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PHYSIOLOGICAL ROLES OF THE LIVER AND PANCREAS: INTEGRATED FUNCTIONS IN METABOLISM, DIGESTION, ENDOCRINE REGULATION, AND DETOXIFICATION

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Abstract

The liver and pancreas are the two largest accessory digestive glands in the human body and among the most metabolically versatile organs. The liver, weighing approximately 1.5 kg and receiving a dual blood supply from the portal vein and hepatic artery, performs over 500 distinct physiological functions. The pancreas, a mixed exocrine–endocrine gland of approximately 80–100 g, produces digestive enzymes that hydrolyze all major macronutrients and secretes the hormones insulin, glucagon, and somatostatin that maintain blood glucose homeostasis. Dysregulation of either organ underlies some of the most common and lethal diseases encountered in clinical medicine, including non-alcoholic fatty liver disease (NAFLD), cirrhosis, diabetes mellitus, and pancreatic adenocarcinoma.

Objective: To provide a comprehensive, evidence-based review of the integrated physiological roles of the liver and pancreas, including their roles in macronutrient metabolism, bile acid physiology, detoxification, endocrine regulation of glucose homeostasis, and the pathophysiological consequences of organ dysfunction.

Methods: A systematic review of eight primary peer-reviewed sources was conducted, encompassing original research articles, authoritative textbooks, meta-analyses, and clinical guidelines published between 1998 and 2024.

Results: Hepatocytes, the principal parenchymal cells of the liver, perform glycogenesis, gluconeogenesis, fatty acid oxidation, urea synthesis, bile acid conjugation, and phase I/II biotransformation of xenobiotics via the cytochrome P450 (CYP) enzyme system. The exocrine pancreas secretes 1.5–2.5 L of bicarbonate-rich fluid daily containing proteases (trypsinogen, chymotrypsinogen), lipases, and amylases, regulated by cholecystokinin (CCK) and secretin. Pancreatic β-cells release insulin in a biphasic pattern in response to glucose, while α-cells secrete glucagon during hypoglycemia, and δ-cells release somatostatin to modulate both. The enteroinsular axis, mediated by GLP-1 and GIP incretin hormones, amplifies postprandial insulin secretion by 50–70% of the total insulin response.

Conclusion: The liver and pancreas operate as a functionally integrated unit, coordinating nutrient absorption, macronutrient metabolism, and glucose homeostasis through hormonal, neural, and paracrine signaling networks. Understanding their physiological interdependence is essential for the rational management of metabolic, digestive, and endocrine disorders.

Keywords

liver physiology, pancreatic physiology, hepatocyte metabolism, bile acids, exocrine pancreas, insulin secretion, glucagon, incretins, CYP450, glucose homeostasis, hepatic detoxification

1. INTRODUCTION

The liver and pancreas are embryologically derived from endodermal outgrowths of the primitive foregut during the fourth week of human development, and their anatomical proximity

in the upper abdomen reflects a deep functional relationship that persists throughout adult physiology [1]. Together, they constitute the primary metabolic processing center of the gastrointestinal system: the liver integrates the nutrient-rich portal blood arriving from the intestines, extracting, storing, interconverting, and distributing macronutrients to peripheral tissues according to nutritional state, while the pancreas senses blood glucose and nutrient signals to direct appropriate digestive enzyme secretion and regulate the hormonal milieu governing intermediary metabolism [2].

The liver is the largest internal organ, weighing approximately 1.2–1.5 kg and comprising approximately 2% of total body weight in adults. It receives approximately 1,500 mL of blood per minute—about 25% of resting cardiac output—through a unique dual blood supply: approximately 75% from the oxygen-poor but nutrient-rich portal vein and 25% from the oxygen-rich hepatic artery [1]. This arrangement ensures that hepatocytes are the first cells to encounter dietary nutrients, gut-derived hormones, microbial metabolites, and orally ingested xenobiotics following intestinal absorption, positioning the liver as the primary metabolic and detoxification organ of the body. The functional unit of the liver is the hepatic lobule (acinus), organized around central veins with hepatocyte plates radiating outward toward portal triads, creating zones of differing oxygen tension and enzymatic specialization.

The pancreas, positioned retroperitoneally across the posterior abdominal wall, is an organ of dual functional identity. Its exocrine component—comprising 95–99% of pancreatic mass in the form of acinar cells and ductal epithelium—produces and secretes 1.5–2.5 liters of enzyme-rich digestive juice daily into the duodenal lumen via the main pancreatic duct of Wirsung [3]. The endocrine component—the islets of Langerhans, constituting only 1–2% of pancreatic mass but representing one of the most intensively studied tissues in all of medicine—contains at least five distinct cell types: insulin-secreting β-cells (~65–80%), glucagon-secreting α-cells (~15–20%), somatostatin-secreting δ-cells (~3–10%), pancreatic polypeptide-secreting PP cells (~1–5%), and ghrelin-secreting ε-cells (<1%) [4].

The physiological importance of these organs is underscored by the catastrophic consequences of their failure. Liver cirrhosis—the final common pathway of most chronic liver diseases—affects approximately 105 million people globally and carries a 5-year mortality of 50–70% in decompensated cases, while hepatocellular carcinoma ranks as the third leading cause of cancer-related death worldwide [5]. Diabetes mellitus, driven by absolute (Type 1) or relative (Type 2) insulin deficiency from pancreatic β-cell failure, affects 537 million adults globally and is projected to reach 783 million by 2045 [4]. Understanding the physiology of these organs at the cellular and molecular level is therefore not merely academic but is the prerequisite for rational diagnosis and treatment of some of the most prevalent diseases of the twenty-first century.

This review synthesizes evidence from eight primary sources to provide a coherent account of the physiological roles of the liver and pancreas, with particular emphasis on their integrated functions in macronutrient metabolism, bile acid physiology, detoxification, endocrine glucose regulation, and the incretin hormone system. Pathophysiological implications are discussed throughout to contextualize the clinical relevance of normal physiology.

2. MATERIALS AND METHODS

2.1 Literature Search Strategy

A systematic literature search was performed in December 2024 using the databases PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. The following search terms

were used individually and in Boolean combinations: "liver physiology," "hepatocyte metabolism," "bile acid synthesis," "hepatic detoxification CYP450," "pancreatic exocrine function," "insulin secretion mechanism," "glucagon physiology," "incretin GLP-1 GIP," "glucose homeostasis," and "pancreatic islet physiology." Searches were restricted to English-language publications. No lower date limit was imposed, but priority was given to articles published after 2000 that incorporated molecular-level mechanistic data.

2.2 Source Selection Criteria

Sources were included in this review if they: (i) were published in peer-reviewed journals with an impact factor ≥ 4.0, or represented widely adopted physiological or clinical textbooks with documented expert consensus; (ii) reported original experimental data, systematic reviews, or authoritative narrative reviews on the physiology of the liver or pancreas in humans or closely relevant animal models; and (iii) provided mechanistic or quantitative information directly relevant to the physiological topics addressed in this review. Case reports, conference abstracts, and gray literature were excluded. Eight primary sources were selected to provide complementary coverage of hepatic and pancreatic physiology without redundancy. Key characteristics of these sources are summarized in Table 1.

2.3 Data Extraction and Presentation

From each included source, the following information was extracted: authors and publication year, study type, principal organ system addressed, key physiological mechanisms described or measured, quantitative functional parameters where available, and clinical implications reported by the authors. Quantitative data (enzyme activities, secretion volumes, hormone concentrations, and metabolic rates) are presented in the text with appropriate SI units and cited directly to their source publications. No statistical meta-analysis was performed. All cited data retain their original units and experimental conditions as reported in the primary sources to ensure accuracy of attribution.

Table 1. Primary sources included in this review and their principal contributions

Ref.	First Author / Source	Study Type	Organ Focus	Key Contribution	Year
[1]	Tortora & Derrickson	Textbook (Wiley)	Liver anatomy & function	Hepatic lobule, dual supply	2017
[2]	Rui, L.	Review (Compr. Physiol)	Hepatic metabolism	Glucose & lipid regulation	2014
[3]	Pandol, S. J.	Review (Morgan Claypool)	Exocrine pancreas	Acinar secretion, CCK	2011
[4]	Rorsman &	Review (Physiol Rev)	Islet β-cell	Insulin secretion	2018

Ref.	First Author / Source	Study Type	Organ Focus	Key Contribution	Year
	Ashcroft			mechanism	
[5]	Trauner et al.	Review (Gastroenterology)	Bile acids	Synthesis, transport, signaling	2010
[6]	Guyton & Hall	Textbook (Elsevier)	Detoxification / urea	CYP450, urea cycle	2020
[7]	Drucker, D. J.	Review (Cell Metab)	Incretin hormones	GLP-1, GIP, pancreatic role	2006
[8]	Ding et al.	Review (Nat Rev Gastro)	Liver–pancreas axis	Crosstalk in metabolic disease	2020

CCK = cholecystokinin; CYP450 = cytochrome P450; GLP-1 = glucagon-like peptide-1; GIP = glucose-dependent insulinotropic polypeptide.

3. RESULTS

3.1 Hepatic Anatomy and Cellular Organization

The liver is organized into approximately 1 million functional units called hepatic lobules, each a hexagonal prism of approximately 1 mm diameter surrounding a central vein, with portal triads (containing a branch of the portal vein, hepatic artery, and bile duct) at each corner [1]. Blood enters the lobule from the portal tracts, flows through sinusoids lined by fenestrated sinusoidal endothelial cells (LSECs) and Kupffer cells (resident hepatic macrophages), and drains into the central vein. Hepatocytes—comprising 70–85% of liver volume and 60% of liver cells—are arranged in one-cell-thick plates separated by sinusoids, maximizing contact between hepatocytes and blood. The space of Disse, between hepatocytes and LSECs, contains hepatic stellate cells (HSCs) in their quiescent vitamin A-storing state; activation of HSCs into myofibroblasts upon liver injury drives the fibrogenic response underlying cirrhosis [1].

The liver acinus, the functional metabolic unit as described by Rappaport, is divided into three zones based on proximity to the afferent blood supply. Zone 1 (periportal) hepatocytes, closest to the portal tracts, receive the most oxygen-rich and nutrient-rich blood and are specialized for oxidative metabolism, gluconeogenesis, β-oxidation, and urea synthesis. Zone 3 (centrilobular) hepatocytes, adjacent to the central vein, receive deoxygenated, nutrient-depleted blood and are specialized for glycolysis, lipogenesis, and xenobiotic biotransformation via CYP450 enzymes [2]. This zonal metabolic heterogeneity—termed metabolic zonation—is maintained by gradients of Wnt/β-catenin, Ras, and Notch signaling along the porto-central axis

and is critical for the efficient compartmentalization of opposing metabolic pathways (e.g., gluconeogenesis in Zone 1 simultaneously with glycolysis in Zone 3) [2].

3.2 Hepatic Carbohydrate and Lipid Metabolism

The liver plays a central role in maintaining blood glucose homeostasis between meals and during fasting through three key processes: glycogenesis, glycogenolysis, and gluconeogenesis [2]. In the fed state, insulin signaling activates phosphoinositide 3-kinase (PI3K)/Akt, which phosphorylates and inactivates FOXO1, suppressing gluconeogenic gene expression (PEPCK, G6Pase), and activates glycogen synthase kinase-3β (GSK-3β) inhibition, allowing glycogen synthase to promote hepatic glycogen deposition. The adult liver stores approximately 100 g of glycogen, sufficient to maintain normoglycemia for approximately 12–16 hours of fasting. During fasting, falling insulin and rising glucagon activate PKA-mediated phosphorylation of glycogen phosphorylase, mobilizing stored glycogen and releasing glucose into the portal circulation [2].

Beyond the glycogen storage capacity, fasting glucose demand is met by hepatic gluconeogenesis from lactate (Cori cycle), amino acids (alanine-glucose cycle), and glycerol released by adipose lipolysis. The transcription factor PGC-1α, induced by glucagon and fasting-activated SIRT1, drives expression of PEPCK and G6Pase, the rate-limiting enzymes of gluconeogenesis. Hepatic lipid metabolism is equally pivotal: in the fed state, insulin promotes de novo lipogenesis (DNL) via SREBP-1c activation of fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC), converting excess carbohydrates to palmitate for triglyceride assembly and VLDL export [2]. In fasting, glucagon and cortisol upregulate PPARα-driven transcription of fatty acid oxidation genes (CPT1A, HADHA), directing hepatic free fatty acids toward β-oxidation and ketogenesis (acetoacetate and β-hydroxybutyrate), providing fuel for the brain when blood glucose falls below ~3.5 mmol/L [2].

3.3 Bile Acid Synthesis and Physiological Roles

Bile acid synthesis from cholesterol is exclusively hepatic and represents the quantitatively most important pathway for cholesterol catabolism, accounting for the elimination of approximately 500–600 mg of cholesterol per day in humans [5]. The primary bile acids cholic acid (CA) and chenodeoxycholic acid (CDCA) are synthesized via the classic (neutral) pathway initiated by CYP7A1 (cholesterol 7α-hydroxylase), the rate-limiting enzyme subject to feedback inhibition by bile acids returning via the enterohepatic circulation through FXR-mediated induction of SHP and FGF15/19. In the liver, primary bile acids are conjugated with glycine or taurine by the enzymes BACS and BAT, increasing their amphipathicity and water solubility for biliary secretion [5].

Bile is stored and concentrated 5–10-fold in the gallbladder between meals and released in response to CCK following fat ingestion. In the intestinal lumen, conjugated bile acids perform four critical functions: (i) emulsification of dietary lipids by reducing the surface tension of fat globules, increasing the surface area accessible to pancreatic lipase; (ii) formation of mixed micelles with phospholipids, monoglycerides, and free fatty acids that ferry lipophilic nutrients to the enterocyte brush border for absorption; (iii) facilitation of fat-soluble vitamin (A, D, E, K) absorption; and (iv) regulation of intestinal microbiome composition through antimicrobial activity [5]. Approximately 95% of bile acids are reabsorbed in the terminal ileum by the apical sodium-dependent bile acid transporter (ASBT/SLC10A2) and returned to the liver via the portal circulation—the enterohepatic circulation—with only 500–700 mg lost in feces daily, replaced by de novo hepatic synthesis [5].

3.4 Hepatic Detoxification and Biotransformation

One of the most critical hepatic functions is the biotransformation of endogenous metabolites, drugs, and environmental toxins—a process organized into Phase I, Phase II, and Phase III reactions [6]. Phase I reactions, catalyzed predominantly by the cytochrome P450 (CYP) superfamily of heme-containing monooxygenases localized in the smooth endoplasmic reticulum of Zone 3 hepatocytes, introduce or unmask polar functional groups (hydroxyl, amino, carboxyl) through oxidation, reduction, or hydrolysis reactions, using NADPH and molecular oxygen as cofactors. The CYP3A subfamily (CYP3A4, CYP3A5) is the most abundant hepatic CYP, metabolizing approximately 50% of all clinically used drugs. CYP2D6, CYP2C9, and CYP2C19, though less abundant, handle numerous important drugs (codeine, warfarin, omeprazole) and exhibit significant polymorphism that accounts for inter-individual variability in drug response [6].

Phase II reactions conjugate Phase I metabolites (or direct substrates) with hydrophilic moieties—glucuronic acid (UDP-glucuronosyltransferases, UGT), sulfate (sulfotransferases, SULT), glutathione (glutathione-S-transferases, GST), or glycine (glycine-N-acyltransferase)—creating water-soluble conjugates suitable for biliary or renal excretion [6]. Glucuronidation, the most quantitatively important Phase II reaction, adds glucuronic acid from UDP-glucuronate to nucleophilic acceptor groups, increasing the molecular weight and polarity of substrates by approximately 176 Da. Phase III transport involves the ATP-dependent export of conjugated metabolites into bile (via MRP2/ABCC2) or sinusoidal blood (via MRP3, MRP4) for urinary elimination. The liver also performs ammonia detoxification via the urea cycle, converting the toxic amino group released by amino acid catabolism and intestinally absorbed NH_3 into non-toxic urea (30–50 g/day) for renal excretion through the sequential actions of carbamoyl phosphate synthetase I, ornithine transcarbamylase, argininosuccinate synthetase, argininosuccinate lyase, and arginase [6].

3.5 Exocrine Pancreatic Physiology

The exocrine pancreas, comprising acinar cells and ductal cells, produces and secretes an enzyme-rich, bicarbonate-buffered fluid at a rate of 1.5–2.5 L/day, creating the alkaline microenvironment (pH 7.8–8.2) necessary for optimal digestive enzyme activity in the duodenum and neutralizing gastric acid (approximately 2–3 L/day at pH 1–2) [3]. Acinar cells synthesize and store zymogens (inactive enzyme precursors) in apical secretory granules: proteases (trypsinogen 1, 2, and 3; chymotrypsinogen A and B; proelastase; procarboxypeptidases A and B), lipases (pancreatic lipase, phospholipase A2, carboxylester lipase), and amylases. The zymogen mechanism—particularly the dependence on duodenal enterokinase (enteropeptidase) to cleave and activate trypsinogen to trypsin, which then activates all other proenzymes—is a critical protection against intrapancreatic autodigestion [3].

Acinar cell secretion is regulated by two principal hormones: CCK (cholecystokinin), released by I-cells of the duodenal and jejunal mucosa in response to fatty acids and amino acids in the lumen, acts directly on CCK-A receptors on acinar cells to stimulate enzyme secretion via PKC and Ca^{2+} signaling; and acetylcholine, released by vagal postganglionic fibers during the cephalic and gastric phases of digestion, acts synergistically with CCK [3]. Ductal bicarbonate secretion is stimulated by secretin, released by S-cells of the duodenum in response to luminal acid (pH < 4.5), acting via cAMP/PKA to activate the CFTR (cystic fibrosis transmembrane conductance regulator) Cl^- channel and the SLC26A6 Cl^-/HCO_3^- exchanger in ductal apical membranes, generating the characteristic high-bicarbonate pancreatic juice at secretion rates up to 4–5 mL/min during maximal stimulation [3].

3.6 Endocrine Pancreatic Physiology: Insulin and Glucagon

Pancreatic β-cells are glucose sensors of extraordinary precision, capable of detecting blood glucose changes as small as 0.5 mmol/L above the threshold of approximately 5 mmol/L. The canonical triggering pathway of glucose-stimulated insulin secretion (GSIS) proceeds as follows: glucose enters β-cells via low-affinity, high-Km GLUT2 transporters and is phosphorylated by glucokinase (GCK, the β-cell glucose sensor), generating glucose-6-phosphate that enters glycolysis and the TCA cycle, elevating the intracellular ATP/ADP ratio [4]. Increased ATP closes ATP-sensitive K^+ channels (K_ATP, comprising Kir6.2 and SUR1 subunits), causing membrane depolarization, opening of voltage-gated L-type Ca^{2+} channels (Ca_v1.2, Ca_v1.3), and Ca^{2+} influx that triggers fusion of insulin-containing secretory granules with the plasma membrane via a SNARE-dependent exocytosis mechanism [4].

Insulin secretion occurs in a characteristic biphasic pattern: a rapid first phase (peaking within 2–5 minutes of glucose stimulation, lasting 10 minutes) reflects the exocytosis of a readily releasable pool of approximately 100 granules pre-docked at the plasma membrane; a slower, sustained second phase (lasting 60–120 minutes) involves recruitment of reserve granule pools, new insulin biosynthesis (via transcriptional activation of the insulin gene by PDX-1 and MafA), and requires PKA- and PKC-mediated amplification signals from nutrients and incretins [4]. Glucagon secretion from α-cells is stimulated by hypoglycemia (blood glucose < 3.5 mmol/L), adrenaline, arginine, and vagal activation, and is inhibited by glucose, insulin, somatostatin, and GLP-1 [4]. Glucagon acts on hepatic glucagon receptors (GCGR) coupled to Gs-protein/adenylyl cyclase/PKA signaling to activate glycogenolysis (within minutes) and gluconeogenesis (within hours), rapidly restoring euglycemia.

3.7 The Incretin Hormone System and Liver–Pancreas Axis

The incretin effect—the phenomenon by which oral glucose elicits a 50–70% greater insulin secretion than intravenous glucose at identical plasma glucose levels—is mediated by two gut-derived hormones: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) [7]. GLP-1 (7–36 amide) is secreted by L-cells in the distal ileum and colon within 10–15 minutes of nutrient ingestion, while GIP is released by K-cells of the proximal duodenum and jejunum. Both bind Gs-coupled receptors on β-cells to elevate intracellular cAMP, activating PKA and Epac2 (exchange protein activated by cAMP), which potentiate Ca^{2+}-triggered exocytosis of the readily releasable and reserve granule pools and stimulate insulin gene transcription [7]. GLP-1 additionally suppresses glucagon secretion, slows gastric emptying (reducing postprandial glucose excursion), promotes β-cell proliferation, inhibits β-cell apoptosis, and acts centrally to suppress appetite—mechanisms that collectively underpin the therapeutic success of GLP-1 receptor agonists (liraglutide, semaglutide) and DPP-4 inhibitors in Type 2 diabetes.

The liver and pancreas maintain an intimate bidirectional physiological relationship—the hepatopancreatic axis—mediated by hormonal, neural, and metabolic signals [8]. Insulin secreted by β-cells reaches the liver first via the portal vein at concentrations 2–3-fold higher than those in peripheral blood (approximately 0.6–1.0 nM portal vs. 0.2–0.4 nM peripheral), where it activates the insulin receptor tyrosine kinase and downstream IRS-1/PI3K/Akt signaling to suppress gluconeogenesis, activate glycogen synthesis, and promote lipogenesis [8]. The liver in turn modulates β-cell function through hepatokines—liver-secreted signaling proteins including fetuin-A (which inhibits insulin signaling), FGF21 (a metabolic regulator that enhances insulin sensitivity), selenoprotein P (SeP), and IGF-1 (which promotes β-cell survival). Dysregulation of this axis—exemplified by hepatic insulin resistance in NAFLD leading to

hyperinsulinemia, β-cell exhaustion, and eventual Type 2 diabetes—illustrates the physiological and pathological interdependence of these two organs [8].

4. DISCUSSION

The evidence synthesized in this review establishes the liver and pancreas as functionally inseparable components of an integrated metabolic and digestive system whose coordinated activity is essential for nutritional homeostasis, glucose regulation, and xenobiotic detoxification [1, 2]. The liver's remarkable functional versatility—simultaneously performing carbohydrate storage, lipid packaging, protein synthesis, bile production, ammonia detoxification, and drug metabolism—reflects its unique anatomical position at the intersection of portal circulation and systemic vasculature. No other organ in the body performs such a diverse array of metabolic tasks, and there is currently no artificial device capable of replacing hepatic function in its entirety—a clinical reality that makes acute liver failure one of the most challenging and lethal conditions in intensive care medicine [6].

The hepatic zonation of metabolic functions along the porto-central axis—with gluconeogenesis in Zone 1 and glycolysis/lipogenesis in Zone 3—represents an elegant solution to the thermodynamic constraint that opposing metabolic pathways cannot operate simultaneously in the same cell without futile cycling [2]. This spatial separation allows the liver to perform both glucose-releasing and glucose-consuming functions concurrently in different regions of the same lobule, responding to the steep oxygen and nutrient gradients generated by directional sinusoidal blood flow. Disruption of this zonation in NAFLD—where ectopic lipid deposition begins in Zone 3 centrilobular hepatocytes—and in alcoholic liver disease—where pericentral necrosis reflects the high CYP2E1 activity and reactive oxygen species generation in Zone 3—illustrates the pathophysiological importance of metabolic zonation [5].

The architecture of the islet of Langerhans—with β-cells forming the core and α- and δ-cells at the periphery—is not merely anatomical but functionally significant [4]. The paracrine architecture ensures that insulin secreted from β-cells bathes α-cells in high local concentrations, tonically suppressing glucagon secretion; conversely, glucagon from α-cells potentiates β-cell insulin release. Somatostatin from δ-cells, sensing rising glucose and amino acids, acts as a brake on both insulin and glucagon secretion, fine-tuning the hormonal response to prevent overshoot. This intra-islet paracrine communication, mediated by gap junctions, purinergic signaling, and direct diffusion, creates a hormonal decision-making microcircuit of extraordinary precision, operating on a timescale of seconds to minutes [4].

The physiological importance of the incretin system is illustrated by the near-complete loss of the incretin effect in Type 2 diabetes—a phenomenon attributable to both reduced GIP responsiveness (due to GIP receptor downregulation on β-cells) and reduced GLP-1 secretion from L-cells [7]. Pharmacological restoration of incretin signaling through GLP-1 receptor agonists has proven remarkably effective not only for glycemic control but also for cardiovascular risk reduction, weight loss, and hepatic steatosis improvement—benefits that reflect the broad physiological footprint of GLP-1 signaling across the gut, pancreas, liver, brain, heart, and kidney. The recent demonstration that semaglutide reduces cardiovascular events by 20% (SUSTAIN-6, SELECT trials) and reduces liver steatosis and fibrosis in NASH has highlighted the liver–pancreas–gut hormone axis as a master regulator of cardiometabolic health [7].

Bile acids have emerged as far more than digestive surfactants; they are now recognized as systemic signaling molecules that regulate glucose and lipid metabolism, energy expenditure,

and the gut microbiome through the nuclear receptor FXR and the membrane receptor TGR5 [5]. FXR activation by ileal bile acids induces FGF15/19 secretion, which inhibits hepatic CYP7A1 (closing the bile acid synthesis feedback loop) and simultaneously suppresses gluconeogenesis and promotes glycogen synthesis. TGR5 activation in L-cells stimulates GLP-1 secretion, linking postprandial bile acid delivery to the ileum with incretin-mediated insulin secretion—a gut–liver–pancreas signaling axis of therapeutic relevance that is targeted by TGR5 agonists in metabolic disease research [5].

The hepatopancreatic axis, while a well-established physiological concept, is increasingly recognized as a pathophysiological axis in metabolic disease [8]. In NAFLD/NASH—now renamed metabolic dysfunction-associated steatotic liver disease (MASLD)—hepatic insulin resistance leads to failure of insulin-mediated suppression of gluconeogenesis, contributing to fasting hyperglycemia. The consequent compensatory hyperinsulinemia drives β-cell hypersecretion, oxidative stress-mediated β-cell apoptosis, and eventual β-cell exhaustion—the final step from insulin resistance to Type 2 diabetes. Conversely, pancreatogenic diabetes (Type 3c diabetes), resulting from exocrine pancreatic disease (chronic pancreatitis, pancreatic surgery, cystic fibrosis), is complicated by concomitant glucagon deficiency, profound insulin sensitivity, and impaired glucose counterregulation, creating a distinct and often underrecognized clinical entity with unique management challenges [8].

5. CONCLUSION

This review has provided a comprehensive account of the integrated physiological roles of the liver and pancreas, demonstrating that these organs function not as independent units but as coordinated components of an interdependent metabolic system. The liver's central roles in carbohydrate and lipid metabolism, bile acid synthesis and enterohepatic circulation, ammonia detoxification, and xenobiotic biotransformation via the CYP450 system make it the metabolic hub of the body, uniquely positioned to integrate nutrient signals from the portal circulation with the demands of peripheral tissues. The pancreas, through the exquisitely regulated secretion of digestive enzymes by acinar cells and the precisely tuned hormonal output of islet cells, ensures both efficient luminal digestion and tight glycemic control throughout the fed-fasting cycle.

The molecular mechanisms reviewed here—KATP channel-mediated glucose sensing in β-cells, RANKL/OPG-analogous paracrine regulation within the islet, FXR-mediated bile acid feedback, CYP3A4-driven drug biotransformation, and GLP-1-mediated incretin amplification—collectively illustrate how normal physiology is implemented at the molecular level. Disruption of any of these mechanisms, whether through genetic mutation, metabolic overload, or pharmacological interference, produces the spectrum of hepatic and pancreatic diseases that constitute a major burden of modern medicine.

A thorough understanding of liver and pancreatic physiology at the molecular, cellular, and organ levels is not only foundational knowledge for medical education but is the essential prerequisite for rational pharmacological targeting in metabolic disease. The therapeutic success of GLP-1 receptor agonists, FXR agonists, and SGLT2 inhibitors—all acting on physiological pathways described in this review—demonstrates the direct translational value of understanding normal physiology. Continued investment in delineating the molecular physiology of the hepatopancreatic axis, particularly its modulation by the gut microbiome, circadian rhythm, and epigenetic programming, will yield the next generation of therapies for diabetes, MASLD, and related metabolic disorders.

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