exhibited marked increases in the expression of spliced X-box binding protein 1 (sXBP1), and inositol-requiring enzyme 1 (IRE1), key transcription factors regulating lipid metabolism, and expression. Conversely, these observations were not present following lurasidone treatment.

Discussion: Our results indicate that pimozide has favorable actions on obesity/T2D-related NAFLD. Whether these actions are dependent on pimozide's ability to inhibit the D2R, or via targeting the IRE1-XBP1 pathway remains elusive.

Abstracts

THE GLP-1 RECEPTOR AGONIST LIRAGLUTIDE ALLEVIATES TYPE 2 DIABETES-RELATED DIASTOLIC DYSFUNCTION IN A PYRUVATE DEHYDROGENASE-DEPENDENT MANNER

Jordan S.F. Chan1,2*, Amanda A. Greenwell1,2 *, Christina T. Saed1,2, Magnus J. Stenlund1,2, Indiresh A. Mangra-Bala1,2, Seyed Amirhossein Tabatabaei Dakhili1,2, Kunyan Yang1,2, Keshav Gopal1,2, Farah Eaton1,2, John R. Ussher1,2

1Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, Canada. 2Alberta Diabetes Institute, University of Alberta, Edmonton, AB, Canada

*Denotes equal contribution

Introduction: Impairments in cardiac energy metabolism are a major contributor to the pathology of diabetic cardiomyopathy (DbCM), which is characterized by diastolic dysfunction. This includes an increased reliance on fatty acid oxidation to meet the heart's energy demands, which coincides with a marked reduction in glucose oxidation. Of interest, several studies have shown that restoration of myocardial glucose oxidation improves cardiac function in type 2 diabetes (T2D). Liraglutide, a glucagon-like peptide-1 receptor (GLP-1R) agonist used for the treatment of T2D that also improves cardiovascular outcomes, can alleviate diastolic dysfunction and increase myocardial glucose oxidation in experimental T2D. However, whether these increases in glucose oxidation explain the liraglutide mediated alleviation of DbCM remains enigmatic. Thus, we hypothesized that the cardioprotective actions of liraglutide would be abolished in mice with T2D and a cardiac-specific deletion of pyruvate dehydrogenase (PDH; PDHCardiac-/- mice), the rate-limiting enzyme of glucose oxidation.

Methods and Results: Male PDHCardiac-/- mice and their myosin heavy chain-α Cre expressing littermates (αMHCCre mice) were subjected to experimental T2D via 10-weeks of high-fat diet supplementation (60% kcal from lard; Research Diets D12492) with a single low-dose injection of streptozotocin (75 mg/kg) provided at week 4. After the induction of experimental T2D, αMHCCre and PDHCardiac-/- mice were randomized to treatment with either vehicle control (VC; saline) or liraglutide (30 µg/kg) twice daily during the final 2-weeks of the protocol, with cardiac function assessed via ultrasound echocardiography pre- and post-treatment. As expected, liraglutide treatment improved glucose homeostasis in both αMHCCre and PDHCardiac-/- mice with T2D but did not produce any notable weight loss with our dose of 30 µg/kg. Furthermore, parameters of systolic function were unaffected by liraglutide treatment in both αMHCCre and PDHCardiac-/- mice with T2D. In contrast, treatment with liraglutide alleviated diastolic dysfunction in αMHCCre mice with T2D, as indicated by an increase and decrease in the e'/a' ratio (1.63 vs. 1.32; $p<0.05$) and E/e' ratio (25.25 vs. 31.52; $p<0.05$), respectively, when compared to VC-treated αMHCCre mice with T2D. Consistent with our hypothesis, liraglutide failed to rescue diastolic dysfunction in PDHCardiac-/- mice with T2D, as evidenced by a lack of improvement in either the e'/a' ratio (1.34 vs.1.24) or E/e' ratio (30.46 vs. 31.29) relative to VC-treated PDHCardiac-/- mice with T2D.

Discussion: Because liraglutide was unable to alleviate diastolic dysfunction in experimental T2D in the absence of myocardial PDH activity, our findings suggest that increases in myocardial glucose oxidation are necessary for GLP-1R agonist mediated improvements of cardiac function in T2D. As such, strategies aimed at increasing PDH activity may represent a novel approach for the treatment of DbCM.

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COMPARING THE FUNCTION AND EFFICACY OF STAGE 6 AND STAGE 7 IPSC-DERIVED ISLET-LIKE CELLS

Zofia Czarnecka, Nidhesh Dadheech, Haide Razawy, Rena Pawlick, AM James Shapiro

Introduction: The Edmonton Protocol revolutionized islet cell transplantation for Type 1 Diabetes in 2000. However, it is limited by islet cell supply and the need for chronic immunosuppression. A new direction of study has emerged with the use of pluripotent stem cells (iPSCs). Pluripotency genomic factors are used to reprogram mature somatic cells back to their embryonic, pluripotent form. iPSCs can then be cultured and differentiated into islet cells through a six-stage process. A seventh stage of extended maturation was recently proposed by Balboa et. al. By altering the composition of the proliferation culture medium, ß-cells underwent cytoarchitecture changes and acquired biphasic glucose-stimulated insulin secretion. We further optimized this seventh stage to increase the efficacy of our stem cell-derived islet cells (SC-islets) and to limit off target growth. We added FGF-R inhibitors to the culture medium to remove off-target cells as well as two different AXL inhibitors further endocrine maturation. Stage 6 and 7 Sc-islets were subsequently transplanted into mice to compare in vivo function and efficacy.

Methods and Results: Human iPSCs were differentiated over 27 days to Stage 6 SC-islets and then matured to Stage 7 endocrine cells over 40 days and transplanted into immunodeficient NSG mice at these two respective time points. No morphological differences were observed in cells between the two stages. Flow cytometry showed that Stage 7 cells maintained their true ß-cell identity and were C-peptide+, ISL1+ and Nkx6.1+. Compared to Stage 6, Stage 7 islets had reduced numbers of non-endocrine cells (<1%) as identified with SLC16A1, CDX2, Ki67, and Oct4 staining. In parallel with flow cytometry, immunohistochemical staining confirmed the presence of mature islet hormones at Stage 7. Specifically, Stage 7 SC-islets demonstrated increased maturation with higher presence of hormones including insulin, NK6.1, MAFA, PDX1 and UCN3.

Discussion: Our refined differentiation protocol permits maturation of stem-cell derived islets into ß-cells that are mono-hormonal and include fewer off-target cells. Our preliminary in vitro data demonstrates that Stage 7 cells maintain ß-cell identity, morphology, and hormone secretion. Our in vivo trials are ongoing however preliminary results at eight weeks post-transplant reveal no obvious tumor or cystic growth in mice at either stage. Mice in both groups demonstrate sustained glycemic control. This lengthened maturation protocol shows promise for producing stem-cell derived human islets with a more efficacious endocrine population while eliminating off-target growth.

Abstracts

MULTI-SCALE MODELING OF *GLAD*-FABRICATED ELECTROCHEMICAL BIOSENSORS FOR DIABETES MONITORING

MohammadAli Maleki Bigdeli1, Abebaw B. Jemere2, Kenneth D. Harris1,2, Wylie Stroberg1

1Department of Mechanical Engineering, University of Alberta, Edmonton, Canada
2National Research Council Canada – Nanotechnology Research Centre, Edmonton, Canada

Background: Exploring alternatives to invasive blood sugar testing, like measuring glucose levels in sweat, saliva, or tears, has made monitoring easier for people dealing with diabetes. Nonetheless, the challenge lies in the relatively lower glucose content in these bodily fluids compared to blood. A recent breakthrough employs nanostructured nickel-oxide electrodes produced through the glancing angle deposition (GLAD) technique. These electrodes have proven highly sensitive, selective, and reproducible in electrochemically determining glucose concentrations in sweat. GLAD involves a single-step physical vapor deposition process that blends oblique angle deposition with dynamic substrate movement. By controlling the substrate's rotation, this technique can control electrode properties such as porosity and film thickness. This level of control holds promise for improving sensor performance. Even with the burgeoning applications of GLAD sensors, a knowledge gap remains regarding how various parameters affect sensor performance. To fill this gap, advanced computational methods offer an avenue for understanding the intricate interplay of parameters without the labor-intensive process of experimentation.

Methods and Results: Our present study introduces a 2D reaction-diffusion model that employs finite element method (FEM) simulation. This model delves into the intricacies of surface-catalyzed reactions occurring in nanostructured GLAD electrodes. Through our model, we embarked on an exhaustive exploration of the impact of GLAD structure depth (electrode thickness) and spacing (electrode porosity), factoring in diverse absorption and catalytic rates. Our findings illuminate the most favorable electrode structures, a crucial advancement in designing enhanced sensors with elevated sensitivity and the ability to detect even minute changes.

Discussion: The current model demonstrates that the optimal electrode porosity is a linear function of the electrode thickness. With an increase in electrode thickness, the optimal nanocolumn separation also increases. Furthermore, the mutual information saturates at a specific electrode thickness for a given electrode porosity. This implies that surpassing a certain electrode thickness does not necessarily lead to an improvement in the glucose sensor operation. This is due to the diffusion, which makes it difficult for molecules to diffuse in the confined spaces within the structure. The current model exhibits limitations that are worth noting. Firstly, the 2D representation restricts the model's ability to accurately capture many of the intricacies inherent in GLAD nanostructures found in real-world scenarios. Future endeavors should therefore aim to generate geometries that closely resemble the actual structures to enhance the model's capabilities. Secondly, the non-dimensional nature of the model enables the estimation of trends; however, to achieve more precise results and comparisons with experimental data, it is necessary to incorporate calculations of reaction rates and diffusion coefficients specific to analytes like glucose.

Abstracts

ETNPPL INFLUENCES LIPOPROTEIN METABOLISM BUT DOES NOT INDUCE FATTY LIVER DISEASE IN MICE

Kholoud Elmihia,e, Kelly-Ann Leonarda, Randy Nelsona,e, Aducio Thiesenc, Robin D. Clugstonb,e, René L. Jacobsa,d,e

a: Department of Agricultural, Food and Nutritional Science, b: Department of Physiology, c: Department of Laboratory Medicine and Pathology, d: Department of Biochemistry, e: Group on the Molecular and Cell Biology of Lipids, University of Alberta.

Background: Ethanolamine phosphate phospholyase (ETNPPL) is an enzyme that irreversibly degrades phospho-ethanolamine (p-ETN) to acetaldehyde, ammonia and phosphate. P-ETN is an intermediate in the Kennedy pathway for phosphatidylethanolamine (PE) biosynthesis. ETNPPL is highly expressed in the liver, mainly hepatocytes. ETNPPL was thought to affect hepatic PE levels, thereby affecting hepatic lipid accumulation through disturbing the hepatic ratio of phosphatidylcholine (PC) to PE. ETNPPL was detected to be downregulated in patients with hepatocellular carcinoma associated with abnormal lipid metabolism. In this study, we aimed to investigate the livers of mice upon genetic deletion of *Etnppl*. Furthermore, ETNPPL was localized in the nucleus where ETNPPL is thought to play a role in the regulation of gene expression.

Methods: Knock-out (KO) and wild-type (WT) mice were generated from heterozygous parents. Four groups of WT and KO male and female mice (n=10-12) were fed a chow diet for 20 weeks. Other sets of groups were fed a western-type diet (WTD) for 24 weeks after 8 weeks of chow diet feeding. Mice were euthanized in the fasted state. Plasma and livers were collected. Plasma lipid species were detected by HPLC and FPLC. Livers were divided into three portions for RNA sequencing, histopathological examination, and HPLC analysis.

Results: Our data showed that KO mice either fed a chow diet or WTD have higher plasma triglycerides (TG) and apolipoprotein B100 than WT, indicating increased plasma VLDL particles. After Poloxamer injection, no difference in plasma TG. The results of RNA sequencing in KO mice showed downregulation in the expression of genes related to cholesterol and lipid metabolism. In addition, plasma cholesterol was increased in KO mice compared to WT mice. The data from RNA sequencing revealed that there is a downregulation in sirtuin signalling in KO mice, hence, I suppose that knocking out *Etnppl* could affect gene transcription. Furthermore, there is no difference in hepatic PC, PE, and TG levels between both groups with normal liver histology. The livers of WT and KO mice fed a WTD showed excessive hepatic lipid accumulation, but no difference was detected between both groups. Interestingly, the differences in plasma lipoproteins were only detected in female mice.

Conclusions:
Knocking out *Etnppl* impacts lipoprotein metabolism without influencing hepatic lipid balance. The exact mechanism requires further investigation.

Abstracts

GLYCINE RECEPTOR ACTIVITY IN β CELLS IS DOWNREGULATED IN TYPE 2 DIABETES AND AFTER HIGH GLUCOSE CULTURE

Amanda Schukarucha Gomes1, Kunimasa Suzuki1, Aliya F. Spigelman1, Patrick E. MacDonald1

1 Alberta Diabetes Institute, Department of Pharmacology, University of Alberta, Edmonton, Alberta, Canada

Background: Glycine receptors (GlyRs) are present in human β cells and contribute to cell depolarization, increasing insulin secretion. However, in type 2 diabetes (T2D), islet GlyR activity is impaired by unknown mechanisms, and the GlyR subunit GLRA1 is reported as one of the strongest downregulated transcripts in islets, with increasing donor HbA1c. We aimed to further investigate how the GlyRs can influence islet function, and if the GlyR dysfunction in T2D is caused by hyperglycemia.

Methods: Glycine receptor-mediated currents were measured using whole-cell patch-clamp in human β cells from donors with or without T2D, or after culture in 5.5 or 15 mmol/L glucose for 2 days. The expression of the GlyR α1, α3, and β subunits mRNA splice variants was compared between islets from donors with and without T2D. Insulin secretion from human islets was measured in the presence or absence of the GlyR antagonist strychnine (10 µM) and quantified by ELISA.

Results: The glycine-evoked currents in β cells from donors with T2D (-0.81±0.51 pA/pF, n=7) were smaller than those measured in cells from donors without diabetes (-12.72±2.38 pA/pF, n=29; $p<0.001$). The β cells cultured in 15 mmol/L glucose for 2 days had smaller glycine-evoked currents (-9.18±1.86 pA/pF, n=18) than those in control media (-17.63±3.53 pA/pF, n =14; $p<0.05$). The expression of most GlyR subunit mRNA splice variants was decreased in islets of donors with T2D, with no evidence of a shift in alternative splicing towards 'non-functional' receptor isoforms. Glucose-stimulated insulin secretion was reduced when 10 µM strychnine was present (AUC = 13.58 ±1.10, versus 23.83 ±2.43 without strychnine; $p<0.05$).

Conclusions: Glycine-evoked currents in β cells are decreased after 2 days of culture with high glucose, showing that hyperglycemia is capable of down-regulating GlyRs. This is similar to the reduced glycine-evoked current in T2D, where we find a decrease in overall GlyR gene expression, but not a shift in GlyR mRNA splicing. In addition, inhibiting the GlyR reduces glucose-stimulated insulin secretion.

Keywords: β-cells, Glycine, Neurotransmitters, Hyperglycemia, Type 2 diabetes.

Abstracts

RURAL RESIDENCE IS ASSOCIATED WITH LIMITED GUIDELINE CONCORDANT CHOLESTEROL MANAGEMENT IN NEWLY TREATED TYPE 2 DIABETES

Danielle K Nagya, Lauren C Breseeb, Dean T Eurichc, Scot H Simpsond

a – Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, 2-35, Medical Sciences Building, 8613 – 114 St., Edmonton, Alberta T6G1C9, Canada
b – Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, 3330 Hospital Drive NW, Calgary, Alberta T2N4N1, Canada
c – School of Public Health, University of Alberta, 2-040F Li Ka Shing Centre For Research, 11203 – 87 Ave NW, Edmonton, Alberta T6G2H5, Canada
d – Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, 2-020C, Katz Group Centre for Research, 11315 – 87 Ave NW, Edmonton, Alberta T6G2H5, Canada

Background: Processes of care, such as the prescribing decisions that clinicians make when managing disease, is an important, understudied factor associated with the differences between rural and urban healthcare. Building on this, our study evaluated guideline concordant processes of cholesterol management in individuals with newly treated type 2 diabetes by place of residence (metropolitan/urban/rural), based on the recommendations from the Canadian Diabetes Association 2013 Clinical Practice Guidelines.

Objectives: We hypothesized that rural-dwelling individuals would be less likely to receive lipid laboratory monitoring or a statin dispensation within the first year of type 2 diabetes management, compared to metropolitan-dwellers.

Methods: We used a retrospective cohort study design with administrative data to examine anonymized patient health records between 1 April 2015 and 31 March 2020 in Alberta, Canada. Adult new metformin users were followed for the first year of their type 2 diabetes management. Place of residence was identified using postal codes. We used multivariable logistic regression to examine the association between lipid laboratory monitoring and place of residence, as well as the association between statin dispensations and place of residence. A sensitivity analysis was performed by excluding those with statin use prior to first metformin dispensation.

Results: Of the 60,222 new metformin users, the mean age was 55 years at first metformin dispensation and 57% were male. At first metformin dispensation, area of residence was distributed as 67% metropolitan, 10% urban, and 23% rural. Considering patient characteristics, comorbid conditions, and concurrent medications, rural residence was associated with a significantly lower likelihood of lipid laboratory monitoring and statin use within the first year of type 2 diabetes management, compared to metropolitan residents (aOR: 0.86; 95% CI: 0.83-0.90) and (aOR: 0.83; 95% CI: 0.79-0.87), respectively. When prevalent statin users were excluded, rural residence continued to be associated with a significantly lower likelihood of statin use (aOR: 0.80; 95% CI: 0.76-0.85).

Conclusions: While cholesterol management is only one measure of guideline recommended type 2 diabetes care, this study highlights the differences in management experienced according to place of residence. The limited adherence to guideline recommended cholesterol management in rural areas is a concerning observation which may result in jeopardized cardiovascular outcomes. Examining other guideline concordant processes of care by place of residence is planned in future analyses as well as health outcomes research.

Abstracts

EXTRA-PANCREATIC ACTIONS OF MLR-1023, A NOVEL ANTIDIABETES DRUG CANDIDATE

Hui Huang, Shay Forget, Jean Buteau

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

Background: The Lyn kinase activator MLR1023 has shown potent glucose-lowering action in both preclinical and clinical models of type 2 diabetes (T2D). We have previously shown that MLR1023 acts (at least in part) through stimulation of β-cell mass expansion. Indeed, activation of Lyn in both mouse models of T1D and T2D promotes β-cell survival and regeneration, which leads to diabetes reversal. However, the effects of MLR1023 in insulin-sensitive tissues remain unknown. In this study, we aimed to investigate the pleiotropic effects of MLR1023 to better understand its anti-diabetes properties.

Methods: Male diet-induced obese (DIO) mice were fed a 60% high-fat diet for 12 weeks and then treated with MLR1023 (30 mg/kg) or vehicle daily for 7 consecutive days. We performed ipGTT, and MRI scans before and after treatment. Liver, and adipose tissue were harvested for histological examinations. Complementary in vitro studies were performed in HepG2 hepatocytes.

Results: A short treatment of 7 days with MLR1023 was sufficient to improve glucose tolerance in DIO mice. This was accompanied by lower hepatic expression of gluconeogenic genes, lower plasma triglyceride and LDL/HDL ratio, and reduced intracellular lipid accumulation in the liver. In vitro, genetic or pharmacological activation of Lyn in HepG2 hepatocytes potentiated insulin signaling, reduced expression of gluconeogenic genes, and inhibited glucose production. MLR-treated mice also displayed reduced adiposity compared to controls. Morphological examination of various fat depots indicated a reduction in retroperitoneal white adipose tissue, more specifically, and a concomitant decrease in macrophage infiltration. MLR1023 also increased UCP1 expression in white adipocytes, suggesting that MLR1023 could stimulate browning.

Conclusion: MLR1023 exerts a panoply of beneficial extra-pancreatic effects, which could participate in its glucose-lowering properties. Our study greatly increases the interest in MLR1023 as a potential anti-diabetes medication.

Keywords: T2D, MLR1023, hepatic gluconeogenesis, adipogenesis

Abstracts

CHARACTERIZING GLUCAGON-LIKE PEPTIDE-1 PRODUCTION IN ALPHA-CELLS

Janyne Johnson, Amy Barr, Wentong Long, Peter Light

Department of Pharmacology, University of Alberta, Alberta Diabetes Institute

Background: Glucagon-Like Peptide-1 (GLP-1) is released from intestinal endocrine cells in response to dietary glucose. GLP-1 enhances insulin production and secretion from pancreatic beta-cells, and supports beta-cell health during metabolic stress. In certain conditions, GLP-1 is produced by pancreatic alpha-cells. Alpha-cell GLP-1 acts on neighbouring beta-cells to improve their function and survival. We aim to identify the molecular mechanism that promotes GLP-1 production in the pancreas so that we may explore this pathway in future drug discovery.

Methods: Alpha-TC1/6 cells are cultured in control conditions (5.5mM glucose + saline vehicle) and proinflammatory conditions (interleukin-6 [IL-6], stromal-derived factor-1 [SDF-1]) for 24-72 hours. We harvest cells and assess changes in proglucagon processing gene transcription and protein expression. Since prohormone convertase 1/3 (PC1/3) is required for GLP-1 processing, we use this as a surrogate marker for downstream GLP-1 production. Similar assays are conducted on FACS-sorted human alpha cells from cadaveric organ donors distributed through IsletCore.

Results: While 72 hours in hyperglycemia elicits a modest 2-fold increase in *PCSK1* (the PC1/3 gene) expression, 72hrs in IL-6 or SDF-1 cause a 5.6-, and 8.5- fold increase in gene expression, respectively. These conditions also impact PC1/3 protein expression and total GLP-1 content. Both conditions significantly alter the proglucagon processing environment and enhance GLP-1 production.

Conclusions: Proinflammatory stimulation by IL-6 and SDF-1 are strong potentiators of *PCSK1* and PC1/3 expression in alpha cells. These conditions promote GLP-1 production, although the exact cell-signalling mechanism has yet to be determined. Based on cell signalling pathways common to both IL-6 and SDF-1's receptors, we have determined that *PCSK1* expression is most likely modulated by the JAK/STAT, PI3K, or Ras/Raf cell signalling cascade. Ongoing experiments aim to identify which intracellular signalling factors are required for cytokine induced *PCSK1*, PC1/3, and GLP-1 production.

Abstracts

METABOLIC PROFILE OF INDIVIDUALS WITH EXCESS BODY WEIGHT: BASELINE FINDINGS FROM THE *PREMIUM* STUDY

Julia Montenegro, Camila L.P. Oliveira, Aloys Berg, Arya M. Sharma, Laurie Mereu, Cristiane Cominetti, Sunita Ghosh, Caroline Richard, Jens Walter, Carla M. Prado

Introduction: Obesity can alter metabolic markers affecting appetite regulation, energy metabolism, and insulin secretion. Understanding the metabolic profile of those with excess body weight can provide insights into the pathophysiology of obesity and its consequences. In this context, our study aimed to profile the metabolic markers in individuals with excess body weight and investigate their correlations with specific components of energy metabolism and body composition.

Methods: A cross-sectional analysis of baseline data from "The Impact of a Powdered Meal Replacement on Metabolism and Gut Microbiota" (PREMIUM) study (NCT03235804) was conducted. Participants (18-50y), with a body mass index (BMI) of 25-37 kg/m2, and no comorbidities were included in this randomized controlled trial. Fasting plasma samples were analysed with MesoScale Discovery® plates for insulin, leptin, ghrelin, adiponectin, glucagon like peptide 1 (GLP-1), and peptide tyrosine-tyrosine (PYY). Energy metabolism was assessed using an indirect calorimeter; including resting energy expenditure (REE) and respiratory exchange ratio (RER; i.e., Volumes of CO2 expired/O2 inspired). Dual energy X-ray absorptiometry (DXA) was used for body composition analysis including data on fat mass (FM; %) and lean soft tissue (LST; kg). Results are reported as mean ± standard deviation or as median (interquartile interval; IQI) according to data distribution. Spearman's correlation test was performed.

Results: We included 52 participants (65.4% females), mean age of 28.0 years (IQI: 23.0 – 33.7), a BMI of 27.79 kg/m2 (IQI: 26.84 – 29.61), and FM of 38.47 ± 6.24%. The majority exhibited high insulin (92.3% >25 mIU/L) and leptin (88.5% >15 ng/mL) levels, while 55.8% had low adiponectin levels (<5 ug/mL). Active ghrelin ranged from 64.9 – 370.1 pg/mL, active GLP-1 from 0.22 – 7.38 pMol/L, and PYY from 63.1 – 460.6 pg/mL, all within what has been observed in the general population. Correlation analyses revealed:

- Age with insulin (Rho= -0.359, p=0.009), adiponectin (Rho= 0.335, p=0.015), and GLP-1 (Rho= -0.318, p=0.022)
- Adiponectin with insulin (Rho= -0.451, p=0.001), ghrelin (Rho= 0.555, p<0.001), and leptin (Rho=0.287, p=0.046)
- Insulin with ghrelin (Rho= -0.392, p=0.005)
- GLP-1 with PYY (Rho= 0.559, p<0.001)
- REE with leptin (Rho= -0.460, p=0.001), adiponectin (Rho= -0.281, p=0.043), and ghrelin (Rho= -0.356, p=0.011)
- RER with GLP-1 (Rho= 0.323, p=0.019) and PYY (Rho= 0.285, p=0.041)
- FM with leptin (Rho= 0.733, p<0.001)
- LST with leptin (Rho= -0.533, p<0.001), adiponectin (Rho= -0.328, p=0.017), and ghrelin (Rho= -0.348, p=0.013)

Discussion: As expected, individuals with excess body weight presented with altered insulin, leptin, and adiponectin concentrations. Correlations between leptin and FM, LST, and REE indicates leptin resistance. Furthermore, correlations between GLP-1 or PYY with RER suggest that these peptides increase carbohydrate oxidation. The observed abnormalities in metabolic markers can contribute to nutrient-specific and overall energy metabolism changes. This could in turn create a feedback loop of weight and fat gains, and increased risks for metabolic diseases such as type 2 diabetes. Our findings emphasize the importance of understanding the interplay between obesity, energy metabolism, and associated metabolic markers.

Abstracts

HEALTHY EATING INDEX SCORE IS ASSOCIATED WITH REDUCED INCIDENCE OF CARDIOVASCULAR DISEASE AS WELL AS A LOWER LEVEL OF NON-FASTING REMNANT CHOLESTEROL IN THE ALBERTA TOMORROW PROJECT

Reihane Taheri1, Olivia Weaver2, Ming Ye2, Donna Vine1, Dean Eurich2, Spencer D Proctor1
1. Metabolic and Cardiovascular Diseases Laboratory, Division of Human Nutrition, University of Alberta. 2. School of Public Health, University of Alberta.

Background: Cardiovascular diseases (CVDs) are the most common cause of morbidity and mortality in diabetes. Dyslipidemia is a major risk factor of CVD in those with diabetes, particularly non-fasting blood lipids (1) . We recently demonstrated that individuals with diabetes from the Alberta Tomorrow Project (ATP) had higher fasting (low-density lipoprotein cholesterol-LDL-C) and non-fasting remnant cholesterol, and these were associated with increased CVD incidence (2). Dietary recommendations in diabetes include healthy-diet patterns and increased n-3 long chain fatty acid intake in an effort to reduce fasting and non-fasting dyslipidemia and lower CVD risk (3, 4) . In this study, we aimed to investigate the relationship of the healthy eating index (HEI) score, dietary n-3 fatty acid intake and blood lipids with CVD incidence in the ATP cohort.

Methods: The ATP cohort enrolled n=52,769 participants aged 35-69 with no history of cancer between 2000-2015. The present study is a subset analysis of ATP participants who had dietary data and developed CVD (incidence) (n=23,248) with mean age of 50.2 yrs (63% females and 37% males). HEI-Canada (2005) was used to calculate a score (0-100) for quality and includes 8 adequacy and 3 moderation components. The relationship between HEI, non-fasting blood lipids as well as the Elixhauser co-morbidity score (0-30) were used to assess the relationship with incidence of CVD.

Results: In our ATP sample (in comparison to those without CVD), those with CVD were significantly older (49 vs 54 years), had higher BMI (28.2 vs 29.8 kg/m 2), a greater intake of carbohydrate (50.3 vs 50.6 %), lower intake of protein (16 vs 15.8 %), a lower HEI score (53.8 vs 52.6) and a higher comorbidity score (Elixhauser of 1.6 vs 2.1). Interestingly, for every 1 unit increase in the HEI score, the Odds Ratio (OR) of developing CVD decreased by 0.97 and 0.98 in females and males, respectively ($p\text{-v}<0.05$). Further, males (but not females) had a mild inverse relationship with n-3 fatty acid intake and CVD (OR = 0.93, ($p\text{-v}<0.05$). However, while there appeared to be a strong relationship between a very low OR for CVD and n-3 fatty acid intake in quartiles up to 1.29 g/day, the relationship did not persist with intakes >1.30g/day. Adjusted multivariate regression in a reduced subset (n=8,458) showed a significant inverse association between HEI score and remnant cholesterol (coef: -0.006 for females and -0.01 for males), TG levels (-0.01 for both males and females) as well as non-HDL-C (-0.008 for both males and females) ($p<0.05$). But there was no other beneficial relationship found between HEI score, LDL-C or n-3 fatty acid intake.

Conclusion: We found a significant inverse relationship with HEI score and the incidence of CVD in this sub-group of the ATP cohort. Minor relationships were associated with increased n-3 fatty intake and lower OR for CVD, and this relationship was more prominent in males. Higher HEI score was found to be associated with reduced levels of non-fasting lipids, including remnant cholesterol (but not LDL-C). These analyses in an Albertan-based cohort, reinforce the importance of maintaining high nutrient quality and n-3 fatty acid intake in the prevention of non-fasting dyslipidemia and CVD.

Abstracts

COMPOSITE SCORES USING FASTING AND STIMULATED C-PEPTIDE ARE EQUIVALENT AND CAN TRACK BETA CELL FUNCTION IN NEW ONSET TYPE 1 DIABETES

Alice L. J. Carr1*, Kimberly S. Collins2, Stephen R. Karpen2, Elnaz Atabakhsh2, Anna Lam 1, Peter N. Taylor3, Colin M. Dayan 3, Peter A. Senior1*

1. Alberta diabetes institute, University of Alberta, Edmonton AB Canada
2. Critical path Institute, AZ, USA
3. Cardiff University School of Medicine, Cardiff, UK

Introduction: Composite scores using fasting samples have been developed to routinely monitor beta cell mass after islet transplantation in type 1 diabetes (T1D). They may also have utility in new onset or T1D prevention trials as an alternative to mixed meal tolerance tests measuring AUC C-peptide.

Methods: We examined if a composite score using stimulated C-peptide was equivalent to fasting C-peptide in estimating beta cell mass in new onset T1D and reflected changes in AUC C-peptide over time. BETA-2 (fasting C-peptide, glucose, insulin dose, HbA 1c) and BETA-2stim (using C-peptide AUC) were calculated in 1312 individuals from the TOMI dataset (median (IQR) age 16y (12,24); 42% F). The dataset comprises 3200 participants within 100 days of diagnosis across 22 studies. Studies meeting their primary end point were deemed positive.

Results: BETA-2 and BETA-2stim were strongly correlated (R 2 =0.96, p<0.0001) and showed good agreement using Bland-Altman plots. Both BETA-2 and BETA-2stim showed changes over time which mirrored those for AUC C-peptide, but both composite scores showed differences between active and control participants in positive studies by 3 months while differences in AUC C-peptide were not seen until 6 months.

Conclusions: Composite scores using fasting C-peptide may provide a simple, sensitive and practical tool to monitor beta cell mass without complex stimulation tests in new onset diabetes.

Alberta Diabetes INSTITUTE

ABSTRACTS

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UNIVERSITY OF ALBERTA

Abstracts

UNDERSTANDING THE IMPACT OF ALTERED PHOSPHATIDYLETHANOLAMINE (PE) METABOLISM IN HEPATOCYTE DERIVED CELLS

Courtney Holdaway, Kelly-Ann Leonard, Randal Nelson, Jelske van der Veen, Chinmayee Das, Richard Lehner, Rene Jacobs

Background: Altered phospholipid metabolism has been shown to induce metabolically associated steaototic liver disease (MASLD) and hepatocellular carcinoma (HCC). Phosphatidylethanolamine (PE) is the second most abundant glycerophospholipid in mammalian membranes and is synthesized primarily through the PE arm of the Kennedy Pathway. It is important for lipid storage/transport and cell proliferation. Ethanolamine phosphate phospholyase (ETNPPL) is a metabolic enzyme expressed in astrocytes and hepatocytes that catabolizes phosphoethanolamine (p-etn). In humans, low ETNPPL expression has been linked to reduced survivability in patients with hepatocellular carcinoma (HCC). Therefore, we investigated the impact of removing p-etn on PE synthesis and overall cellular health.

Methods: To investigate the biological effects of removing p-etn, human Huh7 hepatoma cells were transfected with a plasmid containing mouse ETNPPL cDNA. Immunofluorescence was conducted to visualize the localization of ETNPPL. Cells were treated with 3H-ethanolamine to assess incorporation into p-etn and PE. Proliferation rate of cells was measured using a WST-1 assay. mRNA expression was measured for many tumor suppressor genes, including p53. Lipid accumulation and storage was assessed in primary hepatocytes using lipid droplet immunofluorescent visualization.

Results: Immunofluorescence showed that ETNPPL localized in the nucleus. Radiolabel experiments showed there was a decrease in ethanolamine incorporation into p-etn and PE, and an increased PC/PE ratio in cells expressing ETNPPL. Additionally, cells expressing ETNPPL had increased triglycerides and cholesteryl esters. ETNPPL expressing cells also had a decreased rate of cell proliferation with increased mRNA and protein expression of p53, a tumor suppressor gene. In addition to p53, an increase in expression of four other tumor suppressor genes (CDKN1A, BBC3, BAX, BRCA1) was observed. ETNPPL expressing cells exhibited an increase in levels of acetylated histones H3 and H4 when measured by Western blot. Primary hepatocytes show a decrease in lipid accumulation in etnppl -/- mice.

Discussion: ETNPPL expressing cells exhibited decreased PE synthesis and altered PE metabolism, leading to a decrease in PC/PE ratio. These alterations in PC/PE in addition to increased lipid storage may be associated with MASLD and impaired mitochondrial function. A decrease in ethanolamine incorporation into p-etn confirms that ETNPPL is responsible for removing p-etn from the Kennedy Pathway, and which may be the cause of the observed decrease of PE in these ETNPPL expressing cells. Additionally, human hepatoma cells expressing ETNPPL grew at a slower rate and exhibited increased expression of tumor suppressor genes, which implies that ETNPPL is a tumor supressing enzyme and
may impact HCC. ETNPPL was observed to localize in the nucleus, and an increase in Ac-H3/Ac-H4 was observed; together this may indicate that ETNPPL alters the genome epigenetically to turn on genes for tumor suppression.

Conclusion: ETNPPL observably impacts PE metabolism in the cell. This alteration influences cellular changes that could link ETNPPL to MASLD and HCC.

Funding: Canadian Institutes of Health Research

Abstracts

EGG-DERIVED PC ENHANCES T CELL RESPONSES TO A GREATER EXTENT THAN SOY-PC UNDER THE CONTEXT OF OBESITY

Tianna Rusnak1, Jessy Azarcoya-Barrera1, Alexander Makarowski1, René Jacobs 1, Caroline Richard1

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

Objectives: Obesity is associated with a diminished immune response along with increased systemic inflammation. Phosphatidylcholine (PC), a lipid-soluble form of choline, may support immune function through maintaining immune cell membrane integrity. PC is found in both animal sources, such as eggs, and plant sources, such as soybeans. Our group has shown that feeding PC from both plant and animal sources improves immune function in early life. However, it is unclear if PC from animal and plant sources provide similar immunomodulatory benefits under the context of obesity. Thus, the objective of this study was to determine how PC derived from eggs and soy affects immune cell function.

Methods: Male Wistar rats were randomized to consume one of 4 nutritionally complete, fatty acid composition matched diets (n=10/group) for 12 weeks, all containing 1.9g of total choline/kg of diet but differing in choline forms: 1- Control Low Fat (CLF, 20% fat, 100% free choline (FC)); 2- Control High Fat (CHF, 50% fat, 100% FC); 3- High fat Egg-derived PC (EPC, 50% fat, 100% Egg-PC); 4- High fat Soy-derived PC (SPC, 50% fat, 100% Soy-PC). Immune cell function was measured in splenocytes and mesenteric lymph node (MLN) lymphocytes by ex vivo cytokine production and proliferation after T cell mitogen stimulation, and phenotypes by flow cytometry.

Results: After anti-CD3/anti-CD28 stimulation, the EPC diet normalized splenocyte T cell proliferation relative to the CLF diet, but the SPC diet did not ($p < 0.05$). The SPC diet significantly increased splenocyte IL-2 production after PMA+I stimulation compared to the CHF diet. However, the SPC diet fed group had a lower proportion of splenocytes expressing the IL-2 receptor (CD25+, $p < 0.05$). After PMA+I stimulation, feeding EPC normalized splenocyte production of IL-10 relative to the CLF diet while SPC did not ($p < 0.05$). In MLN lymphocytes, the SPC diet group produced more lL-2 and TNF-α after PMA+I stimulation than the CHF diet, while the EPC diet group did not.

Conclusions: Our results suggest that while both egg- and soy-derived PC may attenuate obesity induced T cell dysfunction, egg-PC enhances to a greater extent peripheral T cell proliferation and cytokines involved in the resolution phase of the inflammatory response (IL-10). However, soy-PC appears to elicit a greater effect on gut-associated immune responses. Since the fatty acid composition of egg-PC and soy-PC molecules differ, this may explain at least in part their differential effect on immune function.

Funding Sources: Egg Farmers of Canada, NSERC

Abstracts

THE ASSOCIATIONS BETWEEN DOCOSAHEXAENOIC ACID (DHA) AND CAROTENOIDS, EXERCISE PATTERNS, AND QUALITY OF LIFE IN WOMEN UNDERGOING NEOADJUVANT CHEMOTHERAPY IN THE DHA-WIN RCT

Claire Douglas1, Susan Goruk1, Kerry S Courneya2, Catherine J Field1

1 Faculty of Agricultural, Life and Environmental Sciences, University of Alberta
2 Faculty of Kinesiology, Sport and Recreation, University of Alberta

Cancer is the leading cause of death worldwide, with breast cancer serving as the most diagnosed type in 2020 (1). Although neoadjuvant therapy is administered to patients to improve surgical resection outcomes and reduce micrometastases, not all individuals achieve a pathological complete response (pCR) (2). Further, certain chemotherapeutic agents alter metabolic function and contribute to weight gain (3). This in turn increases one's risk of diabetes and cardiovascular disease (3, 4). Therefore, it is crucial to understand factors that may improve the efficacy and reduce the side effects of neoadjuvant chemotherapy.

Docosahexaenoic acid (DHA) is an omega-3 polyunsaturated fatty acid that has demonstrated antitumorigenic effects in preclinical models (2). It has also been shown to improve drug-induced side effects, bone health, and chemotherapeutic efficacy when administered during chemotherapy (5). This may, in turn, prevent dose reductions or discontinuation of treatment and contribute to better patient outcomes, including specific dietary habits, exercise habits and quality of life (QoL).

The current study is based on the phase II randomized controlled trial (RCT) evaluating DHA supplementation (4.4 g/day) in women with breast cancer undergoing neoadjuvant chemotherapy (DHA-WIN) (2). The project will investigate changes in specific dietary habits, exercise patterns, and QoL for women that participated in the DHA-WIN clinical trial. Dietary habits will be assessed by measuring plasma carotenoid levels via high-performance liquid chromatography. These molecules are antioxidants found in fruits and vegetables that have demonstrated anticancer effects (6, 7). Circulating carotenoid concentrations serve as biomarkers for fruit and vegetable intake, and the bioavailability of certain carotenoids has been shown to vary depending on fat intake (8, 9). The project will investigate whether chemotherapy or DHA influences circulating carotenoid levels. Completed food frequency questionnaires will also be used to estimate macronutrient energy intake at baseline.

Exercise has been associated with reduced risk, recurrence, and mortality from breast cancer (10). It has also been shown to reduce chemotherapy-associated side effects and improve QoL (11). A separate investigation will look at changes in exercise patterns between and within treatment groups using the Godin Leisure-Time Exercise Questionnaires completed by participants. Potential associations between exercise patterns and QoL, pCR, and treatment completion will also be examined. Lastly, there are mixed findings regarding the effect of DHA on QoL in cancer patients receiving chemotherapy (12, 13). QoL questionnaires completed by participants will be used to investigate a possible association between DHA supplementation and improved QoL.

Please note that statistically analyzed results will be available for several of the aforementioned outcomes prior to ADI research day on September 15, 2023.

Abstracts

METFORMIN AND FIBER COMBINED THERAPY IN ADOLESCENTS WITH OBESITY AND INSULIN RESISTANCE (METFIBER TRIAL): PRELIMINARY BASELINE FINDINGS

Nandini Basuray1, Flavio T. Vieira1,2, Edward C. Deehan3, Geoff D.C. Ball2, Faria Ajamian2, Reena L. Duke2, Eloisa Colin-Ramirez4, Eytan Wine2, Karen L. Madsen5, Carla M. Prado1, Catherine J. Field1, Andrea M. Haqq1,2

1Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, Alberta, Canada. 2Department of Pediatrics, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada. 3Department of Food Science and Technology, University of Nebraska, Lincoln, Nebraska, United States. 4School of Sport Sciences, Universidad Anahuac Mexico, Huixquilucan, Mexico. 5Department of Medicine, University of Alberta, Edmonton, Alberta, Canada.

Background: Obesity is characterized by excessive adiposity and low-grade chronic systemic inflammation, which may impair insulin signaling and induce insulin resistance (IR). Adolescents with obesity are at high risk of developing IR and early-onset of type 2 diabetes mellitus (T2DM). In our ongoing RCT, we assess the effectiveness of metformin (Met) and dietary fibers (DF) alone and in combination in reducing IR in adolescents with obesity. This work aimed to describe participant characteristics and explore cross-sectional associations between demographic, anthropometric, and metabolic variables at baseline.

Methods: Baseline data were collected from October 2021 to June 2023 according to our study protocol (ClinicalTrials.gov NCT04578652). We included 12-18 year olds with a BMI >95th percentile for age/sex, a homeostatic model for insulin resistance (HOMA-IR) >3.16, and a family history of T2DM. Demographic information, medical history, and pubertal stage were collected. BMI and waist circumference (WC) were measured and analyzed based on age/sex. Body composition was assessed using air displacement plethysmography. Participants performed an oral glucose tolerance test (OGTT), allowing us to calculate HOMA-IR, Matsuda index, quantitative insulin sensitivity check index (QUICKI), and incremental area under the curve (iAUC). Other metabolic markers included triglycerides, LDL-C, HDL-C, total cholesterol, high-sensitivity C-reactive protein (hs-CRP), and HbA1c. Pearson/Spearman correlations were performed between anthropometric, body composition, and metabolic markers; statistical significance was considered at $p<0.05$. Preliminary Findings: Fourteen participants (57% females, age: 14.4±1.8 years, BMI z-score: 3.5±1.0, HOMA-IR: 7.87±3.65) were enrolled. Most participants were white (71.4%, n=10) and classified as mid-pubertal stage (57.1%, n=8). Most exhibited obesity-related comorbidities, including hypertension (28.6%, n=4), non-alcoholic fatty liver disease (21.4%, n=3), and hypothyroidism (21.4%, n=3). As expected, all participants demonstrated IR (Matsuda index: 1.3±0.7; QUICKI: 0.29±0.02). The mean iAUC for insulin and glucose were 27281.9±12347.6 µIU*min/mL and 260.3±102.0 mmol*min/L, respectively. Insulin iAUC was positively correlated with IR (HOMA-IR $r=0.71$, $p=0.005$), higher lipids (LDL-C $r=0.63$, $p=0.016$; total cholesterol $r=0.61$, $p=0.021$), and negatively correlated with insulin sensitivity indices (Matsuda index $r=-0.81$, $p<0.001$; QUICKI $r=-0.75$, $p=0.002$). Hs-CRP was positively correlated with BMI ($r=0.68$, $p=0.007$) and percent body fat ($r=0.81$, $p<0.001$), but was not correlated with insulin indices nor lipid markers.

Conclusion: Adolescents with obesity and IR have elevated insulin concentrations that are positively correlated with IR and unfavorable lipid profiles. Increased body fat and higher BMI z-scores were positively correlated with a pro-inflammatory status. These participant baseline features are highly appropriate for describing adolescents with obesity and IR. In this population, Met and DF alone have beneficial effects on the described variables, hence a combination of Met and DF may have a synergistic therapeutic effect to help attenuate obesity-related IR in adolescents and prevent early-onset of T2DM.

Abstracts

AGONISM OF GLUCOCORTICOID RECEPTOR IN THE NUCLEUS OF THE SOLITARY TRACT STIMULATES VLDL-TG SECRETION FROM THE LIVER

Boyan Vasilev*1,2,3, Mantash Grewal1,2,3, Eyram Asem1,2,3, Randal C. Nelson2,3, Audric Moses3,4, Bryan M. Lum1 , Richard Lehner2,3 , Jessica T.Y. Yue1,2,3,5

1Department of Physiology, 2Alberta Diabetes Institute, 3Group on Molecular and Cell Biology of Lipids, 4FoMD Lipidomics Core Facility, 5Neuroscience and Mental Health Institute, University of Alberta.

BACKGROUND: Dysregulated lipid metabolism is a characteristic of diabetes, insulin resistance, and obesity. Increased glucocorticoid (GC) levels and/or action is associated with elevated levels of circulating triglyceride (TG)-rich very low-density lipoproteins (VLDL-TGs). Lipid metabolism is heavily affected by GCs via its direct actions on peripheral organs, e.g. liver, adipose tissue. However, how GCs modulate hepatic VLDL-TG secretion via their actions in the brain is less known. The nucleus of the solitary tract (NTS) in the hindbrain is responsive to various hormones and neural signals and is an important region involved in whole-body metabolism. Here, we aimed to assess how GC action in the NTS affects hepatic TG secretion. We hypothesize that GC receptor (GR) agonism in the NTS stimulates hepatic TG secretion.

METHODS: Sprague-Dawley rats underwent stereotaxic NTS bilateral cannulation and vascular catheterizations to enable simultaneous direct NTS infusions, intravenous injections, and blood sampling. Hepatic TG secretion rates were measured in 10h-fasted rats after intravenous poloxamer injection with concurrent NTS infusions.

RESULTS: NTS GC infusion stimulated TG secretion compared to NTS vehicle controls, but this effect was negated with pharmacological and genetic GR antagonism. Inhibiting Hsp90 chaperone proteins involved in maintaining GR stability and function also prevented NTS GCs from triggering hepatic TG secretion, suggesting that NTS GCs require functional GRs for their lipostimulatory effect. Preliminary data shows that NTS GC infusion increased TG concentrations in VLDL-containing fractions of plasma analyzed by FPLC compared to NTS vehicle. NTS GC-induced hyperlipemia occurred independent of changes in plasma insulin and glucose, but notably, plasma free fatty acids (FFAs) were increased in NTS GC infused rats. Liver CD36 and FATP2/5 protein levels were similar amongst groups, and increased plasma FFAs was associated with increased pHSL:HSL protein levels in white adipose tissue, suggesting a potential FFA-mediated mechanism underlying increased TG secretion.

CONCLUSION: We herein provide evidence that acute GR activation in the NTS stimulates hepatic VLDL-TG secretion and affects adipose tissue lipid metabolism. Increased circulating FFA availability from enhanced lipolysis in white adipose tissue may contribute to the hyperlipidemic effects of NTS GCs. Future studies to assess the role of NTS GC action in diabetic and obesity-related metabolic disease dyslipidemic models are warranted.

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Alberta Diabetes INSTITUTE

2023 RESEARCH DAY

0815-1600 | 1-040 LKS (Oborowsky Degner Seminar Hall) & LKS Foyer

FRIDAY SEPTEMBER 15

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