Metabolic and Clinical Perspectives on the Functions of the Liver

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By
Åke Nilsson and Stefan Lindgren

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About the Authors

Åke Nilsson, MD, PhD is a former professor in medicine/gastroenterology at University of Lund, and Senior Consultant in Gastroenterology at Skane University Hospital Lund, Sweden, where he served as head of the medicine clinic for 6 years, and of the gastroenterology for about 20 years. He has special interests in inflammatory bowel disease, hepatology, clinical nutrition, and intestinal failure. His scientific production is both translational and clinical. After a Ph D in physiological chemistry and a postdoctoral period at Cornell University US, he led a research group that combined translational and clinical research, and which was supported by the Swedish Research Council for more than 30 years. His translational science is linked to phospholipid metabolism and lipid signaling in the gut and liver, and to colon and liver cancer. He has supervised several doctoral students and has written book chapters and recent review articles.

Stefan Lindgren, MD, PhD is a former professor in medicine/gastroenterology at Lund University and Senior Consultant in Gastroenterology at Skane University Hospital, Malmö, Sweden. His main research, clinical and teaching interest is in inflammatory liver and bowel diseases. During the last ten years this has also comprised iron deficiency in relation to systemic inflammation. In addition, he has devoted time and interest to academic education and has held several faculty positions related to undergraduate medical education at Lund University. His academic work has also included national and international roles as leader within both undergraduate and postgraduate education and research. Some international examples are President of World Federation for Medical Education and the European Federation of Internal Medicine. National positions include President of the Swedish Society of Medicine and the Swedish Society of Gastroenterology.

PREFACE

When the liver fails, the patient loses muscle mass, strength, and energy. The skin and whites of the eyes turn yellow, and bowel and brain functions, blood clotting and defense against infections deteriorate. Plasma levels of glucose, lipids, proteins, amino acids, and many hormones become abnormal, and the regulation of blood circulation and renal function fails. The failure discloses that the liver has multiple functions related to the regulation of metabolism, bile secretion, blood coagulation, defense against infection, and production of plasma proteins.

The healthy liver controls blood glucose level, blood lipids, and inflammation, thereby conveying many connections between diet, lifestyle, and health. In many severe diseases, it promotes survival chances and recovery by its role in the redistribution of body resources. Yet, the liver remains remarkably anonymous to many health professionals due to the complexity of its functions.

Many knowledge gaps in liver physiology and biochemistry have been filled during the last decades. Important mechanisms behind bile secretion, nutrient traffic and metabolic regulation have been identified. Many mechanisms behind the liver's key role in the defense against infections, in blood coagulation, and in the body's reaction to trauma and life-threatening diseases have been clarified. Parts of the pathophysiology behind the development of common liver diseases have been elucidated. The new molecular biology and analytical techniques have been crucial to this development.

On the clinical side, liver transplantation, improved treatment of viral hepatitis, refinement of imaging techniques and improved tumor surgery account for remarkable progress. Despite progress, alcohol-related liver disease, and nonalcoholic fatty liver remain major challenges.

Gut bacteria have long been in focus in severe liver disease. The risk of infection is high, and treatment directed against intestinal bacteria also counteracts cerebral dysfunction (encephalopathy) and other complications. The idea that disturbances in our harmonious interaction with gut bacteria have broader implications is not new. The Nobel laureate Eli Metjnikof (1845–1916), who discovered the macrophages, believed that "the majority of our diseases begin in the gastrointestinal tract, when good bacteria can no longer control the bad bacteria". He called this condition dysbiosis, a

term which is today frequently used. Today, most substances in blood and tissues can be quantified while mapping the genes of the host and gut bacteria. The gut-liver interactions are studied extensively. The interpretation of all the new information is complex. Grasping and clarifying the whole is more challenging and interesting than ever.

This book balances an overview and a more in-depth description of important areas. An introductory overview introduces liver functions, nutrient absorption, and energy metabolism, and how the gut and the liver work together. This part introduces a broad metabolic section. We then turn to inflammation biology, discussing the barrier and immune functions of the gut liver axis, the interaction with the gut microbiome, and the role of the liver in the defense against infections. All these aspects are important when we then turn to the pathogenesis of alcohol-related (ALD) and nonalcoholic fatty liver disease (NAFLD), and gallstones, and to liver failure, portal hypertension and the role of the liver in sepsis and in cancer cachexia. Finally, we describe how the liver mediates the beneficial effects of a healthy diet and physical exercise and how the interplay between the liver and the brain influences our well-being.

The book places what the liver does in a clinical context but is not a systematic hepatology book. We hope to make curious readers even more curious and knowledgeable about this fascinating organ. The subject is broad. Many references are to recent reviews, which in turn refer to the thousands of important original articles that are behind today's liver knowledge. It is simply impossible to make original discoveries justice in the reference list of a book in this format.

The book was published in Swedish in 2022 by Studentlitteratur AB Lund Sweden. Translating and revising the book, we have benefitted from the earlier editing work done by Vala Flosadottir, Inger Jänchen and, regarding the illustrations, Jonny Hallberg at Studentlitteratur. Thanks also to Edith Nelander for her watercolor paintings of the interior and the outside of the liver. Finally, thanks to all colleagues with whom we have had fruitful discussions during the preparation of the Swedish version, particularly Professor Eva Degerman (metabolic aspects), Professor Emeritus Lennart Truedsson (gut and liver immunology) and dietician Carina Trägårdh (diet and health aspects).

List of Abbreviations

ABC transporter	ATP binding cassette transporter
Acetyl-CoA	Acetyl-coenzyme A
ADP	Adenosine diphosphate
ALD	Alcohol related liver disease
AMP	Adenosine monophosphate
AMPK	AMP activated protein kinase
ANGPTL4	Angiopoietin-like protein 4
ATP	Adenosine triphosphate
CD 36	Cluster of differentiation 36
CETP	Cholesterylester transfer protein
ChREBP	Carbohydrate response element binding protein
CoA	Coenzyme A
CPT1	Carntine palmitoyl-CoA transferase 1
CREB	Cyclic AMP regulatory element binding protein
CRP	C-reactive protein
CYP2E1	Cytochrome P450 2E1
CYP7A1	Cytochrome P450 7A1
DAMP	Danger associated molecular pattern
EGFR	Epidermal growth factor receptor
F1P	Fructose-1-phosphate
FAD	Flavin adenine dinucleotide
FGF21	Fibroblast growth factor 21
FOXO1	Forhead box protein O
G6P	Glucose-6-phosphate
GABA	gamma-aminobutyric acid
GIP	Gastric inhibitory peptide
GLP-1	Glucagon-like peptide 1
GLUT	Glucose transporter
GPBAR1	G-protein-coupled bile acid receptor 1
GTP	Guanosine triphosphate
HDL	High density lipoprotein
HGF	Hepatocyte growth factor
HMG-CoA	Hydroxymethyl-glutaryl-Coenzyme A
IL-1	Interleukin 1
IL-6	Interleukin 6

LCAT	Lecitin cholesterol acyltransferase
LDL	Low density lipoprotein
LPL	Lipoprotein lipase
LPS	Lipopolysacharide
LXR	Liver X receptor
MMC	Migrating myoelectric complex
mTORC1	Mammailan target of rapamycin complex 1
NAD	Nicotinamide adenine dinucleotide
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NEFA	nonesterified fatty acid
NOD	Nucleotide-binding oligomerization domain like receptor
NPY	Neuropeptide Y
NRF1	Nuclear respiratory factor 1
PAMP	Pathogen associated molecular pattern
PCSK9	Proprotein convertase subtilisin/kexin type 9
PDGF	Platelet derrived growth factor
PEPCK	Phosphoenolpyruvate kinase
PKA	Protein kinase A
PLTP	Phospholipid transfer protein
PPAR	Peroxisome proliferator activated receptor
PUFA	Polyunsaturated fatty acids
PYY	Peptide YY
RGB	Roux-en Y gastric bypass
RIG-I	Retinoic acid inducible gene I like receptor
ROS	Reactive oxygen species
RXR	Retinoid X receptor
SAM	S-adenosyl-methionine
SCFA	Short chain fatty acid
SGLT	Sodium dependent glucose transporter
SREBP	Sterol regulatory element binding protein
TGF-β	Transforming growth factor beta
THF	Tetrahydrofolate
TMA	Trimethylamine
TMAO	Trimethylamineoxide
TNF-α	Tumor necrosis factor alpha
VLDL	very low density lipoprotein

CHAPTER 1

THE LIVER – AN INTRODUCTION

The liver is brown in color, has a smooth surface, and weighs 1200-1500g, i.e., about two percent of body weight. The liver blood flow, however, amounts to 20–25 percent of cardiac output at rest. The liver receives both arterial blood through the hepatic artery, and venous blood from the gastrointestinal tract, the pancreas and the spleen which is collected in the portal vein. About 1200 ml of blood passes through the liver every minute. One-fifth to one-third comes via the liver artery and two thirds to four fifths via the portal vein.

The blood vessels branch in the liver into a fenestrated capillary network designed to facilitate the bidirectional traffic of molecules and molecular aggregates such as lipoproteins, between the blood and liver cells, and the elimination from blood of bacteria, virus, and ageing blood cells. Bile is secreted from the canalicular pole of the hepatocytes into canaliculi which converge into the bile ducts that transport bile into the gallbladder and into the duodenum. A rupture of the blood-rich liver after a trauma can cause terrible bleeding, but the liver itself can help to sort it all out. It forms the clotting factors needed to stop bleeding that can be stopped. When surgical resection of a large part of the liver is needed, it recreates new liver tissue from the part that is left, so that the liver returns to its previous size. No other organ except bone marrow has such regeneration ability.

The liver accounts for 20-30% of our total oxygen consumption. Its brown color is due to the large content of mitochondria and cytochromes, iron-containing enzymes that participate in the aerobic energy production of the mitochondria. All the metabolic transformations and the transport and secretion processes that take place in the liver require a lot of energy.

THE MULTIPLE FUNCTIONS OF THE LIVER

The liver forms a functional unit with the gut. Via the portal blood both absorbed nutrients and material that should be rapidly discarded pass the liver before entering the systemic blood, and the bile secretion supports intestinal functions and secretes waste products. The liver supplies nutrients to other tissues and it receives and uses recirculating nutrients and metabolites, the metabolism at whole body level being coordinated by hormones, cytokines, and nerve impulses. It is also a lead actor in the body's defense against infections and reaction to trauma. Many functions are interconnected. The liver is a logistics center where several functions are coordinated, coregulated, and interconnected. It is therefore not obvious how the functions of the liver should be grouped. We have chosen to introduce them by using four main headings (Figure 1.1):

1. ***Regulation and coordination of metabolism.*** The liver ensures that all organs have access to glucose and other energy sources that they need for the moment, and to materials that are necessary to build and maintain the functions of cells. For this, the liver needs to interact effectively with the intestine, from where nutrients are absorbed, and with the adipose tissue that is the body's largest energy depot. It regulates not only carbohydrate, fat, and amino acid metabolism. The liver also controls intestinal uptake, storage, and distribution of iron, and regulates copper balance via excretion in the bile. Finally, it regulates storage, metabolic conversions and transport of vitamin A and D, and of folate and cobalamins. Since iron has a key role in oxygen transport and aerobic energy metabolism, and both iron, copper and the vitamins are needed for many specific enzymatic reactions, we view these functions as a part of the metabolic regulation.
2. ***Production of bile.*** The liver cells produce bile, which is needed for digestion and uptake of fat and fat-soluble vitamins in the intestine, and for optimal function of the intestinal mucosa including control of bacterial growth in the intestine. Bile secretion also eliminates numerous endogenous and exogenous organic chemical compounds, such as bilirubin, cholesterol, steroid hormone metabolites and metabolites of fat-soluble drugs.
3. ***Key role in the body's response to infection and trauma.*** The liver eliminates a major part of the bacteria, bacterial products, viruses, and material from dead or damaged cells that reach the blood. It produces proteins that participate in the defense against infections and regulate inflammatory reactions, and most of the factors that mediate, regulate and resolve blood clotting.

4. ***Production of plasma proteins.*** The liver produces most of the plasma proteins that generate the colloid osmotic pressure of blood that is needed for normal blood circulation and the partitioning of body fluid between the intravascular and extravascular spaces. A range of plasma proteins produced in the liver have transport functions or other specific biological functions. Immunoglobulins are the only major plasma proteins that are not produced in the liver.

The different functional areas are linked to each other (Trefts, Gannon, and Wasserman 2017). E.g., the production of plasma proteins is also an important part of protein and amino acid metabolism, and of blood coagulation and defense against infections. The conversion and excretion in bile of endogenous and foreign organic chemicals is also a branch of metabolism and metabolic regulation. Infections and trauma strongly affect the regulation of metabolism, in a way that favors survival and recovery. We start, however, by introducing the four main areas of operation. It will gradually emerge how they intervene in each other (Fig. 1.1.).

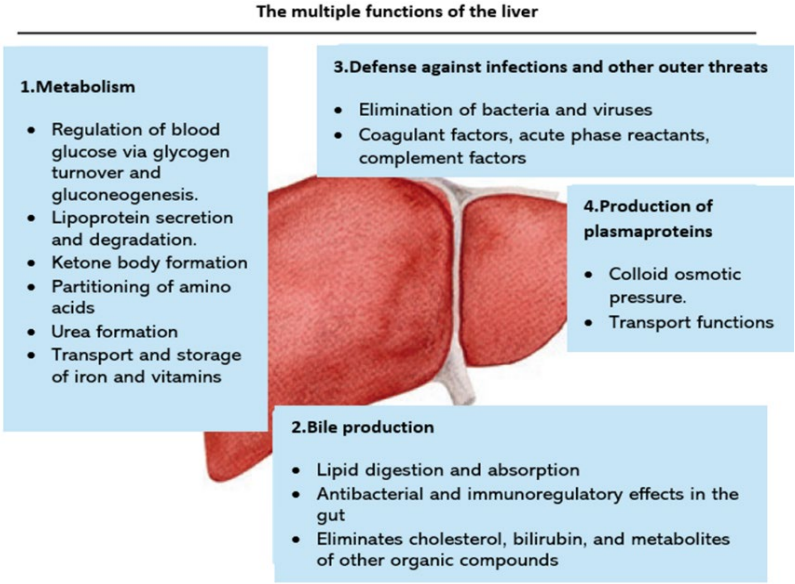

Figure 1.1. The four major areas of operation of the liver. The different areas intervene in each other. The metabolism of carbohydrates, fat and protein is coordinated, and metabolism, bile production, immune functions and blood coagulation have important connections to each other. *Figure: Edith Nelander.*

Regulation and coordination of metabolism

The body's organs need energy sources and materials to build up cells. What is needed is supplied in the diet as carbohydrates, fat, protein, vitamins, and minerals. Metabolic regulation synchronizes utilization with absorption, transport, storage, and mobilization of nutrients. Glucose and fatty acids are the main energy sources. Amino acids contribute a smaller but important part. The role of the liver in the regulation of glucose, fatty acid and amino acid metabolism, and the regulated storage and release of fatty acids in adipose tissue enable continuous tissue access to necessary nutrients. Metabolic regulation adapts to increased needs of individual tissues, e.g., during physical exercise and during activation of the immune system and repair mechanisms in severe disease.

Regulation of glucose metabolism

The liver is a main actor in the regulation of glucose metabolism. Prevention of detrimental falls in blood glucose concentration is vital, since hypoglycemia causes immediate dysfunction of the brain, which has a high obligate glucose consumption. Even other parts of the nervous system, and erythrocytes, are obligately glucose dependent, and all organs use glucose for their energy supply to varying degrees. Glucose is the only energy source from which cells can extract energy without access to oxygen. Glycolysis, i.e., the initial anaerobic stage of glucose metabolism, in which glucose is converted into two molecules of pyruvate, is a flexible energy source. The aerobic oxidation of pyruvate, fatty acids and amino acids to carbon dioxide and water generates greater amounts of energy but cannot replace the functions of glycolysis. The liver regulates blood glucose level by controlling its uptake and release of glucose. This is done by storing and mobilizing glycogen, and by synthesizing glucose (gluconeogenesis). Glycogen is a polymer, which consists of long, highly branched chains of glucose molecules. After a meal containing carbohydrates liver glycogen is synthesized and accumulates. When the influx of glucose from the gut ceases, the liver breaks down stored glycogen and releases glucose into blood. Gluconeogenesis ensures the blood glucose level when glycogen depots are emptied. The availability of nutrients, hormones, and nerve impulses together regulate the liver's balance between storage and release of glucose. Insulin stimulates the formation of glycogen after ingestion of carbohydrates, and glucagon stimulates mobilization from glycogen, and gluconeogenesis, during fasting. In the intestine, the major dietary carbohydrates, i.e., starch, sucrose and lactose are degraded to monosaccharides which are absorbed into

the portal blood. Starch, which is a polymer of glucose molecules, sucrose which is a disaccharide consisting of glucose and fructose, and lactose which is a disaccharide consisting of glucose and galactose, all generate glucose. Although the hepatic uptake of absorbed glucose from portal blood increases with increasing concentration, the glucose concentration increases in systemic blood after a meal. Fructose and galactose are effectively taken up by the liver, mostly during the first pass. Galactose is converted to glucose in the liver and fructose to pyruvate which may in turn generate glucose and fatty acids.

Amino acid distribution and nitrogen balance

Some of the amino acids contained in the body's proteins are essential (indispensable), i.e., they must be supplied in the diet. Others can be formed in the body via metabolic conversions. The liver has a high protein and amino acid turnover, and it sorts out the amino acids that are not needed for protein synthesis, to oxidation and gluconeogenesis. It controls the transport of individual amino acids so that other organs have access to the amino acids they need. When muscles and other extrahepatic tissues oxidize amino acids, the nitrogen is taken care of and recirculated as the amino acids alanine and glutamine. Much of the alanine carbon is used for hepatic gluconeogenesis, and glutamine is used for amino group transfers and synthetic reactions. The liver eliminates amino acid nitrogen by producing urea that is eliminated mainly in urine. In this way, the body maintains its nitrogen balance, i.e., the relationship between the ingested amount of amino acid nitrogen and the amount that is retained in the body's proteins.

The protein in the food is degraded in the intestine, to amino acids that are transported by the portal vein through the liver. The hepatic uptake of amino acids is effective and increases with increasing postprandial concentrations in the portal blood. Uptake kinetics differ between individual amino acids.

Fatty acid transport and metabolism

In the absorptive cells of the small intestine the absorbed fat builds into the triglyceride rich chylomicrons which are transported via intestinal lymph and reach the vein system beyond the liver. The chylomicron fatty acids are distributed between oxidation, and lipid synthesis in the liver and other tissues, and storage as triglycerides in adipose tissue. The liver has a high uptake of non-esterified fatty acids (NEFA) released from adipose tissue and from chylomicron and very low-density lipoproteins (VLDL) triglycerides. It meets a large part of its own energy needs by fatty acid

oxidation. Glucose cannot be formed from fatty acids, but a large part of the energy needed for the gluconeogenesis in the liver comes from fatty acid oxidation. The liver also generates ketone bodies, which are water-soluble partial oxidation products of fatty acids, which other organs can use as an alternative energy source, when supply of glucose is scarce.

The partitioning in the liver of fatty acids between oxidation and synthesis of triglycerides and phospholipids varies with the nutritional state. The generated triglycerides are secreted as triglyceride rich VLDL or temporarily stored as fat droplets in the cytoplasm of the hepatocytes. The liver also has a significant biosynthesis of fatty acids when glucose or fructose is available in excess.

Most of the triglycerides in chylomicrons and VLDL are hydrolyzed by the enzyme lipoprotein lipase in the endothelium of muscles, heart, lung, and adipose tissue. Of the remaining remnant particles most chylomicron remnants are taken up by the liver, whereas VLDL remnants are partitioned between hepatic uptake and further conversion to low density lipoproteins (LDL). Both remnants and LDL are eliminated from blood mainly via the liver's lipoprotein receptors. During the triglyceride lipolysis phospholipids and some peptides are transferred from the surface of the chylomicrons and VLDL to high density lipoproteins (HDL). Whereas remnants and LDL are atherogenic, HDL has antiatherogenic effects. Lipoprotein secretion and elimination by the liver, in combination with the transfer of lipids between lipoprotein classes in blood, regulates fatty acid and cholesterol traffic between tissues and determines the plasma lipoprotein profile.

Redox metal ion and vitamin transport

Iron has a key role in oxygen transport and energy metabolism. Vitamins have multiple functions in energy metabolism and anabolic reactions.

By producing the hormone hepcidin, the liver regulates the iron uptake in the gut and iron release from cells in which it is stored. This hormone inhibits iron absorption in the gut and is released into the blood when iron stores are sufficient. The liver also produces the transport protein transferrin which distributes iron to hematopoietic and other proliferating cells. The copper balance is regulated by a transporter mediated secretion of copper into bile, and the liver derived protein ceruloplasmin transports cupper.

The liver stores vitamin A-esters. It produces retinol-binding protein that transports retinol to retina and other tissues. To become active, vitamin D undergoes two sequential hydroxylation reactions, at position 25 and 1. The activation begins in the liver with the formation of 25-hydroxy-vitamin D. The liver also synthesizes vitamin D transporting protein, which binds

vitamin D and its metabolites. The B-vitamins have important functions in energy metabolism (B1, B2, B3, B5, B7) and in anabolic reactions (folate, B12). Although the liver does not have well defined storage pools of B-vitamins, a high content parallels the high mitochondrial density.

Bile production

Bile contains bile salts, which are detergents that facilitate fat digestion and fat uptake in the gut. The bile salts themselves are mostly absorbed in the lower small intestine and reused for bile secretion. They counteract bacterial growth in the small intestine and influence intestinal barrier and immunological functions, and hepatic lipid and glucose metabolism. These functions may be influenced by bacterial conversion of bile salts in the gut.

By forming bile salts from cholesterol and by excreting cholesterol in bile, the liver maintains the body's cholesterol balance. The loss of cholesterol and bile salts in feces balances the de novo synthesis and dietary supply of cholesterol to keep the body pools of cholesterol constant. Secretion of phospholipids in bile counteracts formation of cholesterol gallstones and enhances emulsification of lipids during digestion, and chylomicron formation after absorption. The phospholipids also have cytoprotective effects in the bile ducts. Many endogenous and naturally occurring organic compounds and lipid-soluble drugs are eliminated in bile after conversion in the liver to more water-soluble products. Bilirubin, which gives bile its yellow color is a breakdown product of heme from hemoglobin and other heme containing proteins.

The key role in infection and trauma

The liver is a vital part of the constitutive immune defense against bacteria and viruses. The liver decreases the risk of developing sepsis, a life-threatening condition in which bacteria multiply in the bloodstream. Some bacteria enter the blood every day. Most bacteria that reach the bloodstream have about an 80 percent chance of being eliminated by the liver, which contains macrophages, that ingest and destroy (phagocytose) bacteria. The stationary liver macrophages (Kupffer cells) interact with other cells in the liver, and with white blood cells and platelets, when viruses, bacteria, and bacterial products are eliminated and destroyed. In infections and trauma anywhere in the body, the liver increases its production of a series of proteins called acute phase reactants, including C-reactive protein (CRP), which assist in the elimination of infectious agents. The liver also produces complement factors that are important for the killing of infectious agents.

The gut and liver collaborate to maintain a controlled interaction with the gut bacteria. In the large intestine there are huge amounts of bacteria, which break down and ferment fiber in plant food, to produce short chain fatty acids (SCFAs) which are used by the host. The gut maintains a selective barrier of mucus, a tight epithelium, and a strong immune system. Normally the intestinal and liver immune systems are tolerant to gut bacteria and certain amounts of bacterial products. They react, however, with severe inflammation if the exposure increases due to defective barrier function, and to the presence of pathogenic infectious agents.

The liver's production of clotting factors is vital. It produces both factors that activate and factors that restrict and regulate blood clotting, and factors that mediate the resolution of thrombi. Fibrinogen, which is converted into fibrin, the net in the blood clot, is produced in the liver. The production of some coagulation factors, including fibrinogen, increases in case of infection and trauma.

Production of plasma proteins

The liver's production of plasma proteins is quantitatively large. The total amount of protein in blood determines the colloid osmotic pressure of the blood plasma, i.e., the force that controls the filtering of extracellular fluid into the interstitial space. The concentration of albumin that makes the greatest contribution to the colloid osmotic pressure in blood plasma is about 40 g/L. Albumin also binds and transports nonesterified fatty acids (NEFA), a variety of other organic substances such as unconjugated bilirubin, and divalent metal ions such as Ca^{2+} and Mg^{2+}. The liver also produces specific transport proteins for iron and copper, hormones, and vitamins. Coagulation factors and complement factors are already mentioned. The only quantitatively large plasma protein group that is not formed in the liver is the immunoglobulins i.e., the antibodies, which are formed by the immune system's B lymphocytes and plasma cells.

THE GUT-LIVER COLLABORATION

What happens in the stomach and intestine determines the course of the absorption of nutrients after a meal. The postprandial portal vein concentrations of nutrients and of hormones secreted from the pancreas and the intestine differ from the concentrations in systemic blood, the differences for individual compounds being related to the efficiency of absorption and first pass hepatic uptake. When the body assimilates nutrients, the pancreas, intestine, and liver collaborate effectively (fig. 1.2). Absorbed monosaccharides

and amino acids are delivered to the portal blood. The fat is delivered to the bloodstream via the chylomicrons of the intestinal lymph, beyond the liver.

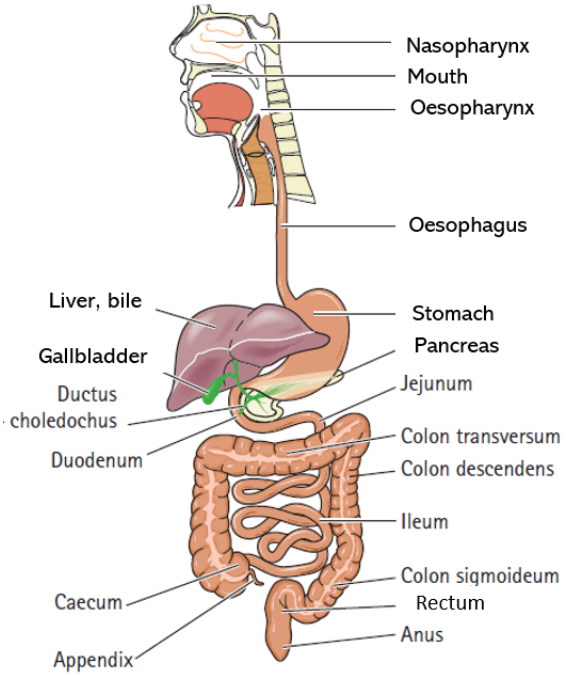

Figure 1.2. Basics of gut-liver interaction. Chewing and saliva decompose, mix, and wet food. The reservoir function of the stomach allows for processing and portion-wise emptying over 2-4 hours. In the duodenum, processed stomach contents, pancreatic juice, and bile from the liver meet. Gastric emptying, pancreatic secretion and gallbladder emptying are well coordinated. Digestion by hydrolysis catalyzed by pancreatic and intestinal enzymes, and uptake via transporters in the intestinal mucosa are effective processes. The small intestine is 4-6 m long, which facilitates almost complete absorption of most nutrients. Plant fiber is, however, digested and fermented by bacteria in the colon, where short chain fatty acids (SCFAs) are produced and absorbed. The intestine receives several liters of water per day in the different secretions and as drink. Water and electrolyte absorption and nutrient absorption are coordinated. Absorbed nutrients reach the portal vein and pass the liver before reaching vena cava. The exception is the absorbed fat that reaches the vein blood via the gut lymph without first passing through the liver. *Figure: Shutterstock.*

The controlled delivery from the intestine

The reservoir function of the stomach, the initial processing of the food and the regulated portion-wise emptying to the duodenum determine the time course of the absorption in the intestine. The ability of the stomach to expand makes it possible to eat much when food is available. The pancreatic enzymes have high capacity and are mixed with food and bile in the duodenum, which makes the digestion of triglycerides, proteins, and starch effective in the proximal small intestine. Intestinal mucosal enzymes complete the digestion, and transporters in the absorptive epithelial cells mediate the uptake of the products.

The gut lacks enzymes of its own to digest the fiber components of plant food, which are mostly large carbohydrate polymers with varying structure. The bacteria in the colon have, however, a wide set of enzymes which decompose plant fiber and ferment much of the products into short chain fatty acids (SCFA) and multiple other products. SCFAs are absorbed and can be used by the colon mucosa or transported on to the portal blood to be used elsewhere in the body.

The functions of the stomach, intestine, pancreas, and liver are coordinated via hormones, nerve signals and by direct effects of the nutrients in the intestine and liver. This regulation is the result of a long-term evolution driven by food availability, and by factors that have gained the best possible links between bodily functions and the utilization of the available food.

The liver assimilates, converts and distributes

The liver is a coordination and distribution center of metabolism. It regulates blood concentrations of nutrients, so that all organs have constant access to the fuel, building blocks and tools they need to maintain cell functions and structures (Figure 1.3 and 1.4). The liver also takes care of metabolites produced by other organs and eliminates or uses them for alternative purposes.

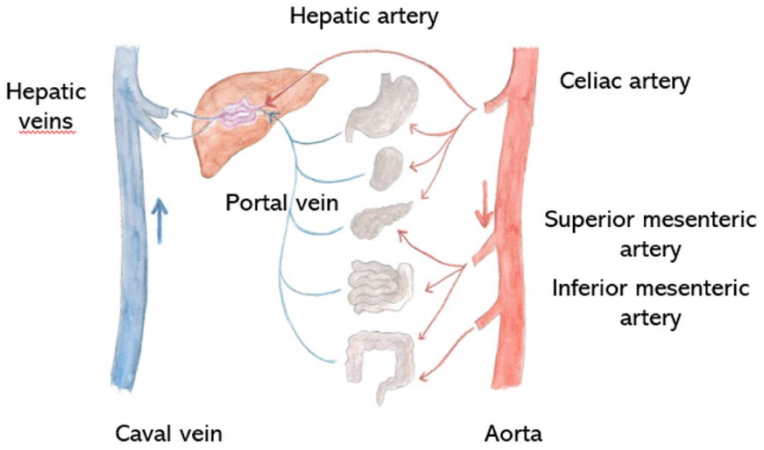

Figure 1.3. Principles of hepatic blood circulation. The liver receives blood from the hepatic artery that is a branch of the celiac artery. The stomach, spleen, pancreas, small intestine, and a major part of the colon, and mesenterial fat and lymph glands, receive arterial blood from three major arteries and collect their venous blood in the portal vein. Hereby about 25 % of the total cardiac output, i.e., of the order 1200 ml/min, passes the liver. This means that the entire volume of blood passes through the liver about two hundred times per day. *Figure: Edith Nelander.*

The adaptation to nutrient access

When logistics works, delivery of raw materials, processing, demand, and distribution are in phase. Inventory is moderate but sufficient to withstand variations in demand. In a normal weight, active individual, who eats a well-composed diet, it works that way. Then the traffic of energy substrates flows as nature intended. The organs of the body get what they need, and blood glucose and plasma lipid levels are kept within narrow limits. Over short periods of time we can vary our diet within broad limits without health disadvantages. The liver adapts its activity to the influx of nutrients from the intestine and to the body's use of the nutrients. It cooperates with the adipose tissue that houses by far the largest nutrient depots in the body. When an excess of nutrients is available the liver secretes lipoproteins that transport fatty acids to adipose tissue for storage as triglycerides, for future needs. If the nutrient supply exceeds the body's demand for too long, the regulation of transport and storage becomes, however, less accurate both in the liver and in the adipose tissue. Blood glucose and blood lipid levels increase, and the storage of fat in adipose

tissue, liver and other organs expand. One may say that the traffic of glucose and lipids is disrupted by queue formation, unclear delivery addresses and overflowing stores. When fasting, the liver ensures that the blood glucose level is maintained, and fatty acids are mobilized from adipose tissue. The whole-body energy metabolism switches towards fatty acid oxidation, and the liver produces ketone bodies from fatty acids to be used as an alternative energy substrate by extrahepatic tissues. Hereby glucose is spared. In severe long-term malnutrition, the tissue deposits eventually become so depleted that there is too little to redistribute. During severe infection, trauma, or other severe disease, the regulation of the body's metabolism is drastically affected. The liver is important when resources are redirected to functions needed for survival, healing, and recovery.

Insulin, glucagon, and other pancreatic and gut hormones, and visceral nerves and their connections with the brain, are important for the regulation of metabolism. They affect both the glucose and lipid metabolism of the liver, adipose tissue and muscles, and the build-up and breakdown of proteins. The supply of nutrition, the functions of the gut-liver axis and the demand of organs for energy substrates and building blocks create, however, the conditions under which the hormones and nervous system act.

Regulating glucose levels is a priority for the liver. The brain is heavily dependent on good regulation of the blood glucose level. Heart and muscles meet a large part of their energy needs by burning fatty acids. The liver and kidneys have a great energy need that is to a large extent met by oxidation of fatty acids. When the liver produces lipoproteins and sends fatty acids to the adipose tissue for storage, it also stores for its own future needs.

The secretion of bile is a functional link between the liver and the intestine. The bile salts not only have detergent effects but also antibacterial effects, and they trigger signals from the gut that affect the functions of the intestinal mucosa and the liver's metabolism.

The effective structure of the liver

The liver is built to receive a large blood flow from the liver artery and the portal vein and to have the best possible exchange of material with the blood (Figure 1.4, 1.5 and 1.6). A flow of 800-1200 ml of blood through the liver every minute means 1100-1700 liters per day (Eipel, Abshagen, and Vollmar 2010). The liver artery and portal vein branch into ever finer branches and finally into wide common capillaries, where the flow is relatively slow despite the large amount of blood passing through. The endothelium lacks basal membrane and has openings that allow efficient traffic of both low molecular substances, macromolecules as plasma

proteins, and aggregates as the plasma lipoproteins, between blood and hepatocytes. The endothelial cells participate in many transport processes. The space between the endothelium and the hepatocytes is called Disse´s space. The capillary area where blood flows from the smallest branches of the portal vein and liver artery to the smallest liver vein branches i.e., the central veins, constitutes a sinusoid, which is the functional unit of the liver (Figures 1.6 and 1.7). The sinusoids are organized into lobules that receive blood from about six portal vein branches and hepatic artery branches (Figure 1.6). Due to the rapid uptake and release of substances and high oxygen consumption, the cells closest to the portal vein and arterial branch are exposed to different concentrations of nutrients and oxygen than the cells closest to the central vein. The term 'zonality' refers to this functional gradient (Figure 1.7 and 1.8). The liver cells are organized into layers where apical cell surfaces with their microvilli are oriented towards Disse's space between the endothelial cells and the bloodstream. Between the hepatocytes bile is secreted into the bile canaliculi which are bounded by tight junctions and the canalicular membrane. The bile is collected in small ducts that merge into larger branches, finally the common large bile duct. Bile is stored and concentrated in the gallbladder. After a meal, more of the content in the gallbladder is emptied into the duodenum.

Adjacent to the endothelium, the phagocytic Kupffer cells are strategically placed. In Disse's space stellate cells, also called vitamin A storing cells are located (Figure 1.7).

Hepatocytes make up the bulk of the mass of the liver and are the seat of most metabolic functions and of bile production. The Kupffer cells are stationary phagocytic cells (macrophages) that are main actors when infectious agents, bacterial components, and materials from aged or damaged cells are phagocytosed and degraded. These important elimination functions are, however, conducted in collaboration with other cell types in the liver. The stellate cells participate in inflammatory reactions in the liver, forming connective tissue matrix. Thereby they contribute to generation of fibrosis and finally cirrhosis in chronically diseased livers. Endothelial cells have important functions in the elimination of viruses and of soluble antigens and have immuno- regulatory functions.

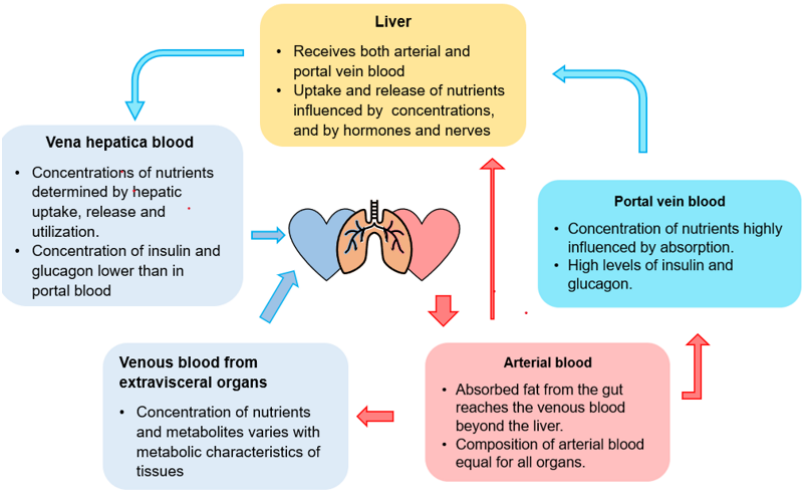

Figure 1.4. The liver is a metabolic hub. The concentrations of nutrients and hormones in portal blood and the net supply of nutrients to the systemic blood vary with food intake and with the first pass uptake by the liver. The liver is difficult to study. Measuring the uptake and release of nutrients in the liver and the liver's exposition to hormones requires measurements of concentrations in both arterial blood, porta blood and liver vein blood, which is technically demanding.