The Liver

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The Liver

- Anatomy
- Microanatomy
- Function
  - Metabolism
    - Carbs
    - Fats
    - AA’s
    - Proteins
  - Storage
  - Drug inactivation and detoxification
  - Immunomodulatory functions
The Liver

• Is the largest gland in mammals
• AND
• The most boring.

• So, today is an ATTEMPT at a quick review (with lots of pictures)...there’s just so much *stuff*

• Followed by an ATTEMPT at making this organ interesting
  – “Sometimes you can’t put a shine on shit”
  • Fisher, B. *Wall of Wo*
Gross Anatomy

- Divided into 4 lobes
  - Right lobe
    - Largest
    - Separated from the left by the falciform ligament
  - Left Lobe
  - Quadrate lobe
    - Four sided
  - Caudate Lobe
Gross Anatomy

- Porta Hepatis
  - Area of vascular entry and bile duct exit
- Ligamentum Venosum
  - Patent at birth
Microanatomy

- Liver is arranged in lobules
- A central vein is surrounded by portal triads
  - Hepatic portal vein
    - Blood from intestines, brings nutrients and toxins
  - Hepatic Artery
    - Via celiac artery, brings O2 and fats
  - Bile ducts
    - Take bile formed by hepatocytes to gallbladder
Microanatomy

- Acinus is the functional unit of microcirculation
- Divided into 3 zones
  - Zone 1 – rich in oxygen, mitochondria
    - Oxidative metabolism and synthesis of glycogen
  - Zone 2 – transition
  - Zone 3 – lowest in oxygen, anaerobic metabolism, Cytochrome P-450
    - Biotransformation of drugs, chemicals and toxins
    - Most sensitive to damage due to ischemia, hypoxia or congestion
Microanatomy

• The paths from the triad to the central vein are fenestrated and discontinuous capillaries
  – Sinusoids
• The sinusoids are lined by hepatocytes and phagocytic Kupffer cells
• Kupffer Cells are the resident macrophages
• Reside in sinusoids
• Engulf antigenic material and senescent erythrocytes
• Account for the largest pool of phagocytes with direct access to blood
  – Very important in clearing portal bacteria (more on all this later)
Blood Flow

- Liver receives 25% of cardiac output
- Hepatic artery provides ~25% of blood flow
- Portal Vein provides ~75% of blood flow
- Drainage is via 3 major hepatic veins (right, middle and left)
  - Short extrahepatic segment before joining IVC
    - Makes surgical access, esp. in emergent situations, difficult
Blood Flow

• Portal pressure usually <10mmHg
• Portal sinusoidal pressure usually 2-4mmHg higher
  – Any increase in portocaval gradient will decrease sinusoidal flow
• Regulation
  – Autoregulation
  – Decreases in portal blood flow cause increased hepatic arterial flow
  – Neural control
    • Both sympathetic and parasympathetic control
Metabolism

• Carbohydrates
  – Glucose, fructose and galactose arrive via portal vein
  – Liver stabilizes serum blood glc by way of the following:
Carbs

- Glucogenesis
  - Fructose, sucrose, lactose and galactose are converted to glucose
Carbs

- **Glycogenesis**
  - Glucose is polymerized into glycogen, and then stored in the liver
- **Glycogenolysis**
  - Glycogen is hydrolyzed to glucose
• **Gluconeogenesis**
  - Triglycerides and amino acids are converted into glucose
• **Balance of all four pathways** mediated by complex hormonal interaction
• Please note the lactate-pyruvate relationship
• The liver is the primary organ that clears lactate from the blood
  – Shuttles it into gluconeogenesis
  – This conversion, however, is diminished in MODS secondary to shifts in global liver function
  – More later.....
Lipids

- Triglycerides, fatty acids and glycerol arrive via hepatic artery
- Ketogenesis
  - Ketone bodies formed from fatty acids after beta oxidation
  - Used as energy sources by brain, myocardium and kidneys
Lipids

- Lipogenesis
  - Synthesis of triglycerides that can be stored or converted
Proteins

- Amino acids arrive via hepatic portal vein
- Deamination
  - Removal of amine groups (NH3) from amino acids and proteins
- Decarboxylation
  - Removal of carboxy groups (-COOH)
Proteins

- Urea synthesis
  - Way by which amine groups are eliminated
  - Ammonia is toxic if it builds up
  - Notice that some of the enzymatic names are familiar given their associated defects
Proteins

• Synthesis
  – Clotting proteins
    • Factors II,V,VII,IX,X,XI,XII,XIII
    • Protein C,S, ATIII, fibrinogen, prothrombin
  – Albumin and Prealbumin
    • Albumin has half life of 20d, prealbumin of 1.9 days, making it a better marker of immediate protein/caloric intake
  – Alpha 1 antitrypsin
    • In liver disease, if decreased, uncontrolled proteolytic activity of lung by elastase can occur
  – Transferrin, haptoglobin, ceruloplasmin, lipoproteins,
Activation of Vitamin D

- The liver converts cholecalciferol (D3) into 25-hydroxycholecalciferol (calcidiol)
Nutrient Storage

• The liver stores energy as
  – Glycogen
  – Lipids

• Also stores
  – Vitamins A, D, E, K and B12
  – Copper and Iron
Bile Formation

• Bilirubin elimination is a critical liver function
• Most bilirubin formed from breakdown of hemoglobin (after being phagocytosed by Kupffer cells), myoglobin and cytochromes
• Emulsified by bile salts
  – A solution of sodium salts and cholic acid
Bile formation

• Little bile acid is required for emulsification
  – Very little made, so mostly conserved via
• Enterohepatic circulation
  – Bile salts and acids are reabsorbed in the terminal ileum
  – Recycled 4-12 times a day
  – Short bowel syndrome occurs with loss of terminal ileal function
    • Malabsorption of vits, fats, b12 and bile acids
    • Bile acids in colon cause osmotic diarrheal state
Drug Biotransformation

- Make drugs more polar for efficient elimination
- Phase I reaction
  - Cytochrome P450 system
  - Oxidation/reduction
  - Mixed function oxidases
- Phase II reaction
  - Conjugation usually catalyzed by UDP-Glucuronyl transferase
Drug Biotransformation

- Drugs with high extraction ratio are affected by changes in hepatic blood flow
  - Propranolol, lidocaine, meperidine
- Poorly extracted drugs are more sensitive to liver’s intrinsic ability to metabolize
  - Diazepam, phenytoin, coumadin
Detoxification of metabolic byproducts

**Glutathione Conjugation**
Detoxifies: Acetaminophen, Nicotine, Pesticides, Heavy Metals

**Required Nutrients**
- Glutathione
- P5P

**Amino Acid Conjugation**
Detoxifies: Benzozate, Aspirin

**Required Nutrients**
- Glycine
- Taurine
- Glutamine
- Arginine
- Ornithine

**Methylation**
Detoxifies: Estrogen, Dopamine, Epinephrine, Histamine

**Required Nutrients**
- S-adenosyl-methionine (SAM)

**Sulfation**
Detoxifies: Intestinal Toxins, Aniline dyes, Neurotransmitters, Estrogen, Testosterone, Steroids

**Required Nutrients**
- Cysteine
- Methionine
- Molybdenum

**Acetylation**
Detoxifies: Sulfur drugs

**Required Nutrients**
- Acetyl-CoA

**Glucuronidation**
Detoxifies: Morphine, Diazepam, Digitalis, Vanillin, Benzoates

**Required Nutrients**
- Glucuronic acid

**Additional Nutrients**
- NAC
- Methionine
- Glutamic acid
- Glycine
- Magnesium
- Potassium
- Methionine
- Choline
- B12
- Folic acid
- Thiamin
- Pantothenic acid
- Vitamin C
Humoral Function

- The liver is involved in catabolism of many hormones
  - Insulin
    - 50% of secreted insulin is degraded on a first pass basis
  - Glucagon
    - Direct secretion of above two into portal circulation amplifies hepatic influence over carb metabolism.
  - GH
  - Estrogens
  - Progesterone
  - PTH
  - Glucocorticoids
  - Thyroid hormone
  - ADH
  - Aldosterone

- Liver dysfunction thus results in endocrine abnormalities
Evaluation of liver function

• ALT and AST
  – Aminotransferases that are present throughout the body
    • AST found extensively in Liver, heart, skeletal muscle and kidney (at about equal amounts)
    • ALT found mostly in liver (and a little in kidney)
  – Elevated in hepatocellular and muscular injury, ALT mostly in just hepatocellular injury
  – Can be 40-50% higher than normal with high BMI
• AST and ALT
  – In BAT, they are useful markers of liver injury
  – Sensitivity and specificity of 92.9 and 100%, respectively for clinically sig liver injury
    • When AST>400 or ALT >250, CT indicated
  – Useful to detect intra-abdominal injury even in absence of hepatic injury
    • When AST>110 or ALT>63, there was radiologically detectable injury following BAT in 87 kids
      • Karaduman D, The role of elevated liver transaminase levels in children with blunt abdominal trauma, Injury, 2003
• GGT
  – Liver is the major source of activity
  – Increased levels indicate liver disease
    • Extrahepatic obstruction
    • Liver cancer
    • Hepatitis
    • Chronic cirrhosis
  – Sensitive, but not at all specific given wide DDx
  – “Useful for detecting cholestasis during parenteral nutrition……and screening for biliary complications after liver transplant”
    • Cabrera, J Gamma-Glutamyltransferase: value of its measurement in paediatrics Annals of Biochemistry, Jan 2002
  – GGT is increased an average of 12-fold above the upper reference limit in 93–100% of those with cholestasis
    • Dufour DR, Diagnosis and monitoring of hepatic injury. I. Performance characteristics of laboratory tests, Clin Chem 2001
• Albumin
  – Major protein in serum, produced by liver
  – Decreased in:
    • protein loss (nephrotic syndrome, burns, protein losing enteropathy)
    • increased albumin turnover (catabolic states, glucocorticoids),
    • decreased protein intake (malnutrition, very low protein diets)
    • liver disease – but must be of longer standing than the half life of albumin (~20d) to see effect
• PT
  – Measures clotting time after addition of prothrombin and TF
  – Associated with activity of Factors X, VII, V, II (prothrombin), and I (fibrinogen)
    • All made by liver
  – PT is reproducibly increased, usually at least 3 s beyond the population mean, in acute ischemic and toxic hepatitis
    • Dufour DR, Diagnosis and monitoring of hepatic injury. I. Performance characteristics of laboratory tests, Clin Chem 2001
• NH3
  – Product of amino acid metabolism and is cleared by Urea cycle in liver
  – High concentrations are seen with
    • deficiency of urea cycle enzymes
    • Liver failure
    • acute or chronic hepatic encephalopathy
      – No relationship between degree of encephalopathy and NH3 level
      – Must be separated from cells with 15 min to prevent artificial elevation
    • Dufour DR, Diagnosis and monitoring of hepatic injury. I. Performance characteristics of laboratory tests, Clin Chem 2001
• Bilirubin
  – Aarrrggghhh…..
  – Please refer to one’s residency in pediatrics
  – For further information,
    • Please ask someone else
Immunomodulation

Seki, S *The liver as a crucial organ in the first line of defense*, Immunological reviews, 2001


Wong, F *Sepsis in Cirrhosis*, Gut 2005
• The liver contains the largest population of phagocytes that have direct contact with the blood
  – Kupffer cells
• Uniquely positioned to be the first organ exposed to intestinally translocated bacteria
• Liver may contain pluripotent stem cells that give rise to all cell lineages
• Most bacteria that enter the blood stream accumulate in the liver and are entrapped by kupffer cells
  – Primary defense against portal bacteremia and endotoxemia
  – In rats 70% of injected viable E.Coli, taken up within 2 hrs by liver
• Kupffer cells release cytokines, namely IFN-gamma and IL-12 that stimulate hepatocytes to produce many acute phase reactants
  – CRP, complements, etc.
• When LPS or bacterial superantigens are injected into circulation of mice, liver monos, but not that of other organs, produced large amounts of IFN-gamma and IL-12
  – In rabbits, injected endotoxin cleared via kupffer cell uptake in the liver
• In response to endotoxin, kupffer cells release large amounts of TNF-alpha
  – TNF enhances procoagulant activity of vascular endothelial cells and increases neutrophil adhesion to endothelial cells – contributing to injury
  – BUT, Liver is able to take up and clear TNF
• NK cells of the liver are implicated in the Shwartzmann reaction – which is LPS initiated organ failure and death after second LPS exposure – through IFN-gamma sensitization of kupffer cells and t-cells, which then release lots of IL-1 and TNF
  – So, liver NK cells are both important effectors of defense, but can sensitize the host too strongly, triggering MODS
• Kupffer cells are potent scavengers for systemic and gut derived inflammatory mediators (TNF), toxic products (endotoxin) cytokines and bacteria
  – Play a crucial role in limiting the systemic inflammatory response
• Because of all the above, hepatic dysfunction may promote systemic bacterial or endotoxin spillover, which may be involved in pathogenesis of SIRS
  – Can occur even if other liver functions are intact
• Liver dysfunction, in absence of synthetic alterations, also leads to an increase in intestinal bacterial translocation
Liver NK cells are also major antimetastatic effector cells
- Inhibit tumor mets in the liver AND, tumor mets in other organs by migrating

The number of the liver’s effector cells (NK, kupffer and T-cells) are influenced by diet
- These cells are decreased in the liver in mice fed pathogen free diets
- Intestinal bacterial flora thus plays an important immunoregulatory role both in preventing overgrowth, and, ostensibly, by providing the liver’s cells with stimulus for proliferation
• Hepatocytes, in response to many mediators (TNF, IL-1, IL-6) will modify their metabolic pathway towards gluconeogenesis
  – Urea cycle, in mice, is depressed, decreasing arginine production
    • Uncouples NOS, which results in increased oxidant stress
• Hepatocytes increase synthesis and release of acute phase proteins (CRP, fibrinogen, LPS binding protein etc)
  – Enhance host immune response
  – Synthetic upregulation enhanced by influence of kupffer cells
  – However, AAP’s contribute to the procoagulant state via
    • Inhibition of protein C
    • Increased C4 binding protein (binds protein S)
    • Decreases liver synthesis of protein C and AT
    • Increased CRP promotes expression of TF
Finally…..

• So, the liver may be the start, the catalyst and the regulator of the systemic inflammatory response syndrome.

• Has an enormous potential for therapeutic intervention given its many important roles in starting, aggravating and regulating systemic inflammation

• Not so boring, now, is it?