NASPGHAN Physiology Education Series

Fat Digestion: Bile Acid Physiology, micelles, and chylomicrons

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Overview (slides 4-7)

Gastric Lipolysis (slides 8-10)
Recall that normal lipolysis begins in the stomach. Through mechanical and chemical means, a reasonable amount of fatty acids are liberated here. Fatty acids help make more stable emulsion particles because they are more hydrophillic. Continued trituration eventually squirts the chyme into the duodenum.

The duodenum receives chyme with smaller emulsion particles because of the mechanical work done by the stomach and because the emulsion particles are more 'stable' with the addition of fatty acids released during gastric lipoysis. The emulsion particles in the duodenum immediately encounter bicarbonate and the pH begins to rise. Neutral pH and the addition of bile salts and phospholipids further stabilizes the emulsion particles because more fatty acids are ionized at neutral pH and because bile salts and phospholipids coat the emulsion particles. The bulk of lipolysis then occurs in duodenum and jejunum, while the products of lipolysis eventually make there way into micelles.

Gastric lipolysis is little discussed but may be important for infants and children with pancreatic disorders. It is interesting to note that different mammals have lipase either in the stomach OR in the saliva. These enzymes are quite similar in structure and activity. Human gastric lipase can be detected in amniotic fluid by 24 weeks of age. It has particular characteristics that are noted on this slide. It can be found in the upper body of the stomach. Its preference for MCTs and pH optima in the acidic range are worth keeping in mind when thinking about patients with fat malabsorption. Studies typically demonstrate that up to 30% of lipid hydrolysis can take place in the stomach. This gastric 'predigestion' facilitates digestion in the duodenum. It increases the stability of the fine emulsion in the duodenum and provokes release of CCK via the liberated fatty acids.

Fatty acids produced via gastric lipase-induced digestion of triglyceride become further ionized at the neutral pH of the duodenum and move to the surface of the emulsion particles. This serves to both stabilize the emulsion, and lead to some fatty acid diffusion to the intestinal surface, which serves as a signal for CCK release as noted before.

Bile acid physiology (slides 11-29)

Bile is mostly water. The solids in bile contain micelles filled with the fat-soluble organic components noted such as phospholipids and fatty acids. Other important components include trace minerals and xenobiotics.

Bile salts are important molecules. Their functions are myriad. They include the micellar solubilization of fats discussed below, but also serve as enzymatic co-factors for bile salt-dependent lipases, solubilizers of xenobiotics, heavy metals, and cholesterol in the bile, regulators of colonic fluid secretion, antimicrobial agents in the gut, and promoters of thermogenesis in brown fat.

Bile acid synthesis occurs via two pathways: the classical pathway (neutral pathway), which utilizes microsomal cholesterol 7a-hydroxylase (CYP7A1), or by mitochondrial sterol 27-hydroxylase (CYP27A1) of the alternative (acidic pathway). The pathway we discuss here is the classical pathway. The classical pathway begins with7a-hydroxylation of cholesterol catalyzed by CYP7A1, which is thought to be the rate-limiting step in BA synthesis. The classical pathway of BA synthesis occurs exclusively in the liver and gives rise to the two primary BA: cholic acid and chenodeoxycholic acid. An intermediate product is actually measurable in the blood (C4) and its blood concentration reflects the activity of the hepatic CYP7A1.

Bile salts are able assist in the intraluminal digestion and mucosal absorption of fat because of their **amphipathic** structure--- one side of the molecule is nonpolar, and the other side is variably polar, especially when molecules are ionized at a neutral pH. Thus acting like detergents, these molecules are able to keep emulsions stable so that lipolysis can occur on emulsion particle surfaces. Most importantly, these molecules also act to solubilize products of lipolysis in nanoparticle side micelles.

Primary bile acids become secondary bile acids in the distal small intestine. Bacteria change the structure of the bile acids usually by adding an –OH or removing an oxygen– these species are called ‘secondary bile acids’. Bacterial ALSO deconjugate bile acids, which means that they remove the amino acid side chains.

The **enterohepatic circulation** conserves bile acids and provides for their re-use during digestion. The majority of bile salts, conjugated primary and secondary bile salts, are reabsorbed via **sodium-coupled carrier-mediated uptake** by ileal absorptive cells, and then return to the liver via the mesenteric-portal venous system. Specific transporters export bile salts to the interstitium from basolateral surface of enterocytes. Complexed with albumin, bile acids then travel through portal blood to the sinusoidal membrane, where they are taken up by specific transporters. A very small amount of bile salt (~700mg) enters the colon each day, some of which is deconjugated and absorbed passively (~200mg), while most (~500mg) is lost in the feces.

The organ-level regulation of bile secretion is very similar to the regulation of pancreatic secretion. It is for this reason that bile ducts in patients with cystic fibrosis get plugged with viscous bile, because CFTR is also responsible for much of the electrolyte and fluid secretion from the bile duct epithelium.

As with the pancreas, infants may have a few reasons to have small bile acids pools. Ileal update of bile acids matures late in infancy. In addition, the ability of the immature liver to synthesize new bile acids is limited. Thus, early infants may have bile salt insufficiency, and this possibility may have clinical implications when combined with additional abnormalities in the intestinal tract.

Duodenal Lipolysis (slides 30-35)

Pancreatic lipase works at the surface of emulsified lipid droplets, depicted in this picture. Co-lipase, also binds to the surface of the emulsion particle. In the presence of bile acids, lipase activity is diminished, most likely because lipase is displaced from the surface of lipid droplets by bile acids. Co-lipase functions to re-associate pancreatic lipase with the lipid droplet, and optimize its enzymatic activity. Pancreatic lipase then continues to convert triglyceride on the surface of the emulsion to fatty acids and 2-monoglyceride. For these reactions to be optimal, the environment has to be right. This environment includes neutral pH, adequate mixing, and adequate amounts of materials (enzymes bile salts). These factors can be altered in disease and result in varying degrees of incomplete lipolysis.

Micelles (slides 36-46)

Micelle formation allows substances that have little water solubility on their own to act as if they are. This is a fascinating feat. Bile salts gather together in nano-size particles and package products of lipolysis in their interiors, which allows micelles to achieve mixing in the aqueous phase similar to standard water-soluble molecules.

Bile salts are needed in relatively high concentration in the small intestine in order to form micelles. However, overproducing bile salts is likely a bad idea because they are toxic, being detergents as well. This gets worked out because bile salts are re-circulated 2-3 times per meal because of their enterohepatic circulation. In adults, this may be about 2-3 grams of bile salts excreted in the bile per hour while a meal is being digested. Recall that the total pool size is about 4-6 grams. This connects to the reasonably easy possibility that the concentration of bile salts may not achieve the required concentration in the small intestine. This threshold is termed ‘critical micellar concentration’ (CMC). Achieving the CMC is dependent on intact enterohepatic circulation.

Understanding the physical chemistry of lipid phase transitioning in the intestine is only important for our purposes in explaining how there can be any fat absorption when bile salt concentration is below the CMC. When there are adequate bile salts, lipolytic products are water-soluble and absorption at the brush border is nearly complete. How is it that there can be up to 70% of dietary fat absorption in the absence of bile? In health, the intestine is long and there is some equilibrium between the lamellar vesicles and the aqueous phase, in which fatty acids can diffuse to the brush border. This occurs more readily for medium chain fatty acids, which have more intrinsic water solubility than long chain fatty acids.

It is apparent that a substantial amount of fat can be absorbed even if bile salt concentrations are insufficient to form micelles. Because fat-soluble vitamins are entirely nonpolar, they will not have appreciable equilibrium between the aqueous phase and the lamellar vesicles. This is the reason that fat-soluble vitamin deficiencies will develop in states of bile acid insufficiency unless water-miscible or parenteral vitamins are supplied.

Transport and Chylomicron Physiology (slides 47-56)

Micelles deliver products of lipolysis to enterocyte membrane for passive diffusion but also facilitated diffusion via noted transporters. Products of lipolysis and cholesterol enter endoplasmic reticulum and are re-esterified– there are likely proteins that participate in the chaperoning of absorbed products to the ER membrane.TGs and esters packaged in 'prechylomicrons', and bud off in specialized pre-chylomicron transport vesicles (PCTVs). PCTVs fuse with Golgi apparatus which finalizes lipoprotein coat, and sends vesicles filled with mature chylomicrons to fuse with basolateral membrane for release into the interstitium. Cholesterol and plant sterols can be ejected from enterocyte by energy dependent pump –mutations in DNA that encode these pump proteins cause a condition called sitosterolemia, one of the inherited dyslipidemias characterized by xanthomas, hyperlipidemia, early atherosclerosis, and hemolytic anemia.

Structure of lipoproteins or chylomicrons includes phospholipids oriented with their polar group toward the aqueous environment of plasma. Free cholesterol is inserted within the phospholipid layer. The core of the lipoprotein is made up of cholesterol esters and triglycerides. Apolipoproteins are involved in the secretion of the lipoprotein, provide structural integrity, and act as cofactors for enzymes or as ligands for various receptors.

Chylomicrons are the largest of the lipoprotein particles. They account for the white layer in plasma that is spun following a fatty meal, since they are packed with lipid and are less dense than water. As a side note, chylomicrons are large enough not to fit through the fenestrae in the liver sinusoids– they must deliver their payloads to peripheral tissue endothelial cells and become remnants before they can be processed by the liver.

Lymph drains from lacteals into larger and larger channels ultimately draining into the cisterna chyli in the retroperitoneum. Then, lymph flows up the thoracic duct typically emptying into the confluence of the left subclavian and left internal jugular veins. It will now be obvious how a surgical misadventure in the abdominal or thoracic cavities could lead to chylous fluid losses into these spaces.

Medium-chain triglycerides are important to discuss. We know that medium-chain triglycerides are hydrolyzed in the stomach preferentially, and that have increased water solubility without the need for micelles. But post-transport, they have additional unique pathways. Medium chain fatty acids move through cells without the need for repackaging. They may also move paracellularly. In either case, they accumulate basolaterally in the interstitium, where they can diffuse into capillaries and bind to albumin. Then, they make there way into the portal blood and to the liver for processing or to the systemic circulation for distribution to periphery as a fuel source. It is apparent that medium-chain fats do not employ chylomicrons for access to the systemic circulation.

Clinical correlation with lymphangiectasia and chylomicron retention disease reinforces the importance of different pathways for absorption between long chain and medium chain fatty acids.