Banting & Best Diabetes Centre
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HOW SUGAR AFFECTS FAT IN THE BLOOD AND RISK OF HEART DISEASE

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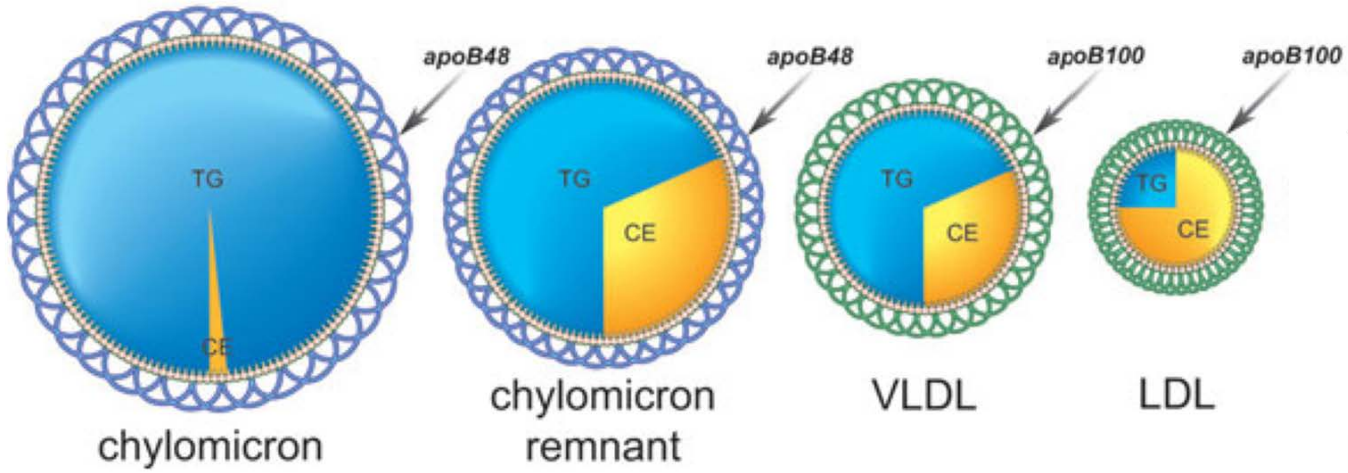
INTRODUCTION

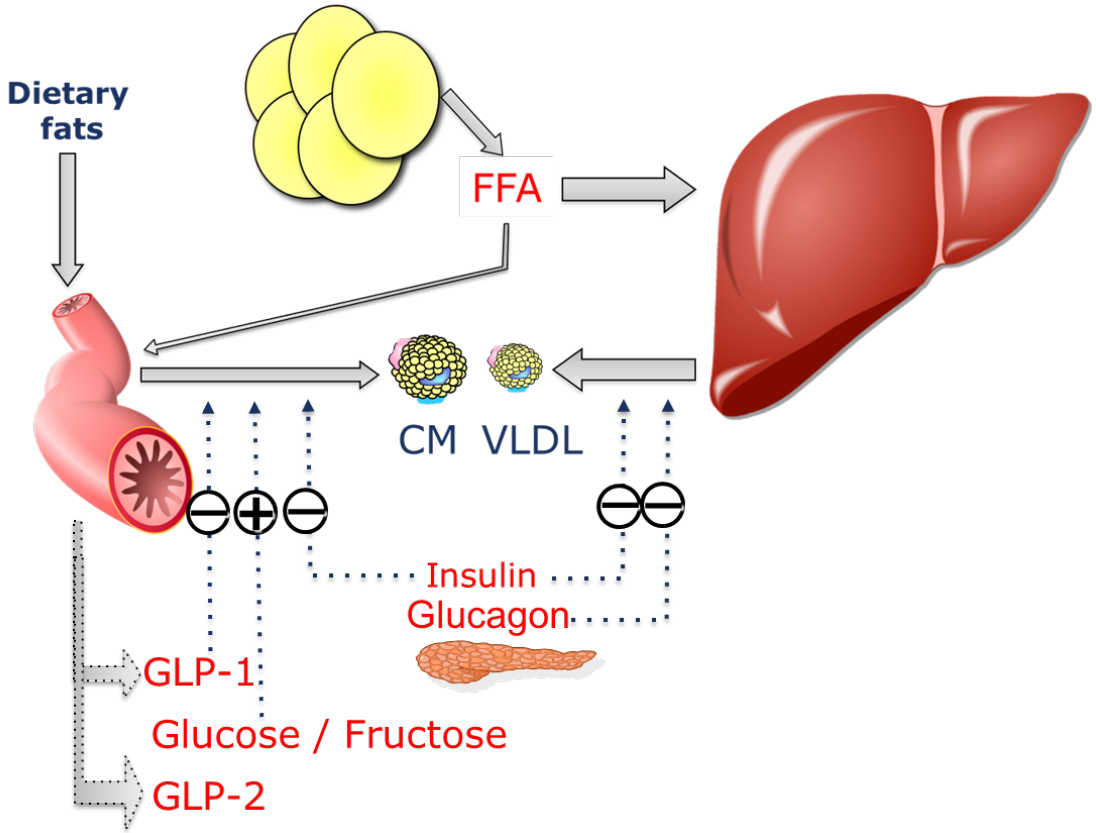
- Patients with type 2 diabetes and pre-diabetes often have high levels of fat (triglycerides) in the blood which can lead to heart disease
- Fat in the diet is packaged into special particles called chylomicrons by the intestine. This helps fat move around the body and get into tissues that can use it for energy
- How the intestine puts fat into these particles is regulated by hormones, what you eat and by your nervous system



de Graaf et al., 2015. *ApoB in Clinical Care*

INTRODUCTION

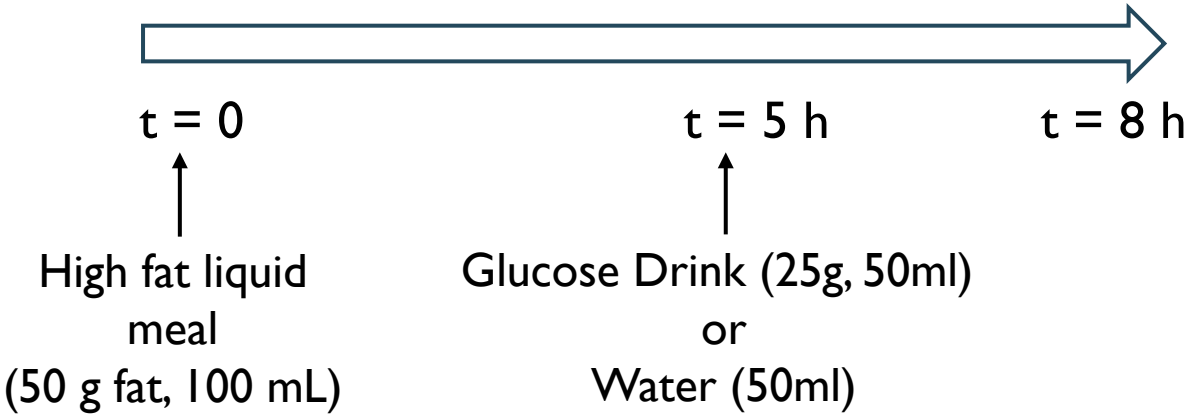
Nutrients and hormones influence how fat particles are made by the liver and intestine



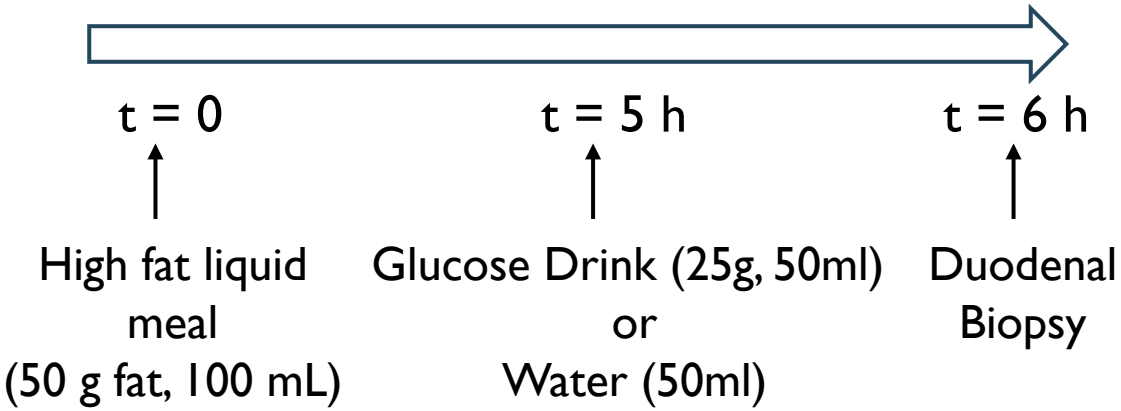
METHODS

How does glucose affect how the intestine packages fat from the diet, in humans?

Protocol A: Plasma Sampling
Crossover Design



Protocol B: Duodenal Biopsy
Parallel Arm Design



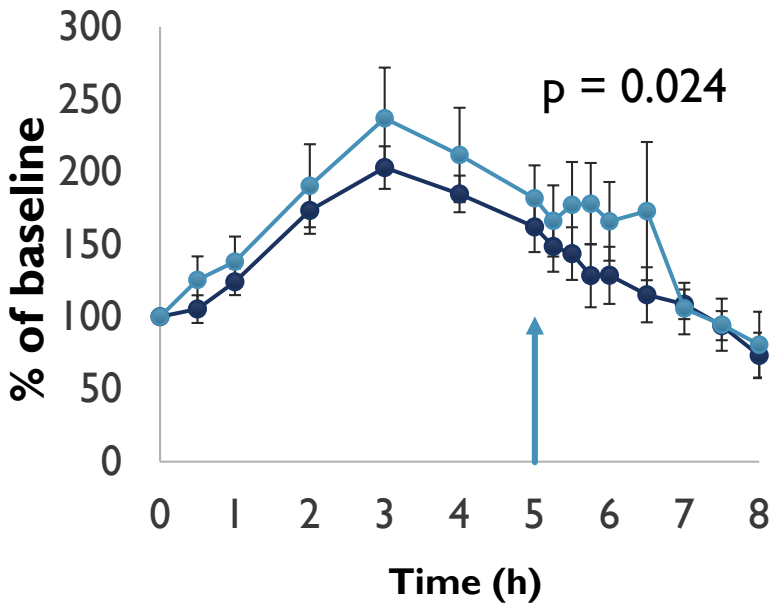
Xiao et al., *CMGH* 2019; 7:313-337.

PATIENT AND PUBLIC INVOLVEMENT

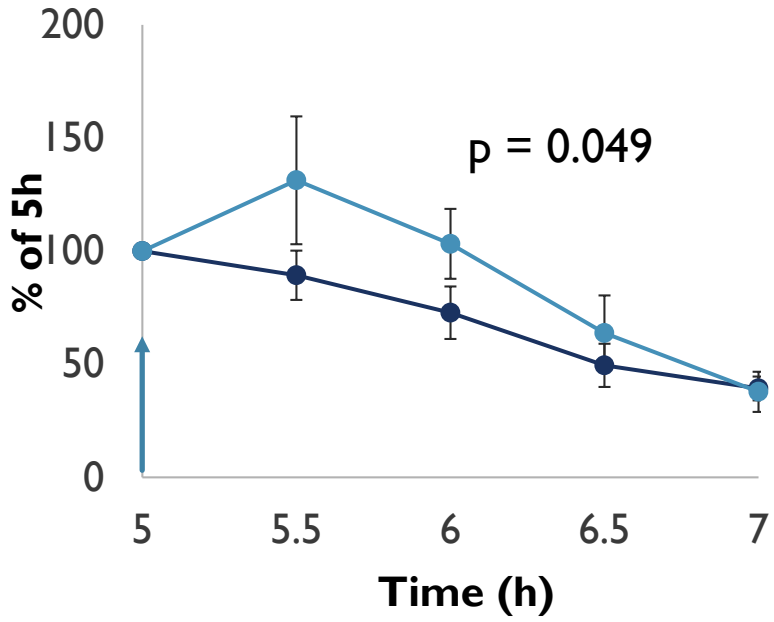
- The risk of developing heart disease is known to be a major concern for patients with type 2 diabetes
- Understanding how the foods we eat affect this could help develop ways to fight heart disease for patients with type 2 diabetes
- We used healthy volunteers to first understand how this works in healthy individuals and are now recruiting people with obesity and insulin resistance to see how this changes in those states
- We consulted with subjects who are recruited in the biopsy study to understand what aspects of the study concern them and how to help alleviate these concerns? Ex: fear of anaesthesia, fear of side effects
  - Amended the study protocol to allow patients to go home between the fat drink and glucose drink, and the research nurse stayed with them for a few hours after the procedure to make sure they were feeling well

RESULTS

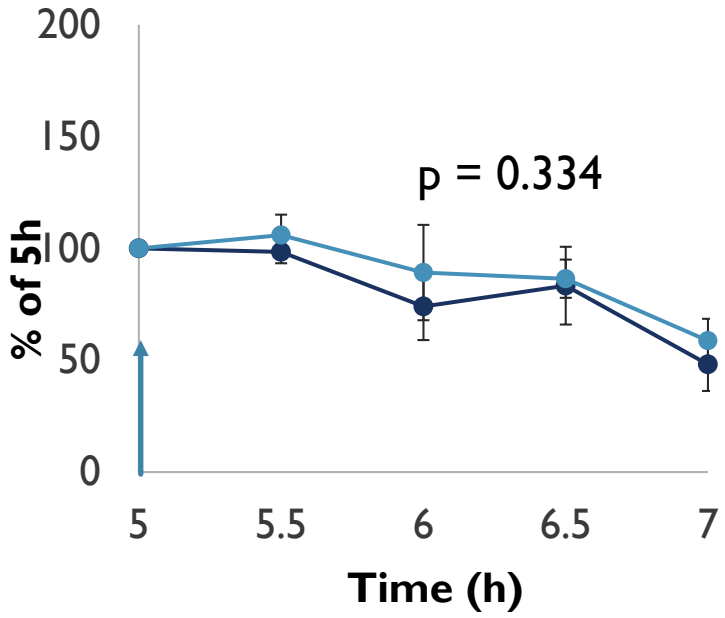
PLASMA TG



CHYLOMICRON-TG



VLDL-TG



Xiao et al., *CMGH* 2019; 7:313-337.

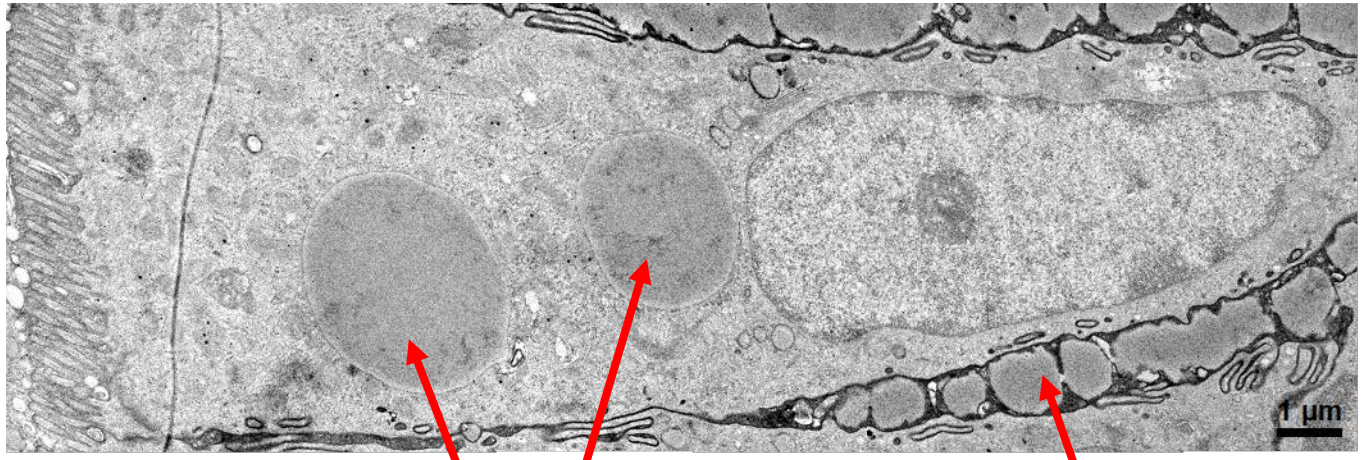
ELECTRON MICROSCOPY OF INTESTINAL TISSUE

t = 0 → High fat liquid meal (50 g fat, 100 mL)

t = 5 h → Glucose (25 g, 50 mL) or Water (50 mL)

t = 6 h → Duodenal Biopsy

Apical membrane

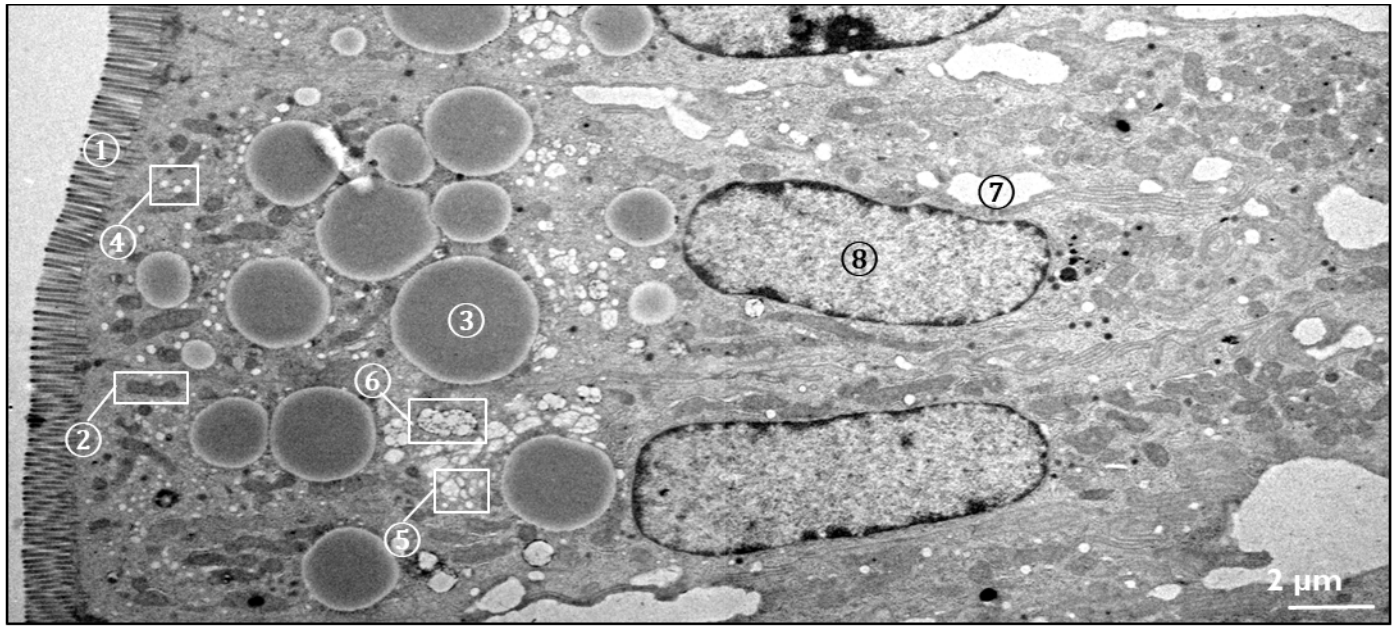


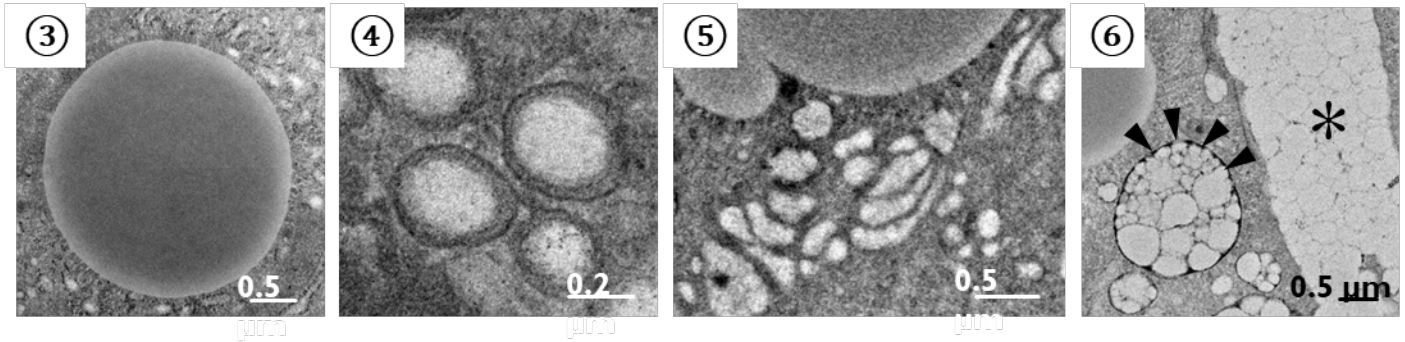
Basolateral membrane

Cytosolic lipid droplets

Secreted chylomicrons

FAT FOUND THROUGHOUT THE CELL OF THE INTESTINE





① Microvilli
② Mitochondria
③ Cytoplasmic Lipid Droplet (CLD)
④ TAG in ER lumen
⑤ TAG in Golgi apparatus
⑥ TAG in secretory vesicles
⑦ TAG in intercellular space
⑧ Nucleus

Hung et al. 2017 Biochim Biophys Acta 1862:6

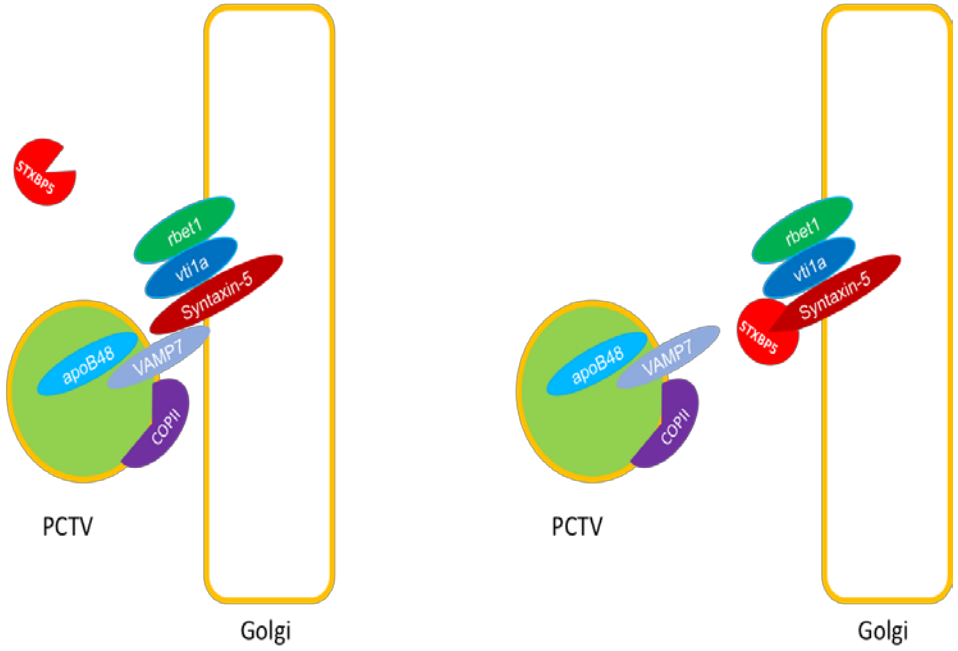
RESULTS

Uniprot Accession	Protein Name	Gene Name	Fold Change	T Test p-value	Function
Q5T5C0	Syntaxin-binding protein 5	STXBP5	-6.8628	4.72E-22	Protein Folding/Transport

STXBP5

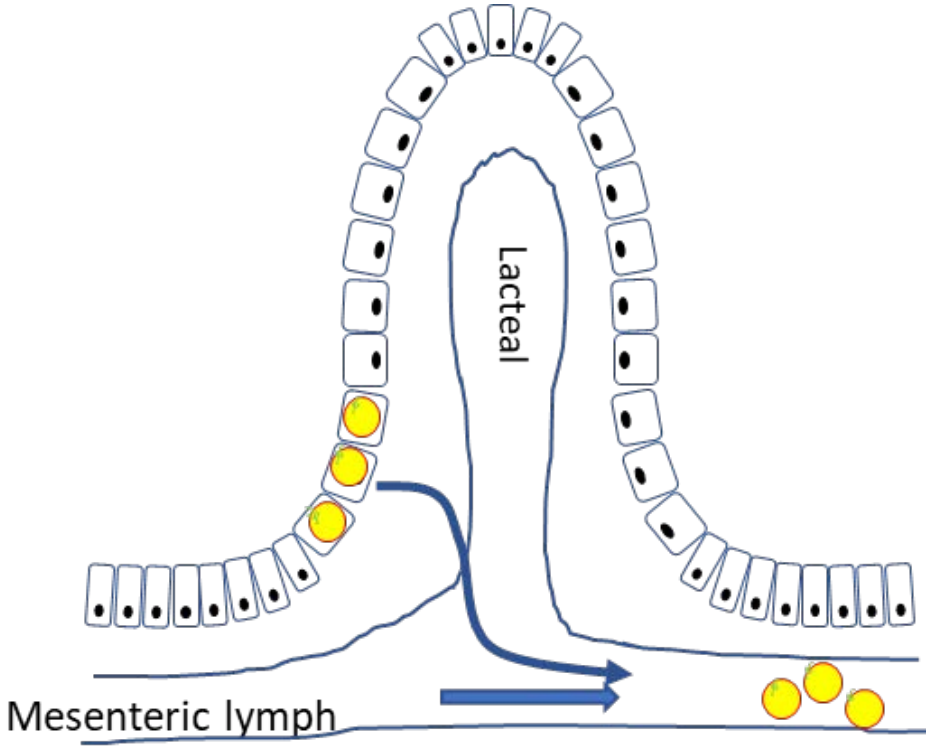
- Glucose caused levels of this protein to go down in intestinal tissue
- Negative regulator of SNARE protein assembly, which is a key part of fat packaging in the intestine

SNARE ASSEMBLY IN ENTEROCYTES – POTENTIAL ROLE FOR STXBP5



Xiao et al., *CMGH* 2019; 7:313-337.

RESULTS



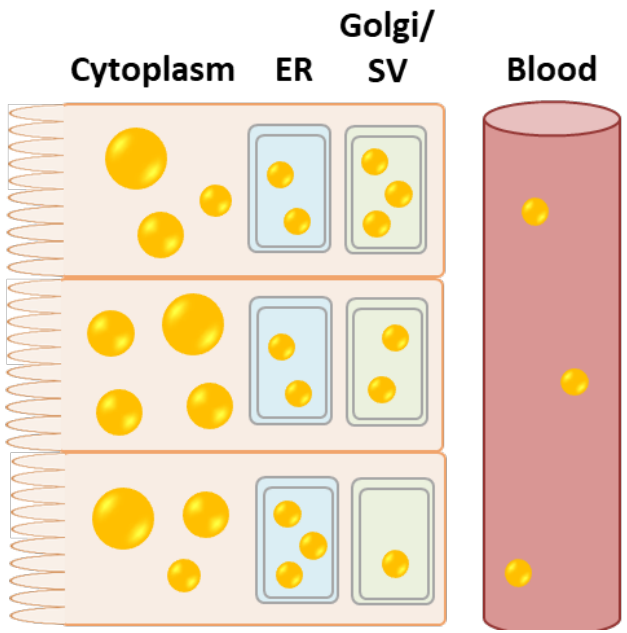
Results in studies using rats:

- When we investigate this phenomenon in rats, we find similar effects
- Glucose causes fat that is stored in the intestine to move out of the cell
- This doesn't occur when parts of the pathway are disrupted

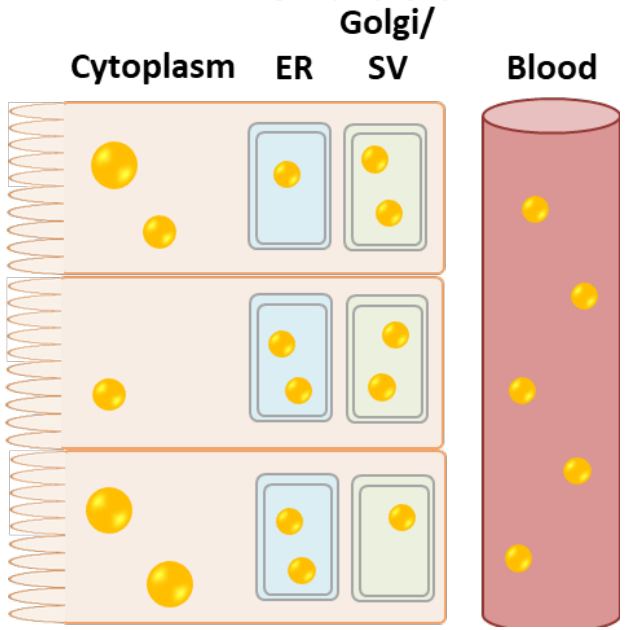
Stahel et al., *ATVB* 2019; 39:31565-73.

DISCUSSION

WATER



Glucose



- In humans, glucose causes fat from a previous meal to be pushed out of the intestine, into the blood
- STXBP5 might be one of the factors that helps glucose stimulate fat secretion from the intestine
- Similar findings were found in animals which allows us to explore in more detail how it happens

Xiao et al., *CMGH* 2019; 7:313-337.

CONCLUSIONS

- When we eat fat, some of it stays within the intestine and can be released into the blood many hours after a meal
- Drinking glucose (sugar) can trigger release of these stored fats, most likely releasing fat that is stored within the cell
- This demonstrates that high glucose levels, like in diabetes, can increase the risk for heart disease
- Determining how glucose does this could help us develop treatments that prevent the rise in blood fats, particularly in people with type 2 diabetes

LESSONS LEARNED

- It is important to discuss concerns about the study protocol with participants to make sure we come up with solutions that suit them and don't affect the study
- When we study these effects in people with type 2 diabetes, we will discuss how they think the glucose drink will affect them and allow them to adjust the dose if they have concerns