we found that Fyn-dependent phosphorylation of Tgm2 regulates autophagy. It has been reported that Tgm2 forms complexes with p53 and p62 (a known autophagy regulator) to mediate degradation of p53 at autophagosome in cancer cells and p53 functions as a DKD inducer. We found that p53 expression was decreased in Tgm2 knock-downed HK2 cells suggesting that Tgm2-p62-p53 complex also modulates autophagy in RPTC. We previously showed that Fyn and autophagy is regulated by energy status, therefore we next examined whether energy levels changed the subcellular localization of p53, p62 and Tgm2 in HK2 cells *in vivo*using the marker, Aquaporin 1. Confocal microscopic studies revealed that *ad libitum*-fed mice showed increased punctate of p62 in RPTC suggesting that autophagy was reduced. Fyn, Tgm2 and p53 shaped the dotted form mainly in the basement membrane of the cells. Interestingly, all these molecules moved to the cytoplasm in fasted state, where decreased p62 punctations were observed indicating increased autophagy. More importantly, in HFD fed mice, diet-induced rodent models of metabolic disorders, we found that protein expression of p53 was increased due to decreased levels of degradation with inhibition of autophagy implicated by decreased p62 punctations in RPTC. Taken together, these data suggest that the metabolic status may regulate Fyn to not only phosphorylate Tgm2 and modulates Tgm2-p62-p53 complex but also change their co-localizations of Fyn, p53 and Tgm2 in RPTC to regulate autophagy leading to pathogenesis of DKD.

Diabetes Mellitus and Glucose Metabolism

DYSREGULATED METABOLIC RESPONSE

The IgG Antibody Paradox in Insulin Resistance: Pathogenic and Therapeutic

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Chronic low-grade inflammation and mitochondrial dysfunction are hallmarks of insulin resistance. However, the mechanisms by which the immune system can propagate systemic insulin resistance remains poorly understood. IgG antibodies are a critical component of immunity and display paradoxical properties. IgG can propagate inflammation by crosslinking Fc receptors activating innate immune cells, and conversely, when given intravenously at high doses (1–2 g/kg intravenous immunoglobulin), actively suppress inflammation. Here, we demonstrate that IgG can exert similar paradoxical properties on glucose metabolism. IgG can elicit insulin resistance, and conversely, when given at high doses, promote insulin sensitivity in a diabetic mouse model. IgG, through its Fc-mediated interactions, suppresses insulin-induced mitochondrial function as well as insulin signaling. Modulation of insulin-dependent mitochondrial respiration by serum or purified IgG highly correlates (R2 = 0.70) with the quantitative measurement of insulin sensitivity accessed by the modified insulin suppression test. Our studies indicate that IgG antibody glycosylation is critically important to these conflicting actions. In mice and humans, the progression of insulin resistance is associated with reduced IgG Fc region sialylation, and administration of asialylated IgG is sufficient to cause insulin resistance in IgG null mice. On the other hand, a single administration of high-dose IgG significantly improved insulin and glucose tolerance as well as plasma glucose levels lasting over 72 days post-administration. These results demonstrate new insights into the systemic nature of insulin resistance, a novel mechanism of the disease, and an innovative therapeutic strategy for treating type 2 diabetes.

Diabetes Mellitus and Glucose Metabolism

DYSREGULATED METABOLIC RESPONSE

The Role of TGFβ Ligands and Signalling on Insulin Resistance in Skeletal Muscle in Women With PCOS

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Polycystic ovary syndrome (PCOS) is the most common female endocrinopathy affecting metabolic and reproductive health of 8–13% of reproductive-age women. Insulin resistance (IR) appears to underpin the pathophysiology of PCOS and is present in approximately 38–95% of women with PCOS. This underlying IR has been identified as unique from, but synergistic with, obesity-induced IR (1). Skeletal muscle accounts for up to 85% of whole-body insulin-stimulated glucose uptake; however, in PCOS this is reduced by about 27% when assessed by a euglycaemic-hyperinsulinaemic clamp (2). Interestingly, this reduced insulin-stimulated glucose uptake observed in skeletal muscle tissue is not retained in cultured myotubes (3), suggesting that *in vivo* environmental factors may play a role in this PCOS-specific IR. Yet, the molecular mechanisms regulating IR remain unclear (4). A potential environmental mechanism contributing to the development of peripheral IR may be the extracellular matrix remodelling and aberrant transforming growth factor beta (TGFβ) signalling. Previous work demonstrated that TGFβ superfamily ligands are involved in the increased collagen deposition and fibrotic tissue in the ovaries, and suggested that these ligands may be involved in the metabolic morbidity associated with PCOS (5). In this study, we investigated the effects of TGFβ1 (1, 5 ng/ml), and the Anti-Müllerian hormone (AMH; 5, 10, 30 ng/ml), a TGFβ superfamily ligand elevated in women with PCOS, as causal factors of IR in cultured myotubes from women with PCOS (n=5) and healthy controls (n=5). TGFβ1 did not have a significant effect on insulin signalling but induced expression of some ECM related genes and proteins, and increased glucose uptake via Smad2/3 signalling in myotubes from both groups. Conversely, AMH did not appear to activate the TGFβ/Smad signalling pathway and had no significant impact on insulin signalling or glucose uptake in any of the groups. In conclusion, these findings suggest that TGFβ1, but not AMH, may play a role in skeletal muscle ECM remodelling/fibrosis and glucose metabolism in PCOS but does not have a direct effect on insulin signalling pathway. Further

research is required to elucidate its contribution to the development of *in vivo* skeletal muscle IR and broader impact in this syndrome. **References:** (1) Stepto *et al., Hum Reprod* 2013 Mar;28(3):777–784. (2) Cassar *et al., Hum Reprod* 2016 Nov;31(11):2619–2631. (3) Corbould *et al., Am J Physiol-Endoc* 2005 May;88(5):E1047-54. (4) Stepto *et al., J Clin Endocrinol Metab*, 2019 Nov 1;104(11):5372–5381. (5) Raja-Khan *et al., Reprod Sci* 2014 Jan;21(1):20–31.

Diabetes Mellitus and Glucose Metabolism

DYSREGULATED METABOLIC RESPONSE

The Short-Term Impact of Roux-en-Y Gastric Bypass on Enteroendocrine Hormone Distribution and Density in Rhesus Macaques

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Roux-en-Y gastric bypass (RYGB) surgery results in profound weight loss and improvements in glucose homeostasis through a likely combination of malabsorption and changes in GI tract signaling. One component of GI tract signaling implicated in RYGB effects are enteroendocrine hormones, which are produced along the tract and regulate GI tract motility, pancreas exocrine and endocrine functions, including insulin release, and central nervous system control of feeding. While RYGB has been shown to cause post-prandial serum increases of several enteroendocrine hormones, the mechanism for how this occurs in the GI tract is still unknown. The current study examined GI tract tissue 13 weeks after RYGB or sham-surgery combined with pair-feeding (Sham/PF) in adult rhesus macaques. In situ hybridization analysis revealed no RYGB-induced changes compared to Sham/PF animals in the overall distribution of enteroendocrine hormones, with cholecystokinin (CCK) and glucose-dependent insulinotropic peptide (GIP) cells found predominantly in the proximal small intestine and preglucagon, encoding glucagon-like peptide-1 (GLP-1), and peptide tyrosine tyrosine (PYY) cells found predominantly in the ileum and colon. Immunohistochemistry was performed to further characterize the impact of RYGB on enteroendocrine cell density. No differences were observed in CCK cell densities in the proximal tract following RYGB, nor were there any differences in PYY and GLP-1 densities in the distal intestine. The only observed difference was an increase in serotonin and chromogranin A cell densities in the ileum of the RYGB group compared to the Sham/PF group. Serotonin has diverse actions from regulating GI tract motility to central nervous system signaling via the vagus nerve. Additional studies are planned to investigate how this up-regulation of serotonin may impact metabolic physiology after RYGB.

Diabetes Mellitus and Glucose Metabolism

DYSREGULATED METABOLIC RESPONSE

Use of Intranasal Insulin as Neuroprotection From Hyperglycemia in Rat Model of Extremely Preterm Infants

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Background: Hyperglycemia is common in extremely preterm infants (EPI) and is a risk factor for increased mortality and morbidity, including abnormal neurodevelopment. Hippocampus-mediated cognitive deficits are common in this population. In a rat model of insulinopenic hyperglycemia, abnormal neurochemistry in the hippocampus was found, with lactate, glutamate (Glu):glutamine (Gln) ratio lower and Phosphorylated Creatinine (PCr):Creatinine (Cr) higher. Intranasal insulin has been shown to improve cognitive function in animal models of Alzheimer's disease and type 2 diabetes mellitus, as well as in adult human studies of Alzheimer's disease. No study has previous investigated the use of intranasal insulin on preventing the long-term effects of hyperglycemia in the EPI population. **Objective:** To determine whether administration of intranasal insulin during early postnatal days would negate the effects of hyperglycemia on the developing hippocampus in neonatal rat model of streptozotocin (STZ)-induced hyperglycemia. **Design/Methods:** STZ (80mg/kg IP) was injected on postnatal day (P) 2, and littermates in the control group were injected with an equivalent volume of citrate buffer. STZ pups were randomized to intranasal insulin, 3U twice daily from P3-P6 (STZ + INS) or left untreated (STZ). Neurochemical profile (consisting of 20 metabolites, PCr:Cr and Glu:Gln ratios) of the hippocampus was evaluated using ultra-high-field (9.4 T) magnetic resonance spectroscopy (MRS) on P7 (acute effects) and P56 (long-term effects) compared with the control group (CON)(N=6/group). **Results:** Mean glucose values from P3-P6 were higher in STZ groups (STZ = 279.0 +/- 132.2 mg/dL, STZ+INS = 274.4 +/- 89.5 mg/dL, CONT = 128.4 +/- 15.1 mg/dL). The neurochemical profile was different at both P7 and P56. On P7, compared with the control, the taurine (Tau) was higher in the STZ groups ($p = 0.007$. At P56, PCr:Cr was higher in the STZ group compared to CONT and STZ+INS groups ($p = 0.04$). No difference noted between the STZ+INS and CONT groups. No other metabolites were altered. **Conclusion:** Neonatal hyperglycemia alters the acute and long-term neurochemical profile in the hippocampus of developing rats. The increase in PCr:Cr ratio in the STZ group indicates lower demand for ATP and PCr, secondary to decreased neuronal activity, which has been demonstrated in previous studies. PCr:Cr ratio of the STZ+INS group was no different than control, indicating that intranasal insulin reverses the negative effect on neuronal activity caused by neonatal hyperglycemia.

Diabetes Mellitus and Glucose Metabolism

DYSREGULATED METABOLIC RESPONSE

Young Adult LEW.1WR1 Rats Develop Dysregulated Islet Function and Impaired Liver Insulin Responses