Physiology team

Summary

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Bilirubin metabolism

Explain the fate of RBCs?

When the RBCs become Senescent (fragile) >> get lysis intravascularly or extravascularly by Liver & spleen >> release Hemoglobin

What happens to **Hemoglobin**?

Split to:

Globin > broken- down into AA >> stored

Heme >>Iron > transported by transferrin >> stored for erythropoiesis

>> bile pigment (Porphyrin) >> Biliverdin by Biliverdin reductase >> bilirubin

which **plasma proteins** will combine with **free bilirubin** to form a water soluble compound (**hemobilirubin**) ??

albumin and globulin

how the bilirubin absorbed through the hepatic cell membrane ??

mediated by a carrier protein (active transport) & combined with **Y & Z proteins** that trap the bilirubin inside the cells.

So hemobilirubin dissociates into **protein and free bilirubin**.

What are the substances conjugate with bilirubin ??

- 80% with **Glucuronic acid**
- 10% with sulphate >> bilirubin sulphate
- 10% others

how the bilirubin get conjugated with **Glucuronic acid ??**

one bilirubin + 2 uridine diphospho-glucuronic acid (UDPGA) >> bilirubin diglucuronide (cholebilirubin)

catalyzed by the enzyme **glucuronyl transferase** in the smooth ER.

>> actively secreted by the liver cells into the bile canaliculi

which substances responsible for the color of **bile**??

Bilirubin >> yellow-green of bile

Explain the fate of conjugated bilirubin??

- **Small amount returns to the PLASMA:**
  either directly into the liver sinusoids or indirectly from the bile ducts or lymphatics.
- **Small amount > de-conjugated> absorbed by the small intestine into the portal blood to the liver > conjugate again and excreted in the bile (entero-hepatic-circulation of bile pigments).**
- **The majority passes via the bile ducts to the intestine > transformed through bacterial action into urobilinogen which is highly soluble**

What is the fate of urobilinogen ??

- **70% converted into stercobilinogen >oxidized to stercobilin >> feces**
- **20% reabsorbed by intestinal mucosa> portal vein>liver > bile (entero-hepatic-circulation of urobilinogen)**
- **10% excreated in urine > oxidized to urobilin**

how can we differentiate between conjugated & unconjugated bilirubin??
By **Van den Bergh reaction:**

- **A direct Van den Bergh reaction:**

Conjugated bilirubin + Diazo reagent ⇒ Purple color

- **an indirect Van den Bergh reaction:**

Un-conjugated bilirubin + Ethanol ⇒ Free bilirubin
Free bilirubin + Diazo reagent ⇒ Purple color

- **Biphasic Van den Bergh reaction:**

blood contains both **conjugated and unconjugated bilirubin**.
purple color appears without adding alcohol and is intensified after adding it.

Transport of bilirubin in plasma occurs in two forms :

UN-CONJUGATED BILIRUBIN	CONJUGATED BILIRUBIN
Indirect reacting bilirubin-hemobilirubin	Direct reacting bilirubin-cholebilirubin
The chief form of bilirubin in the blood	Present in low conc. in the blood
Bound to albumin	Bound to glucuronicacid
Not filtered through renal glomeruli	Filtered through renal glomeruli
Not present in urine	Excreted in urine
Fat soluble	Water soluble
Toxic substance	Non-toxic substance

In which cells organelles The glucuronyl transferase system catalyzes the formation of the glucuronides of a variety of substances ??
smooth endoplasmic reticulum

which substances can cause marked proliferation of the smooth endoplasmic reticulum in the hepatic cells, with a concurrent increase in hepatic glucuronyl transferase activity??
barbiturates, antihistamines, anticonvulsants

which substances used for the treatment of of a congenital disease in which there is a relative deficiency of glucuronyl transferase (type 2 UDP-glucuronyl transferase deficiency)??
Phenobarbital

What are the other substances excreted in the bile ??
Cholesterol & alkaline phosphatase
It's blood level increased in case of jaundice due to intra or extra hepatic obstruction of the bile duct

jaundice

What is Jaundice ?

The yellow coloration of the skin , sclera . mucus membranes and deep tissues

What is the main cause of jaundice ?

Large quantities of free or conjugated bilirubin in the ECF

When does the skin begin to appear jaundiced ?

If the total bilirubin concentration in the plasma more than 2 mg/dl

At which level dose subclinical jaundice occur ?

It occurs if the total bilirubin concentration level from 0.5 to 2 mg/dl

Classification of jaundice :

1. Prehepatic (hemolytic) jaundice *in hemolytic jaundice the live excretory function in not impaired .

causes	Plasma concentration of bilirubin	Urine and stool characteristics	Van der reaction
-It results from excess production of bilirubin **-Excess RBC lysis is commonlythe result of:** **1- Autoimmune disease** **2- Hemolytic disease of the newborn** **3- Rh- or ABOincompatibility** **4- Structurally abnormal RBCs (Sickle cell disease)** **5- Breakdown of extravasated blood.**	**Concentration of free bilirubin (hemobilirubin) will be more than normal , and won't be filtrated by the kidney**	**-urine is free from bilirubine (acholuric jaundice)** **- the stools will appear more darker than normal due to excessive stercobilin formation**	**Indirect**

2.Hepatic (hepatocellular) jaundice :

This is due to :

- Impaired uptake of bilirubin int the hepatic cells
- Disturbed itra cellular protein binding or conjugation
- Disturbed active secretion of bilirubin in to bile canliculi

causes	Plasma concentration of bilirubin	Urine and stool characteristics	Van der reaction
-The causes may be due to: **1-Damage of liver cells e.g., viral hepatitis, drugs,** **2-chemical, alcohol, or toxins.** **3-Autoimmune hepatitis.** **4-Genetic errors in bilirubin metabolism.** **5-Genetic errors in specific proteins.**	**Both types of bilirubin (conjugated and unconjugated) → present in blood in high concentration due to :** **-the diseased liver cells are unable to take all the unconjugated hemobilirubin → increase its concentration in the blood.** **- intrahepatic biliary duct obstruction → regurgitation of CB in to blood**	**-urine appears dark brown due to filtration of excess CB** **-stools appear pale grayish due to deficiency of stercobilin**	**biphasic**

How to differentiate between jaundice due to biliary obstruction and hepatic jaundice ?

-in biliary obsrtructin : ALT goes up and down (pulsatile increase) and bilirubin concentration in the blood is high

-in hepatic jaundice : ALT shows persistent increase for a long period of time (months)

3.postheoatic (obstructive) jaundice :

*the rate of bilirubin formation and conjugation is normal but the CB can't pass in to the small intestine → returns back into the blood

causes	Plasma concentration of bilirubin	Urine and stool characteristics	Van der reaction
-caused by an obstruction of the biliary tree : **1..intraheoatic bile duct obstruction :** **-drugs , primary biliary cirrhosi and cholangitis** **2. extrahepatic bile duct obstruction :** **- gall stone , cancer of the pancreatic head and cholangiocarcinoma** .	**-concentration of the conjugated bilirubin in blood will be high .**	**-urine appears dark brown (liquorice) due to filtration of conjugated bilirubin .** **-urine free from urobilinogen** **-stools appear clay in color due to absence of stercobilin**	**direct**

	Prehepatic hemolytic	Hepatic Hepatocellular	Posthepatic Obstructive
Unconjugated	↑	↑	Normal
Conjugated	Normal	↑	↑
VDB	Indirect	Biphasic	Direct
AST & ALT	Normal	↑	Normal
ALP & yGT (γ glutamyl transpeptidase)	Normal	Normal	↑
Urine bilirubin	Absent	Present (dark brown)	Present (liquorice)
Urine urobilinogen	Present	Present	Absent
Stercobilin	↑ Darker	↓ Pale grayish	Absent (Clay Color)

When does neonatal jaundice resolve ?
In the first 10 days

What is the cause of neonatal jaundice ?
Immaturity of enzymes involved in bilirubin conjugation

What is kernicterus ?
It is a mental retardation due to crossing of uconjugated bilirubin the BBB (unconjugated bilirubin is a hydrophobic substance)

How to treat neonatal with hyperbilirubinemia ?
-phototherapy with UV light → to converts unconjugated bilirubin (wate insoluble) to conjugated bilirubin (water soluble)
-exchange blood transfusion

COLON
What are the most important Characteristics of the colon??
has many crypts of Lieberkühn , mucous- secreting goblet cells
what are the Functions of the large intestine ??

- Function of the large intestine
- Reabsorb water and compact material into feces.
- Store fecal matter prior to defecation.

The physiology of different colon regions ?

- Ascending colon: Specialized for processing chyme delivered from the terminal ileum.
- Transverse colon : Specialized for the storage and removal of water & electrolytes from feces.
- Descending colon : A conduit between the transverse and sigmoid colon. This region has the neural program for power propulsion that is involved in defecation reflex.
- The rectosigmoid region, anal canal, together with pelvic floor musculature: maintains fecal continence.

What is the type of secretion in the colon?
mainly mucus, no digestive enzymes.
What are the functions of the **mucus**?
1- It neutralizes against any acids present.
2- It protects against irritation.
3- It helps to lubricate feces.
What will happen if the segment of large intestine irritated by bacterial infection??
the mucosa secretes large amount of water & electrolytes in addition to the alkaline mucus > This dilute the irritating factors and causes rapid movement of the feces toward the anus.
Which substances will absorbed & secreted in absorptive part which is the the proximal half of the colon??
1. Water absorption, about 0.5- 1.5L/day
2. Na+ is actively absorbed (in the presence of Na+-K+ ATPase) at the basolateral membrane to blood.

3. K+ is secreted into the lumen of colon
4. Cl- is absorbed in exchange for HCO3- which is secreted.
5. Vitamins as Vit. K, biotin, B5, folic acid and some Amino Acid and short chain Fatty Acid resulting from bacterial fermentation of CHO are absorbed.
6. drugs ex.aspirin
7. bile salts

what are the actions of the bacteria in the colon??

1. Synthesis of vitamin K and some B group vitamins as folic acid, biotin, thiamine and B12
2. Deconjugation and decarboxylation of Bile salts. .
3. Break down of bile pigments to produce stercobilinogen
4. Decarboxylation of some AA to produce amine and histamine
5. Break down of urea by bacterial urease to ammonia.
6. Fermentation of undigested CHO

What is the function of ileocecal valve??

prevents backflow of contents from colon into small intestine.

It remains closed and open only when???

intestinal peristaltic wave reaches it.

What are the factors will stimulate contraction & relaxation of ileocecal??

Stimulation that Contract ileocaecal valve	stimulation that relax ileocaecal valve.
Distension of the cecum , Secretin , Ach and alpha adrenergic	Gastrin , B adrenergic and CCk

Motility in the colon

Mixing movements (haustration)	Propulsive (mass) movement	antiperstalsis
Cecum + ascending colon	Transverse + descending colon	at the junction of ascending and transverse colon > cecum (in the orad direction)
Contraction of circular & longitudinal muscles > haustration at the same time move slowly to analward	constrictive ring occurs at a distended point in the colon > forcing the fecal material mass down the colon persist for only 10 min to half an hour	Give sufficient time for absorption
For absorption , predominant	Programmed for defecation	

What are the initiation factors of mass movement ??

1. Gastrocolic & duodenocolic reflexes
2. Irritation of the colon
3. Intense stimulation of parasympathetic NS
4. Over distension of a segment of the colon.

What is the direct neural control of the contractile behavior of the colon??

The intramural plexuses

What are the Stimulatory & inhibitory enteric motor neurons ??

Stimulatory: Ach & substance P

Inhibitory: VIP & NO

What is the type of receptor the detect the distention of the RECTUM ??

Mechanoreceptors

Defecation is a spinal reflex which is influenced by higher center that's why a person with spinal cord injury & infants have fetal incontinence

RES :

What is the new term of reticuloendothelial system??
mononuclear phagocyte system
RES is an essential component of which system??
Immune system
Define thr RES ??
It is a network of connective &ssue fibers inhabited by phagocytic cells such as macrophages ready to attack and ingest microbes .
what are the cellular component of RES??

1. **monocytes**
2. **endothelial cells**
3. **macrophage**

where can we find monocytes & endothelial cells ??
monocytes in the blood
endothelial cells in bonemarrow,spleen,lymphnode

what are the differences between fixed & mobile macrophages??

Fixed Macrophages	Mobile Macrophages
more common	Less common
filter and destroy objects which are foreign to the body such as bacteria, viruses	can group together to become one big phagocytic cell in order to ingest larger foreign particles

What are the types of MACROPHAGES ??

Macrophage differ depending on the organs in which they reside

liver	Kupffer cells
brain	Microglia
lymph nodes, bone marrow, spleen	Reticular cells
subcutaneous tissues	Tissue histiocytes
lungs	Alveolar cells

All types of macrophages are derived from monocyte except kidney macrophage, derived from??? mesangial cell.

Explain the Transformation of monocytes to macrophage??

- increase Cell size

- increase Number and complexity of intracellular organelles. "Golgi,mitochondria, lysosomes"

-I increase ntracellular digestive enzymes

how much the monocyte will stay in the circulation then go to the tissue & transformed to macrophage?? 10_20 hours

what are the general features of RES??

- **Phagocytosis: (direct)**
- **Immune function: processing antigen and antibodies production (indirect)**
- **Breakdown of aging RBC.**
- **Storage and circulation of iron.**

Where is the site of B & T cells maturation??

T-cell maturation in the Thymus

Spleen is Site of B cell matura-on into plasma cells, which synthesize antibodies in its white pulp and initiates humoral response.

What are the Lymphoid Organs??

1. **Thymus**
2. **Lymph node**
3. **Spleen**

What are the differences between white & red pulp ??

- **White pulp: Thick sleeves of lymphoid tissue, that provides the immune function of the spleen.**

- **Red pulp: surrounds white pulp, composed of Venous sinuses filled with whole blood and Splenic cords of reticular connective tissue rich in macrophages.**

What are the general functions of spleen??

- **Haematopoiesis (Hemopoiesis): fetal life.**
- **site for destruction of RBCs specially old and abnormal .**
- **Blood is filtered through the spleen.**
- **Reservoir of thrombocytes and immature erythrocytes.**
- **Recycles of iron.**

What are the immune functions of spleen??

1. **Because the organ is directly connected to blood circulation, it responds faster than other lymph nodes to blood-borne antigens.**
2. **Destruction and processing of antigens.**
3. **Reservoir of lymphocytes in white pulp.**
4. **Site for Phagocytosis of bacteria and worn-out blood cells**
5. **Site of B cell maturation**
6. **Removes antibody-coated bacteria along with antibody-coated blood cells.**
7. **It contains (in its blood reserve) half of the body monocytes within the red pulp, upon moving to injured tissue (such as the heart), turn into dendritic cells and macrophages that promoting tissue healing.**

What are the indications of Spleenectomy??

Hypersplenism , Primary spleen cancers , Haemolytic anaemias , Idiopathic thrombocytopenic purpura (ITP) , Trauma , Hodgkin's disease and Autoimmune hemolytic disorders

What are the ricks and complications of spleenecomy??

bacterial infection or post splenectomy sepsis , prone to malaria , Inflammaion of the pancreas and collapse of the lungs , Excessive post-operative bleeding and Post-operative thrombocytosis and thrombosis.

Coagulation Mechanisms

What is the mechanism of blood coagulation??

physiological balance between (procoagulants) and (anticoagulants).

What will happen if the balance disturbed??

⇑ procoagulants (⇑ clotting) ⇒ thrombosis (blocking of Blood Vessels)

⇑ anticoagulants (⇑fibrinolysis) ⇒ bleeding

What does **Hemostasis mean??**

prevention or stoppage of blood loss.

What is the importance of the Coagulation??

To form of fibrin meshwork (Threads) to form a CLOT

what is the rule of prothrombin activator??

Activate prothromin(factorII) (plasma protein) to THROMBIN (protein enzyme) after long intrinsic or short extrinsic pathways

what is the rule of THROMBIN??

- **Change fibrinogen (factor I) (plasma protein) into fibrin (insoluble protein)**
- **stimulates platelets to release ADP & thromboxane A2**
- **Activates factor V XIII**

Which factors will give us strong fibrin ??

Fibrin-stabilizing factor (XIII) + Calcium

What are the factors triggered Intrinsic & Extrinsic Pathways??

- **Intrinsic pathway: The trigger is the activation of factor XII by contact with foreign surface, injured blood (all clotting factors present in the blood).**
- **Extrinsic pathway : Triggered by material released from damaged tissues (tissue thromboplastin) factor III .**

What is the importance of the fibrinolysis??

Break down of fibrin by naturally occurring enzyme plasmin therefore prevent intravascular blocking.

what is the rule of tissue plasminogen activators (t-PA)??

activate plasminogen to PLASMIN

what is the rule of PLASMIN??

Digests intra & extra vascular deposit of Fibrin → fibrin degradation products (FDP)

What is the unwanted effect of PLASMIN ??

digestion of clotting factors

how the PLASMIN is controlled??

By Tissue Plasminogen Activator Inhibitor (TPAI) & Antiplasmin from the liver

What is the uses of Tissue Plasminogen Activator ??

used to activate plasminogen to dissolve coronary clots

how our body prevent blood clotting in the normal vascular system??

- **Endothelial surface factor:**

- **Smoothness of the ECS.**
- **Glycocalyx layer**
- **Thrombomodulin protein**

- **Fibrin fibers**
- **Antithrombin III**
- **Heparin**

How the fibrin fibers prevent blood clotting??

Adsorbs 90% of thrombin to removes it from circulating blood

How the Heparin prevent blood clotting??

combines with Antithrombin III and quickly removes thrombin from blood heparin found in Liver, lungs, mast cells, basophils

what are the factors that require vitamin K for their synthesis??

Prothrombin, Factor VII, Factor IX, Factor X (2,7,9,10)

What are the characteristics of Hemophilia??

↑ bleeding tendency , males , X- linked disease

which factors will be deficient in hemophilia A & B??
Factor VIII deficiency (hemophilia A) (8=A)
Factor IX deficiency (hemophilia B) (9=B)
What dose <u>Thrombocytopenia</u> mean??
Very low number of platelets in blood (< 50,000/µl)