



# Dietary Fat Composition Directly Affects Insulin Secretion in Type-2 Diabetes

Joshua C. Neuman<sup>1</sup>, Allison L. Brill<sup>2</sup>, Harpreet K. Brar<sup>2</sup>, Kelsey M. Connors<sup>2</sup>, and Michelle E. Kimple<sup>2</sup>

Departments of Nutritional Sciences<sup>1</sup> and Medicine, Division of Endocrinology, Diabetes, and Metabolism<sup>2</sup>, University of Wisconsin-Madison, Madison, WI 53705.



## Introduction

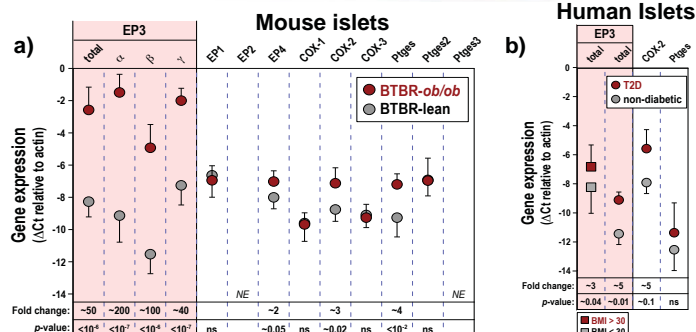
Type 2 diabetes is a serious public health problem that is proposed to reach epidemic proportions in the coming decades. Dietary interventions with omega-3 ( $\omega$ -3) polyunsaturated fatty acids (PUFAs), such as those in fish oil, have been proposed as potential therapy for many chronic conditions, including type 2 diabetes; however, the direct impact of PUFAs, including both  $\omega$ -6 and  $\omega$ -3, on insulin secretion are inconclusive. Delineating the specific cellular mechanisms and signaling cascades of  $\omega$ -6 and  $\omega$ -3 PUFAs in insulin secreting  $\beta$ -cells is necessary to establish their role in  $\beta$ -cell function. Our lab investigates the role of the prostaglandin E receptor 3 (EP3), whose primary natural ligand is the  $\omega$ -6 PUFA-derived prostaglandin E2 (PGE2). Previous work in our lab identified the up-regulation EP3 expression in addition to increased PGE2 production in type 2 diabetic mouse and human islets. This up-regulation in PGE2 ultimately reduced glucose stimulated insulin secretion. The primary focus of this project is to determine whether PGE2 production can be altered by modulating the cellular  $\omega$ -6 vs.  $\omega$ -3 PUFA composition and whether this protects diabetic  $\beta$ -cells from becoming dysfunctional.

## Background

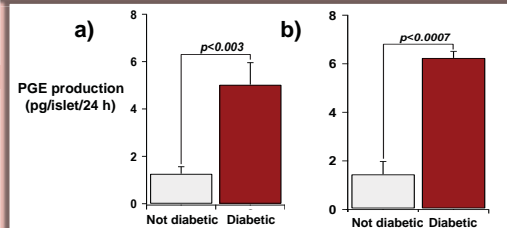
1. The BTBR ob/ob mouse: A model of type 2 diabetes with  $\beta$ -cell dysfunction



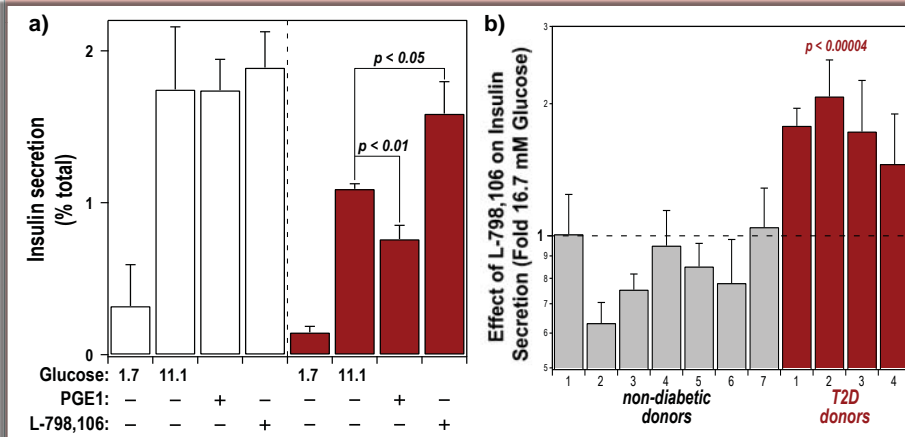
2. Both the cellular receptor, EP3, and PGE2 forming enzyme expression are upregulated in type 2 diabetic islets: (a) mouse and (b) human



3. PGE2 production is increased in both type 2 diabetic a) mouse and b) human islets.

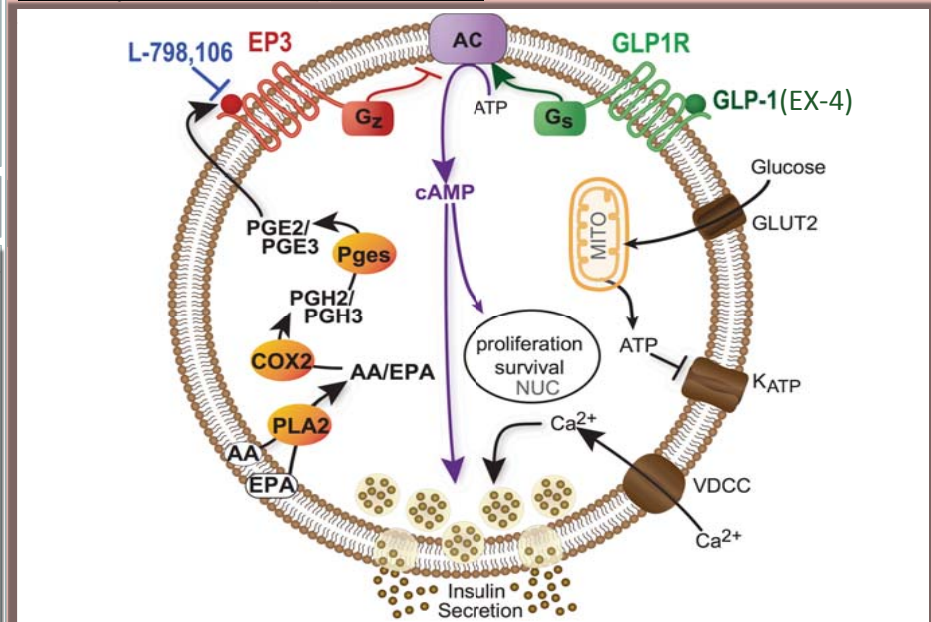


4. L798,106, a compound that prevents activation of the EP3 receptor, improves insulin secretion in both a) mouse and b) human type 2 diabetic islets.



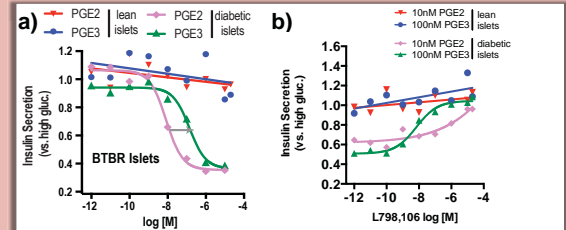
## Specific Aim & Hypothesis

5. Determine the effect of enriching insulin secreting  $\beta$ -cells with arachidonic acid (AA,  $\omega$ -6 fatty acid) and eicosapentaenoic acid (EPA,  $\omega$ -3 fatty acid) in regulating insulin secretion in the non-diabetic and diabetic state. Cellular membrane-bound AA and EPA compete for the same downstream metabolic enzymes. Our hypothesis, based on strong preliminary data, is that  $\beta$ -cells enriched with EPA will improve  $\beta$ -cell function, reduce PGE2 production, and effectively restore diabetic  $\beta$ -cell function.

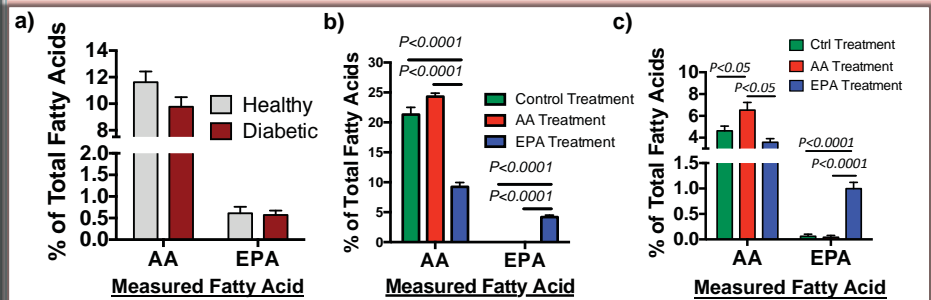


## Methods and Results

6. PGE3 reduces insulin secretion through the EP3 receptor similarly to PGE2 in type-2 diabetic islets. PGE3, which is derived from EPA, and PGE2, an AA-specific metabolite, were added in increasing concentrations in islets isolated from both healthy (BTBR Lean) and diabetic (BTBR ob/ob) islets. Ten times the amount of PGE3 compared to PGE2 is required to elicit the same reduction in insulin secretion only in diabetic islets (a). We confirm this reduction occurs through the EP3 receptor as we relieve this inhibition by adding the EP3-specific antagonist L798,106 (b).

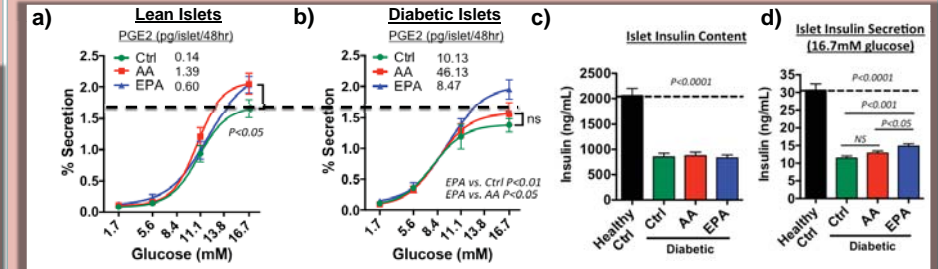


7. Islet phospholipid composition is reflective of diet and can be altered *in vivo* and *in vitro*. Phospholipid composition of both diabetic (BTBR ob/ob) and healthy (BTBR lean) mouse islets fed a standard chow diet did not differ in their islet phospholipid composition (a). However, islet phospholipid composition can be altered when BTBR Lean mice are fed a diet enriched with AA or EPA for 6 weeks (b). Furthermore, we can achieve similar changes in isolated BTBR Lean islets incubated with AA or EPA *in vitro* (c).

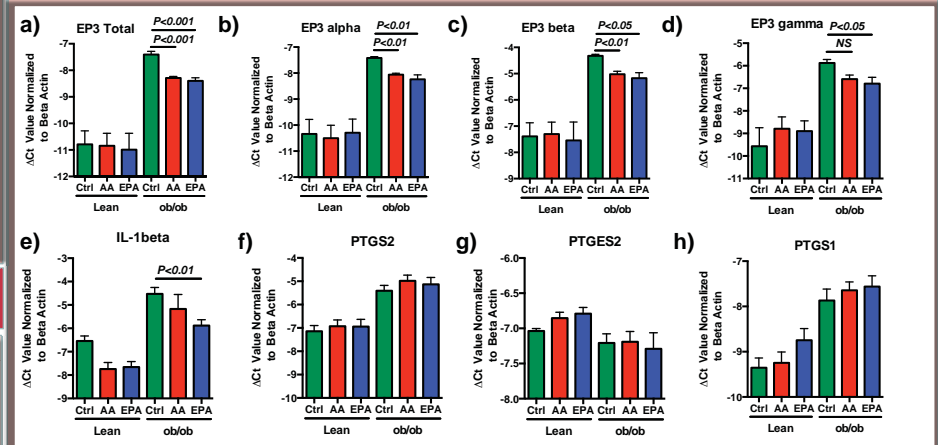


## Methods and Results

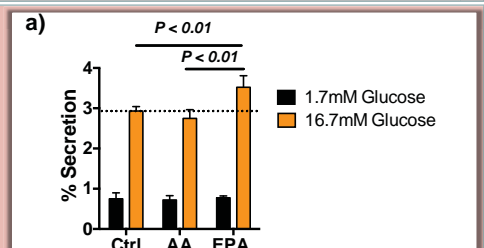
8. AA and EPA affect lean and diabetic mouse islets differently. Following a 48-hour incubation, AA and EPA enhance insulin secretion compared to control in lean islets (a) but only EPA potentiates insulin secretion in diabetic islets (b). We predict that changes in prostaglandin production (b) contributes to the enhanced secreted insulin in the EPA treatment (d) since there is no difference in insulin content (c).



9. AA and EPA alter EP3 gene expression in diabetic islets among other genes associated with prostaglandin production. BTBR ob/ob treated with AA and EPA had reduced total EP3 expression, including the 3 known splice variants (a,b,c,d). Moreover, there was a reduction in the cytokine IL-1 $\beta$ , a known modulator of prostaglandin production (e).



10. EPA but not AA potentiates insulin secretion in human islet donors. Human islets treated with EPA for 48-hours led to a statistically significant increase in insulin secretion at high, 16.7mM glucose conditions when compared to both control and AA treatments.



## Conclusions and Future Directions

- EPA and AA islet composition is directly related to dietary intake
- EPA provides protection against  $\beta$ -cell dysfunction in diabetic islets, presumably through a change in prostaglandin production and subsequently EP3 signaling
- EPA and AA can reduce EP3 expression but this change does not rescue the reduction in insulin secretion in the AA condition potentially due to increased PGE2 production
- Future directions are: 1) determine if antagonism of the EP3 receptor further rescues  $\beta$ -cell function in fatty acid treated diabetic islets and 2) determine changes in other prostaglandins by mass spectrometry to help explain phenotype

## Acknowledgements

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