Alberta Diabetes
INSTITUTE

2019 RESEARCH DAY

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

FRIDAY SEPTEMBER 27

KEYNOTE SPEAKER

Michael Riddell, PhD

Professor, School of Kinesiology and Health Science,
York University, Toronto, Canada

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Program

2019 ADI RESEARCH DAY

Friday September 27

LISTER CENTRE, Maple Leaf Room, University of Alberta

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

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

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ALBERTA DIABETES INSTITUTE

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NOTE FROM THE DIRECTOR

Welcome to the 2019 Alberta Diabetes Institute Research Day. Wow how time flies, it doesn't seem like a year since the last Research Day. Perhaps the miserable summer weather has affected my shorter-term memory! However, my long-term memory informs me that we should celebrate 20 years since the first patients were enrolled in the Edmonton Protocol. Kudos to those researchers involved in this initial landmark procedure and to those currently involved in developing the next generation(s) of cell-based therapies right here at the ADI. Furthermore, insulin was discovered 98 years ago with key contributions made by Dr. James Collip, a UofA Biochemistry Professor. The 100th anniversary of this event is just around the corner. In the last year we have also established the Helmholtz International Graduate School for Diabetes, in partnership with the Diabetes Center at the Helmholtz Zentrum Munchen (Munich). Look out for the 2nd call for interested students later this fall!

With respect to this research day: it is intended to provide a forum to showcase the research efforts of our **ADI Trainees.** The podium presentation session is 3 sessions of 5 speakers each and the poster session takes place immediately after lunch from 1:00-2:30 pm allowing enough time for the judges and attendees to visit all the posters. The ADI Trainee Working Group are excited to once again organize and host the **"Trainee Lunch with the Speaker"** event – all ADI Trainees presenting (podium / poster) and the ADI TWG members are invited to attend.

Please take time to attend the podium presentation sessions and stop by each poster to see what exciting research our trainees are doing! Remember, for some of our trainees it will be the first time presenting their research in front of an audience of their peers, supervisors and principal investigators. Today is about giving you our trainees, as the next generation of diabetes researchers, an opportunity to present your most recent exciting results and ideas.

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

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

Best Regards,

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

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MORNING SESSION

WELCOME		
0830-0844	Dr Peter Light Director, ADI	Welcome & Overview

KEYNOTE SPEAKER		Introduction – Kim Ho (Chair, ADI Trainee Working Group)
0845-0945	Dr Michael Riddell York University, Toronto	Exercise and Type 1 Diabetes
0946-0954	REFRESHMENT BREAK	GLACIER ROOM

SESSION 1		Chair – Dr Jessica Yue
0955-1005	Abrar ALAM Summer Student Supervisor: Dyck	FECAL MICROBIOME TRANSPLANTS FROM RESVERATROL-FED MICE IMPROVES GLUCOSE HOMEOSTASIS IN OBESE MICE
1006-1016	Diva NIAZ Graduate Student Supervisor: Simpson & Necyk	PATIENTS WITH TYPE 2 DIABETES HAVE A HIGHER LIKELIHOOD OF POOR MEDICATION ADHERENCE IN THE YEAR PRIOR TO AN INCIDENT DEPRESSIVE EPISODE COMPARED TO MATCHED PATIENT CONTROLS
1017-1027	Shubham SONI Graduate Student Supervisor: Dyck	GENETICALLY ELEVATING CIRCULATING KETONES REDUCES CARDIAC INFLAMMATION AND PROTECTS FROM HEART FAILURE
1028-1038	Stephanie CARLIN Graduate Student Supervisor: Jacobs	ROLE OF INTESTINAL DE NOVO PHOSPHATIDYLCHOLINE SYNTHESIS IN LIPID METABOLISM.
1039-1049	Wentong LONG Postdoctoral Fellow Supervisor: Light	VITAMIN D MAY BE AN IMPORTANT ENDOGENOUS PARTIAL AGONIST OF TRPV1 AND MAY PLAY A CRITICAL ROLE IN TYPE 1 DIABETES.
1050-1100	REFRESHMENT BREAK	GLACIER ROOM

SESSION 2		Chair – Dr Andrew Pepper
1101-1111	Bethany WOLLIN Summer Student Supervisor: Richard	EGG-PHOSPHATIDYLCHOLINE IMPROVES OBESITY-RELATED IMMUNE DYSFUNCTION
1112-1122	Jake SZETO Summer Student Supervisor: Shapiro	IN VIVO EXPANSION OF REGULATORY T-CELLS IN ISLET TRANSPLANTATION: THE ROLE OF TUMOR NECROSIS FACTOR SUPERFAMILY RECEPTOR 25 (TNFRSF25)
1123-1133	Emilie BEAULIEU-BAYNE Graduate Student Supervisor: Yue	GLUCOREGULATORY EFFECTS OF HYPOTHALAMIC GLUCOCORTICOID ACTION IN VIVO
1134-1144	Linnet IMMARAJ Postdoctoral Fellow Supervisor: Febbraio	ROLE OF ENDOTHELIAL CD36 FATTY ACID UPTAKE
1145-1155	Nicole OFOSU Postdoctoral Fellow Supervisor: Campbell-Scherer	DIABETES AND OBESITY IN VULNERABLE ETHNOCULTURAL COMMUNITIES: IDENTIFYING CARE GAPS THROUGH A PARTICIPATORY, MULTIDISCIPLINARY LENS

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AFTERNOON SESSION

1200-1255	LUNCH BREAK	GLACIER ROOM

TRAINEE EVENT

1200-1255	Trainee LUNCH with Keynote Speaker Dr Michael Riddell **PRAIRIE ROOM**	• TRAINEES / Dr Riddell Round Table Discussion – organized by ADI Trainee Working Group • INVITED PARTICIPANTS – ADI Trainees Presenting at Research Day & ADI TWG Members and Dr Riddell

POSTER PRESENTATIONS

1300-1430	21 Posters	• Posters located at the back of Maple Leaf Room • 2 poster judges per category • Poster presenters have 5 minutes in total to present their poster (3 min presentation to the judges with 2 minutes for Q&A)

SESSION 3 — Chair – Dr Gavin Oudit

1435-1445	Steven QIU Summer Student Supervisor: Chan	EFFECTS OF EARLY LIFE AMOXICILLIN EXPOSURE ON PANCREATIC DEVELOPMENT IN PIGLETS
1446-1456	Mahmoud GHEBLAWI Graduate Student Supervisor: Oudit	ANGIOTENSIN-CONVERTING ENZYME 2 KNOCKOUT LEADS TO WORSENED CARDIOVASCULAR FUNCTION IN DIABETIC MICE
1457-1507	Heather HINZ Graduate Student Supervisor: Yardley	THE ASSOCIATION OF EXERCISE BLOOD GLUCOSE ON POST-EXERCISE HYPOGLYCEMIA IN TYPE 1 DIABETES
1508-1518	Dhruvesh PATEL Graduate Student Supervisor: Field	SUPPLEMENTATION OF ARACHIDONIC ACID AND DOCOSAHEXAENOIC ACID DURING SUCKLING PERIOD AFFECTS SPLENOCYTE FUNCTION OF EX-VIVO CYTOKINE PRODUCTION IN BROWN NORWAY RAT OFFSPRING AT WEANING
1519-1529	Birbickram ROY Postdoctoral Fellow Supervisor: MacDonald	MEMBRANE EXCITABILITY OF HUMAN ISLET CELLS WITH DISTINCT HETEROGENEITY MARKER EXPRESSION

WRAP UP & PRIZES

1545-1600	WRAP UP, AWARDS, & PRIZES	Facilitated by Dr Peter Light

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KEYNOTE SPEAKER

Michael Riddell, PhD

Dr. Riddell is Professor & Graduate Program Director at the School of Kinesiology and Health Science Faculty of Health, York University, Toronto, Canada.

Dr. Riddell has published over 170 original research articles, 23 book chapters, and one globally referenced patient guidebook on the metabolic and hormonal responses to exercise and stress in health and diabetes. He currently holds research grants from various government agencies, foundations and industry partners totaling in excess of $5M. His research team uses a broad selection of innovative models and techniques to discover how regular exercise, stress and diabetes influence metabolism and health. Riddell's team of students and fellows are advancing new therapeutic approaches and technologies that will enable people living with diabetes to exhibit better metabolic control with fewer burdens. Presently, he is helping to develop an "exercise-smart" artificial pancreas for active people living with type 1 diabetes (NIH and JDRF funding). He is leading studies on new strategies for improved blood sugar balance during exercise and sport (industry and foundation funds) and he is overseeing work done on the effects of somatostatin on glucose metabolism (NSERC). Riddell is an author on several international guidelines on exercise and diabetes and he leads teams in establishing community-based sport programs that enhance the translation of research findings to families of children living with type 1 diabetes. He is considered the international authority on exercise and stress hormones and how they affect diabetes metabolism.

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PRIZES

Prize announcements at 15:45-16:00

ORAL PRESENTATION AWARDS

- 1 Best Award & 1 Honourable Mention :: Summer Student Trainees
- 1 Best Award & 1 Honourable Mention :: Junior Trainees (MSc)
- 1 Best Award & 1 Honourable Mention :: Senior Trainees (PhD / Postdocs)

POSTER PRESENTATION AWARDS

- 1 Best Award & 1 Honourable Mention :: Summer Student Trainees
- 1 Best Award & 1 Honourable Mention :: Junior Trainees (MSc)
- 1 Best Award & 1 Honourable Mention :: Senior Trainees (PhD / Postdocs)

DOOR PRIZES

- Door prize draws at end of ADI Research Day (courtesy of Alberta Diabetes Foundation)

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2	Diva NIAZ MSc Student	SIMPSON & NECYK	PATIENTS WITH TYPE 2 DIABETES HAVE A HIGHER LIKELIHOOD OF POOR MEDICATION ADHERENCE IN THE YEAR PRIOR TO AN INCIDENT DEPRESSIVE EPISODE COMPARED TO MATCHED PATIENT CONTROLS
3	Shubham SONI MSc Student	DYCK	GENETICALLY ELEVATING CIRCULATING KETONES REDUCES CARDIAC INFLAMMATION AND PROTECTS FROM HEART FAILURE
4	Stephanie CARLIN PhD Student	JACOBS	ROLE OF INTESTINAL DE NOVO PHOSPHATIDYLCHOLINE SYNTHESIS IN LIPID METABOLISM
5	Wentong LONG Postdoc Fellow	LIGHT	VITAMIN D MAY BE AN IMPORTANT ENDOGENOUS PARTIAL AGONIST OF TRPV1 AND MAY PLAY A CRITICAL ROLE IN TYPE 1 DIABETES
6	Bethany WOLLIN Summer Student	RICHARD	EGG-PHOSPHATIDYLCHOLINE IMPROVES OBESITY-RELATED IMMUNE DYSFUNCTION
7	Jake SZETO Summer Student	SHAPIRO	IN VIVO EXPANSION OF REGULATORY T-CELLS IN ISLET TRANSPLANTATION: THE ROLE OF TUMOR NECROSIS FACTOR SUPERFAMILY RECEPTOR 25 (TNFRSF25)
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12	Mahmoud GHEBLAWI MSc Student	OUDIT	ANGIOTENSIN-CONVERTING ENZYME 2 KNOCKOUT LEADS TO WORSENED CARDIOVASCULAR FUNCTION IN DIABETIC MICE
13	Heather HINZ MSc Student	YARDLEY	THE ASSOCIATION OF EXERCISE BLOOD GLUCOSE ON POST-EXERCISE HYPOGLYCEMIA IN TYPE 1 DIABETES
14	Dhruvesh PATEL PhD Student	FIELD	SUPPLEMENTATION OF ARACHIDONIC ACID AND DOCOSAHEXAENOIC ACID DURING SUCKLING PERIOD AFFECTS SPLENOCYTE FUNCTION OF EX-VIVO CYTOKINE PRODUCTION IN BROWN NORWAY RAT OFFSPRING AT WEANING
15	Birbickram ROY Postdoc Fellow	MACDONALD	MEMBRANE EXCITABILITY OF HUMAN ISLET CELLS WITH DISTINCT HETEROGENEITY MARKER EXPRESSION

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FECAL MICROBIOME TRANSPLANTS FROM RESVERATROL-FED MICE IMPROVES GLUCOSE HOMEOSTASIS IN OBESE MICE

Abrar Alam, Ty T. Kim, Miranda M. Sung, Emmanuel Denou, Carrie-Lynn M. Soltys, Nikole J. Byrne, Grant Masson, Heekuk Park, David S. Wishart, Karen L. Madsen, Jonathan D. Schertzer and, Jason R. B. Dyck

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

Background: Obesity and type 2 diabetes (T2D) are global epidemics and the number of individuals affected by T2D is rising. Resveratrol (resv), a polyphenolic compound that can be found in a variety of plant-based foods, has shown promising results in the prevention and treatment of T2D. While oral administration of resv is able to improve glucose homeostasis in obese individuals, the majority of ingested resv will pass unmetabolized to the colon because of its low bioavailability. In fact, it is possible that the interaction of resv with the gut microbiota is a major mechanism by which resv improves glucose homeostasis in obesity. Based on this, our hypothesis is that fecal microbiome transplants (FMT) from healthy resv-fed mice is sufficient to improve glucose homeostasis in obese mice.

Methods: Conventional raised 8 week-old C57Bl/6 mice were maintained on a high-fat high-sucrose diet for 6 weeks to induce impaired glucose homeostasis. Following this, fecal matter was transplanted from donor mice maintained on either a control diet (Chow) or a Chow + 0.4% resv diet for 8 weeks to obese mice. Additionally, to confirm that live bacteria are required for the beneficial effects of FMT, the same experiment was repeated with a heat-killed fecal slurry.

Results: While ingestion of resv for 2 weeks is not sufficient to rescue impaired glucose tolerance in obese mice, obese mice receiving resv-FMT show improved glucose tolerance and peripheral insulin signaling within 11 days of the first transplant. FMT using heat-killed resv slurry also show improvements in the glucose tolerance of obese mice.

Conclusion: Our findings demonstrate that FMT from resv-fed mice is more potent and efficacious than an oral treatment of resv, and highlight the potential importance of non-living bacterial, metabolites or other components of the fecal material as a central mechanism by which resv improves glucose homeostasis in obesity.

Keywords: Resveratrol, FMT, Glucose homeostasis

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PATIENTS WITH TYPE 2 DIABETES HAVE A HIGHER LIKELIHOOD OF POOR MEDICATION ADHERENCE IN THE YEAR PRIOR TO AN INCIDENT DEPRESSIVE EPISODE COMPARED TO MATCHED PATIENT CONTROLS

Diva Niaz, Candace Necyk, Scot Simpson
Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta

Background: Good adherence to antihyperglycemic medications contributes to blood sugar control and decreases the risk of complications. Although depression is an accepted risk factor for poor adherence in diabetes, studies examining this association are either cross-sectional or measure adherence rates after depression is diagnosed. Our objective was to measure medication adherence among newly treated patients with type 2 diabetes prior to an incident depressive episode.
Methods: This retrospective cohort study was conducted on new metformin users in Alberta Health's administrative data between 2008 and 2018. A validated case definition of International Classification of Disease (ICD) 9 and 10 codes was used to identify subjects with an incident depressive episode occurring at least one year after metformin initiation. Control subjects who never had an active depressive episode were randomly assigned an index date from subjects with a depressive episode. We defined poor adherence as having ≤80% of days covered by metformin within the year prior to the index date. Multivariate logistic regression was conducted to adjust for baseline characteristics and examine the association between depression and adherence.
Results: We identified 165,056 new metformin users, mean age was 57 (14.0) years, 73, 821 (44.72%) were female and 5136 (3%) had an incident depressive episode at least one year after initiating metformin. The mean time between metformin initiation and an incident depressive episode was 3.1 (1.6) years. A total of 113,560 (68%) control subjects were randomly assigned an index date. The mean proportion of days covered in the year before the index date was significantly lower for subjects with a depressive episode (55.5% [39.0%]) compared to controls (60.0% [38.1%]) ($p<0.001$). After adjusting for other comorbidities, drug therapy, number of clinician visits, prior hospitalizations and other characteristics at baseline, subjects with a depressive episode were more likely to have poor adherence compared to controls (adjusted odds ratio 1.33; 95%CI 1.25,1.41).
Conclusions: These results suggest that poor adherence to oral antihyperglycemic medications appears in the year prior to an incident depressive episode. This study is part of a larger project to identify whether depression is a modifiable risk factor for adherence to oral antihyperglycemic medications in patients with type 2 diabetes. Next steps are to analyze adherence trajectories prior to an incident depressive episode, in hopes of helping clinicians better identify patients with type 2 diabetes and depression at risk of nonadherence to antihyperglycemics.

Key Words: Adherence, Type 2 Diabetes, Depression, Antihyperglycemics

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GENETICALLY ELEVATING CIRCULATING KETONES REDUCES CARDIAC INFLAMMATION AND PROTECTS FROM HEART FAILURE

Shubham Soni, Nikole J Byrne, Shingo Takahara, Mourad Ferdaoussi, Ahmed Darwesh, Rami Al Batran, Mya Schmidt, Abrar Alam, John M Seubert John R Ussher, Jason RB Dyck

Department of Pediatrics, Cardiovascular Research Centre, FoMD, University of Alberta

Background: The failing heart has metabolic defects which impair ATP production and contractile function. Recent studies show that the failing heart upregulates ketone metabolism and may rely on ketones as a fuel. Ketones, namely β-hydroxybutyrate (βOHB), are produced in low glucose conditions, such as fasting. Furthermore, βOHB may be beneficial in heart failure (HF) as a more energy-efficient substrate, as well as a signaling molecule as seen acutely. Thus, chronically elevating circulating βOHB levels beyond what is normally observed in HF may serve as a novel therapy to improve cardiovascular outcomes in patients with HF.

Methods: To determine whether endogenously elevating circulating ketones may improve cardiac function in HF, we used a tamoxifen-inducible skeletal muscle-specific knockout of succinyl-CoA:3-ketoacid-CoA transferase (smSCOT-KO), the rate limiting enzyme in ketone catabolism. SmSCOT-KO and wildtype littermate mice were subjected to transverse aortic constriction (TAC) surgery to generate pressure overload-induced HF. Echocardiography, immunoblot analysis, gene expression, and histological analysis were performed.

Results: SCOT expression was significantly reduced in skeletal muscle of smSCOT-KO compared to wildtype mice ($p<0.001$) without changes in cardiac muscle SCOT expression. SmSCOT-KO resulted in a 1.5-fold increase in fasted circulating βOHB ($p=0.01$). Interestingly, this rise in circulating βOHB was associated with protection from TAC-induced decline in systolic (47% vs 32% ejection fraction; $p=0.0042$) and diastolic (E/E'; $p=0.002$) function in smSCOT-KO compared to wildtype littermates. This protective effect was also consistent with parameters of cardiac hypertrophy, fibrosis, and markers of cardiac inflammation and macrophage infiltration.

Conclusion: Together, these data are the first to show that chronically increasing circulating ketones, via a smSCOT-KO, prevents cardiac dysfunction and reduces cardiac inflammation in mice with pressure overload-induced HF. Thus, chronically elevating circulating ketones in HF may be a novel therapeutic approach in the chronic management and treatment of HF.

Key words: Heart failure, Ketones, β-hydroxybutyrate, SCOT, Inflammation

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ROLE OF INTESTINAL *DE NOVO* PHOSPHATIDYLCHOLINE SYNTHESIS IN LIPID METABOLISM

Stephanie Carlin[1], John Kennelly[1], Ariel Quiroga[2], Hailey Fedoruk[1], Kelly-Ann Leonard[1], Randal Nelson[3], Richard Lehner[2,4] and René Jacobs[1, 3]

[1]Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, Alberta, Canada. [2]Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada. [3]Department of Biochemistry, University of Alberta, Edmonton, Alberta, Canada. [4]Department of Cell Biology, University of Alberta, Edmonton, Alberta, Canada.

Background: Phosphatidylcholine (PC) is vital for the structural integrity of mammalian membranes and is the primary phospholipid in bile and plasma lipoproteins. In intestinal cells, PC can be synthesized from dietary choline which uses the enzyme CTP:phosphocholine cytidylyltransferase alpha (CTα) to regulate flux. Intestinal PC can also be obtained from luminal supply (dietary and biliary sources). Our lab has created an intestinal-specific CTα gene knockout mouse (iCTα$^{-/-}$), which has reduced *de novo* PC synthesis. Previous analysis has shown that high fat diet (HFD) fed iCTα$^{-/-}$ mice have reduced postprandial lipid secretion and weight gain. This data shows the importance of intestinal PC synthesis for proper lipid metabolism.
Hypotheses: My objective is to understand the mechanisms by which intestinal PC availability regulates dietary lipid handling. I hypothesize that increasing dietary lipids exacerbates fatty acid malabsorption in iCTα$^{-/-}$ mice.
Methods: To determine whether increased dietary lipids impact the lipid malabsorption phenotype, control and iCTα$^{-\backslash-}$ mice were fed diets with increasing lipid content (4, 20, 40 or 60 % fat/calorie). Plasma and tissues were collected for analysis. To determine if reduced lipid absorption is influenced by *in vivo* effects, such as hormonal regulation, intestines from control and iCTα$^{-\backslash-}$ mice were isolated, everted and segmented. The intestinal sacs were then incubated in a buffer containing radiolabelled oleic acid and choline. Intestinal sacs and serous buffer were collected for analysis.
Results: Preliminary data from the mouse diet study show reduced intestinal PC levels regardless of lipid content, while plasma triglyceride (TG) levels were reduced only in iCTα$^{-\backslash-}$ mice fed a 60 % HFD. Preliminary data from tissue culture show reduced radiolabelled PC, PE and TG. These results indicate that iCTα$^{-\backslash-}$ mice have reduced PC synthesis and impaired fatty acid absorption.
Conclusion: In conclusion, dietary lipids may be responsible for some of the observed phenotype in iCTα$^{-\backslash-}$ mice, but not all. As well, intestines isolated from iCTα$^{-\backslash-}$ mice appear to maintain lipid malabsorption, even in the absence of *in vivo* influences. Further research will need to be conducted to fully understand the role of PC in lipid metabolism.
Keywords: Phosphatidylcholine, lipid regulation, small intestine

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VITAMIN D MAY BE AN IMPORTANT ENDOGENOUS PARTIAL AGONIST OF TRPV1 AND MAY PLAY A CRITICAL ROLE IN TYPE 1 DIABETES.

Wentong Long[1,2], Mohammad Fatehi[1,2], Rashmi Panigrahi[3], Shubham Soni[1,2], Rees Kelly[4], Brett Boonen[5], Koenraad Philippaert[1,2], Amy Barr[1,2], Dominic Golec[1,2], Scott Campbell[1,2], Yi Yu[1,2], Morganne Held[1], Katarina Ondrusova[1,2], Matt Hubert[1,2], M. Joanne Lemieux[3], Troy Baldwin[4], Peter Light[1,2]

[1.]Department of Pharmacology, Faculty of Medicine & Dentistry. [2]. Alberta Diabetes Institute. [3.]Department of Physiology, Membrane Protein Disease Research Group. [4.]Medical Microbiology & Immunology, Faculty of Medicine & Dentistry, University of Alberta, Edmonton, Canada. [5.] Katholieke Universiteit Leuven.

Background: Type 1 Diabetes (T1D) results in the immune destruction of β-cells. Recent studies suggest supplementation of vitamin D along can significantly improve patients' β-cell function and glycemic control possibly by dampening naïve T-cell activation. However, most of these studies are observational, and the underlying cellular mechanism for this effect has not been elucidated completely, especially as naïve T-cells possess absent or very low VDR expression. Therefore, the effects of Vitamin D on naïve T-cells may involve a VDR-independent pathway. Interestingly, TRPV1 channel activation is necessary for naïve T-cell activation. Our initial data show that Vitamin D (25OHD) can partially activate TRPV1 and can inhibit capsaicin induced TRPV1 activity. We propose that vitamin D is a partial agonist of TRPV1, through direct binding to TRPV1 and modulating naïve T-cell activation.
Methods: TRPV1 over-expressing HEK cells; mouse $CD4^+$ T-Cells; mouse TRG; Single channel and whole cell patch clamp; calcium imaging; flow cytometry; *in-silico* modeling and docking.
Results: Interestingly, our single channel recordings indicate that, at physiologically concentration, 100 nM 25OHD increases hTRPV1 open probability yet antagonizes the stimulatory effects of capsaicin, which suggest that 25OHD is a partial agonist of TRPV1. Additionally, our electrophysiological data demonstrates that both the 25OHD and 1,25OHD can inhibit capsaicin, but not pH, stimulated TRPV1 activities, suggesting the lipophilic 25- and 1,25OHD interact with hTRPV1 in the same binding sites as capsaicin. Previous studies show that phosphorylation of hTRPV1 through PKC augments capsaicin
-mediated TRPV1 activation. Our experiments reveal that 25OHD opposes this PKC effect. *In silico* modeling and docking of 25OHD to the TRPV1 structure indicates that 25OHD binds to hTRPV1 in the upper region of the vanilloid binding pocket as capsaicin and capsazepine, supporting the concept that vitamin D binds directly to TRPV1 channels. Moreover, activation of CD4+ naïve T-cells is reduced by 25OHD in a VDR-independent manner.
Conclusion: These novel findings provide evidence that vitamin D is a partial agonist of TRPV1, and vitamin D binds to TRPV1 in the same vanilloid binding pocket as capsaicin but with a different configuration. These discoveries advance our knowledge of the underlying cellular mechanism by which vitamin D may beneficially reduce naive T-cell activation in autoimmune diseases such as T1D.
Key words: Vitamin D, TRPV1, Type 1 diabetes

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EGG-PHOSPHATIDYLCHOLINE IMPROVES OBESITY-RELATED IMMUNE DYSFUNCTION

Wollin B[1], Veida-Silva H[1], Juarez-Platas M[1], Azarcoya-Barrera J[1], McDougall C[1], Goruk S[1], Richard C[1]
[1]Department of Agricultural, Food & Nutritional Science, Faculty of ALES, University of Alberta

Background: Low-grade systemic inflammation and immune dysfunction are common features of many chronic diseases, including obesity and type 2 diabetes. In rodents, consuming a high fat diet has been shown to decrease T-cell function, potentially through the generation of a pro-inflammatory environment and increased gut permeability. Choline is an essential nutrient required for several biological processes including immune system development. Previous data from our group has shown that phosphatidylcholine (PC), a form of choline, improves the T-cell response early in life. The objective of this study was to determine if PC can improve the immune dysfunction associated with a high fat diet in rats.
Methods: At 4 weeks of age, male Wistar rats were randomized to consume one of three nutritionally complete diets: 1- free choline low-fat (control), 2- free choline high-fat (FCHF), and 3- PC high-fat (PCHF). The diets differed in the form of choline but contained equal amounts of total choline. At 13 weeks of age, rats were terminated and immune cells were isolated from spleens. *Ex vivo* cytokine production after stimulation with mitogens, phorbol 12-myristate 13-acetate plus ionomycin (PMA+I) and pokeweed, was measured by ELISA to determine immune cell function. Immune cell subsets were determined by flow cytometry.
Results: Despite no significant change in body weight among diet groups, rats fed the FCHF diet had a lower production of IL-2 (a marker of proliferation) and TNF-α by splenocytes stimulated with PMA+I (a T cell mitogen) compared to rats fed the control diet (both $P< 0.05$). Feeding a FCHF diet led to a higher production of IL-1B and IL-6 by pokeweed-stimulated splenocytes compared to the control diet (both $P< 0.05$). No change was observed in cytokine production after PMA+I or pokeweed stimulation between the PCHF and control diet. Rats fed the FCHF and the PCHF diet tended to have a higher and lower proportion of helper T cells expressing the CTLA-4 (CD4+CD152+ cells), respectively, compared to the control diet ($P=0.059$).
Conclusion: We demonstrated that adding PC to a high-fat diet normalizes both T and B cell responses after immune challenge. PC seems to increase T cell proliferation which can be partly explained by the lower expression of CD152 that inhibits T cell responses. PC also lowers the pro-inflammatory response of antigen-presenting cells to a mitogen. Altogether, our findings suggest that PC counteracts some aspects of obesity-related immune dysfunction.
Key words: Immunology, phosphatidylcholine, high-fat diet, inflammation

IN VIVO EXPANSION OF REGULATORY T-CELLS IN ISLET TRANSPLANTATION: THE ROLE OF TUMOR NECROSIS FACTOR SUPERFAMILY RECEPTOR 25 (TNFRSF25)

Jake Szeto, Braulio A. Marfil-Garza, Sirtaj Jhutty, Mark Farinas, Zhe Fan, Sofia Varelas, Rena Pawlick, A.M. James Shapiro
Department of Surgery, Faculty of Medicine and Dentistry, University of Alberta

Background: Islet transplantation is an effective treatment for patients with type 1 diabetes complicated with severe hypoglycemia and hypoglycemia unawareness. One major limitation is the need for lifelong immunosuppression to prevent immune rejection. Regulatory T-cells (Tregs) are a subset of CD4+ T cells that regulate or suppress other cells in the immune system. Current evidence suggests Treg expansion promotes immunological tolerance to allogeneic grafts by modulating effector T-cell responses. Tregs intrinsically express TNFRSF25, whose stimulation using agonistic antibodies has been shown to expand Treg numbers in vitro and in vivo. Herein, we test a novel agonistic anti-TNFRSF25 antibody. Our objective is to assess whether this antibody increases Treg numbers in vivo and if this increase leads to improved outcomes and immunological tolerance in a murine allogeneic islet transplantation model.
Methods: In a C57BL/6 mouse model, three treatments were injected intraperitoneally: 1) Control (0.9% NaCl, n=2), 2) anti-TNFRSF25 (10 mg/kg, n=2), and 3) streptozotocin (STZ) (175 mg/kg, n=2). Baseline whole blood flow cytometry was performed prior to each treatment, and daily thereafter for ten days. Treg percentage (defined as CD3+ CD4+ FoxP3+ cells) from CD3+ CD4+ cells (CD4+ T cells) was measured over time. To assess synergy between drugs, control mice were then treated with both STZ and anti-TNFRSF25.
Results: While the number of Tregs in the control group did not change significantly over time, both STZ and anti-TNFRSF25 administration significantly increased Treg numbers with peaks at day 4 and 6, respectively. The anti-TNFRSF25 group showed a higher Treg percentage (29.1%) at peak levels as compared to control (16.6%) and STZ-treated mice (23.9%) (repeated measures one-way ANOVA, p=0.004). No changes in CD4+ and CD4- T cells were observed with any treatment, suggesting the effect is specific to the Treg population. Combined STZ/anti-TNFRSF25 treatment followed a similar pattern, albeit with slightly higher Treg numbers as compared to both STZ and anti-TNFRSF25 treatments alone (p=ns).
Conclusion: Administration of anti-TNFRSF25 agonist effectively increases Treg numbers in vivo and its effect is specific to this cell population. Co-administration of STZ does not abrogate the effect of anti-TNFRSF25. Treg expansion has the potential to mitigate immune rejection and promote immunological tolerance in islet transplantation. We are increasing our sample size to corroborate our preliminary findings and will further complement with transplant studies in a mouse allograft model.

Keywords: Islet transplantation, Regulatory T-cells, Type 1 diabetes, Tumor necrosis factor, Lymphocytes.

GLUCOREGULATORY EFFECTS OF HYPOTHALAMIC GLUCOCORTICOID ACTION *IN VIVO*

Emilie Beaulieu-Bayne, Miguel Cardoso, Hyejun Kim, Shuling Yang, Jessica T.Y. Yue
University of Alberta, Edmonton, AB, Canada

Background: Diabetes is characterized by dysregulated glucose homeostasis that leads to hyperglycemia, due in part to increased hepatic glucose production (GP) and insulin resistance. Excessive levels and/or action of glucocorticoids (GCs) are associated with obesity, insulin resistance, and hyperglycemia. We aim to delineate a mechanism of GC action in the mediobasal hypothalamus (MBH) that modulates GP in normal and pre-obese rodents.

Methods: Male SD rats underwent stereotaxic MBH bilateral cannulation and intravenous (iv) and intraarterial catheterization to enable simultaneous direct infusions into the MBH, iv infusions, and blood sampling, respectively. Mildly hyperinsulinemic-euglycemic clamps with tracer dilution methodology combined with MBH GC infusion ± GC receptor (GR) inhibition enables measurement of GP and utilization while assessing MBH GC interaction with its MBH receptors independent of changes in plasma insulin, glucagon, and glucose levels.

Results: MBH GC infusion potently stimulates GP and lowers the requirement for exogenous glucose infusion without altering glucose utilization. This effect is mediated via GRs since co-infusion of GR antagonist mifepristone, or a HSP90 inhibitor, negates the ability of MBH GCs to increase GP. MBH GCs similarly increased glucose excursions during iv glucose tolerance tests, which was reversed with concomitant MBH mifepristone infusion. Rats fed with high fat diet (HFD) for 3 days had altered glucose kinetics and increased basal plasma corticosterone, insulin, and blood glucose levels without changes in body weight. Chronic MBH GR inhibition with MBH GR shRNA lowered GP compared to MBH mismatch control HFD rats with MBH vehicle infusions, suggesting that blocking excessive MBH GC action resulting from HFD-feeding attenuates GP to improve glucose homeostasis.

Conclusion: We provide novel evidence that MBH GC action modulates GP in healthy and pre-obese rats. Importantly, targeted inhibition of MBH GC action may help improve glucose regulation in obesity-related metabolic disease.

Acknowledgements: This work is supported by Diabetes Canada and NSERC. EBB is supported by CIHR CGS-M. JTYY is supported by a Diabetes Canada Scholar Award.

Key words: Metabolism, Diabetes, Glucocorticoids, Mediobasal Hypothalamus

ROLE OF ENDOTHELIAL CD36 FATTY ACID UPTAKE: -

Linnet Immaraj, Maria Febbraio

Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta

Background: Hyperlipidemia from over-nutrition leads to increased levels of plasma fatty acids (FA) and modified lipoprotein ligands, which trigger endothelial cell-proinflammatory and oxidative stress pathways. Our hypothesis is that CD36, as a major EC receptor for these pro-inflammatory ligands and FA, contributes to the development of dysfunctional EC directly. Dysfunctional endothelium, critical in atherosclerosis initiation, is also a hallmark of insulin resistance.

Methods: EC CD36 knockout (CD36°) mice were created using flox/flox CD36 mice created in our lab and tie2e cre mice, which targets endothelium while sparing bone marrow, a common issue with other EC-targeting cre mice. To compare metabolic and fatty acid related parameters, we performed IP glucose tolerance testing, insulin tolerance testing, lipoprotein analyses, and whole-body composition analysis using dual-energy x-ray absorptiometry (DXA) system (UltraFocus^{DXA} by Faxitron).

Results: EC CD36° mice showed significantly lower blood glucose levels compared with controls ($p<0.05$). Age matched male mice showed significantly lower body weight and decreased glucose levels after overnight fast ($p= 0.0297$). Both male and female EC CD36° mice had a decrease in total cholesterol and an increase in triglycerides (TG), with significant differences in the distribution of cholesterol and TG across the lipoprotein pools. Body composition analysis showed that EC CD36° exhibited significant decreased bone mineral density (male, $p= 0.0025$; female, $p < 0.0001$) and bone mineral content (male, $p < 0.0001$; female, $p= 0.0170$) compared to controls. Age matched male and female EC CD36° mice also showed significantly lower body weight by DXA analysis (male, $p= 0.0070$; female, $p= 0.0479$).

Conclusion: Our data suggest that in EC CD36° mice, metabolic and fatty acid related parameters exhibit significant differences compared to control mice. It has been established that CD36 deficient mice exhibit low bone mass phenotype however, it was surprising to observe this effect in EC CD36°.

Keywords: EC CD36. Fatty acid uptake. Glucose. Insulin. DXA.

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DIABETES AND OBESITY IN VULNERABLE ETHNOCULTURAL COMMUNITIES: IDENTIFYING CARE GAPS THROUGH A PARTICIPATORY, MULTIDISCIPLINARY LENS

Nicole N. Ofosu[1], Thea Luig[1, 2], Yvonne Chiu[6], Roseanne O. Yeung[5, 3], Karen K. Lee[4], Denise Campbell-Scherer[1, 2, 5]
[1]Department of Family Medicine, [2]Physician Learning Program, [3]Division of Endocrinology & Metabolism, [4]Division of Preventive Medicine, Faculty of Medicine & Dentistry, University of Alberta | [5]Alberta Diabetes Institute | [6]Multicultural Health Brokers Cooperative

Background: Ethnocultural newcomer communities to Canada experience dramatic increases in diabetes, obesity and related diseases. Addressing clinical and social determinants of health for diabetes and obesity prevention and management is important because of the disproportionate burden of poverty, immigration-related stresses, and deteriorating health they face. Consequently, developing contextually appropriate interventions is a complex problem, requiring deep understanding of their unique situation and context. Building on the previous work of the 5AsT Research Program and our broad stakeholder engagement, our project seeks to understand care and service gaps from a multidisciplinary lens. We aim to explore how to work together with people with lived experience and communities to develop sustainable solutions to improve diabetes and obesity care for these ethnoculturally diverse and vulnerable populations.
Methods: A multi-method, collaborative, participatory approach involving partnerships with the Multicultural Health Brokers (MCHB) Cooperative and Edmonton Southside Primary Care Network. We are working with a community advisory group to guide the research process and building a coalition of stakeholders across different sectors to explore implications for policy and practice.
Results: We co-created an 18-month research project to generate insights to support diabetes and obesity care in vulnerable ethnocultural populations. The project has successfully secured funding from the Novo Nordisk Alberta Diabetes Fund. We are collecting and integrating the following: 1) Population data (demographic, clinical, material and social deprivation data); 2) Qualitative data (community members, MCHB, and primary care provider data); and 3) Community resources and built environment data. Our outputs will include: a) Prototype of an individual physician dashboard; b)Culturally appropriate, clinically relevant extension of the 5AsT intervention; c) Map of existing and missing resources in the built environment; and d) Resource kit for healthcare and community resources for primary care providers' use.
Conclusions: Our coalition and outputs will build the foundation for next-phase intervention development, implementation, and scaling-up.
Key words: vulnerable immigrant population, primary care, diabetes, obesity, participatory

THE EFFECTS OF EARLY LIFE AMOXICILLIN EXPOSURE IN PIGLETS ON PANCREATIC ISLET DEVELOPMENT

Steven Qiu, Carla Sosa Alvarado, Benjamin P. Willing, Catherine B. Chan

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

Background: Amoxicillin is a pediatric broad-spectrum antibiotic which has well-documented efficacy and side effects like its impact on the gut microbiota. In human infants, many studies have associated early life antibiotics treatments with an increased risk of developing metabolic disorders such as diabetes and obesity in later childhood. Previously, we used an amoxicillin-treated neonatal piglet model to study microbiome-related effects on islet morphology and insulin secretion. We found that while gut microbiome composition changes were transient, changes in pancreatic islet function, morphology and development remained detectable at post-natal day (PND) 14, 21 and 49. Supporting findings in the previous human studies, piglets also had a decrease in glucose tolerance at PND 49 that was normalized by PND 77 suggesting an increased susceptibility to metabolic disorders during this period. These results suggest an important role for the neonatal gut microbiome in normal, healthy pancreatic islet development. Hence, we seek to elucidate amoxicillin's effects on pancreatic growth by studying the morphology, proliferation and apoptosis of different pancreatic cell types at PND 7 when microbiome changes induced by antibiotics are most profound.

Methods: Piglets were orally administered amoxicillin (30mg/kg/day) or a placebo twice daily from birth until they were euthanized at PND 7 for sample collection (n=7 per group). Pancreatic tissue samples were fixed, dewaxed and rehydrated before immunostaining was carried out. Slides were stained using anti-Ki67 antibodies to detect proliferation, or a TUNEL assay for apoptosis. The slides were then double stained with anti-insulin or glucagon antibodies to detect β or α-cells respectively, then mounted with ProLong Gold Antifade Mount with DAPI. Stained slides were tile-scanned and analyzed to generate measures of β- and α-cell area, β- and α-cell proliferation and apoptosis and other parameters. The results were then analyzed using unpaired t-tests with $\alpha = 0.05$.

Results: While amoxicillin treated piglets had higher overall pancreatic (predominantly acinar cell) apoptosis rates (difference of 1.88±0.83 in %TUNEL-positive cells out of total cells, p=0.043, n=7 pairs), neither proliferation nor apoptosis of β- or α-cells were significantly different. Furthermore, β-cell, α-cell, β/α-cell ratio and estimated total islet mass were not significantly different between the treatment and control group.

Conclusion: Early life administration of amoxicillin to piglets appears increase the apoptosis rate of non-β and non-α-cells but the proliferation and apoptosis rates of islet cells do not seem to be affected. Islet morphology as indicated by β- and α-cell mass also appear to be unaltered by amoxicillin treatment at PND 7. This suggests that the effects of amoxicillin-induced microbiome disturbances on pancreatic islets could be mediated through changes in acinar or ductal cells and may not yet be detectable at PND7.

Keywords: Antibiotics, pancreas, β-cells, α-cells, proliferation, apoptosis, immunostaining

ANGIOTENSIN-CONVERTING ENZYME 2 KNOCKOUT LEADS TO WORSENED CARDIOVASCULAR FUNCTION IN DIABETIC MICE

Mahmoud Gheblawi[1], Ratnadeep Basu[2], Wang Wang[2], Jessica Desaulniers[2], Faqi Wang[2],Cory Wagg[2], Gary Lopaschuk[2], Zamaneh Kassiri[1], Gavin Y. Oudit[1,2]

[1]Department of Physiology,[2]Department of Medicine, Faculty of Medicine and Dentistry

Background: In diabetic individuals, the renin-angiotensin system (RAS) is chronically upregulated, generating excessive amounts of angiotensin II (Ang II). Sustained Ang II release promotes cardiovascular remodeling and endothelial cell damage. Resulting vascular endothelial dysfunction leads to inflammation, insulin resistance, and metabolic imbalances. A therapeutically promising member of the RAS, angiotensin-converting enzyme 2 (ACE2), degrades Ang II into angiotensin 1-7 (Ang 1-7), acting as a negative regulator of the RAS. Ang 1-7 further activates its own therapeutic pathways through the Mas receptor restoring cardiovascular function and endothelial integrity. We aim to show that ACE2 knockout furthers diabetic cardiovascular dysfunction and that ACE2 therapy can alleviate these adverse cardiovascular effects.

Methods: WT, ACE2KO, *db/db*, and *db/db* ACE2KO double mutant mice were evaluated at six months of age, with a subset of *db/db* mice receiving rmACE2 either subcutaneously or via adeno-associated virus-9 (AAV9) gene therapy. The diabetic phenotype was assessed through EchoMRI analysis of body composition, glycated hemoglobin quantification, oral glucose tolerance tests, and urinary creatinine to albumin level quantifications. Cardiac structure and function were examined through transthoracic echocardiography and catheter conductance pressure-volume loops. Vascular endothelial cell function was assessed through femoral artery flow-mediated dilation response in addition to wire myography isovolumetric contractility of the 3rd order mesenteric artery.

Results: Preliminary results indicate that ACE2KO further exacerbates the diabetic cardiovascular phenotype with worsened diastolic function and advanced endothelial dysfunction. Administration of ACE2 attenuates the development of diabetic cardiomyopathy and results in improvement of vascular function.

Conclusions: These results provide a novel insight into the role ACE2 plays in the prevention of diabetic cardiovascular complications and hopefully translate into future personalized treatment.

Keywords: renin-angiotensin system, HFpEF, hypertension, insulin resistance

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THE ASSOCIATION OF EXERCISE BLOOD GLCUOSE ON POST-EXERCISE HYPOGLYCEMIA IN TYPE 1 DIABETES

Heather Hinz, Carla Prado, Normand Boulé, Jane Yardley

Faculty of Kinesiology, Sport, and Recreation, University of Alberta

Background: Exercise is recommended for everyone, including people with type 1 diabetes (T1D). In addition to barriers encountered by people who do not have T1D (e.g., work pressures, time, and weather), people with T1D also contend with a fear of hypoglycemia. This includes fear of overnight hypoglycemia, which can be fatal. A recently published consensus on exercise for people with T1D recommends starting exercise with glucose between 8.0-10.0 mmol/L. Some people with T1D start exercise at a higher blood glucose as a strategy to reduce the risk of hypoglycemia. Currently it is unknown if exercise at different glucose concentrations has different effects on glucose over the subsequent 12 hours.

Methods: 11 recreationally active participants with T1D (3 male and 8 female) completed the study. After a graded exercise test to volitional exhaustion, 60% of the peak rate of oxygen consumption was calculated for the exercise sessions. Participants were randomized to either start with blood glucose between 8.0-10.0 mmol/L (MOD) or 12.0-14.0 mmol/L (HI). All participants had a continuous glucose monitoring (CGM) sensor inserted 24 hours before the first exercise session. Both exercise sessions took place before dinner, with at least 72 hours between sessions. During each session, participants cycled for 45 minutes at 60% of their peak oxygen consumption. Capillary blood glucose was monitored throughout. We then analyzed the CGM data in two periods: between 6:00 pm and 12:00 am, and between 12:00 am and 6:00 am.

Results: The average blood glucose during exercise was 8.3 mmol/L in MOD and 11.9 mmol/L in HI ($p=.00003$). However, blood glucose immediately post exercise was no longer different between conditions ($p=.10$). When looking at both post-exercise time periods, there was no overall difference between HI and MOD conditions in time spent in hyperglycemia ($p=.129$) or euglycemia ($p=.095$). The time spent in hypoglycemia after both sessions was 1%.

Conclusion: There is no difference in respect to post exercise hypoglycemia between the MOD and HI conditions.

Keywords: type 1 diabetes, exercise, glucose

SUPPLEMENTATION OF ARACHIDONIC ACID AND DOCOSAHEXAENOIC ACID DURING SUCKLING PERIOD AFFECTS SPLENOCYTE FUNCTION OF EX-VIVO CYTOKINE PRODUCTION IN BROWN NORWAY RAT OFFSPRING AT WEANING

Dhruvesh Patel, Susan Goruk, Caroline Richard and Catherine J. Field Department of Agricultural, Food and Nutritional Science, Faculty of Agricultural, Life and Environmental Sciences, University of Alberta

Background: The immune system is immature at birth and long chain polyunsaturated fatty acids (LCPUFA) plays an important role in its development. In healthy rodent models, we have shown that docosahexaenoic acid (DHA, an omega (n)-3 LCPUFA) with arachidonic acid (ARA) supplementation in the suckling and/or weaning diet have a beneficial programming effect on immune cell function later in life in healthy rodents. We aimed to determine the programming effect of supplementing the maternal diet with DHA and ARA during suckling on the immune system development in the offspring, later in life, using allergy sensitive rodent model.
Methods: Pregnant Brown Norway rats were randomized to consume nutritionally adequate high fat diets; ARA+DHA diet (0.8%DHA and 0.4%ARA of total fat, n=20) or control diet (0%DHA and ARA of total fat, n=16) from 5 days before parturition to the end of 3-week suckling period. During weaning, the pups were then fed the control diet for additional 5 weeks. At 8-weeks of age, all the pups were euthanized, spleens were collected and splenocytes isolated for lipid analysis and *ex-vivo* stimulation with or without phorbol myristate acetate +ionomycin (PMAi), lipopolysaccharide (LPS) or the food protein, ovalbumin (Ova) for 72 hours. Cytokines were measured in the supernatant by ELISA.
Results: There were no differences in food intake, bodyweight, and liver weight, however, spleen weight tended to be higher ($p=0.06$) in ARA+DHA group compared to control group pups. In splenocytes incubated without mitogen, TNFα production was higher in ARA+DHA group ($p<0.06$) than control group. Splenocytes from ARA+DHA group produced the same amount of IL-2, IL-10 and TNFA-α but more IL-6 (30%) and less IL-10 ($p<0.02$) after stimulation with PMAi and LPS, respectively. Similarly, Ova-stimulated splenocytes produced less IL-10 ($p=0.02$) in ARA+DHA group vs. control. Feeding the maternal diet supplemented with ARA+DHA during suckling period resulted in a lower fatty acid composition of n6 LCPUFA such as, ARA, 22:4n6 and 22:5n6 in splenocyte phospholipid than control group at 8-weeks. No differences were observed at 8 weeks in n3 LCPUFA (EPA, DPA or DHA) in splenocytes.
Conclusion: Supplementing the maternal diet with ARA+DHA during suckling period had a programming effect on the ability of splenocytes to respond to T cell mitogens, a bacterial antigen and a food protein that might be due to a lower content of n6 LCPUFA in the membrane.

Keywords: Arachidonic acid; Docosahexaenoic acid; Immune system development

MEMBRANE EXCITABILITY OF HUMAN ISLET CELLS WITH DISTINCT HETEROGENEITY MARKER EXPRESSION

Birbickram Roy**,** Austin Bautista, Patrick E MacDonald

Department of Pharmacology, University of Alberta, Edmonton, AB

Background: Pancreatic α and β-cells regulate blood glucose level by releasing glucagon and insulin, respectively, a process disrupted in diabetes. These electrically excitable cells are functionally heterogeneous, and much attention has been devoted to identify the underlying electrophysiological, metabolic, and transcriptomic diversity using animal models, and to a lesser extent, human cells. We recently reported data using linked electrophysiological profiling and single-cell RNA sequencing (patch-seq) in human islet cells that showed, among other things, heterogeneity of Na+ channel currents amongst sub-populations of α and β cells. This suggests that islet cell sub-populations differ in their inherent excitability, although this was not tested directly. We are now directly investigating excitability and action potential firing of single human islet cells coupled with a single-cell RT-qPCR panel for twelve genes to identify cell-types and sub-populations.

Methods: Islets were isolated from human pancreas and dispersed into single cells for whole-cell patch clamp measurement of membrane properties. 150 μm thick pancreas slices were prepared from the tail region of human donor pancreata using a vibratome. Electrophysiological assessment was performed using a patch pipette solution containing (in mM): 115 K-gluconate, 15 KCl, 10 NaCl, 10 EGTA, 10 HEPES and 3 mM MgATP (pH 7.2 with KOH). The extracellular bath contained (in mM): 140 NaCl, 3.6 KCl, 1 MgCl2, 1.5 CaCl2, 0.5 NaH2PO4, 5 NaHCO3, 10 glucose and 10 HEPES (pH 7.4 with NaOH). Following electrophysiological measurement, single-cells were collected into lysis buffer, and cDNA synthesis, preamplification, and qPCR was performed using a commercial kit and validated assays.

Results: Our preliminary results validate the heterogeneous expression of markers such as *RBP4* and *LOXL4* in human dispersed and -cells, respectively. We also confirm that these cell types exhibit distinct resting and active membrane properties, with -cells firing action potentials at a higher frequency compared with -cells, and demonstrate considerable heterogeneity in resting membrane potential, action potential amplitude, and other parameters within each cell type. Finally, while this demonstrates differential excitability amongst islet cells with differing molecular profiles, we also show that our experimental approach is applicable in adult human pancreatic slices, allowing electrophysiological characterization of islet cells in their native microenvironment and mapping of functions to known transcriptomic markers.

Conclusion: Human islet cells display great variability in membrane excitability properties.

Keywords: islet cell excitability, electrophysiology, functional heterogeneity, marker expression

DIFFERENCES IN 'NATURAL' AND 'INDUCED' ABO ANTIBODY IN FEMALE *VS.* MALE WILD-TYPE MICE

Bushra Anjum[1], Ibrahim Adam[2,3], Jordana Fersovich[1], Maurits Sulzer[1], Jean Pearcey[1,3,4], Kesheng Tao[1,3,4], Bruce Motyka[1,3,4] and Lori J. West[1-5]
[1]Dept. Pediatrics; [2]Dept. Medical Microbiology & Immunology; [3]Alberta Transplant Institute; [4]Canadian Donation & Transplantation Research Program; [5]Depts. Surgery and Laboratory Medicine & Pathology; University of Alberta

Background: ABO histo-blood group incompatibility is a barrier in solid organ transplant due to the presence of `natural' preformed ABO antibodies (Ab). However, ABO-incompatible (ABOi) heart transplantation is successful in infants as ABO Ab are low/absent. A better understanding of the specificity of natural ABO Ab and how they are produced may allow for successful ABOi transplantation at older ages. To study ABO Ab development and ABOi transplantation we developed a mouse model and showed that ABO Ab develop naturally with age and can be `induced' following sensitization (eg, with human A/B erythrocytes) in wild-type (WT) mice. Herein, we sought to determine the isotype (IgM/IgG) and subtype (I-VI) specificity of ABO Ab produced naturally or induced by sensitization as a function of age and sex in WT mice.

Methods: WT BALB/c mice were assessed for natural ABO Ab production over time (n=32/39, female/male; age 1-18 months), or challenged with human A erythrocytes (5 weekly intraperitoneal injection) beginning at 5 weeks of age to measure induced ABO Ab (n=13/8, female/male; age 1-3 months). Blood samples were collected by tail bleed and plasma ABO Ab titre and ABO Ab isotype and subtype specificity determined by hemagglutination assay and ABH glycan microarray, respectively.

Results: Female mice produced markedly higher natural anti-A and anti-B ABO Ab compared with male mice. With age, natural ABO Ab shifted from an IgM to IgG isotype in females but remained predominantly IgM in males. Most natural ABO Ab was specific to subtypes III/IV with specificity to subtype II absent or very low. In contrast, following A-antigen sensitization both female and male mice produced IgM and IgG anti-A Ab with specificities for all subtypes (I-VI).

Conclusion: Male and female mice show distinct differences in ABO Ab production depending on whether ABO Ab are produced naturally or induced by sensitization. It will be important to explore mechanisms for these sex differences and relevance to ABOi transplantation in humans.
Keywords: ABO histo-blood group antigens, ABO antibodies, sex differences

THE ROLE OF CADHERINS IN THE DEVELOPMENT OF NEONATAL PIG ISLETS POST TRANSPLANTATION

Seanna Menard, Kaja Matovinovic, Wenlong Huang, Ashley Tuttle-Farkas, Gina R. Rayat Department of Surgery, Faculty of Medicine and Dentistry, University of Alberta

Background: Type 1 Diabetes Mellitus is a disease in which the islet beta cells in the pancreas are destroyed, resulting in hyperglycemia. Xenotransplantation of neonatal pig islets is a potential method of treatment. Single islet cells in neonatal pigs are observed to be scattered throughout the pancreas, however as the cells mature it is found that they migrate to form a clustered structure. This migration may be contributed to the roles of certain types of cell adhesion molecules (CAMs) called cadherins. Cadherins are thought to maintain and control cell-cell interactions by mediating aggregation of endocrine cells, and this is required for the typical cell organization of islets. The roles of cadherins have not been extensively studied in pig islets until now.

Methods: Neonatal pig islets from varying ages of pigs are isolated and transplanted under the kidney capsule of immune-deficient B6 rag-/- mice. Blood glucose levels are monitored weekly and the mice were euthanized at 4 time points: 1, 30, 50, and 200 days post islet transplantation. The kidney grafts were harvested following euthanization. These tissues were processed, sectioned and were then stained following immunohistochemistry staining protocols using antibodies to islet precursor cells, endocrine hormones, neurons, and the cadherins, in order to identify the amount and the types of cadherins at these time points.

Results: At 1, 30, and 50 days ptx all mice remained diabetic although as time went on their blood glucose levels slowly decreased. At 126 days ptx, most mice were achieving normal glycemia. These mice were able to lower their BGL during a glucose tolerance test. At 1 day ptx insulin, glucagon, and somatostatin positive cells were observed to be randomly scattered across grafts; however, by 50 days ptx these cells formed clustered structures.VE-cadherin as well as CK7 was less present as islets mature. VE-cadherin was also less present in grafts originating from older pigs. By 50 days ptx, E-cadherin was observed to be in the same area as endocrine cells (alpha, beta, and delta islet cells). PGP 9.5 was found in the same location as endocrine cells with the most intense staining at 30 days ptx

Conclusions: After cell migration, an increased production of insulin and glucagon and a decreased expression of VE-cadherin and CK7 occurs, indicating that by the final time point VE-cadherin and CK7 may not be required to the extent they were in the earlier time points. PGP9.5 is present where endocrine cells are. Expression of E-cadherin increases over time, with the most amount of staining at 50 days post- transplant, which leads us to believe that E-cadherin may play a role in the development of the islet and is important in the maintenance of the islet structure and functioning.

Keywords: islet transplantation, neonatal pig islets, cadherin, and diabetes

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Title: BARRIERS TO ACCESSING DIABETES CARE FOR VULNERABLE URBAN POPULATIONS: OPPORTUNITIES FOR IMPROVING PATIENT EXPERIENCES

Julie A Saby, Kate Kerber, Fariba Kolahdooz, Jane de Pauw, Se Lim Jang, Meeka Otway, Melinda Laboucan, Kinley Dyce, Yashar Rahimogliturk, Sangita Sharma
Indigenous and Global Health Research Group, Department of Medicine, Faculty of Medicine & Dentistry, University of Alberta

Background: Approximately 3 million Canadians live with diabetes. Effective diabetes management requires frequent, repeated interactions with the healthcare system to prevent significant complications. However, individuals who face challenges within the healthcare system, such as patients within a vulnerable population, may encounter additional barriers to diabetes management.
Methods: Baseline data collection for The CARE Project, a large 5-year, mixed-methods intervention study funded by the Royal Alexandra Hospital Foundation, involved 392 one-on-one interviews with adults in Edmonton accessing services at community organizations: two drop-in services, one shelter, one medical travel boarding home, and one hospital emergency department. A survey collected information on demographic characteristics, health status, and perceived unmet need for care. Open-ended questions were asked about barriers to accessing health care services, and opportunities for improvement. Data were entered on a tablet using REDCap version 8.1.1, and analyzed using SAS version 9.4, and NVivo Pro version 12. A subanalysis of the initial data was undertaken to look at 49 participants (13%) who self-reported a diagnosis of Type 1 or Type 2 Diabetes Mellitus to look at the access to care and experiences with chronic disease management.
Results: Respondents ranged in age from 24 to 78 years. Nearly half (47%) self-identified as Indigenous. Housing instability was reported by 36% of participants residing in Edmonton. 27% of respondents reported moderate to severe food insecurity in the past month. 78% reported more than one existing health condition in addition to diabetes, with an average of 6 prescription medications per respondent. Perceived unmet need for care was reported by 69% of respondents, meaning there was at least one healthcare service the respondent wanted to access but could not. Four main themes impacting healthcare access and experience for respondents with diabetes were identified, including: communication with and between healthcare providers, respect and caring, time limitations within the healthcare system, and financial/socioeconomic barriers.
Conclusions: General population studies on healthcare access for patients with diabetes may not be sufficient for understanding barriers to and opportunities for improving care amongst structurally vulnerable populations with significant co-morbidities and high rates of perceived unmet need for care. There is a need to reduce common access barriers and increase continuity of care between service users, community support services, and healthcare providers, particularly for structurally vulnerable patients with diabetes.
Key Words: Diabetes, healthcare access, needs assessment, perceived unmet needs

EXPRESSION OF ETNPPL, A NOVEL REGULATOR OF HEPATIC LIPID METABOLISM, IS UPREGULATED BY FORSKOLIN

Haresh Sureshkumar, Jelske N. van der Veen, Randal C. Nelson, Kelly-Ann Leonard and Rene L. Jacobs
Group on the Molecular Biology of Lipids, Department of Biochemistry and Department of Agricultural, Food and Nutritional Sciences, University of Alberta

Background- Nonalcoholic fatty liver disease (NAFLD) is a progressive disorder of the liver that arises from an accumulation of fat in the liver not caused by alcohol consumption. The primary cause for the disease is obesity and it affects 75% of individuals who are obese. Preliminary data from our group show that ethanolamine-phosphate phospho-lyase (ETNPPL) is a novel enzyme involved in hepatic lipid metabolism. The biochemical function and transcriptional regulation of EtnPPL, however, has not been elucidated.
Objective- Our objective is to explore the role of ETNPPL in the development of NAFLD and how the expression of ETNPPL is regulated.
Methods- Western type diet-fed mice were injected with AAV to overexpress EtnPPL in the liver and hepatic lipid metabolism was evaluated. Primary hepatocytes and cell lines expressing endogenous ETNPPL were used to investigate the regulation of ETNPPL.
Results- From our in vivo experiments, we found that mice which over-expressed EtnPPL developed NAFLD. After qPCR analysis, we found that genes involved in *de novo* fatty acid synthesis were greatly upregulated. Genes which were upregulated include *Acac1*, *Fas*, *Acly*, and *L-Pk*. This suggests that over-expression of ETNPPL causes an increase in fatty acid synthesis. The mechanism however of this up-regulation is not yet clear. To investigate transcriptional regulation, hepatocytes were treated with several compounds know to be involved in lipid metabolism. Forskolin (FSK) showed a significant up-regulation of EtnPPL. FSK, like glucagon, increases cAMP, suggesting that EtnPPL might be regulated by fasting/feeding.
Conclusion- We demonstrate that hepatic overexpression of ETNPPL results in NAFLD, possibly due to an increase in lipogenesis. Moreover, ETNPPL seems to be regulated by nutritional status and could thus be important for the fasting response in the liver.
Keywords: Liver, lipids, non-alcoholic fatty liver disease, nutritional regulation

FISH OIL AND METFORMIN TO TARGET DYSLIPIDEMIA AND CARDIOMETABOLIC RISK IN HIGH-RISK WOMEN WITH POLYCYSTIC OVARIAN SYNDROME

Olivia Weaver[1], Mahua Ghosh[2], Katerina Maximova[3], Spencer Proctor[1], Donna Vine[1]

1. Metabolic and Cardiovascular Disease Laboratory, Department of Agricultural, Food and Nutritional Science, Faculty ALES
2. Division Endocrinology and Metabolism, Faculty Medicine and Dentistry
3. School of Public Health, University of Alberta.

Background: Polycystic Ovarian Syndrome (PCOS) is an endocrine-metabolic disease that affects up to 18% of women of reproductive age and is highly associated with the metabolic syndrome (MetS): obesity, insulin resistance and dyslipidemia, and increases the risk of early development of Type 2 Diabetes (T2D) and Cardiovascular disease (CVD). Atherogenic dyslipidemia occurs in >70% of women with PCOS and includes high fasting plasma triglycerides (TG), LDL-C, non-HDL-C or ApoB, and low HDL-C. Metformin is commonly prescribed to improve glucose sensitivity in PCOS but has been reported to have limited effects on blood lipids. Furthermore, treatments for dyslipidemia are limited due to safety and efficacy. Fish oil (FO) and Icosapentyl ethyl supplementation have been shown to reduce fasting TG, but the effectiveness of FO in combination with metformin is unknown in conditions of the MetS and PCOS. The aim of this pilot study was to determine the effect of FO in combination with metformin on fasting blood lipids and glucose-insulin indices compared to FO and metformin treatment alone in high-risk women with PCOS.

Methods: Women 18-30 years of age with PCOS (n=30) participated in a randomized clinical trial. Intervention groups included: metformin (Met), FO, or FO+Met treatment for 12 weeks. Inclusion criteria consisted of PCOS diagnosis, BMI >25 kg/m^2, elevated fasting plasma triglycerides, impaired insulin sensitivity and/or diagnoses of T2D. Fasting (overnight fast 16hrs) plasma lipids, insulin, glucose and endocrine hormones were analysed using standard U of Alberta Hospital calorimetric and ELISA protocols. Data was analyzed using ANOVA ($p<0.05$) (GraphPad 8.0).

Results: FO+Met treatment significantly reduced fasting plasma TG from baseline compared to other treatment groups. Met and FO+Met treatment groups tended to reduce LDL-C, and non-HDL-C, as well as blood glucose, fasting insulin and HOMA-IR. However there were no significant effects of treatments on insulin-glucose indices or endocrine hormones.

Conclusion: FO+Met combination treatment significantly reduces fasting plasma TG levels in women with PCOS. A larger and longer-term trial is warranted to determine the efficacy of this treatment to improve plasma TG, apoB-lipoproteins and atherosclerotic CVD risk.

Keywords: PCOS, Metformin, Fish oil, Lipids, Triglyceride

ROLE OF INTESTINAL DE NOVO PHOSPHATIDYLCHOLINE SYNTHESIS IN LIPID METABOLISM

Stephanie Carlin[1] , John Kennelly[1] , Ariel Quiroga[2], Hailey Fedoruk[1] , Kelly-Ann Leonard[1] , Randal Nelson[3], Richard Lehner[2,4] and René Jacobs[1,3]

[1]Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, Alberta, Canada. [2]Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada. [3]Department of Biochemistry, University of Alberta, Edmonton, Alberta, Canada. [4]Department of Cell Biology, University of Alberta, Edmonton, Alberta, Canada

Background: Phosphatidylcholine (PC) is vital for the structural integrity of mammalian membranes and is the primary phospholipid in bile and plasma lipoproteins. In intestinal cells, PC can be synthesized from dietary choline which uses the enzyme CTP:phosphocholine cytidylyltransferase alpha (CTα) to regulate flux. Intestinal PC can also be obtained from luminal supply (dietary and biliary sources). My lab has created an intestinal-specific CTα gene knockout mouse (iCTα -/-), which has reduced de novo PC synthesis. Previous analysis has shown that high fat diet (HFD) fed iCTα -/- mice have reduced postprandial lipid secretion and weight gain. This data shows the importance of intestinal PC synthesis for proper lipid metabolism.

Hypothesis: My objective is to understand the mechanisms by which intestinal PC availability regulates dietary lipid handling. I hypothesize that increasing dietary lipids exacerbates fatty acid malabsorption in iCTα -/- mice. Methods: To determine whether increased dietary lipids impact the lipid malabsorption phenotype, control and iCTα -\- mice were fed diets with increasing lipid content (4, 20, 40 or 60 % fat/calorie). Plasma and tissues were collected for analysis. To determine if reduced lipid absorption is influenced by in vivo effects, such as hormonal regulation, intestines from control and iCTα -\- mice were isolated, everted and segmented. The intestinal sacs were then incubated in a buffer containing radiolabelled oleic acid and choline. Intestinal sacs and serous buffer were collected for analysis.

Results: Preliminary data from the mouse diet study show reduced intestinal PC levels regardless of lipid content, while plasma triglyceride (TG) levels were reduced only in iCTα -\- mice fed a 60 % HFD. Preliminary data from tissue culture show reduced radiolabelled PC, PE and TG. These results indicate that iCTα -\- mice have reduced PC synthesis and impaired fatty acid absorption.

Conclusion: In conclusion, dietary lipids may be responsible for some of the observed phenotype in iCTα -\- mice, but not all. As well, intestines isolated from iCTα -\- mice appear to maintain lipid malabsorption, even in the absence of in vivo influences. Further research will need to be conducted to fully understand the role of PC in lipid metabolism.

Keywords: Phosphatidylcholine, lipid regulation, small intestine

THE GUT MICROBIOME IN PRADER-WILLI SYNDROME (PWS): UNIQUE BACTERIAL AND FUNGAL PROFILES

Shima Afhami[1§], Hein Min Tun[2], Ye Peng[2], Suisha Liang[2], Edward C. Deehan[1§], Karen Madsen[3§], Lucila Triador[1§], Jens Walter[1§], Andrea M Haqq[1,4§]

[1]Department of Agricultural Food & Nutritional Science; [2]School of Public Health, University of Hong Kong; [3]Department of Medicine;[4]Department of Pediatrics; [§]University of Alberta

Background: PWS is the most common syndromic form of childhood obesity and is characterized by failure to thrive during infancy followed by abnormally increased appetite (hyperphagia) and progressive obesity. The pathogenesis of hyperphagia and weight gain in PWS is poorly understood and management strategies have been met with limited success. The gut microbiome has been implicated in several metabolic disorders such as obesity and diabetes; however, the specific role of the gut microbiome in PWS and childhood obesity is not fully understood.

Methods: Stool samples, a 3-day dietary record, a hyperphagia questionnaire, and anthropometric measures were collected. Bacterial (16S rRNA via Illumina) and fungal (ITS2) sequences were characterized. Operational taxonomic units (97% clustering via Mothur), differences in α- & β-diversity indices and differential abundance testing (LDA Effect Size) were assessed between PWS and control groups. Canonical correspondence analysis (CCA), microbial co-occurance networks and random forest classifier models were applied to discern microbial signatures amongst groups.

Results: Fifty children aged 3-17 (male and female) were recruited [n=25/group]. There was greater bacterial richness (Chao1) in the PWS-group. No differences in other diversity indices were noted for the bacterial profile. Beta-diversity (Bray-Curtis) was significantly different for the fungal profile in both groups. CCA showed that several factors contributed significantly to shaping the bacterial and fungal communities (PWS status, age, weight, sex, diet, hyperphagia score). Differences in hyperphagia scores and dietary intake were observed between groups, with specific taxa correlating to these differences. Differentially abundant taxa were identified between 1) PWS and CON groups (weight-class adjusted), 2) within the different weight-class subgroups of each group. Distinct microbial occurrence networks were observed among groups (stratified by weight). Machine learning models identified microbial predictors for weight status that were unique for the PWS group.

Conclusions: An understanding of the unique gut microbial profile of children with PWS has the potential to unveil more personalized approaches for effective treatment of excessive weight gain and hyperphagia, ultimately leading to improvements in overall health and quality of life.

Key words: Prader-Willi Syndrome, obesity, microbiome, hyperphagia

BRAIN GLUCOCORTICOID ACTION ON LIPID METABOLISM

Miguel Cardoso, Mark Wang, Emily J. Ling, Hongju (Jennifer) Lee, Emilie Beaulieu-Bayne, Jessica T.Y. Yue

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

Background: Aberrant lipid homeostasis is a feature of diabetes and obesity. This metabolic imbalance is associated with excessive levels and/or actions of glucocorticoids (GCs) and contributes to dyslipidemia including elevated hepatic triglyceride (TG)-rich very low-density lipoprotein (VLDL-TG) secretion. The mediobasal hypothalamus (MBH) is a nutrient and hormone sensing brain region that regulates whole-body lipid metabolism and VLDL-TG secretion. We aimed to assess GC action in the MBH in regulating VLDL-TG secretion in health and diet-induced hyperlipidemia.
Methods: Sprague Dawley rats received stereotaxic MBH cannulation and vascular catheterizations to enable direct MBH infusions, intravenous (i.v) injections, and blood sampling. Plasma TG levels and the rate VLDL-TG secretion were measured in 10h-fasted rats following i.v poloxamer injection with concomitant MBH infusions.
Results: In healthy rats, direct MBH GC infusion increased VLDL-TG secretion compared to controls. MBH GC action is mediated via its receptor (GR) since mifepristone (GR antagonist) co-infusion, chronic inhibition of GRs in the MBH with GR shRNA, or inhibition of heat shock protein 90 (required for *in vivo* GR function) negated the MBH GC-induced increases in VLDL-TG secretion. High-fat diet (HFD)-fed rats had both elevated basal plasma GC levels and hepatic TG secretion compared to healthy rats. Remarkably, chronic MBH GR loss-of-function lowered VLDL-TG secretion in HFD induced hyperlipidemic rats, independent of changes in body weight.
Support: Diabetes Canada, NSERC, Canadian Lipoprotein Conference.
Keywords: VLDL-TG, Glucocorticoids, Mediobasal Hypothalamus

IDENTIFYING THE INFLUENCE OF FOOD LITERACY ON DIET QUALITY IN CHILDREN AND YOUTH: A CRITICAL REVIEW

Samantha Cyrkot, Justine Turner, Andrea Haqq, Diana Mager

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

Backgrounds: Developing healthy eating patterns in children is important in the prevention and treatment of chronic disease into adulthood. Food literacy addresses the concepts of food and nutrition knowledge, food skills, self-efficacy and confidence, ecological factors, and food decisions. Understanding the attributes of food literacy and how this contributes to food choices made by children may promote positive health outcomes and assist in delivering appropriate health interventions for children with chronic diseases such as Type 1 Diabetes (T1D). This critical review evaluated the influence of food literacy on diet quality (DQ) in healthy school-aged (4-18y) children and youth.
Methods: Three databases were searched: Medline, Embase, and CINAHL. Key search terms included food literacy, nutrition literacy, DQ, children, and youth. Studies were excluded if they were a) not relevant, b) did not discuss DQ or dietary intake, c) adult study d) written in non-English, e) case studies/review papers, and/or f) non full-text. Validated tools were used to assess food literacy and DQ.
Results: A total of 268 records were identified and screened. Thirteen articles from 2006 to 2019 were reviewed including parental, child and teacher/health worker assessments of food literacy. Studies utilized quantitative (n=9), qualitative (focus group, interviews; n=3), and mixed methodology (n=1) to examine food literacy. In 6 quantitative studies, food literacy was associated with improved child DQ, improved vegetable/fruit intake and/or dairy intake, lower sugar intake, and/or energy balance in children, $p<0.05$. In contrast, one study utilizing both quantitative and qualitative methodology, indicated an inverse association between food literacy and DQ. Parental involvement, role modeling and the school environment were identified in three studies as important factors in improving food literacy and DQ in youth.
Conclusion: Improved food literacy may result in increased DQ in children. Consistent research methods used to evaluate food literacy in children is warranted to ensure that the effects of these factors on health outcomes in children is determined. This is particularly warranted in children on specialized diets that are used in the management of chronic disease, such as T1D.

Keywords: Food Literacy, Nutrition Literacy, Diet Quality, Children, Youth

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INVESTIGATING THE EFFECTS OF 2-AMINOADIPIC ACID ON HUMAN ISLET FUNCTION

Matthew Hubert[1], Amy Barr[1], Scott Campbell[1], Katarina Ondrusova[1], Wentong Long[1], Koenraad Philippaert[1], Mohammad Fatehi[1], Dominic Golec[1], Peter Light[1]
Department of Pharmacology, Faculty of Medicine and Dentistry, University of Alberta

Background: 2-aminoadpic acid (2-AAA) has been found to be an accurate biomarker for future development of diabetes. Investigation of over 2000 patients found that patients in the upper quartile of initial blood 2-AAA levels showed a 2-4x higher incidence of diabetes development over the next 12-13 years. Mouse models and in-vitro static murine and human islet cultures both suggested that 2-AAA increases low glucose insulin release. Additionally, previous 2-AAA studies indicate 2-AAA's toxicity to glial cells by the inhibition of glutathione production. This toxicity inducing inhibition could also be taking place in β-cells, as the affected transporters and enzymes are present and required in both cell types.

Methods: Isolated human islets were cultured overnight, treated with buffer containing 2-AAA, and perifused at 2.5mM glucose and then 11.1μM glucose. Changes in insulin secretion were measured over time. The rat β-cell line INS-1 was cultured overnight in 96 well plates and subjected to either buffer containing 2-AAA along with H_2O_2 and/or 20mM high glucose. Reactive oxygen species (ROS) and necrosis were measured after treatment.

Results: Our data suggests that 2-AAA does not modify insulin secretion from human islets at low or high glucose. Additional INS-1 cell data suggests that 2-AAA can lead to an increased level of cellular necrosis but not cellular ROS during acute β-cell stress.

Conclusions: It is possible that the effects on insulin secretion seen in mouse islets are not replicable in human islets. We propose that increased diabetes incidence in patients with high 2-AAA levels may instead be due to the detrimental effects of 2-AAA on β-cell health. Further experiments will examine 2-AAA's effect on isolated mouse and human islet ROS and necrosis. With a better understanding of 2-AAA's effects we will be in a better position to prevent the non-diabetic patients with high blood 2-AAA levels from developing diabetes.

Keywords: 2-Aminoadipic Acid, Diabetes, Islet, ROS

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Does Exercise Timing Affect Glucose Concentrations in Type 2 Diabetes?

Munan, M., Dyck., R., Houlder, S., Yardley, J., Prado., C., Boulé, N.G

Background: It is well known that exercise can improve glycemic control in individuals with type 2 diabetes (T2D). However, the glycemic response to exercise is highly variable. One of the primary causes of variability in response to a single bout of exercise may be timing in relation to meals. The timing of exercise may affect glycemic responses to subsequent meals but there is currently no consensus on the optimal time for exercise in individuals with T2D. The results from the Exercise, Physical Activity and Diabetes Glucose Monitoring (E-PAraDiGM) protocol found no significant difference in 24-hour glucose when exercise was performed 3-4 hours after lunch. The present study, a follow-up to the E-PAraDiGM protocol, sought to determine if this result was due to exercise timing.

Methods: Fourteen individuals with T2D were recruited and wore continuous glucose monitors (CGM) for 12 days. All participants completed the following four conditions following a randomized cross-over design, with at least 48 hours between sessions: i. morning exercise before breakfast (MorEX) ii. afternoon exercise 3-4 hours after lunch (AftEX), iii. evening exercise 30 minutes after dinner (EveEX), and iv. seated control (CON).

The exercise protocol consisted of 50 minutes of walking at 5.0 km/hr and 0.5% incline (approximately equivalent to 3.5 metabolic equivalents). Standardized meals were provided for two days in each condition. Macronutrient profile was based on Diabetes Canada Guidelines of ~55% carbohydrate, ~30 fat, and ~15% protein.

Results: Eight males and six females were included in the analysis. On average they were 65 ± 9.0 years old and had T2D for 10.5±6.8 years. The mean A1C for participants was 6.7 ± 0.6%. Thirteen participants were treated with oral hypoglycemic medications and one controlled their diabetes through diet and exercise. Mean 24-hour CGM glucose in the four conditions was 7.4 ± 0.7 mmol/L, 7.3 ± 0.7 mmol/L, 7.5 ± 0.8 mmol/L and 7.5 ± 0.7 mmol/L in the MorEX, AftEX, EveEX and CON conditions respectively. Overall, there was no significant difference in mean 24-hour glucose among the four conditions (P=0.55).

Conclusion: Fifty minutes of walking at three different times of day did not lower 24-hour glucose concentrations in people with T2D. These findings are not consistent with other studies of this nature. The reasons why exercise was not effective at lowering glucose are unclear.

Key words: Exercise Timing, Type 2 Diabetes, Continuous Glucose Monitors

DIETARY PHOSPHATIDYLCHOLINE SUPPLEMENTATION DECREASED ATHEROSCLEROSIS DEVELOPMENT IN *LDLR*$^{-/-}$ MICE

Paulina Aldana-Hernández[1], Jessy Azarcoya-Barrera[1], Kelly-Ann Leonard[1], Caroline Richard[1], Jonathan M. Curtis[1], Catherine J. Field[1], René L. Jacobs[1,2]
[1]Department of Agricultural, Food and Nutritional Science, [2]Department of Biochemistry, University of Alberta

Background: Choline, an essential nutrient, is required for cell membranes, lipoprotein secretion and methyl-group metabolism. The two major forms of choline in the diet of the North American population are free choline and phosphatidylcholine (PC). It has been identified that eggs, dairy and meat are the major dietary sources of choline, majority as PC moiety. Excess of dietary choline can be metabolized to mainly trimethylamine (TMA) by the gut microbiota. TMA is rapidly absorbed by the enterocytes and oxidized to trimethylamine N-oxide (TMAO) in the liver by a group of enzymes called flavin-containing monooxygenases. Epidemiological studies suggest that plasma TMAO is a biomarker for atherosclerosis. Some scientists suggest lower eggs and meat intake would reduce PC consumption and thus reduce atherosclerosis development. The objective of this study was to investigate whether the form of dietary choline, free choline or PC, influences atherosclerosis development in *Ldlr*$^{-/-}$ mice.
Method: For 12 wk *Ldlr*$^{-/-}$ male mice (aged 8-10 wk) were randomly fed one of the three 40% high fat diets (with 0.5% of cholesterol): Control (0.1% choline, CON), choline-supplemented (0.4% choline, CS), or PC-supplemented (0.1% choline and 0.3% choline from PC, PCS) diet. After the dietary intervention, the animals were euthanized, and tissues and blood collected. Aortic atherosclerotic plaque area, plasma choline, and lipid metabolites were quantified. Plasma choline metabolites were measured by hydrophilic interaction chromatography for liquid chromatography–tandem mass spectrometry. Plasma lipoprotein fractions were measured by fast protein liquid chromatography. VLDL secretion was measured following Poloxamer 407 injection.
Result: The PCS group had significant lower atherosclerotic lesions while having 2-fold higher plasma TMAO levels compared with both CON and CS groups ($p<0.05$). We found that PCS increased plasma HDL-cholesterol and decreased VLDL-cholesterol; however, VLDL secretion was not affected by dietary treatment.
Conclusion: Dietary PC supplementation decreased atherosclerosis development, despite increasing plasma TMAO. Changes in lipoprotein might explain partly the reduction in atherosclerotic plaque, however, the mechanism behind this observation is unclear.
Keywords: Choline, TMAO, PC, Atherosclerosis, *Ldlr*$^{-/-}$ mice

ASPROSIN LEVELS IN CHILDREN WITH PRADER-WILLI SYNDROME (PWS)

Maha Alsaif[1], Mohammadreza Pakseresht[1], Carla M Prado[1], Catherine J. Field[1], Atul Chopra[2] and Andrea M Haqq[1,3]

[1]Department of Agricultural, Food & Nutritional Science, [2]Case Western Reserve University, [3]Department of Pediatrics, University of Alberta, Edmonton

Introduction: Asprosin is a newly discovered hormone produce by the white adipose tissue that stimulates glucose production and is correlated with insulin resistance. It increases after fasting and decreases with food intake, utilizing the same signaling pathways as ghrelin. Both asprosin and ghrelin are orexigenic hormones. PWS is a unique clinical model of disordered satiety and paradoxical hyperghrelinemia. However, it is not clear if asprosin levels are altered in children with PWS. The aim of our study was to measure serum asprosin in children with PWS and controls and to assess its relationship to metabolic hormones and percentage of body fat.

Methods: Fasting and 1-hour post meal serum of asprosin were measured in ten children with PWS (9F/1M, 5.1-17.9 y) and seven controls (1F/6M, 6.8-17.1 y). Hormones including: glucose, insulin, acyl ghrelin and leptin were measured and homeostatic model assessment insulin resistance (HOMA-IR) was calculated. Body composition was measured by air displacement plethysmography. Groups were compared for %fat, fasting and 1-hour post-meal using the Mann-Whitney U Test; Correlation between fasting and post-meal asprosin, and other fasting hormone levels were determined using Spearman's Rank-Order correlation.

Results: PWS and controls were of similar BMI z-score; however, the PWS group included more females and were younger (p=0.05). Children with PWS had lower fasting of glucose and HOMA-IR (p=0.04 and p=0.05). Fasting asprosin, insulin, percent body fat and leptin were comparable between groups. However, children with PWS had higher fasting of acyl ghrelin (p=0.02). Fasting asprosin and 1-hour post-meal asprosin did not differ between groups. Fasting asprosin was positively correlated with percent body fat and BMI z-score (r_s=0.70, p=0.04 and r_s=0.90, p<0.01) in children with PWS only.

Conclusion: Serum asprosin was positively correlated with adiposity-related parameters in children with PWS, including percent body fat and BMI-z score; no significant correlations were found in controls. Future larger-scale studies in children with PWS and obesity (with and without insulin resistance) is needed to confirm our findings.

Key words: Prader-Willi syndrome, Asprosin, Glucose, Insulin

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FEEDING A MIXTURE OF CHOLINE FORMS DERIVED FROM BUTTERMILK EARLY IN LIFE IMPROVES GROWTH AND IMMUNE SYSTEM MATURATION

Jessy Azarcoya-Barrera[1], Catherine J. Field[1], Susan Goruk1, Yves Pouliot[2], Jonathan M. Curtis[1], René L. Jacobs[1], Caroline Richard[1].

[1]Department of Agricultural Food and Nutritional Science, University of Alberta, Edmonton, Alberta. [2]STELA Dairy Research Center, Institute of Nutrition and Functional Foods (INAF), Université Laval, Québec, Québec.

Background: Choline is an essential nutrient important for the immune system development. Previously we have demonstrated that providing a diet with a mixture of choline forms (phosphatidylcholine (PC), glycerophosphocholine (GPC) and free choline (FC)) to lactating dams led to an anti-inflammatory response later in life, as compared to FC. However, the impact of sphingomyelin (SM), another form of choline, on the immune system development remains unclear. Buttermilk is an important source of SM and PC. The objective of this study was to determine the impact of feeding buttermilk-derived choline forms during lactation and weaning on the maturation of the immune system.
Methods: During the second week of gestation, Sprague-Dawley dams were randomized to one of the three nutritionally adequate experimental diet: 1-Control (100% FC), 2-Buttermilk (37% PC, 34% SM, 17% GPC, 7% FC, 5% Pcho) and 3-Placebo (50% PC, 25% FC, 25% GPC). Diets all contained the same amount of total choline (1.9 g/kg of diet), were matched for total macro- and micronutrients content and were fed to dams *ad libitum* throughout the lactation period. At weaning, pups continued on the same diet as their mom for 7 weeks. At 10 weeks of age, pups were euthanized and immune cell phenotypes and *ex vivo* cytokine production by splenocytes stimulated with Concanavalin A (ConA) were measured by flow cytometry and ELISA, respectively.
Results: Pups fed the buttermilk diet had a higher bodyweight (p <0.01) when compared to the placebo and control diets. Although the subset of cytotoxic (CD8+) T cells was only higher in pups fed the placebo diet, both the buttermilk and placebo diets increased the proportion of cytotoxic (CD8+) T cell population expressing a memory marker (CD27+) and transferrin receptor (CD71+) when compared to the control diet (all $p < 0.05$). Feeding pups with the buttermilk or the placebo diet led to higher production of IL-2, IFN-y and IL-6 by ConA-stimulated splenocytes (all $p < 0.05$) vs. the control diet. Splenocytes from pups fed the buttermilk and the placebo diet produced more TNF-α and IL-10, respectively, when compared to the control diet (both $p < 0.05$).
Conclusion: Feeding pups with buttermilk-derived choline forms promoted better growth. Feeding diets that are high in lipid soluble forms of choline (i.e. both buttermilk and placebo diets) during lactation and the weaning period resulted in an enhanced T cell response after immune challenge and promoted the maturation of the immune system. Finally, providing a mixture of choline forms with more PC (i.e. placebo diet) favors an anti-inflammatory response by improving the ability of splenocytes to produce the regulatory cytokine IL-10.
Key words: choline forms, pregnancy, weaning period, immunology, spleen.

ESTABLISHING A CASE DEFINITION AND CASE-FINDING ALGORITHM TO DESCRIBE THE SEX DIFFERENCES IN YOUNG-ONSET ADULT METABOLIC SYNDROME USING ELECTRONIC MEDICAL RECORD DATA FROM A PRIMARY CARE SETTING IN NORTHERN ALBERTA

Jamie J. Boisvenue, Carlo U. Oliva, Donna P. Manca, Jeffrey A. Johnson, Roseanne O. Yeung
School of Public Health, University of Alberta, Edmonton, Alberta, Canada;

Background: The prevalence of young-adult onset metabolic syndrome (MetS) in Canada remains poorly reported in primary care due to barriers including variation in case definitions and the use of a multitude of electronic medical record systems (EMRs). Our study aims to establish a case definition and case-finding algorithm to describe the prevalence and patterns of young onset MetS between sexes.

Methods: Using a cross-sectional study design, we developed a case definition and case-finding algorithm for the identification of MetS using EMR data from the Northern Alberta Primary Care Research Network (NAPCReN), a part of the Canadian Primary Care Sentinel Surveillance Network (CPCSSN). Our sample consisted of young-adults aged 18-40 years who attended a NAPCReN clinic between July 29, 2015 and July 29, 2018. Descriptive analysis stratified by sex and MetS status was performed for components of MetS. The prevalence of CPCSSN validated disease definitions for depression, diabetes, hypertension, and osteoarthritis were calculated.

Results: The sample consisted of n=15 766 patients of whom 63.4% are female with a mean age 30.9 5.8 years. The prevalence of MetS was 4.4% and did not differ between sexes. Overall, females had more favourable values for MetS risk factors than males in all physical exam and laboratory diagnostic measures whereas among those with MetS, females had worse outcomes than males for BMI and HbA1c and had higher proportions of depression (20.2% vs 13%), diabetes (21.6% vs. 9.1%), and osteoarthritis (2.9% vs. 2.2%). Importantly, among all patients attending primary care with a BMI 25 kg/m2 females had a higher proportion of missing measures than males for high-density lipoprotein cholesterol (83.8% vs 74.6%), triglyceride (82.8% vs. 72.9%), and hemoglobin A1c (70.4% vs. 66.0%). Fasting blood glucose was missing in the vast majority of individuals with an elevated BMI (F 83.7%, M 84.5%).

Conclusions: Females with MetS had worse metabolic outcomes and were missing more data than their male counterparts. The developed case definition may help inform formal validation of MetS in CPCSSN.
Keywords: Metabolic Syndrome, young adults, primary care EMR

SENP1 in Compensation and Failure of Insulin Secretion with High-Fat Diet

Haopeng Lin[1], Kunimasa Suzuki[1], Mourad Ferdaoussi[1], Nancy Smith[1], Aliya F. Spigelman[1], Xiaoqing Dai[1], Austin Bautista[1], Patrick E MacDonald[1].
1. Department of Pharmacology and Alberta Diabetes Institute, University of Alberta, Edmonton, Canada

Background: Pancreatic β-cells adjust their ability to secrete insulin according to metabolic status. Functional up-regulation of insulin secretion may precede increases in islet mass in mice on high fat diet (HFD). We previously identified SENP1 as a key factor that amplifies insulin secretory responses by deSUMOylating targets at the exocytotic site. However, the involvement of SENP1 in the regulation of β-cell functional compensation, and decompensation in T2D, remains unclear.

Methods: We studied β-cells of human donors, wild-type (WT) mice, or β-cell-specific SENP1 knockout mice and littermate controls generated by crossing $SENP1^{fl/fl}$ and Ins1-Cre knock-in lines (βSENP1-KO). Mice were on chow or high fat diet from 2 days to 8 weeks. We measured glucose tolerance, insulin secretion, single-cell exocytosis, and intracellular Ca^{2+} responses. We also performed structure-function studies of recombinant SENP1 activity and redox-sensing.

Results: In humans without diabetes, β-cell exocytotic capacity and insulin secretion are increased at elevated BMI (>25). Increased β-cell exocytosis was also seen in WT mice fed HFD for 2 days (before any change in islet mass or glucose tolerance), and up to 4 weeks. This is not due to increased Ca^{2+} responses, but to an increase in β-cell exocytotic capacity. We show that this response is dynamic and dependent on cellular redox state. *Senp1* mRNA expression is increased in islets of HFD mice, where it acts as a redox-sensor to control β-cell exocytotic capacity. Finally, βSENP1-KO mice lack compensatory increases in β-cell exocytosis and insulin secretion, and show rapidly worsened IP glucose tolerance following 2-day HFD. Interestingly, after 4-week and 8-week HFD, oral glucose tolerance was more severely impaired than IP glucose tolerance, suggesting a contribution from reduced incretin effect. This was substantiated by an inability of DPPIV inhibition to improve glucose tolerance in βSENP1-KO mice.

Conclusion: β-cells up-regulate their capacity to mount an exocytotic response upon metabolic challenge. This requires SENP1 as a redox-dependent effector, and over a longer term HFD is required for the compensatory contribution of the incretin pathway.

Keywords: SENP1, compensation, HFD

Donor CD8α Cells Overcome Age Dependent Resistance to Chimerism Allowing Tolerance to Fully Allogeneic Islets in Autoimmune Diabetic NOD Mice

Jiaxin Lin[1,2], Rena L. Pawlick[1,2], Louis Boon[3], A.M. James Shapiro[1,2], Colin C. Anderson[1,2]

[1]Department of Surgery, University of Alberta, [2]Alberta Diabetes and Transplant Institutes, University of Alberta, [3]Bioceros BV, Utrecht, Netherlands

Background: A reduced intensity conditioning protocol is desired for inducing hematopoietic chimerism, the most efficacious method for generating tolerance to donor organs. We previously showed that donor chimerism is achievable in pre-diabetic, non-obese diabetic (NOD) mice with a T cell depletion based conditioning protocol. Here, our goal is to develop a protocol for inducing chimerism and tolerance to allogeneic islets in NOD recipients that have become diabetic, which is believed to be an even more challenging model.

Methods: We preconditioned pre-diabetic young (8 week old) and old (15-20 week old), as well as old-diabetic (12-26 week old) NOD mice with lymphocytes from fully mismatched FVB mice (d-10), cyclophosphamide (d-8), antibodies against CD4/8/90 (d-6, -1, 4, 9, 14), and busulfan (d-1). FVB islets and/or bone marrow transplantation (BMT) were done at d0. FVB $CD8\alpha^+$ cells were injected in a group of diabetic mice at d19. Blood glucose was assessed weekly. Flow cytometry was used to detect chimerism.

Results: We determined that age rather than overt diabetes is associated with the resistance to chimerism. We induced transient chimerism in old-diabetic NOD mice with significantly prolonged survival of donor islets in chimeric mice. Recipient T cells in diabetic NOD mice were depleted as efficiently as in pre-diabetic NOD mice but rebounded quickly. Levels of chimerism and donor T cells were lower in diabetic recipients at early time points compared to young pre-diabetic NOD mice. The delayed infusion of donor $CD8\alpha^+$ cells facilitated the establishment of a high level and stable multilineage donor chimerism and the acceptance of donor islets without the presence of graft versus host disease.

Conclusion: Donor CD8α cells overcome age dependent resistance to chimerism allowing tolerance to fully allogeneic islets in autoimmune diabetic NOD mice.

Key words: NOD mice, hematopoirtic chimerism, tolerance, islet transplantation

Late-Breaking Abstract

CURRENT AND EMERGING THERAPIES FOR MANAGING HYPERPHAGIA AND OBESITY IN PRADER-WILLI SYNDROME

Qiming Tan[1], Camila E. Orsso[2], Lucila Triador[1], Joan C. Han[3], Timo D. Müller[4], Andrea M. Haqq[1,2]
1. Dept. of Pediatrics, University of Alberta, Edmonton, AB, Canada; 2. Dept. of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, AB, Canada 3. Dept. of Pediatrics, University of Tennessee, Health Science Center, Memphis, TN, USA; 4. Institute for Diabetes and Obesity, Helmholtz Diabetes Center at Helmholtz Zentrum München, Neuherberg, Germany.

Background: Prader-Willi syndrome (PWS) is a complex multisystem genetic disorder. Individuals with PWS experience excessive weight gain and severe hyperphagia with food compulsivity in early childhood, which often leads to the development of life-threatening obesity and metabolic complications. Effective treatments for appetite suppression and weight control are currently unavailable for PWS patients. Our aim to further understand the pathogenesis of PWS led us to carry out a comprehensive search of the current and emerging therapies for managing hyperphagia and uncontrollable weight gain in PWS.
Methods: An English-language literature search was performed using PubMed and the following keywords: `PWS' and `therapy' or `[drug name]' and `PWS'. Articles presenting data from current standard treatments in PWS and also clinical trials of pharmacological agents in the pipeline were selected. Reference lists and pharmaceutical companies' websites were reviewed to detect relevant sources, including unpublished study results, ongoing clinical trials, and research plans. The data source ClinicalTrials.gov was also used to identify ongoing clinical trials.
Results: Current standard treatments include dietary modifications, exercise, and growth hormone replacement, which appear to have limited efficacy for appetite and weight control in patients with PWS. The long-term safety and effectiveness of bariatric surgery in PWS remains unknown; hence surgical intervention should be considered only when patients with PWS have strong medical indications for such procedure. Novel pharmacological agents, including oxytocin and carbetocin, unacylated ghrelin analogs, glucagon-like peptide-1 receptor agonists, cannabinoid receptor antagonists, and potassium channel activators, are under development. In addition, combinatorial pharmacotherapy, such as tesomet, is also being investigated. Preliminary findings have shown that employing combination treatments may produce metabolic benefits superior to what can be accomplished with mono-therapies.
Conclusion: To date, there is no effective therapy to halt disease progression and alleviate obesity in PWS patients. However, new mechanistic insights into the cause of hyperphagia and weight gain in PWS have revealed an expanding list of molecular targets for novel pharmaceutical agents. Some drugs have shown promise in clinical investigations and, if approved, will bring great choices into the PWS pharmacological armamentarium. With the progress that we have made in our understanding of PWS, an effective treatment is an exciting prospect for the near future.
Key words: Prader-Willi Syndrome, PWS, hyperphagia, obesity, therapy

NON-INVASIVE PRINTABLE TATTOO SHAPE MICROWAVE RESONATOR WITH ZERO POWER CONSUMPTION FOR GLUCOSE MONITORING

Masoud Baghelani[1], Zahra Abbasi[1], Peter Light[2], Mojgan Daneshmand[1]

[1]Department of Electrical and Computer Engineering, Faculty of Engineering, University of Alberta
[2]Alberta Diabetes Institute, Faculty of Medicine and Dentistry, University of Alberta

Background: The World Health Organization estimate that there are >500M people worldwide who have diabetes. Diabetes is primarily characterized by poorly controlled blood glucose concentrations that, if allowed to remain chronically high (hyperglycemia), result in the development of serious and life-threatening diseases such as stroke, heart attacks, heart failure, kidney failure, adult blindness and amputation. Moreover, many patients also experience episode of very low blood glucose (hypoglycemia) that can rapidly lead to coma and death. The most common glucose-sensing technology in use today are finger-prick based glucose strips, although this requires sampling many times per day and the continual purchase of the consumable once-use strips. As such patient compliance to regular glucose monitoring is often not possible. Newer glucose-sensing technologies include the placement of a thin needle-like sensor under the skin. Although this technology removes the need for finger-prick blood sampling and can sample glucose levels every few minutes, it is expensive and requires the insertion of a new sensor every 10 days or so. Therefore many patients cannot take advantage of this technology. What is really required is a non-invasive, reliable and cheaper technology that measures glucose in real-time.

Methods: In this research a new chip-less technology based on printed microwave split ring resonators technology has been developed. According to removing of its substrate, the presented sensor results a great sensitivity which is an ideal feature for very low concentration levels of glucose. The sensor is actually a simple printable metallic trace electromagnetically coupled with a reader without requirement of any any wired contact with zero power consumption for the sensing element. The reader could be embedded in a smart watch and monitor the blood glucose level continuously.

Results: Multiple experimental results verify the impressive performance of the presented sensor. First of all, a return-to-zero test has been done to a sample with 100mM of glucose concentration in horse serum with saline and consistent results were achieved. As low concentration glucose samples as 1mM/lit in serum and saline over a shaved mice skin for modeling real life application over a Pyrex glass have been tested and considerable sensitivity of as high as 50KHz/1mM of resonance frequency shift has been achieved. The experiments were continued up to 30mM/lit concentration of glucose with relatively linear results.

Conclusion: Due to its ultra high sensitivity, zero power consumption and small size chipless printable microwave resonator tag seems to be an excellent candidate for next generation wearable sensors and results from this research presents its potential for revolutionizing the method of health parameters monitoring and consequently health care system.

Keywords: Microwave resonator sensor, real time glucose monitoring, wearable sensors with zero power consumption

Pancreatic α-cells Function and Identity in Human T2D

Xiaoqing Dai[1], Joan Camunas-Soler[2], Linford Briant[3], Aliya Spigelman[1], Kuni Suzuki[1], Stephen R Quake[2], Seung K Kim[2], Patrick E MacDonald[1]
[1]Alberta Diabetes Institute, University of Alberta, Canada
[2] Stanford University, US
[3] OCDEM, University of Oxford, UK

Background: Glucagon is synthesized and released by pancreatic α-cells and, along with insulin, maintains blood glucose within the physiological range. In type 2 diabetes (T2D) the release of glucagon becomes dysregulated.
Methods: We used whole-cell patch-clamp to study exocytosis and ion channel function of human and mouse α-cells; glucagon secretion was measured by ELISA.
Results: Opposite to what is observed in β-cells, depolarization-induced exocytosis in α-cells is enhanced at low glucose (LG, 1 mM), and inhibited by high glucose (HG, 5-20 mM). This is reversed in α-cells from T2D donors, which display a β-cell-like phenotype where HG amplifies exocytosis. Using Ca^{2+} channel inhibitors we found that LG increases, and HG suppresses, P/Q-type Ca^{2+} currents in human α-cells which are specifically linked to glucagon exocytosis. Perifusion of mouse islets indicated that direct depolarization (20 mM KCl) was much more effective at stimulating glucagon secretion at 1 versus 5 mM G, and this could not be accounted for by changes in insulin. We found that α-cell exocytosis and glucagon secretion are both enhanced in high fat diet (HFD)-fed mice (10-14 weeks), where we observe a shift from P/Q-type to L-type Ca^{2+} channel control of glucagon exocytosis. Furthermore, a leftward shift in Na^{+} current inactivation, more closely resembles a β-cell phenotype. Both mouse and human α-cells require Aristaless-related homeobox (Arx) to specify α-cells fate. Acute knockdown of *Arx* α-cells by siRNA produced a similar "β-cell-like phenotype" in α-cells identified by glucagon immunostaining. Finally, we applied dual patch-clamp and single cell RNA sequencing (patch-seq) together with computational modelling of α-cell phenotypes to both human and mouse α-cells. These data not only suggest cell- to-cell heterogeneity in α-cell function that is linked to distinct transcriptional profiles, but also indicate α-cell dysfunction is limited to a sub-set of cells marked by elevated expression of lineage markers.
Conclusion: Our data provides some important information to link human α-cells functional and transcriptional phenotypes and provide new information to understand normal function of α-cells and determinants of glucagon secretion in health and diabetes.

Keywords: pancreatic α-cells, glucagon, exocytosis

EFFECTS OF DIETARY SUPPLEMENTATION WITH ARACHIDONIC ACID AND DOCOSAHEXAENOIC ACID IN THE MATERNAL DIET ON DEVELOPMENT OF THE SMALL INTESTINE

Masaya Shimada[1, 2], Dhruvesh Patel[2], Susan Goruk[2], Marnie Newell[2], Catherine J. Field[2]

[1]Department of Applied Life Science, Faculty of Applied Biological Sciences, Gifu University
[2]Department of Agricultural, Food and Nutritional Science, Faculty of Agricultural, Life and Environmental Sciences, University of Alberta

Background: Rat pups ingest fatty acids from breast milk as major nutrients during the suckling period. For this reason, fatty acids in the maternal diets are essential during the development of various organs in rat pups. Long chain polyunsaturated fatty acid such as arachidonic acid (ARA) and docosahexaenoic acid (DHA) are thought to be important for not only immune system development but also crypt to villus maturation accompanied with expression of digestive enzymes and nutrient transporters in the small intestine. Therefore, in this study, we examined effects of dietary supplementation with a mixture of ARA and DHA in the maternal diet on developmental parameters (including villus height, crypt depth, villus height to crypt depth ratio (VH/CD ratio) and a differentiation marker, sucrase activity) in the jejunum of rat pups.

Methods: Pregnant Brown-Norway rats 5 days before parturition were randomized to consume ARA+DHA (0.4 g ARA+0.8 g DHA/100 g fat) or control (no ARA+DHA) diet during suckling (until 3 weeks age). After the suckling period, the rat pups both in the ARA+DHA maternal diet (n = 6) and control maternal diet (n = 8) were fed the control diet until 8 weeks age. After euthanizing 8-week pups, jejunum sections were collected and used for H&E staining and sucrase activity assay.

Results: Villus height and crypt depth were not different in the two groups, whereas sucrase activity and VH/CD ratio tended to be higher (1.4-fold and 1.3-fold, respectively, $p < 0.1$) in the ARA+DHA group than in the control group. However, the sucrase activity was positively correlated with the villus height ($p < 0.05$).

Conclusion: ARA+DHA in the maternal diet may be an important factor for development of villus in the rat pup jejunum. In addition, sucrase activity induced by ARA+DHA in the maternal could be reflective of higher villus height in the rat pup jejunum.

Key words: Arachidonic acid, Docosahexaenoic acid, Maternal Diet, Small Intestine, Sucrase

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