PHY3102 Lecture notes (SAMPLE): **Nutrition, metabolism and body weight**

SAMPLE NOTES, FULL EDITION IS ORDERED AND COMPLETE.

Week 2 Lecture 3 Macronutrient release & regulation: Part 2

What maintains plasma glucose, 4 mechanisms:

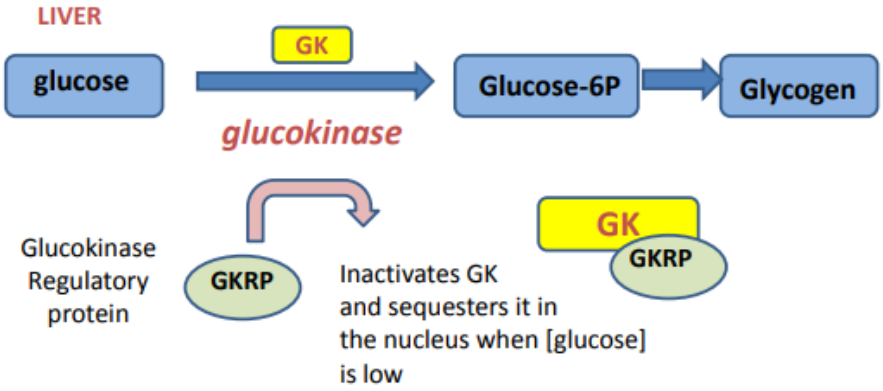
Anabolic effects of insulin are opposed by catabolic effects of glucagon

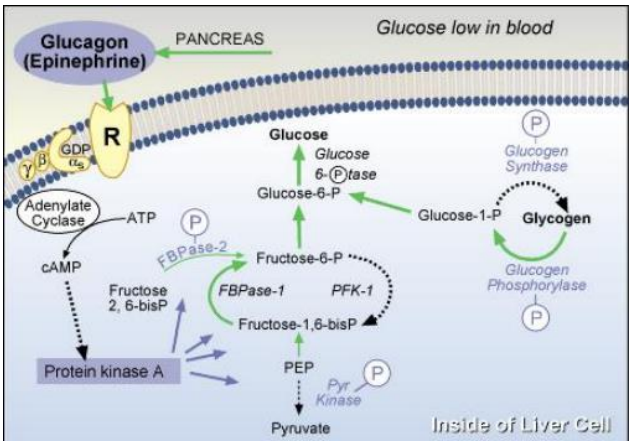
Process after a meal vs after a 24 hour fast

Regulating glucose metabolism:

1. Covalent modification

- reversible attachment of a group onto the enzyme that makes it inactive
- eg: glucokinase- the rate controlling enzyme for hepatic glucose clearance, when you no longer need to be releasing glucose from liver to circulation
- When glucagon actives the glucagon receptor Protein Kinase A is able to re-phosphorylate enzymes allowing glucose formation from glycogen and fructose

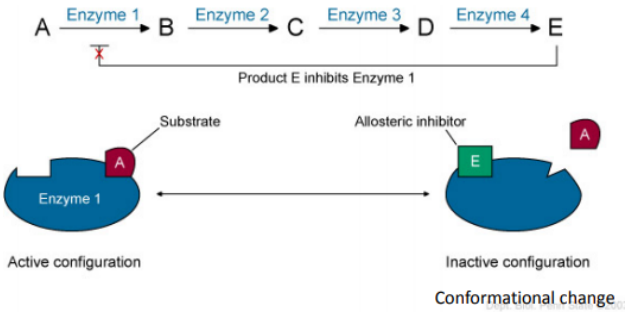


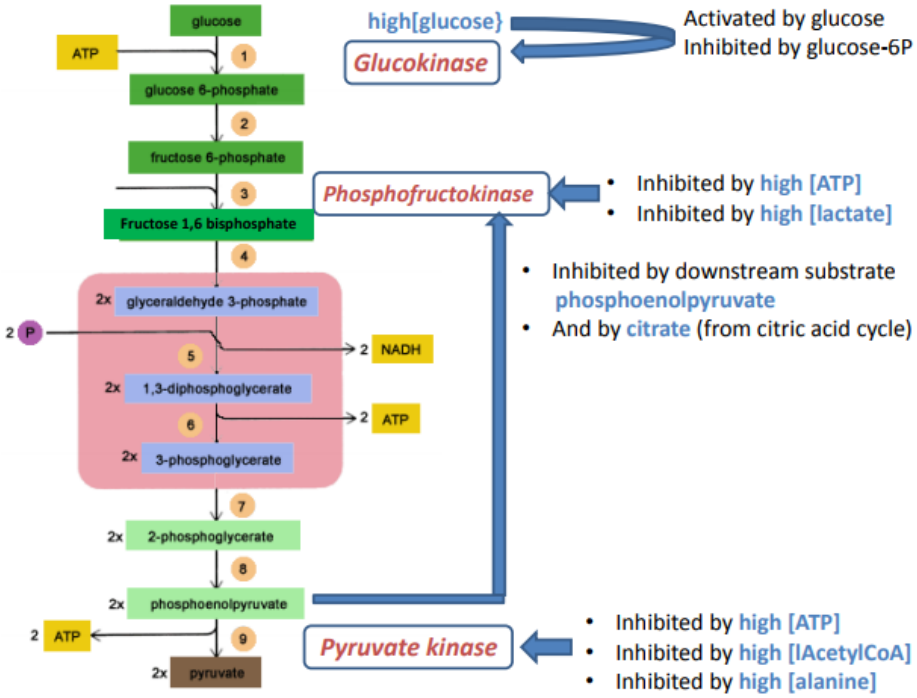


Detect by pancreas→ glucagon released→ binds to receptor, causes conformation change and intracellular signalling process (C-AMP upregulation in cytosol), catalysed by ATP→ Activates protein kinase A. PKA can then phosphorylate other substrates→ promote activity (glycolysis)

2. Allosteric inhibition-

- a downstream product inhibits further enzyme action
- Product E then inhibits enzyme 1
- Reversible





this is common in glycolysis, used to regulate substrate of CAC such as adequate pyruvate to inhibit phosphofructokinase which the regulatory point for usage of glucose.

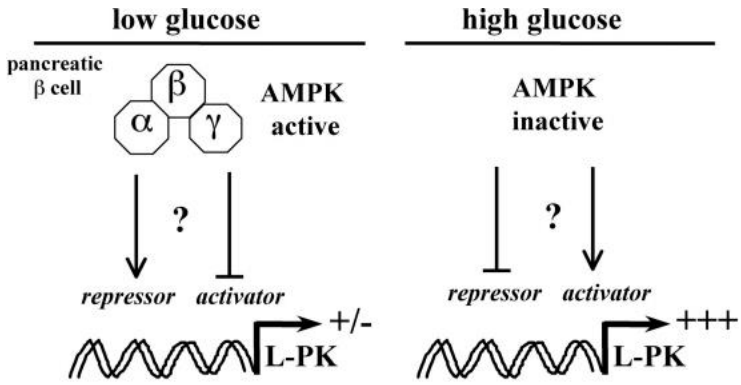
High glucose→ activates hexokinase (in muscle)

Citrate from moving pyruvate to A-CoA, for oxidation in CAC, which acts to regulate glucose

↓ plasma glucose→ ↓ glycolytic pathway in liver

3. Hormone regulated gene transcription
   - Hormones are signalling to alter gene transcription important for enzyme production
   - Meal consumed, ↑ plasma [insulin], transcriptional change in liver
   - ↓ glycogen breakdown
     –↓ glycogen phosphorylase & G-6Pase
     –↑ glycogen synthesis, ↑ glucokinase, & glycogen synthase
   - ↑ Glycolysis
     – transcription glucokinase gene, synthesis of fructose 2,6-bisphosphate, stimulates pyruvate kinase
   - Inhibits gluconeogenesis
     – ↓ transcription of PEPCK, ↓ activity FBPase & G6Pase
   - Promotes lipogenesis
     – ↑ acetyl CoA carboxylase , ↑ fatty acid synthase (↑ TAG)
     – Promotes protein synthesis (reduces degradation)

Role of AMPK in the regulation by glucose of the L-PK gene transcription in pancreatic β cell:

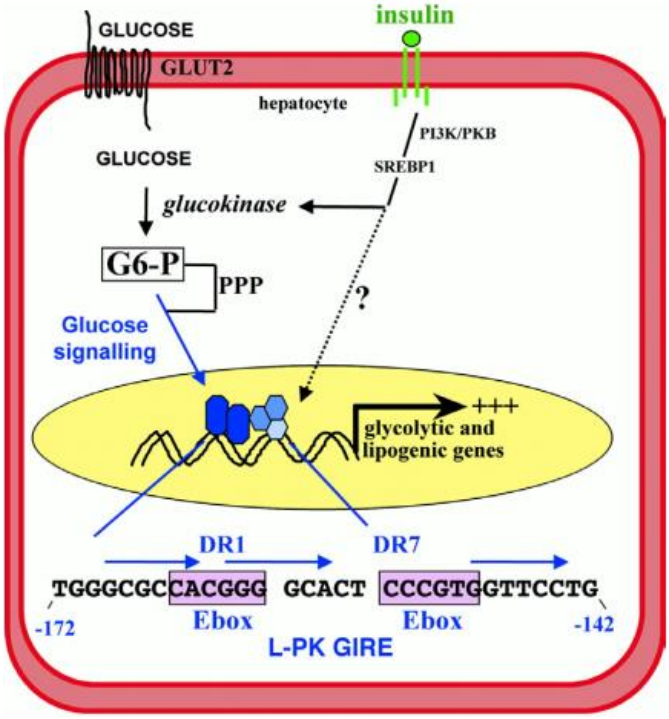


Presents of glucose can directly impact on transcriptional changes, was thought to be indirect.

AMP kinase changes in high/low glucose. L type Pyruvate kinase gene is more present in high glucose

Unclear as to whether activation of amp kinase under low glucose conditions, whether or not it is working through increasing repression activity or inhibiting activator.

Role of glucose and insulin in the transcriptional regulation of glycolytic and lipogenic genes in the liver:



Glucose moves in→ activation of glucokinase stimulatied by insulin binding, gluco-6-phosphotase→ leading to response of L-PK in gene from insulin and glucose.

4. direct action of hormones
    - Main hormones:
        i. insulin
        ii. glucagon*
    - During stress:
        i. Epinephrine
        ii. cortisol*
    - During growth: growth hormone* (especially during growth)

(*elevate blood glucose and fatty acids to provide fuels)

Note: postprandial responses are important as exaggerated responses to meals, lipid and glucose, can be a risk factor for CHD. Also time of day meal is eaten. Energy density of food.

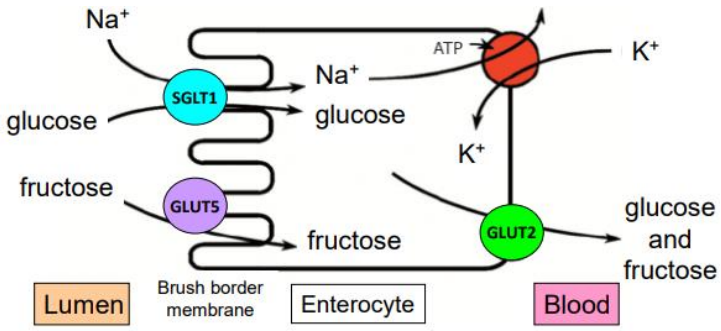
Consider sugars:

- Is there any difference in how the fructose and glucose are absorbed?

	Saturday	Monday
fructose	9.6 g	36.8 g
glucose (incl. starch)	68.1 g	48.8 g
fructose + glucose	77.7 g	85.6 g
Percent glucose	(88%)	(57%)

- How much fructose and glucose enter the blood from each breakfast?

Sugar transporters:



- SGTL1: actively transports glucose across the brush border membrane, this process requires Na+ and uses ATP
- GLUT5: transports fructose across the brush border membrane, this process continues by facilitative diffusion
- GLUT2: transports fructose and glucose from the enterocyte into the blood
- Glucose does not need breaking down. Starch does

Absorption of fructose:

- Fructose absorption occurs more slowly than glucose (gives lower GI, doesn't directly increase plasma glucose)
- Absorption limit for fructose is quantitatively limited ~ 50g at single time. Limited transporters
- Non-absorbed fructose moves into colon, cause of fructose intolerance in people who have lower fructose load
    i. Fermented by bacteria

ii. Causes digestive symptoms

- Glucose consumed with fructose, the total amount of fructose that can be absorbed is increased
- Provides evidence of another disaccharidase transport system evolved to handle break-down products of sucrose

Fat:

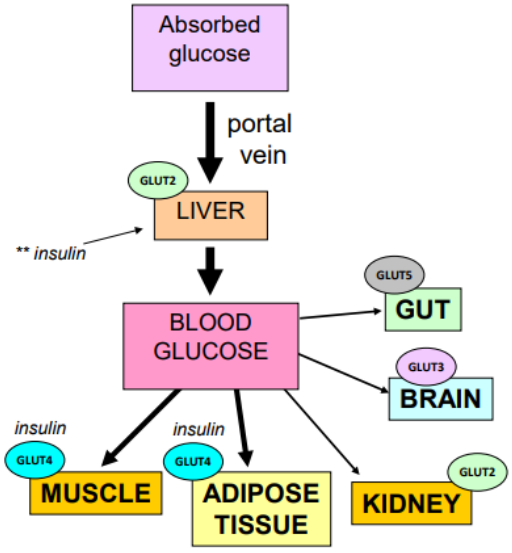
- After fructose consumption, fat is more likely to be stored than oxidised

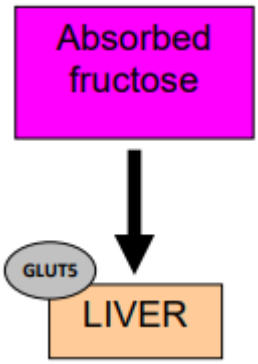
Questions:

- Why is there a difference in blood insulin after each breakfast?
- Is more glucose or more fructose metabolised in the liver?
  i. Some glucose is metabolised in the liver, or stored or passed into circulation. Fructose is metabolised in the liver, however, it cannot be determined which is metabolised more.
- Why are more TAGs formed after the Monday meal than after the Saturday meal?

Factors that increase insulin secretion:

- Rise in blood GLUCOSE (detected by Pancras)
- Rise in serum free fatty acids (to promote storage of lipids)
- Rise in serum amino acids
- Gastrointestinal hormones – Gastrin (from stomach), CCK, secretin, GIP
- Other hormones - GLP-1, growth hormone, cortisol
- Autonomic stimulation - Acetylcholine i.e. stretch receptors in stomach and intestine
- Insulin resistance, obesity (compensatory mechanism)→ hyperinsulinemia
- N.B: FRUCTOSE does not directly stimulate insulin secretion. It is metabolised and indirectly increases insulin release from metabolic processes
- Most of the glucose leaves the liver and is used in other tissues
- Fructose is primarily metabolised in liver
- Different glut transporters move glucose to particular tissues, only glut 4 is responsive to insulin





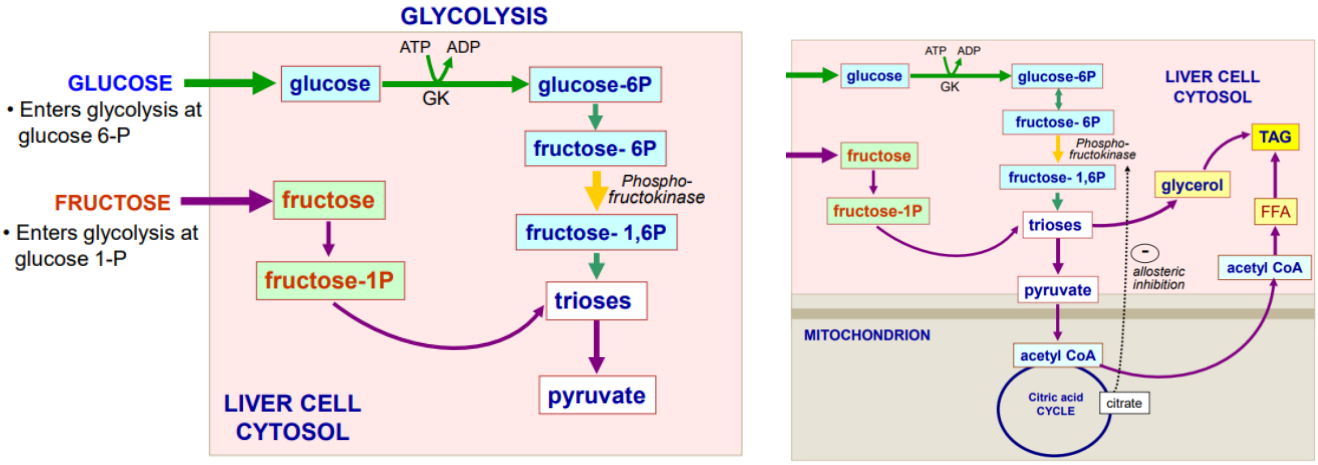
Glucose:

- Regulated formation of acetyl CoA
- Entry into glycolytic pathway is regulated by phosphofructokinase

Fructose:

- Higher amounts of TAG formed in the liver

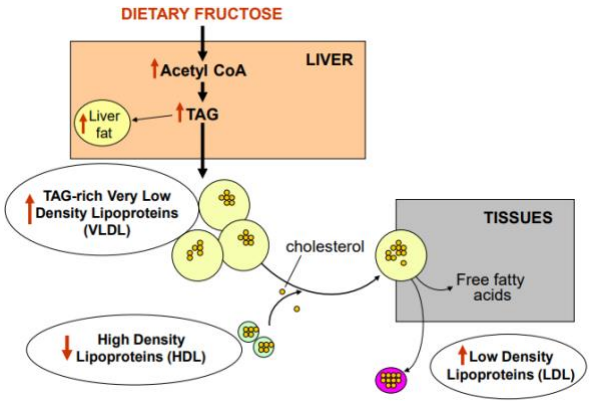
- Unregulated formation of acetyl CoA (which may cause negative effects, stored as fat)
- A better substrate for glycogen synthesis in liver than glucose
- Bypasses phosphofructokinase. Entry unregulated. Also, fructose may have greater effect in activating genes for lipogenesis.



Glucose enter→ Glucose 6-phosphate

Points of regulation:

- Fructose enters below PFK, into trioses. You can stop the pyruvate at fructose-6P down, at PFK to stop glucose coming into liver.
- To stop fructose coming into the liver… can't be done, hence unregulated.



Deterioration of blood lipid profile:

- High circulating triglycerides, ↑LDL, ↓HDL.
- LDL is susceptible to oxidation, causing deposits on arterial walls, → blockage
- ↓HDL→ less removal of LDL

Week 8 Lecture 13: Leptin, energy homeostasis, obesity and cardiovascular parameters

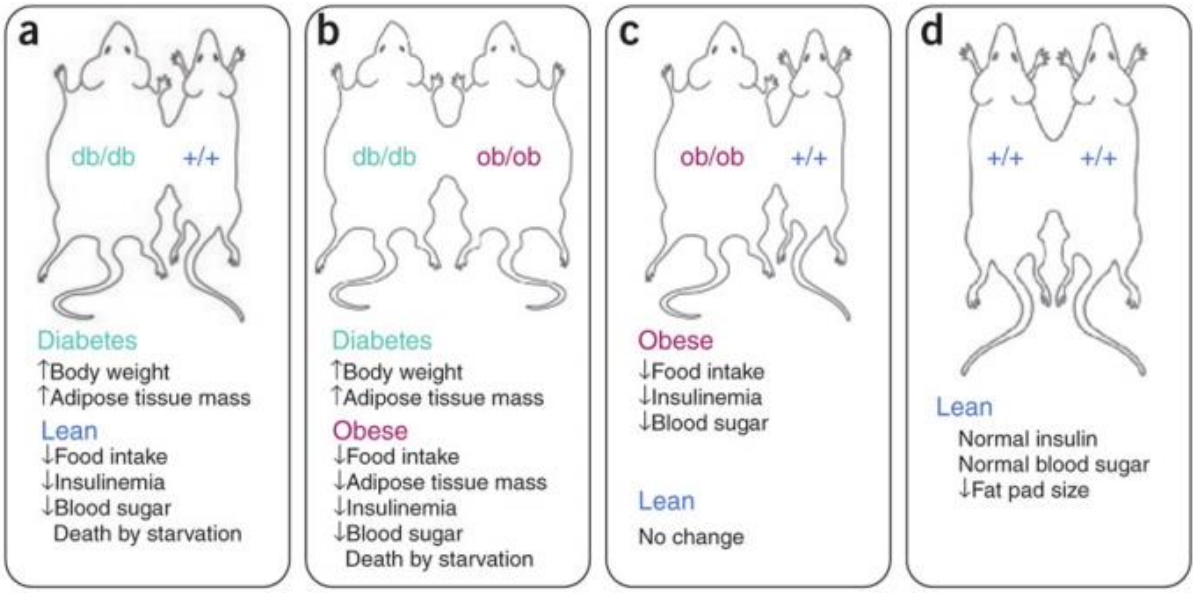
Leptin:

- Product from fat cells

- Daily injections normalised Ob mice
- Decreased body weight, body fat
- Improves insulin and glucose sensitivity
- Increases temperature, metabolic rate and activity
- from adiposities in adipose 7ssue
- Plasma leptin levels significantly correlate to whole body adipose tissue levels

Parabiosis experiment:

- Connecting the circulation of 2 animals



- Db mice do not express the leptin receptor, they still express leptin

Normally:

- Behavior: Hypophagia (decreased food intake)
- Endocrine system: Increases TRH gene expression; interacts with HPA and growth hormone axis; modifies GnRH pulse
- ANS: increases sympathetic tone, decreases parasympathetic tone; increases energy expenditure

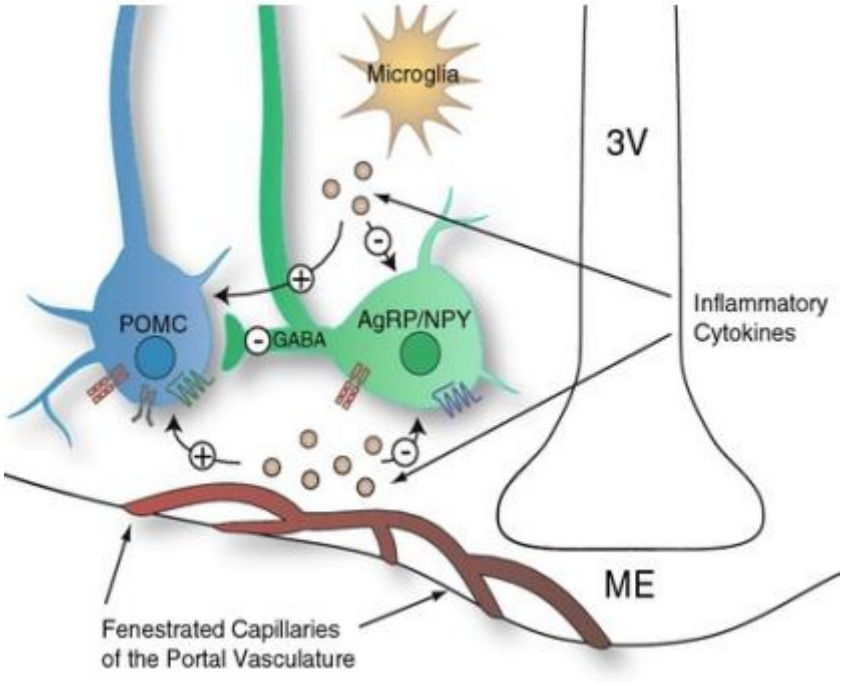
Endogenous hyperleptinemia (individual produce) does not reduce appetite or increase energy expenditure in obese rodents and humans. This is termed leptin resistance.

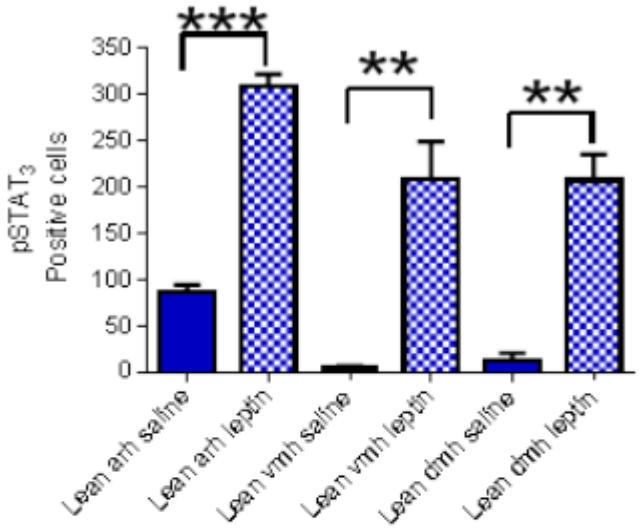
In the brain:

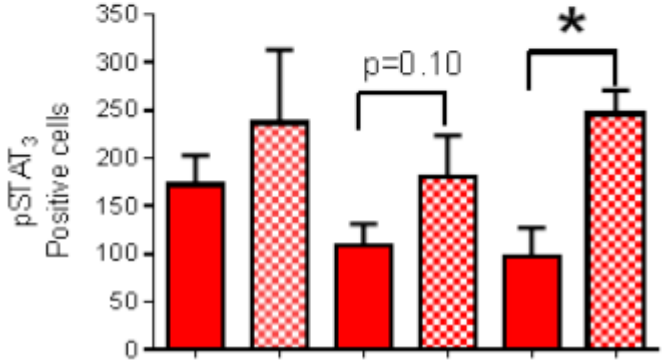
- Leptin receptors are found throughout the body, however high population are found in the hypothalamus
- In obesity, the neurons in the ARC loss there responsiveness to leptin
- In the ARH the NPY and POMC neurons both express leptin receptors
- Leptin inhibits NPY/AgRP
- Excites POMC

Arcuate nucleus:

- Located next to the median eminence (3rd ventricle)
- Gets highest concentration of signals from plasma
- Incomplete bbb
- Neurons located within the arcuate can directly sense the concentrations of various compounds, hormones, lipids, cytokines in the bloodstream.







pSTAT3:

- Marker of leptin receptor signalling
- Leptin binding causes phosphorylation of stat-3
- DIO baseline there is already increase in p-stat expression due to elevated leptin,
- definition of leptin resistance when leptin does not elevate pstat3

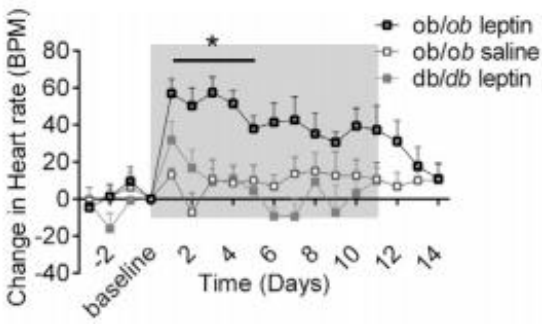
Despite the Arcuate nucleus of the hypothalamus (ARH) of DIO mice becoming resistant to leptin in obesity, the Dorso Medial Hypothalamus (DMH) of DIO mice remains responsive to leptin

SUMMERY:

- Leptin resistance is an inability of exogenous leptin to increase pSTAT3 to a significantly greater level.
- Only the ARH appears to reach threshold and suffer 'leptin resistance' in obesity.
- Despite being unable to induce a decrease in food intake, leptin in obesity is still able to increase themogenic response and blood pressure.
- Leptin increases sympathetic neve activity.
- Giving lean mouse leptin, increase in SNA without effecting food intake and body weight
- Hence there may be a different set of neurons regulating different physiological actions of leptin.
- Leptin administered in the Dorsal medial hypothalamus increases sympathetic tone to BAT in spite of resistance
- Pre-administering Leptin receptor antagonist (competitive) in DMH blunt the increases iBAT temperature in control and DIO mice, showing DMH role in thermogenic response
- Blocks peripheral actions
- Acutely in Anesthetized lean Sprague-Dawley rats leptin administered into the DMH increased HR and MAP

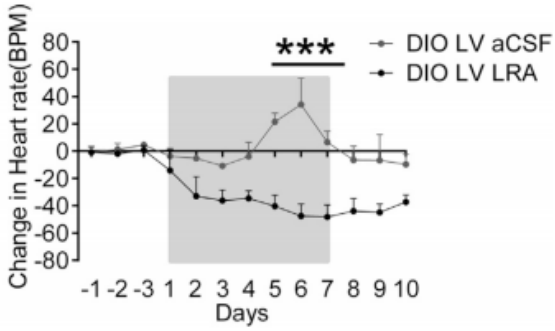
Leptin and blood pressure in obesity:

- Obesity, excess fat is not the cause of hypertension, elevated leptin concentration is.
- DIO mice are the only mice to have elevated HR and SNA
- leptin can increase blood pressure and heart rate in obese leptin deficient (ob/ob) mice but not in db/db, leptin receptor deficient mice.



- Antagonist does not change food intake or bodyweight
- Hence leptin in obese animals is increasing BP and HR

• Blockage of leptin actions in the brain in obese hypertensive mice, reduces heart rate and blood pressure



Antagonist in the DMH:

- Blockage of leptin actions in the Dorsomedial hypothalamic region of the brain in obese hypertensive mice, reduces heart rate and blood pressure (similar to whole brain)
- When leptin receptors are removed, there is an eventual loss in SBP
- Knock down of the leptin receptors with AAV Cre in the DMH region in obesity reduces systolic blood pressure.
- Re activation of the leptin receptors in the DMH region in obese leptin receptor deficient mice elevates heart rate and systolic blood pressure.
- Shows that elevated leptin during obesity and responsive leptin receptors in DMH causes raises CV diseases
- Leptin increases activation of cell
- Inhibiting the DMH leptin receptor expressing neurons via opening glycine channels results in reduction in BP and HR (done by administering virus to leptin receptor Cre expressing animal, which can be activated or inhibited)

Leptin and human BP:

- People who don't produce leptin have lower SBP, no change in DBP

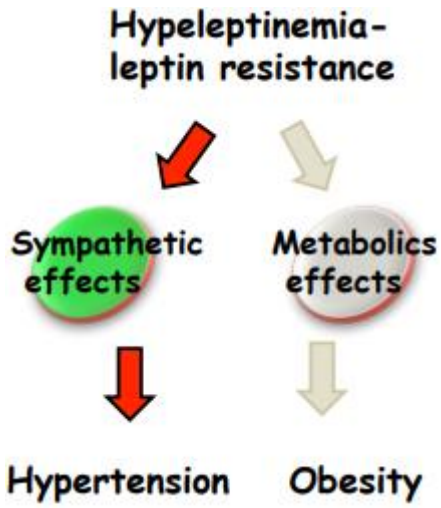
Peripheral leptin action on blood pressure:

- Leptin induces endotheliumdependent NO-mediated vaso relaxation

- Blunted in obesity
- Leptin action is mediated through Akt pathway

Selective leptin resistance:

- There is resistance to the appetite- and weight-reducing actions of leptin but preservation of the sympathetic actions.
- It is due to some hypothalamic centers (eg. DMH) are able to respond to leptin despite the leptin resistance in arcuate neurons



Week 12 Lecture 23: Bariatric Surgery as a treatment for morbid obesity

Obesity is escalating. It is categorised using BMI criteria. Overweight has 3 categories, class 1, 2 & 3. Class 2&3 are legible for bariatric surgery.

Comorbidities: Obstructive sleep apnea, NAFLD, polycystic ovarian syndrome, Coronary heart disease, diabetes, cancer, osteoarthritis.

Bariatric surgery: procedure that tames hunger, introduced a feeling of satiety, drive bodyweight loss by resetting setpoint to a lower level 20-30% weight loss, with max 60%, and improved glycaemic control. It is shown to be the most effective on %body weight loss.

- Eligibility: Usually a BMI over 40 or between 35-40 + comorbidities
- Bariatric surgical procedures: Laparoscopic adjustable gastric band, Roux en Y gastric bypass (more aggressive procedure by reorganising GIT, food is shuttled from oesophagus to duodenum, sleeve gastrectomy (simple removal of stomach section). All work by restricting food intake and absorption
- The procedure is largely due to the discretion of the clinician, patient preference or funding.
- Sleeve gastrectomy is becoming increasingly popular, this is due to effectiveness
- Study: LAGB has a slower onset compared to Rou-en-Y gastric bypass
- Compared to gastric (17kg), there is greater weight loss in the sleeve gastrectomy (35kg) in the first 12 months
- LAGB: insertions of an adjustable silicone ring around the proximal aspect stomach below the gastroesophageal junction. Injection of fluid can be adjusted in band
- Sleeve gastrectomy: using a smaller stomach sleeve, it restricts amount of food taken in before feeling full. May cause an increase in pressure and leakage leading to infection. Working to reduce this pressure may reduce benefits of weight loss.
- Strict guidelines follow these procedures like diet, i.e consumption of high caloric milkshake can bypass restrictive mechanism of LAGB
- Impact on nutrition, and deficient which occur, i.e with RYGB, which require lifelong nutritional supplements as normal metabolism is compromised. Iron and b12. Less pronounced in sleeve
- Follow up issues with LAGB as band needs adjusting to optimise

LAGB: results in 50% weight loss, gradual, not restrictive, no change in gastric emptying, reversible, impacts on T2DM is secondary to weight loss.

RYGB: approximately 50% weight loss, procedure is malabsorptive of calories and nutrients, requirements for vitamins, suggestions in increases in mortality (improved quality), irreversible, increased release of gut derived hormones; GLP1, PYY, Oxyntomodulin reducing gastric emptying. Resolution of T2DM (90% of patients taken off medication) possible related to reduction in caloric intake, however may not be permanent, as it is masked by large caloric reduction.

Sleeve: longer term results, initial 60-80% EWL. Dramatic weight loss, improved glycaemic control, irreversible, long term assessments are unclear. Implications that the reduction in body weight is driven by dramatic reduction ghrelin from stomach, this however was disproven and major drivers are changes in GRP1, PYY? Complication can include gastroesophageal reflux and leakage, leading to reoperation, possible hypertrophy of stomach.

T2DM:

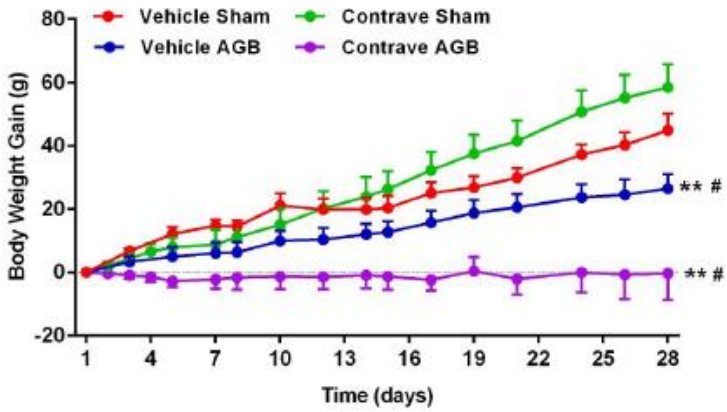
- Bariatric surgery is suggested as a treatment to those who are resistant to the pharmacological agent such as metformin.
- Sleeve may be more appropriate in high weight and glucose dysregulation
- Duration of diabetes, beta cell dysfunction, the promotion of inulin from GRP1 mediated mechanism from gut does nothing as pancreas cannot secrete insulin
- Improvement in postprandial secretion of L cell peptides such as GLP1 from enhanced distal intestinal nutrient delivery (enteroendocrine cells). Possible relation to ghrelin secretion
- Bile acids perturbation in mediating the positive effects

Mechanism:

- In gastric band, there are hormonal (changes in gut derived hormones) as well as neural (changes in vagal sensory activity.
- Study: in rates, following first inflation and 2nd, there is an impact on body weight gain to reduce fat mass (preferential for abdominal region), with no impact on lean or bone mass.
- Hormonal changes include elevation in GLP-1 and PYY. No changes in Ghrelin
- Inflation activates neurons in vagal sensory afferents to the brain stem.
- Study: capsaicin, removing vagal afferents, causes response to food intake reducing effects, and weight is not lost.

New therapies are looking at pharmacotherapy as well as bariatric to enhance satiety and increase energy expenditure. With surgery, there is a reduction in energy expenditure.

- Lean patients have high level of BAT activity compared to obese (low).
- Contrave (bupropion and naltrexone) was selected to reduce appetite and elevate energy expenditure.
- Contrave is used in conjunction with gastric banding to target acute period following surgery. (sub-effective dose) Possible synergistic effect?
- Contrave elevates BAT activity



Sleeve mechanism

- Decrease ghrelin (orexigenic), elevate GLP-1 +PYY
- Study: 3 groups: sham, sleeve and pairfed (same amount as sleeve)
- Sleeve results in a dramatic reduction in food intake
- Similar daily intakes occur 4 weeks after surgery
- Reduction in bodyweight gain (maintained after 30 days)
- Pairfed lost less weight
- In response to sleeve, there is elevation in BAT activity
- Pairfed showed reduced BAT activity
- Removing neural input to BAT reduces weightloss by 50%