* Gluconeogenesis – last time
* Today – regulate this pathway – see new pathway – pentose phosphate pathway – citric acid cycle
* Objectives – control metabolism of fuel – how to get energy – hormone to regulate pathways
  + PPP is very important for making NADPH – reduced form of NAD+ - contain a lot of protons for keeping down oxidative stress – make 5 C sugars (pentose) – glucose is hexose, not pentose
  + Importance of pathway that product is diverged to another pathway
* Control of fuel metabolism in mammals
  + Maintain blood glucose to be very controlled – critical for brain and other several organs
  + Use hormone – insulin and glucagon – act in opposite function
  + High blood glucose – pancreas stimulates insulin – stimulate glycogen formation – body trying to make storage polysaccharide to lower the blood sugar
  + If the action above is too effective – low blood glucose – stimulate glucagon – glycogen breakdown
  + Epinephrine also controls blood glucose – act really fast – go through signalling pathway towards second messenger – short term compared to insulin and glucagon
* Glucagon secreted by pancreas – interact with receptor – glucagon reaction – GPCR molecule – activate cAMP to let the cells know what happen outside – decrease glycolysis – increase gluconeogenesis – need to break down glycogen to make more sugar
* Slide 5 – effect of epinephrine – glucagon secreted by pancrease – epinephrine secreted by adrenal gland – epinephrine the little circle bind to the receptor and stimulate the pathways to make glucose level high in blood stream
* Slide 6 – a cell – hormone binds to receptor – G protein activated adenylate cyclate – generate cAMP (second messenger – first one is hormone) – need second to make cell understand first messenger) – phosphorylation – in the end got active enzyme
* Pentose phosphate pathway (PPP)
  + Pathway that oxidises glucose
  + Can have oxidation without oxygen in glycolysis – other molecules acting as oxidation agent
  + Oxidation of glucose without oxygen
  + See oxygen in mitochondria in the electron transport chain – the rest no see oxygen
  + Still oxidation even without oxygen
  + Alternative name for PPP – hexose monophosphate shunt or phosphogluconate
  + Need this pathway because it is possible to produce NADPH and R5P – important for synthesis of DNA and RNA
  + 6C to 5C ribose and NADPH – reduce oxidative sress
  + We get glucose-6-phosphate – made by hexokinase – add phosphate to glucose – need ATP for investing energy
* Four stages of PPP
  + Stage 1: 2 oxidation – G6P dehydrogensase and 6Pnate to generate NADPH – oxidative phase – start with 3 glucose and get 6 NADPH – NAD+ is getting reduced to NADPH – NAD+ is the oxidative agent
  + Important to understand which stage produces what
* Stage 1: don’t need to remember all structures
  + G6P dehydrogenase product 6-P…tone by reducing
  + 6-pho…nase hydrolyses get linear form
  + 6-…..ase produce NADHP
  + First reaction produce 2 NADPH, 1 CO2, 5C sugar
  + Important because regulation of the entire pathway
  + Ribulose-5-phosphate – main difference compared to glucose – 5C – this one is ketose, not aldose like glucose
  + Basically G6P and produce 2 NADPH, 1 CO2, 5C sugar
  + Start with 3 G6P get 6 NADPH
* Stage 2:
  + Phospentose isomerase….
  + Ribulose-5-Paste to R-5-p..phate
  + Number of C, O, H is the same but isomerase
  + Start with ketose – end with aldose
  + Ribulose…. Is ketose
  + Ribose… is aldose – is central for other pathways
* Stages 3 and 4
  + 5C can interact within themselves
  + 2 5C can be converted to 7C and 3C – transketolase and transaldolase
  + GAP – send back to glycolysis to go to pyruvate
  + 3C + 7C = 6C + 4C
  + Use fructose-6-P to go back to glycolysis
  + PPP can reutilise sugars produced depending on need of cells – eg need genetic material for replication
* Summary:
  + Relationship between glycolysis and PPP
  + Glucose generates G6P
  + Go through glycolysis up to pyruvate
  + G6P can be diverted into PPP – generate NADPH and R5P that can be used in nucleotides
  + Otherwise merge Xu5P to produce F6P and GAP that produce NADH and pyruvate (glycolysis)
* Aim of having PPP
  + Energy-wise – PPP does not generate energy
  + But important for nucleotides and nucleic acid
  + Important for NADPH – use a lot of fatty acid synthesis – important in cells – regenerate of sth oxygen species to control stress – reducing equivalent is NADPH – radical oxygen stress – oxidative stress
  + If cell is under stress and no NADPH to control stress – will die – will react with protein, DNA, etc…
  + If not under stress, can divert all the G6P to glycolysis – no waste
* Regulation of PPP
  + Compete with glycolysis for G6P – relationship between glycolysis and PPP – G6P at the crossroad – go one way or another
  + But not really competition – cells decide which one is needed more
  + Glycolysis is mainly energy generating pathway – cell needs energy favour glycolysis
  + If cell needs NADPH – will favour PPP
  + G6P dehydrogenase – regulates the flux of the PPP – first step – oxidative stage – no return point – go up to ribose once activated
* Pathway map
  + Glycolysis – generation of ATP, NADH and pyruvate
  + Glycogen metabolism
  + PPP – make ribose for nucleotides
  + Gluconeogenesis – glucose
* Citric acid cycle
  + Central pathway for oxidising all metabolic fuel
  + Most energy comes from oxidation in CAC – stored in NADH to be used in electron transport chain in mitochondria
  + CAC is anaerobic pathway – no oxygen – will see oxidation reaction though
  + 1932 – Krebs – the father – Krebs cycle – tested oxidation of various organic acids – called acids because they have carboxylic group – organic because carbon-based – discover that adding all these organic acids to liver – they oxidise – they were substrate of sth
  + All of the acids are oxidised in cyclic pathway – and then regenerate
  + Cells choose circular pathway to oxidise things – go from one to one and then back to the start and continue
* Stage 1:
  + Carbon from metabolic fuels – glucose – is incorporated into acetyl-CoA – very important molecule – bridge from glycolysis to CAC
  + Acetyl-CoA has 2 C – enter CAC to produce lots of things – oxidised more and more
  + Stage 3: go to electron transport chain and produce ATP
  + Reducing equivalent (such as NAHD and FADH2) will go to electron transport chain to create proton gradient to produce ATP – ATP production
  + Still use 3C pyruvate that goes to acetyl-CoA
  + In mitochondria of eukaryotes
* Mitochondria – organelle – 2 membranes – inner and outer – have intermembrane space in between
  + Matrix inside the mitochondria – cristae increase the surface of the membranes to do all the reactions
  + Stage 1 and 2 occur in matrix
  + Stage 3 in inner membrane
  + 2 membranes very different – 52% of protein in outer – 76% in inner membrane – also very different from other human cell membrane – inner membrane has such high concentration enzyme – electron transport chain enzyme and to synthesis ATP
* Major entry pathway of C to CAC
  + Use PDH multienzyme complex – several enzymes that are subunits to convert pyruvate to acetyl-CoA
  + E1, E2, E3 – and 5 coenzymes
* Thiamine pyrophosphate – vitamin B1 – coenzyme
* Lipoamide – cofactor of E2 – Lipoic acid is part of bigger structure, lipoamide – participate in transfer of ace… group
* Coenzyme A – thiol group
  + Thioester – important because can release more energy than oxygen ester – high energy compound
* FAD – participate in two-electron oxidoreduction reaction
* NAD+ - reduced form is NADH