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PHYSIOLOGICAL ROLES OF THE LIVER AND PANCREAS: INTEGRATED METABOLIC, SECRETORY, AND REGULATORY FUNCTIONS IN HUMAN HOMEOSTASIS

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ABSTRACT: Background: The liver and pancreas are anatomically adjacent, developmentally related, and functionally inseparable organs that together orchestrate the central metabolic, digestive, endocrine, and detoxification functions essential to human homeostasis. The liver performs over 500 distinct physiological functions including glucose buffering, lipoprotein metabolism, plasma protein synthesis, bile acid production, and xenobiotic biotransformation. The pancreas provides both exocrine digestive enzyme secretion and endocrine glucose-insulin regulation through its acinar and islet cell compartments.

Objective: To provide a concise, integrated review of the principal physiological roles of the liver and pancreas, encompassing metabolic zonation, hepatic glucose and lipid metabolism, bile secretion, pancreatic exocrine and endocrine function, the incretin axis, and the hepatopancreatic regulatory relationship.

Methods: A systematic review of eight primary authoritative sources—including physiology textbooks, specialist organ physiology reviews, and original research articles—published between 2006 and 2024 was conducted.

Results: The liver processes 70–80% of portal glucose via glycogen synthesis (insulin-dependent) and supplies glucose via glycogenolysis and gluconeogenesis during fasting. Bile acid synthesis (primary: cholic and chenodeoxycholic acid via CYP7A1) produces 500–700 mL bile daily, regulated by the FXR-FGF19 enterohepatic axis. The pancreatic β-cell glucose-stimulated insulin secretion (GSIS) mechanism operates via KATP channel closure and calcium-triggered exocytosis; incretins (GLP-1, GIP) amplify GSIS by 70%. Hepatic insulin resistance and β-cell dysfunction converge to produce type 2 diabetes through overlapping pathways including ectopic lipid accumulation and glucolipotoxicity.

Conclusion: The liver and pancreas function as a tightly integrated hepatopancreatic axis whose coordinated responses to nutritional state, hormonal signals, and neural inputs maintain metabolic homeostasis. Disruption of this axis—through non-alcoholic fatty liver disease, insulin resistance, or β-cell exhaustion—produces the spectrum of metabolic disease that constitutes the primary challenge of contemporary internal medicine.

Keywords: liver physiology, pancreas physiology, hepatic glucose metabolism, glycogen synthesis, gluconeogenesis, bile acids, CYP7A1, insulin secretion, GSIS, glucagon, GLP-1, incretin axis, hepatopancreatic axis, metabolic homeostasis, NAFLD

1. INTRODUCTION

The liver—the largest internal organ (1,200–1,500 g in adults) receiving dual blood supply from the hepatic artery (25%) and portal vein (75%)—and the pancreas (70–110 g, both exocrine acinar tissue and endocrine islets of Langerhans) share embryological origin from the posterior foregut endoderm, anatomical proximity at the hepatoduodenal ligament, and profound

functional interdependence through the portal circulation and entero-insular hormonal axis [1]. Together, they manage the metabolic consequences of each meal—absorbing, processing, storing, and distributing macronutrients—and maintain glucose, lipid, and amino acid homeostasis during the alternating fed and fasted states that characterize human physiology [2].

The clinical importance of these organs is reflected in the global burden of their diseases: non-alcoholic fatty liver disease (NAFLD) affects 25% of adults worldwide and is the most rapidly increasing indication for liver transplantation; type 2 diabetes mellitus (T2DM)—rooted in pancreatic β-cell dysfunction and hepatic insulin resistance—affects 537 million adults globally; and pancreatic exocrine insufficiency contributes significantly to malnutrition in chronic pancreatitis, cystic fibrosis, and post-surgical states [3]. Understanding the integrated physiology of the hepatopancreatic axis is therefore essential both for preclinical education and for interpreting the pathophysiology of the most prevalent non-communicable diseases. This review synthesizes evidence from eight primary sources to provide a focused account of the principal physiological functions of the liver and pancreas and their integrative regulation.

2. MATERIALS AND METHODS

A systematic literature search was conducted in PubMed/MEDLINE, Web of Science, and institutional library databases using the terms: "liver physiology metabolism," "hepatic glucose glycogen," "bile acid synthesis CYP7A1," "CYP450 biotransformation," "pancreatic exocrine secretion CCK," "glucose-stimulated insulin secretion KATP," "glucagon hepatic gluconeogenesis," and "GLP-1 incretin axis." Eight primary sources—authoritative physiology textbooks, comprehensive organ-specific reviews, and original experimental studies published between 2006 and 2024—were selected to provide complete coverage of all review topics. A summary of key physiological functions covered by the eight sources is presented in Table 1, and an integrated overview of the principal functions of both organs is presented in Table 2.

Table 1. Primary sources included in this review

Ref.	First Author	Pub. Type	Organ Focus	Primary Topic	Key Contribution
[1]	Hall & Hall (Guyton)	Textbook (Elsevier)	Liver & Pancreas	Organ physiology	Standard physiology reference
[2]	Rui, L.	Review (Compr Physiol)	Liver	Hepatic energy metabolism	Glucose, lipid, protein metabolism
[3]	Rinella et al.	Review (Lancet)	Liver	NAFLD/MASLD physiology	Hepatic steatosis mechanisms
[4]	Trauner et al.	Review (Dig Dis)	Liver	Bile acid physiology	FXR-FGF19 enterohepatic axis

Ref.	First Author	Pub. Type	Organ Focus	Primary Topic	Key Contribution
[5]	Pandol, S.J.	Monograph (Colloquium)	Pancreas	Exocrine pancreas	CCK/secretin; CFTR; acinar
[6]	Rorsman & Ashcroft	Review (Physiol Rev)	Pancreas	Beta-cell GSIS	KATP, Ca^{2+}, insulin exocytosis
[7]	Drucker, D.J.	Review (Cell Metab)	Pancreas / gut	Incretin hormones	GLP-1, GIP, GLP-2 physiology
[8]	Meier & Nauck	Review (Diabetologia)	Pancreas	Incretin effect	70% postprandial insulin by GLP-1

3. RESULTS

3.1 Hepatic Structure and Metabolic Zonation

The liver's functional unit—the hepatic lobule—is organized around a central vein, with hepatocytes arranged in radiating cords between portal triads (portal vein, hepatic artery, bile duct) and the central vein [1]. This architecture generates an oxygen and nutrient gradient from the periportal zone (zone 1, O_2 tension 60–65 mmHg, first to receive portal blood) to the centrilobular zone (zone 3, O_2 tension 25–35 mmHg), creating functional metabolic zonation: gluconeogenesis, β-oxidation, urea synthesis, and bile acid conjugation predominate in zone 1 hepatocytes exposed to high-oxygen portal blood; glycolysis, lipogenesis, and CYP450-mediated biotransformation predominate in zone 3 [2]. This zonation is not fixed but dynamically regulated by Wnt/β-catenin signaling gradients and by the Hippo pathway effector YAP, which reprogram hepatocyte gene expression according to position within the lobule—a plasticity that enables the liver to shift its overall metabolic output in response to feeding, fasting, and hormonal signals [2].

3.2 Hepatic Glucose and Lipid Metabolism

In the postprandial state, portal glucose concentrations rise to 8–12 mmol/L, activating hepatic glycogen synthesis via insulin-stimulated dephosphorylation of glycogen synthase (GS) kinase-3 (GSK-3) and phosphoprotein phosphatase-1 (PP1), increasing glycogen synthase activity and storing 70–80 g of glycogen in the adult liver [2]. The liver's glucokinase (GK, hexokinase IV) has a high Km for glucose (~10 mmol/L) and is not subject to product inhibition, enabling proportional glucose phosphorylation across the postprandial glucose range—making the liver a glucose buffer that removes approximately 30% of ingested glucose from the portal blood before it reaches the systemic circulation [1]. During fasting, falling insulin and rising glucagon activate glycogen phosphorylase (via PKA-mediated phosphorylation) and stimulate gluconeogenesis from lactate, alanine, and glycerol via upregulation of phosphoenolpyruvate

carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), maintaining fasting plasma glucose between 3.9 and 6.1 mmol/L [2].

Hepatic lipid metabolism centers on the balance between fatty acid oxidation (FAO) and de novo lipogenesis (DNL) [2]. In the fasted state, elevated glucagon activates hormone-sensitive lipase in adipose tissue, releasing non-esterified fatty acids (NEFAs) into the portal circulation; hepatic malonyl-CoA levels fall (inactivating CPT-1 inhibition), enabling mitochondrial fatty acid import and β-oxidation to provide acetyl-CoA for the TCA cycle and, in prolonged fasting, for ketogenesis (producing β-hydroxybutyrate and acetoacetate as alternative fuels). In the fed state, insulin activates SREBP-1c (sterol regulatory element-binding protein 1c) via the PI3K/Akt/mTORC1 pathway, upregulating ACC, FAS, and SCD-1 for de novo lipogenesis; triglycerides are packaged into VLDL (with apolipoprotein B-100) and secreted into the circulation. Chronic excess—through high carbohydrate intake, fructose-driven DNL, or insulin resistance—exceeds VLDL secretory capacity and produces hepatic steatosis, the defining lesion of NAFLD [3].

3.3 Bile Synthesis, Secretion, and the Enterohepatic Axis

The liver produces 500–700 mL of bile daily, its primary organic solutes being bile acids, phospholipids, and cholesterol [4]. Primary bile acids—cholic acid (CA) and chenodeoxycholic acid (CDCA)—are synthesized from cholesterol via the classical pathway (rate-limiting enzyme: CYP7A1, cholesterol 7α-hydroxylase) or the alternative pathway (CYP27A1 → CYP7B1). After conjugation with glycine or taurine in hepatocytes (increasing their aqueous solubility and reducing passive reabsorption), conjugated bile acids are secreted by BSEP (bile salt export pump, ABCB11) across the canalicular membrane. In the ileum, 95% of bile acids are reabsorbed by the ASBT (apical sodium-dependent bile acid transporter) and returned via the portal vein to hepatocytes—the enterohepatic circulation. Ileal FXR (farnesoid X receptor) activation by bile acids induces FGF19 secretion, which acts on hepatic FGFR4/β-Klotho receptors to suppress CYP7A1 transcription in a negative feedback loop that maintains bile acid pool homeostasis [4]. Beyond digestion (emulsification of dietary lipids), bile acids function as signaling molecules: hepatic FXR activation suppresses DNL (via SHP-mediated SREBP-1c inhibition), and intestinal TGR5 activation by secondary bile acids (deoxycholic acid, lithocholic acid—produced by gut bacterial 7α-dehydroxylation) stimulates GLP-1 secretion from enteroendocrine L-cells [4].

3.4 Pancreatic Exocrine Function

The exocrine pancreas—comprising 80–85% of pancreatic mass—consists of acinar cells (secreting digestive enzyme precursors) and ductal cells (secreting bicarbonate-rich fluid) [5]. Acinar cells contain zymogen granules densely packed with digestive enzymes: proteases (trypsinogen, chymotrypsinogen, proelastase, procarboxypeptidases A and B, released as inactive zymogens activated by duodenal enterokinase), pancreatic lipase and co-lipase (hydrolyzing triglycerides at the sn-1 and sn-3 positions), pancreatic amylase (cleaving α-1,4-glycosidic bonds in starch), and phospholipase A2. Ductal cells, stimulated by secretin (released from S-cells of the duodenal mucosa in response to luminal acid), secrete a bicarbonate-rich fluid (HCO_3^- up to 140 mmol/L, pH 7.8–8.0) via apical CFTR channels and NBC1 basolateral bicarbonate transporters, neutralizing gastric acid and providing the alkaline pH optimal for pancreatic enzyme activity [5]. Cholecystokinin (CCK), released from I-cells in response to luminal fatty acids and peptides, is the primary stimulant of acinar enzyme secretion, acting on CCK-A receptors on acinar cells and on vagal afferent neurons (which activate acinar cells via the vagovagal reflex), producing 1.5–2.5 L of pancreatic juice daily [5].

3.5 Endocrine Pancreas: Insulin, Glucagon, and the Incretin Axis

The islets of Langerhans—comprising 1–2% of pancreatic mass but receiving 10–15% of pancreatic blood flow—contain β-cells (65–80%, insulin), α-cells (15–20%, glucagon), δ-cells (5%, somatostatin), PP-cells (< 5%, pancreatic polypeptide), and ε-cells (ghrelin) [6]. Glucose-stimulated insulin secretion (GSIS) operates through a well-defined biophysical mechanism: glucose enters β-cells via GLUT2 (low-affinity, high-capacity transporter), is phosphorylated by glucokinase (the β-cell's glucose sensor, Km ≈ 10 mmol/L), and undergoes glycolysis and mitochondrial oxidation, raising the ATP/ADP ratio. Elevated ATP closes KATP channels (Kir6.2/SUR1 subunits), depolarizing the plasma membrane and opening voltage-gated L-type Ca^{2+} channels, triggering Ca^{2+}-dependent insulin granule exocytosis [6]. This triggers a biphasic insulin secretion: a rapid first phase (granules docked at the plasma membrane, lasting 5–10 minutes) followed by a sustained second phase (recruitment of reserve granules, lasting 60–120 minutes). Glucagon secretion from α-cells is stimulated by hypoglycemia (< 3.9 mmol/L), amino acids, and sympathetic activation, and suppressed by glucose, insulin, and somatostatin; it activates hepatic glycogenolysis via cAMP/PKA-mediated glycogen phosphorylase activation [1].

The incretin effect—the amplification of postprandial insulin secretion by gut-derived hormones—accounts for 50–70% of total insulin released after an oral glucose load compared with an isoglycemic intravenous glucose infusion [8]. Two incretin hormones mediate this effect: glucagon-like peptide-1 (GLP-1), a 30-amino acid peptide derived from proglucagon (GCG gene) in intestinal L-cells via PC1/3 cleavage; and glucose-dependent insulinotropic polypeptide (GIP), secreted from K-cells of the proximal small intestine [7]. Both bind Gs-coupled GPCRs on β-cells (GLP-1R and GIPR), raising cAMP and activating PKA and Epac2 to potentiate Ca^{2+}-dependent exocytosis. GLP-1 additionally inhibits glucagon secretion from α-cells, delays gastric emptying, and suppresses appetite via central GLP-1R in the hypothalamic arcuate and paraventricular nuclei. The incretin effect is markedly reduced in T2DM (incretin deficiency and resistance), providing the mechanistic rationale for GLP-1 receptor agonist therapy [7]. Both incretins are rapidly degraded by dipeptidyl peptidase-4 (DPP-4, plasma half-life 1–2 minutes), the target of the gliptin class of antidiabetic agents [8].

Table 2. Principal physiological functions of the liver and pancreas: mechanisms and homeostatic significance

Function	Organ	Key Molecules / Pathway	Homeostatic Significance
Hepatic glucose metabolism	Liver	Glycogen synthesis/glycogenolysis; gluconeogenesis (PEPCK, G6Pase)	Maintains fasting normoglycemia (3.9–6.1 mmol/L)
Lipid metabolism	Liver	VLDL secretion; β-oxidation; ketogenesis; bile acid synthesis (CYP7A1)	Provides energy substrates; cholesterol homeostasis
Protein & urea	Liver	Albumin, clotting factors (I–XIII); urea	Oncotic pressure; haemostasis; ammonia

Function	Organ	Key Molecules / Pathway	Homeostatic Significance
synthesis		cycle (CPS1, OTC, ASS1)	detoxification
Biotransformation	Liver	CYP450 Phase I/II; glucuronidation; sulfation; glutathione conjugation	Detoxification of drugs, xenobiotics, bilirubin
Exocrine secretion	Pancreas	Acinar cells: amylase, lipase, trypsinogen; CCK/secretin stimulation	Macronutrient digestion; alkaline pH in duodenum
Insulin secretion (GSIS)	Pancreas β-cells	Glucose → ↑ATP → KATP channel closure → Ca^{2+} influx → insulin exocytosis	Glucose uptake (GLUT4), glycogen synthesis, lipogenesis
Glucagon secretion	Pancreas α-cells	Hypoglycemia / amino acids → glucagon → hepatic glycogenolysis + gluconeogenesis	Opposes insulin; maintains glucose during fasting
Incretin axis	Pancreas / gut	GLP-1 (L-cells) + GIP (K-cells) → potentiate GSIS; GLP-1 inhibits glucagon	Amplifies postprandial insulin 2–3-fold (70% of response)

4. DISCUSSION

The liver and pancreas function as a dynamic dyad whose cross-organ communication is bidirectional and multi-modal [1, 2]. Portal venous blood delivers glucose, amino acids, short-chain fatty acids, and pancreatic hormones directly from the gastrointestinal tract to the liver, making the liver the first responder to every meal. Hepatic glucose uptake and glycogen synthesis are enhanced by portal hyperglycemia and amplified by insulin signaling through IRS-1/PI3K/Akt cascade; simultaneously, hepatic insulin extraction (approximately 50% of first-pass) modulates systemic insulin concentrations available to peripheral tissues. Conversely, the liver communicates with the pancreas through hepatokines—FGF21 (which enhances β-cell insulin secretion), IGFBP-1, and fetuin-A (which impairs insulin receptor signaling)—establishing a hepato-insular feedback axis whose dysregulation contributes to the hyperinsulinemia and eventual β-cell exhaustion of T2DM [3].

The convergence of hepatic and pancreatic pathophysiology in metabolic syndrome and T2DM illustrates the clinical importance of understanding these organs as an integrated system rather than independent entities [3, 6]. Hepatic steatosis (ectopic lipid accumulation in NAFLD)—driven by excess DNL from fructose overload, impaired VLDL secretion, or reduced β-oxidation—generates ceramides and diacylglycerols that activate PKCε and IKKβ, inhibiting IRS-2 signaling and producing hepatic insulin resistance. The consequent hyperinsulinemia initially compensates through β-cell hypersecretion, but chronic glucolipotoxicity (elevated glucose + elevated free fatty acids acting synergistically) induces mitochondrial dysfunction, oxidative stress, and β-cell apoptosis—progressively reducing insulin secretory capacity and producing the combined hepatic insulin resistance/β-cell failure characteristic of overt T2DM. This mechanistic understanding directly informs therapeutic targets: GLP-1 receptor agonists address both hepatic steatosis (by reducing DNL via cAMP/PKA-mediated SREBP-1c suppression) and β-cell preservation (by enhancing GSIS and reducing glucotoxic apoptosis), as confirmed in NASH clinical trials [7].

The bile acid-incretin connection identified through TGR5 signaling provides an elegant example of the liver-gut-pancreas functional axis [4, 7]. Hepatically synthesized bile acids—whose composition is modulated by the gut microbiome through 7α-dehydroxylation of primary to secondary bile acids—activate intestinal TGR5 receptors on L-cells, stimulating GLP-1 secretion and thereby amplifying postprandial insulin secretion. This pathway explains why bariatric surgery (particularly Roux-en-Y gastric bypass), which dramatically increases ileal bile acid delivery, produces rapid and often insulin-independent T2DM remission before significant weight loss occurs. The bile acid-TGR5-GLP-1 axis is now a validated therapeutic target: UDCA (ursodeoxycholic acid) and synthetic TGR5 agonists are under clinical evaluation for T2DM and NASH management, while the FXR agonist obeticholic acid has demonstrated anti-fibrotic effects in NASH, bridging hepatic and metabolic disease management [4].

5. CONCLUSION

The liver and pancreas constitute a functionally integrated hepatopancreatic axis that maintains metabolic homeostasis through complementary and mutually reinforcing physiological mechanisms: the liver buffers postprandial glucose and lipid surges, produces bile acids for digestion and metabolic signaling, and performs biotransformation; the pancreatic exocrine compartment provides the enzymatic machinery for macronutrient digestion; and the endocrine islets—through the coordinated secretion of insulin, glucagon, and the amplifying incretin hormones GLP-1 and GIP—orchestrate the minute-to-minute metabolic adaptation to feeding and fasting. Understanding these mechanisms at the molecular level reveals the pathophysiological basis of the most prevalent non-communicable diseases—NAFLD, T2DM, and metabolic syndrome—and identifies the therapeutic targets that modern pharmacology is increasingly able to exploit. For preclinical physiology education in Uzbekistan and the broader Central Asian medical curriculum, mastery of the hepatopancreatic axis provides the essential physiological framework for understanding internal medicine, endocrinology, and gastroenterology throughout a physician's clinical career.

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