Physiology of Digestion

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Iqbal Hyder, Poonooru Ravi Kanth Reddy, and Joydip Mukherjee

Abstract

Digestion is a process by which foods are broken down chemically and mechanically into smaller units that can be then absorbed. The organs of digestive system facilitate this process via movement of nutrients, water, and electrolytes from the external environment into the body's internal environment. The broad functions of digestive tract include secretory and motility functions that ultimately aid in digestion and absorption. Apart from the enzymes secreted from the gut itself, there is significant contribution from other organs like liver and pancreas in the process of digestion. Both secretory and motility functions of gastrointestinal (GI) tract are tightly regulated by intrinsic control mechanism via enteric nervous system apart from direct control of vagus nerve. In addition to the neural control, the GI tract is also controlled by hormones secreted by GI tract itself that predominantly act in autocrine and paracrine manner. The avian digestive system is modified to accommodate flight. This chapter focuses on all of the above discussed aspects with additional excerpts on recent advances.

I. Hyder
College of Veterinary Science, Sri Venkateswara Veterinary University, Garividi, Andhra Pradesh, India

P. R. K. Reddy
Veterinary Dispensary, Animal Husbandry Department, Taticherla, Andhra Pradesh, India

J. Mukherjee (✉)
Department of Veterinary Physiology, West Bengal University of Animal & Fishery Sciences, Kolkata, West Bengal, India

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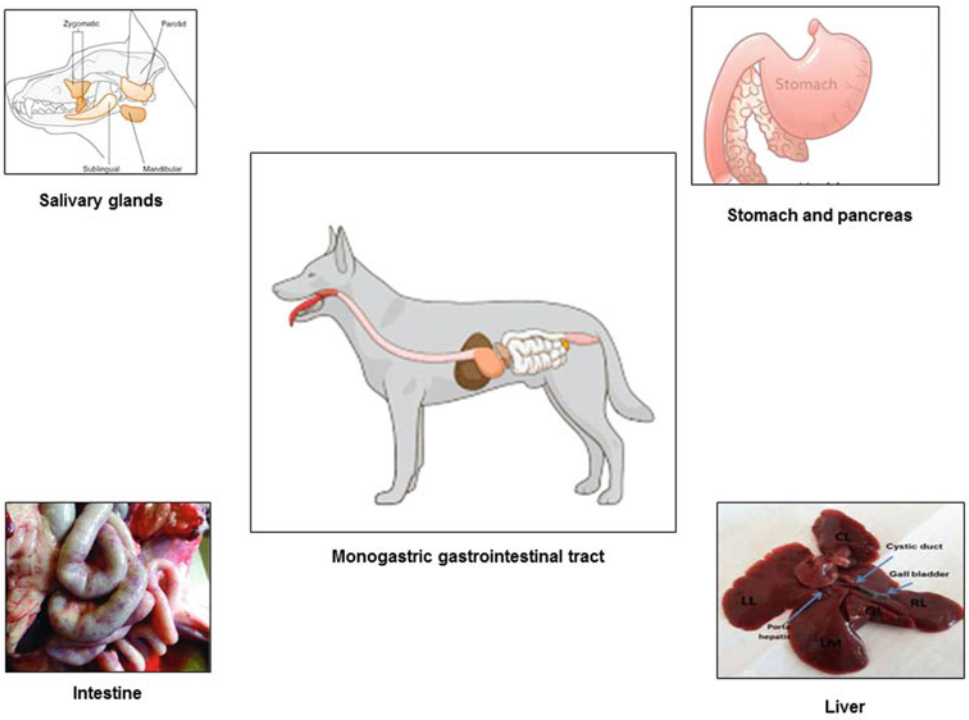
Graphical Abstract



Description of the graphic: Monogastric digestive tract is a long hollow tube extending from the mouth to anus together with some accessory organs in between. The digestion process starts at the mouth cavity by mechanical force of mastication/chewing. The saliva lubricates feed particles for swallowing. The enzymes present in the saliva partially digest the feed. The feed enters into the stomach through oesophagus. Stomach secrets gastric HCl and enzymes to digest proteins. The final stage of digestion is occurred at the small intestine with brush boarder enzymes. The absorption of nutrients occurs at the small intestine. The liver produces bile that helps in the digestion and absorption of lipids.

Keywords

Monogastric digestion · Secretions of GI tract · Absorption · Avian digestion

Learning Objectives

- general overview of digestive system in monogastric digestion
- gastrointestinal motility and its control
- secretory functions of digestive system and its control
- digestion and absorption of nutrients
- physiology of avian digestive system

13.1 Monogastric Digestion

13.1.1 Overview of Monogastric Digestion

The digestion is a complex process of feed intake, conversion of the complex feed into their simplest form by mechanical and biochemical processes, absorption of the nutrients and their assimilation together with the removal of undigested feed materials. The process of digestion starts at the oral cavity where mastication reduces particle size of the ingested feed and incorporates saliva into ingesta for swallowing. The stomach facilitates grinding and mixing of the food along with digestion of proteins with the help of acid and enzymes. Once the chime passes into the small intestine, it is mixed

with pancreatic enzymes and membrane bound enzymes in the enterocytes to convert the complex feed materials into their simplest form for absorption. The gastrointestinal system is the portal through which nutritive substances, vitamins, minerals, and fluids enter the body.

13.1.1.1 Functional Anatomy of Gastrointestinal Tract in Different Domestic Animals

The digestive tract of different species shows numerous structural and functional modifications from their primitive forms to accommodate their wide range of diets and habitats (Table 13.1). The elementary canal or the gastrointestinal [GI] tract is a hollow tube comprises mouth, pharynx, oesophagus, stomach, small intestine, large intestine, and rectum along with the accessory organs like salivary glands, pancreas, and liver. Animals are classified according to their diet in natural conditions as herbivores, omnivores, and carnivores.

The wall of the entire GI tract is made up of four basic layers, from the lumen towards the outside viz. mucosa, submucosa, muscularis, and serosa.

13.1.1.1.1 Mucosa

There are three layers of mucosa:

1. Innermost layer of epithelium made up of non-keratinized stratified squamous cells lines along the lumen to provide protection against wear and tear particularly in the mouth, oesophagus, and the anal canal. In the stomach and intestine, the stratified squamous cells gradually turn into columnar cells to carry out the specific functions of secretion and absorption.
2. In the middle, a layer of areolar connective tissue called lamina propria contains many blood vessels and lymphatic vessels to supply the mucosa and carry the absorbed nutrients of digestion. The lamina propria also contains many lymphatic nodules called mucosa-associated lymphoid tissue (MALT) that facilitates protection against microbes of food origin. MALTs are prevalent in tonsils, small intestine, appendix, and large intestine.
3. The smooth muscle layer arranged in outer longitudinal and an inner circular layer responsible for the local movements of the mucosal layer is called muscularis mucosa. This layer makes the mucosal membrane of the stomach and small intestine into folds to increase the surface area for digestion and absorption.

13.1.1.1.2 Submucosa

This connective tissue layer contains blood vessels and nerves in the form of a plexus apart from lymphatic tissue and glands. The submucosal plexus is highly developed in intestines whereas in stomach and oesophagus such ganglionated plexus is poor to sparsely developed. In larger mammals, the intestinal submucosal plexus is of two types. The inner Meissner's plexus is situated at serous end of muscularis mucosa and outer Schabadasch's or Henle's plexus is adjacent to circular muscle layer at the luminal side.

13.1.1.1.3 Muscularis

The muscularis layer consists of muscle fibres arranged in two layers viz. an outer longitudinal and an inner circular. In the mouth, pharynx and upper one third of the oesophagus it has voluntary skeletal muscle fibres that regulate swallowing.

Table 13.1 Modifications in GI tract according to the type of animal

Characteristics	Herbivore	Carnivore	Omnivore
Facial muscles	Well developed	Reduced to allow wide mouth gape	Reduced
Jaw motion	No shear; more side to side and front-to-back	Shearing, minimal side to side	Shearing, minimal side to side
Major muscle	Masseter and Pterygoid	Temporalis	Temporalis
Mouth opening	Small	Large	Large
Teeth (Incisors)	Broad, flattened, and spade shaped	Sharp and pointed	Sharp and pointed
Teeth (canines)	Short or long (for defence) or none	Long, sharp, and curved	Long, sharp, and curved
Teeth (molars)	Flattened with cusps	Sharp, jagged, and blade shaped	Sharp blades and/or flattened
Stomach type	Simple or multiple chambers	Simple	Simple
Acidity of the stomach	Less acidic (pH 3–4)	Highly acidic (pH 1)	Highly acidic (pH 1–2)
Length of small intestine in Comparison to body length	12–27 times	4–6 times	10–14 times
Caecum	Very well developed	Reduced	Moderately developed
Colon	Long, complex, sacculated	Simple, short, and smooth	Simple, short, and smooth
Length of body: Length of GIT	Horse—1:12 Cattle—1:20 Sheep—1:27	Dog—1:6 Cat—1:4	Pig—1:16

The rest of the portions are lined by smooth muscle fibres regulated by the autonomic nervous system. The muscularis layer is responsible for the movement of the GI tract to facilitate mixing and propulsion of food.

13.1.1.1.4 Serosa

This is the outermost layer consisting of areolar connective tissue and simple squamous epithelium (mesothelium). It is also called adventitia in the oesophagus where it is made up of only the areolar connective tissue without mesothelium.

13.1.1.2 Mechanical Factors Involved in Digestion

The mechanical factors are principally required for physically breaking down feed particles into their smaller forms for effective chemical digestion. It involves prehension, followed by mastication and deglutition (Swallowing of food).

13.1.1.2.1 Prehension

Prehension is the grasping and conveying of food into the oral cavity. The act of prehension varies between species. Cattle use protrusible tongue and incisors of lower jaw for prehension, horses use upper lip, tongue, and incisor teeth to collect food. In sheep and goat, the mobile upper lips are involved in prehension. Pigs use lower lips for prehension while the dogs and cats grasp their prey with forelimbs and carry into the mouth by the movements of head and jaw. In cats, papillae of the tongue (dorsal lingual spicules) help in pushing the feed into the oral cavity.

13.1.1.2.2 Drinking

The drinking is facilitated by suction of fluids by creating negative pressure in horse, cattle, sheep, and goat. Dog and cat use their ladle shaped tongue for drinking. It is vigorously extended and retracted to carry the liquid into the mouth. The negative pressure inside the mouth cavity created by backward tongue movement forces the milk to enter inside the mouth during suckling.

13.1.1.2.3 Mastication (Chewing)

Mastication is the act of chewing by the movement of jaw, tongue, and cheeks that facilitates grinding, moistening, and lubricating the food after mixing with the saliva. Mastication increases the surface area of the feed particles for better enzymatic digestion. Mastication involves rhythmic movements of mandible accompanied by extension of tongue called linguo-mandibular reflex. The presence of feed in the oral cavity stimulates tongue and oral receptors. The sensory inputs via trigeminal, facial, and glossopharyngeal nerves are carried to brainstem and efferent inputs via trigeminal nerve reach to masticatory muscles. In herbivores, mastication is facilitated by lateral movement of the lower jaw. Chisel shaped molar teeth and sharp-edged lower teeth help in grinding of feed particles. Incisor teeth are used for cutting the food. In ruminants, the modified dental pads together with the lower jaw help to cut the feed materials due to the absence of upper incisors. Masseter and pterygoids muscles are very prominent in herbivores. Masseter muscle helps to close the jaw and facilitates forward movement. Pterygoids muscles help to grind the feed by side-to-side jaw movement. Temporal muscles are prominent in carnivores that help to close the jaw and allow the teeth to sink into pray. The lateral and forward jaw movement are restricted in canines due to smaller masseter and pterygoid muscles.

13.1.1.2.4 Deglutition

It is a highly complex reflex that delivers ingesta or fluids from mouth to the stomach through pharynx and oesophagus. It starts as a voluntary act then becomes an involuntary reflex during its execution. Deglutition is facilitated by coordinated motor activities involving the muscles of tongue, pharynx, and oesophagus. Deglutition centre is situated at the medulla. The complex mechanism of deglutition is controlled by lower motor neuron, vagus, hypoglossal, glossopharyngeal nerves, and motor parts of trigeminal nerve. In the voluntary phase of deglutition, the ingested feed materials are converted into bolus by the tongue and pushed back into the pharynx. The pharyngeal pressure receptors (sensory nerve endings) detect the presence of bolus and stimulate deglutition centre to initiate swallowing reflex (involuntary phase). At the beginning of the involuntary phase of deglutition, the breathing is completely stop followed by the elevation of soft palate to close the pharyngeal opening of the nasopharynx. That restricts the entry of feed into the internal opening of the nostrils. To close the oral opening of pharynx, tongue is pressed against hard palate. The glottis is pulled under the epiglottis to ensure the blocking of laryngeal opening followed by the constriction of arytenoids cartilage that prevents the feed to enter into the respiratory passage. After the closure of all pharyngeal openings, the muscular contractions along the wall of the pharynx, push the bolus towards oesophageal opening. The feed enters into the oesophagus after the relaxation of upper oesophageal sphincter.

13.1.1.3 Gastrointestinal Motility

The motility of GI tract results from coordinated contractions of smooth muscle to propel, retain, and mix the ingesta. The motility of the GI tract also facilitates the movement of ingesta around the absorptive surface for efficient absorption. The GI motility can be of three types, propulsive motility to propel the ingesta in forward direction. The propulsion of feed materials is achieved through wave-like muscle contractions called peristalsis. It is occurred through contraction and relaxation of circular and longitudinal smooth muscles of gastrointestinal tract. Peristalsis is of two types.

Primary peristalsis is induced by swallowing and secondary peristalsis is induced by oesophageal distension. The peristalsis is achieved by alternating relaxation and contraction of distal and proximal muscles of GI tract. Retentive motility ensures the retention of feed at a particular segment of GI tract. A combination of both propulsive and retentive motility is also occurred. The time taken by the ingesta to travel from one portion of the GI tract to another is called transit time. Propulsive motility decreases transit time and retentive motility decreases it.

13.1.1.3.1 Motility of the Oesophagus

The oesophagus is a muscular tube extends from the pharynx to the stomach. The upper oesophageal sphincter is formed in part by the cricopharyngeal muscle and lower oesophageal sphincter is surrounded by the crural diaphragm. Upon deglutition, the relaxation of the upper oesophageal sphincter allows the passage of the food bolus into the oesophagus. The upper portion of the oesophagus consists of striated muscles and their activities are regulated by central controlling mechanisms like swallowing reflex. The lower part of the oesophagus is made of smooth muscles that exhibit peristaltic movements under central and intrinsic controlling mechanisms. Normally, the lower oesophageal sphincter is tightly closed under the influence of gastrin and vagal parasympathetic stimulation to prevent stomach contents and acid from entering the oesophagus. In most species, opening of the lower oesophageal sphincter is mediated by vasoactive intestinal polypeptide (VIP) accompanied by peristaltic waves that propels the bolus into the stomach. The peristalsis in oesophagus is of two types, primary and secondary. Primary peristalsis refers to bolus-induced oesophageal contractions upon swallowing whereas secondary peristalsis refers to distension-induced contractions independent of swallowing.

13.1.1.3.2 Gastric Motility

The motility of the proximal stomach is characterized by continuous weak contraction that allows gentle propelling of feed into the distal stomach. The proximal stomach also has adaptive relaxation property as it stores feed. Adaptive relaxation facilitates to accommodate large volume of feed without increasing the intraluminal pressure. Vagal stimulation suppresses the muscular contraction in the proximal stomach to facilitate adaptive relaxation process. It is of great importance in carnivores like wolves and lions to ingest large volume of meat from prey available only once every few days. In contrast, horse has a relatively small stomach with a very limited capacity for distension.

The distal stomach facilitates the grinding of feed by intense slow wave activity with frequent muscular contractions. The propulsive motility begins at the junction of proximal stomach and moves towards pylorus where finely ground and liquefied materials pass through the duodenum. Sometimes the ingesta are propelled back to the proximal stomach for proper grinding.

Reflexes Associated with Gastric Emptying

Gastro-gastric Reflex: The distension of the gastric reservoir initiates excitatory reflexes to stimulate antral contractions. In contrast, the inhibitory reflexes are induced by antral distension for relaxation of the stomach.

Duodenal Control: Gastric emptying is inhibited by nutrients entering the duodenum designated as "Duodenal control". The feedback-inhibition of gastric emptying is elicited by various stimuli. Hydrochloric acid, osmolality of the chyme, and an increased amount of nutrients entering the small intestine reduce the rate of gastric emptying. The afferent vagal fibres act as the receptors for glucose, osmolality, hydrochloric acid, amino acids, and long-chain fatty acids. Gastrointestinal hormones are also involved in the feedback regulation. One of the most important hormones is cholecystokinin (CCK) that mainly causes relaxation of the reservoir and delays emptying. Peptide YY and the glucagon-like peptide (GLP-1) also inhibit gastric emptying. Secretin and gastric inhibitory polypeptide (GIP) also reduce gastric motility whereas gastrin increases it.

13.1.1.3.3 Motility of Small Intestine

The peristaltic waves at the proximal part of intestine are rapid and far spreading which gradually become shorter and slower towards the distal gut to achieve different transit rates along the intestine. Under physiological conditions, small intestine exhibits five different contractile patterns.

Peristaltic waves: These are circular constrictions propagating aborally associated with an aboral relaxation or inhibition of the muscle, respectively, to facilitate an aboral transport of chime. In dogs, the propagation velocities of the peristaltic waves are 7–12 cm/s in the duodenum, 4–7 cm/s in the jejunum, and 0.7–0.8 cm/s in the ileum.

Stationary contractions (segmenting contractions): It occurs as segmental contractions at single sites. By means of segmenting contractions, the chyme is pushed orally and aborally at a localized area for the mixing of the luminal contents.

Clusters of contractions: These are complex contractile patterns characterized by several short repetitive contractions pushing the chyme a few centimetres aborally followed by a partial backflow during the period of relaxation. These types of contractions are required for mixing of chyme and frequently seen after a fat meal.

Migrating motor complex (MMC): It is a cyclic motor pattern of the GI tract exhibited during the inter-digestive state. It is appeared as clusters of contractions divided into four phases that propagate over a longer intestinal segment.

Phase I is called quiescent phase as no contractions occur during this phase. In phase II, random contractions occur. Phase III is characterized by a rapid contraction with the highest amplitude and duration that occur suddenly. The amplitude and duration of contractions are decreased in phase IV. MMC is present in rats, sheep, rabbits, pigs, dogs, and cows. MMC is generally occured during inter-digestive periods, but ad libitum feeding has no effect of MMC in sheep, pigs, and rabbits. But MMC is disrupted when the animals ingest feed once or twice a day. Four phases of MMC are not recognizable in rats and mice; hence, in this species MMC can be described as phase-I-like and phase-III-like contractions that occur in every 12–15 min. In dogs, large particles such as bones, stones of peaches, or insoluble tablets are forced into the intestine by the onset of the inter-digestive motility.

Giant contractions: These are characterized by large amplitude and a long duration. These types of contractions are seen in the ileum of dogs, pigs, and horses during inter-digestive period. In pigs, giant contractions are also observed during digestive period. The giant contractions completely occlude the intestinal lumen and propagate slowly to aboral direction pushing the luminal contents distally and cleaning the intestine; hence, they are also called "stripping wave". Aboral giant contractions of the small intestine are the typical contractile pattern in diarrhoea.

13.1.1.3.4 Motility of Large Intestine

The large intestine serves as fermentation chambers wherein microbial digestion takes place. The faeces are also produced in the large intestine after the absorption of water. These two functions require proper mixing and transport of digesta. Different parts of large intestine show different contractile patterns.

1. peristaltic and antiperistaltic waves
2. aborally migrating segmenting contractions
3. haustral movements and
4. aborally propagating giant contractions

Peristaltic and antiperistaltic waves: These are characteristic motor patterns of the caecum and proximal colon. Waves with shallow circular constrictions followed by low retropulsion is causes by an intensive mixing of chyme.

Aborally migrating segmenting contractions: These are unique contractile patterns of the large intestine frequently seen in the species producing faecal boli, also in carnivores. In dogs and horses, they are called "colonic motor complex" (CMC). The segmenting contractions separate the digesta into boli. In contrast to the segmenting contractions of the small intestine, the segmenting contractions of large intestine represent long-lasting circular constrictions that occur simultaneously at adjacent sites with slow distal movement.

Haustral movements: Haustra are the small-segmented pouches of large intestine. Movements of the haustra are characterized either by alternating contractions and relaxation resulting in mixing of digesta or by an oral or aboral rolling movement causing transport of liquids in a definite direction. Haustral movements are frequently associated with the migrating segmenting contractions.

Aborally propagating giant contractions: These are characterized by large amplitude, long duration, and slower propagation velocity in comparison to peristaltic waves. They facilitate pronounced aboral transport of digesta.

13.1.1.3.5 Defecation

It is the act of expelling faeces from the digestive tract through the anus. Defecation requires a complex and synchronized interactions between gastrointestinal system, nervous system, and musculoskeletal system. The anal opening is guarded by internal anal sphincter and external sphincter made of involuntary circular smooth muscle and voluntary striated muscle, respectively. The faecal contents are channelized into the rectum by peristalsis of colon. The filling of rectum stimulates mechanoreceptors of the wall of the rectum to initiate defecation reflexes. The reflexes are of two types.

Intrinsic reflex: It is mediated by enteric nervous system (myenteric plexus) after the distension of rectal wall. It causes peristaltic waves in descending colon, sigmoid, and rectum followed by relaxation of internal anal sphincter to allow a small amount of faeces to pass through to the anal canal. It is called the recto-anal inhibitory reflex frequently used for anal sampling.

Defecation reflex (Parasympathetic): In the reflex, the signals for rectal filling first transmitted into the spinal cord and then back to the descending colon, sigmoid, rectum, and anus through parasympathetic nerve fibres in the pelvic nerves. These parasympathetic signals result strong peristaltic waves followed by relaxation of the internal anal sphincter to clear the bowl. Strong contractions generate a pressure gradient between the rectum and anal canal for defecation. After the defecation, external anal sphincter regains its normal tone and maintains continence.

13.1.1.3.6 Emesis

Vomiting or emesis is the forceful oral expulsion of gastrointestinal contents by the contractions of the gut and the thoraco-abdominal musculature. The urge to vomit is called nausea. Vomiting is the act of defence intended to remove toxins, drugs, and pathogens entered into the body through enteral or parenteral route. Vomiting centre is situated at the medulla oblongata includes the reticular formation and the nucleus tractus solitarius. The vomiting centre receives inputs from four principal areas namely gastrointestinal tract, vestibular region, chemoreceptor trigger zone (CRTZ), and cerebral

cortex. Out of these four regions, the CRTZ is closest to the vomiting centre as it lies between the medulla and the floor of the fourth ventricle. CRTZ is devoid of blood–brain barrier thus the irritants can easily pass through it. The peripheral stimuli such as toxic substances and pathogens and pathology of GI tract induce the release local emetic neurotransmitters like serotonin to stimulate vomiting centre. The motion sickness and opioid analgesics act via vestibular region to stimulate vomiting centre by releasing histamine and acetylcholine. Pain and anxiety induce stimulate vomiting centre through thalamus and cerebral cortex. CRTZ has receptors for neurokinin, mu/kappa opioids, and dopamines. The mechanism of vomiting includes relaxation of muscle of stomach and lower oesophageal sphincter followed by closing of pylorus. The intra-thoracic pressure is decreased due to expansion of chest cavity and closure of glottis. Finally, the upper oesophageal sphincter closes and the gastrointestinal contents are expelled by antiperistalsis activity. Carnivores and most omnivore mammals are emetic species. But rodents are non-emetic species that lack a vomiting reflex.

Know More. . .
The rodents have long abdominal oesophagus, and they lack neurological component for vomiting reflex. Hence, they are unable to vomit.

13.1.1.4 Control of GI Functions

The gastrointestinal (GI) tract function is very well regulated at various levels. These controls can be classified as myogenic, neurogenic, and endocrine controls.

13.1.1.4.1 Myogenic Control

The contractions of GI smooth muscles are derived from the electrical activity across the membranes of smooth muscle cells. The resting membrane potential of smooth muscle cells is between −50 and −60 mV. In contrast to nerves and other types of muscle cells, the membrane potential of smooth muscle cells fluctuates spontaneously. The electrical activity of GI smooth muscles is initiated from interstitial cells of Cajal (ICC) that surround the circular and longitudinal smooth muscles. ICC resembles Purkinje cells of heart with rhythmic oscillating properties hence called "pacemakers of the guts". The characteristics features of ICCs include small cell bodies with elongated processes, numerous mitochondria, abundant intermediate filaments, few ribosomes, and endoplasmic reticulum. The gap junctions facilitate the communications between ICCs and other smooth muscles to propagate the electrical signals. There are morphologically distinct ICC in different locations of GI tract. Majorities of ICCs are abundant in the myenteric plexus (Auerbach's plexus) called ICC of the myenteric plexus (ICC-MY or ICC-MP) or ICC of Auerbach's plexus (ICC-AP). IC-SM (submucosal ICCs) are located at the submucosal surface of the colon; IC-DMP are cells along the intestinal deep muscular plexus; IC-IM are the intramuscular cells in oesophagus, stomach, and colon. ICCs generate a spontaneous rhythmic membrane potential between 65 and 45 mV called basic electrical rhythm (BER) by the activation of L-type voltage-dependent calcium channels that allow the entry of calcium into smooth muscle cells. The BER itself does not cause muscle contraction.

The electrical activity across the membranes of GI smooth muscles shows two patterns namely slow waves and spike potentials. The slow waves are generated as a result of partial depolarizations when the membrane potential fluctuates between 5 and 15 mV. Slow waves sweep along the digestive tube for long distances. The frequency of slow waves varies along the different sections of the digestive tract, it is 10–20 times per minute in the small intestine and 3–8 times per minute in the stomach and large intestine in dogs. Slow wave activity is the intrinsic characteristics of smooth muscle independent to nervous stimuli.

Slow waves are generated as partial depolarization; they are unable to elicit contractions. Rather, they coordinate or synchronize muscle contractions in the gut to initiate a second type of depolarization event called "spike potentials". Spike potentials are true action potentials generated when the slow waves pass over the area of GI smooth muscle sensitized with neurotransmitters of the enteric nervous system. The spikes contain both depolarizing and repolarizing components result due to calcium influx and potassium efflux, respectively.

13.1.1.4.2 Neurogenic Control

The GI system is innervated by the enteric nervous system and the autonomic nervous system.

The enteric nervous system (ENS): It is the intrinsic nervous system of the gut together with pancreas and gall bladder, composed of mesh-like system of 500 million neurons. It is also called "Gut brain" as it is independent of the central nervous system. ENS receives information form the mechanical and chemical receptors stimulated by sight smell and presence of feed. ENS is composed of an outer myenteric or Auerbach's plexus situated between longitudinal and circular muscle layer. Another inner submucosal plexus known as Meissner's plexus situated at the submucosa of the intestinal wall. Both the excitatory and inhibitory motor neurons of myenteric plexus innervate the intestinal smooth muscles and secretomotor neurons project to the mucosa. The secretomotor activities are initiated through various neurotransmitters. The neurotransmitters for relaxation of GI smooth muscles are nitric oxide, pituitary adenylate cyclase-activating peptide, vasoactive intestinal peptide (VIP), and purine. Whereas tachykinins and acetylcholine are responsible for intestinal contraction.

The submucosal ganglia are composed of different types of neurons like intrinsic primary afferent neurons (IPANs), interneurons, secretomotor, and vasodilator neurons.

With these neural components, the enteric nervous system (ENS) exhibits neural reflexes to control and coordinate motility, secretion, and blood flow.

The autonomic nervous system (ANS): This system includes sympathetic and parasympathetic systems. The sympathetic nervous system is inhibitory to GI muscles and glands. However, the sympathetic system regulates blood flow in the GI system. The parasympathetic nervous system has both excitatory and inhibitory control over the gastric functions. The parasympathetic system comprises vagus (oesophagus, stomach, pancreas, upper large intestine) and pelvic nerves (lower portion of large intestine, rectum, and anus). The vagus nerves synapse with myenteric motor neurons and control them by nitric oxide (inhibitory actions) and acetylcholine/neurokinins (excitatory actions).

Hypothalamic Control of GI Functions

The hypothalamus plays a pivotal role in regulating appetite and energy expenditure by sensing the metabolic signals from leptin, amylin, cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and ghrelin. Distinct hypothalamic areas play a critical role in controlling GIT functions, especially with respect to feeding and satiety. Lateral hypothalamus (LHA) acts as "feeding centre" to promote food intake and weight gain whereas ventromedial hypothalamic nucleus (VMH) acts as "satiety centre" that favours weight loss. The sub-populations of arcuate (ARC) neurons express a variety of neuropeptides including orexigenic (appetite stimulant) Agouti-related protein (Agrp), Neuropeptide Y, and the anorexigenic (appetite suppressor) pro-opiomelanocortin (POMC). These neurons are highly responsive to metabolic status and regulate energy intake by modulating melanocortin-4 receptor (MC4R). In response to these metabolic signals, hypothalamus coordinates with multiple brain regions through neuronal circuits. The area postrema (AP), on the caudal brainstem, regulates satiation in response to metabolic signals.

13.1.1.4.3 Endocrine Control

The GI hormones can be classified into endocrines, paracrine, and neurocrine based on their mode of delivery. Hormone gastrin, secretin, cholecystokinin (CCK), motilin and gastric inhibitory polypeptide (GIP), or glucose-dependent insulinotropic peptide (GIP) are secreted from the enteroendocrine cells into the blood stream hence categorized under endocrines. Somatostatin and histamine are secreted as paracrine fashion to their local target tissue. Some hormones act through both endocrine and paracrine mechanisms like pancreatic polypeptide, glucagon-like peptide-1 (GLP-1), and peptide YY. Neurocrine hormones like enkephalins, vasoactive intestinal peptide (VIP), and gastrin release peptide (GRP) are secreted from postganglionic non-cholinergic neurons of the enteric nervous system. The roles of different hormones in GI functions are summarized in Table 13.2.

13.1.2 Secretory Functions of GI Tract

The primary functions of the GI tract are the digestion and absorption of feed. Different parts of GI system secrete a wide range of chemical substances to assist digestive and regulatory processes of GI function. Salivary glands, stomach, pancreas, gall bladder, and intestine are the predominant organs that contribute GI secretions. There are several anatomically distinct glands in the epithelial surface of GI tract. Single cell mucous glands like goblet cells contribute to mucous secretion in response to irritation. Small intestine is equipped with specialized secretory cells at the epithelial invaginations called Crypts of Lieberkühn. The glandular part of stomach contains deep tubular cells (oxyntic gland) that secret acid and pepsinogen. The salivary glands and the pancreas are complex acinar glands situated outside of the elementary canal, but their acinar secretions are poured into the GI tract. The glands of GI system are stimulated by direct contact of food. The tactile, chemical, and wall distension activates ENS that stimulates the glands for secretion. Parasympathetic stimulation increases the secretions of glands of upper GI tract. The GI secretions are also influenced by endocrine factors.

13.1.2.1 Salivary Secretions

Saliva is the collective secretions of three major salivary glands (Table 13.3) and numerous minor salivary glands situated at the mucous membrane of oral cavity. Shape, size, and number of salivary glands are varied among animal species. The functional capabilities of salivary glands are also varied. In majority of species, it lubricates the feed bolus, aids digestion, and protects the oral cavity. But, in some arthropods, saliva is used to prepare threads for the cocoons.

Other than three main salivary glands, sheep, and cattle have paired inferior molar salivary glands. There are some minor salivary glands in animals like buccal, palatine (palate), labial (lips and cheeks), and pharyngeal (pharynx). Dorsal buccal gland of dogs is also called zygomatic salivary gland. It is a sero-mucous gland situated at the zygomatic arch and ducts open at caudal parotid papilla in the oral cavity.

Salivary glands can also be classified on the basis of their secretory contents. Parotid, inferior molar, palatine, and buccal glands secret more bicarbonate hence called alkaligenic glands. In contrast, submaxillary, sublingual, and pharyngeal are called mucogenic glands as they secret more mucin.

Table 13.2 Roles of different hormones in GI functions

Name	Source	Functions
Gastrin	G cells in the stomach and duodenum	Stimulates parietal cells in the stomach for acid secretion Growth of intestinal mucosa Inhibition of secretin and GIP
Cholecystokinin (CCK)	I cells in the duodenum and jejunum	Contraction of the gallbladder Inhibition of gastric emptying Stimulation of pancreatic enzymes and bicarbonate secretion
Secretin	S cells in the duodenum	Inhibition of gastrin and acid secretion Stimulation of biliary secretion Stimulation of pancreatic bicarbonate secretion
Glucose-dependent insulinotropic polypeptide (GIP) (Previously known as gastric inhibitory polypeptide	K cells in the duodenum and jejunum	Stimulation of insulin secretion Induction of satiety Stimulation of lipoprotein lipase
Glucagon-like peptide-1 (GLP-1)	Intestinal L-cells	Inhibition of gastric emptying Induction of satiety
Somatostatin	D cells of stomach, duodenum, and pancreatic islets	Inhibition of pancreatic and gastric exocrine functions Inhibition of the motility of stomach and the gut
Histamine	Intestinal enterocytes	Stimulation of gastric acid secretion
Peptide YY	L cells at the distal GI tract	Reduction of feed intake
Enkephalin	Postganglionic non-cholinergic neurons of the enteric nervous system	Inhibition of intestinal fluid and electrolyte secretion
Vasoactive intestinal peptide (VIP)	Postganglionic non-cholinergic neurons of the enteric nervous system	Relaxation of GI smooth muscles Stimulation of pancreatic and biliary secretions Inhibition of gastric acid secretion
Gastrin release peptide (GRP)	Postganglionic non-cholinergic neurons of the enteric nervous system	Stimulation of gastrin release
Motilin	Entero-endocrine cells (Mo cells) in the upper small intestine	Increases gastrointestinal motility

Table 13.3 Types of major salivary glands

Name	Anatomical Position	Type	Name of duct	Site of secretion	Nerve supply
Parotid	Under the ear and vertical ramous of mandible	Serous	Duct of Stensen	Either side in the vestibule of mouth cavity	Glossopharyngeal and Trigeminal nerve
Submaxillary or Mandibular	Intramandibular space	Mixed (Sero-mucous)	Ducts of Wharton	Either side of frenulum of tongue	Lingual and facial nerve
Sublingual	Base of tongue	Mucous	Duct of Bartholin Duct of Rivinus	Either side of frenulum of tongue	Lingual and facial nerve

13.1.2.1.1 Functional Anatomy of Salivary Gland

The glands are lobular and each lobule comprises acini and duct. The individual salivary secretory unit is called salivon. Each salivary acinus is lined by glandular epithelial cells surrounding a central lumen. The secretions from these glandular cells are poured into these lumens. The acini are of three types based on their nature of secretions viz. serous, mucous, and mixed (sero-mucous). The serous types of cells appear dark in haematoxylin and eosin (HE) stain due to plenty of zymogen granules. In contrast, mucous-secreting cells look empty under HE stain. Serous demilunes is the characteristic feature of mixed type of glands where serous part remains compressed at the periphery of a mucous acinus. Serous glands produce thin, watery, and enzyme-rich secretions. Mucous cells secret thick and viscoid mucous. There are specialized modified smooth muscle cells called

myoepithelial cells surrounding the acinus. These cells have long cytoplasmic processes spread like a basket, hence called basket cells. The contraction of myoepithelial cells increases the ductal pressure that leads to salivary secretions.

There are four generations of salivary ducts viz. intercalated, striated, excretory, and main collecting duct. The striated duct is active and involved in reabsorption of electrolytes.

13.1.2.1.2 Composition and Rate of Salivary Secretion

The composition of saliva varies greatly among species and types of glands (Table 13.4). In non-ruminants, the secretions of submaxillary and parotid glands are hypotonic during basal or unstimulated secretions. The concentration of sodium chloride and bicarbonate increases with the secretory flow rates and at maximum flow rate it is isotonic in nature. But the ruminant saliva is isotonic at any flow rate though reciprocal changes in phosphate and bicarbonate concentration is noted at increased flow rates. The secretions of the parotid glands are continuous. The flow rate of parotid glands is about 2 mL/min at rest and 30–50 mL/min during rumination. Total salivary gland flow rate is 60–160 L/day in cow and 6.0–16 L/day in sheep. Free flow of submaxillary and sublingual glands is seen during chewing of normal meat in dogs. Parotid secretion occurs only during feed intake in horse. Ruminants have numerous minor salivary glands viz. buccal, pharyngeal, palatine, inferior molar, and labial. The composition of saliva is depicted in Fig. 13.1.

Table 13.4 Ionic composition of saliva (mmol/L) in different species at maximum flow rate

	Parotid gland			Submandibular gland		
Species	Na^+	K^+	HCO_3^-	Na+	K+	HCO_3^-
Sheep	160–175	9–10	113–140	20	7	23
Dog	80–110	6–14	50	70–100	12–15	10–30
Cat	–	–	–	40–51	9–10	26
Rabbit	110–140	10	12–30	50–100	10–40	25

Hornbuckle et al. (2008)

13.1.2.1.3 Control of Salivary Secretion

The salivary glands receive both efferent innervations of sympathetic and parasympathetic nervous system which mainly act synergistically on the salivary glands.

Sympathetic supply: The pre-ganglionic fibres originate from thoracic nerves and terminate at superior cervical ganglion after passing cervical sympathetic chain. The postganglionic adrenergic nerves originate from superior cervical ganglion and supply the blood vessels of salivary glands. The sympathetic stimulation causes myoepithelial cell contraction by norepinephrine. But, at the later phase of secretion, the sympathetic stimulation leads to thick mucin-rich salivary secretion mediated by vasoconstriction.

Parasympathetic supply: Parasympathetic stimulation comes from superior and inferior salivary nucleus located in the pons and medulla. Superior salivary nucleus supplies submandibular and sublingual salivary glands and inferior salivary nucleus supplies parotid glands. The sensory stimulation is carried by trigeminal and glossopharyngeal nerves. The afferent impulses are carried to the salivary glands by facial and glossopharyngeal nerves to cause vasodilation and

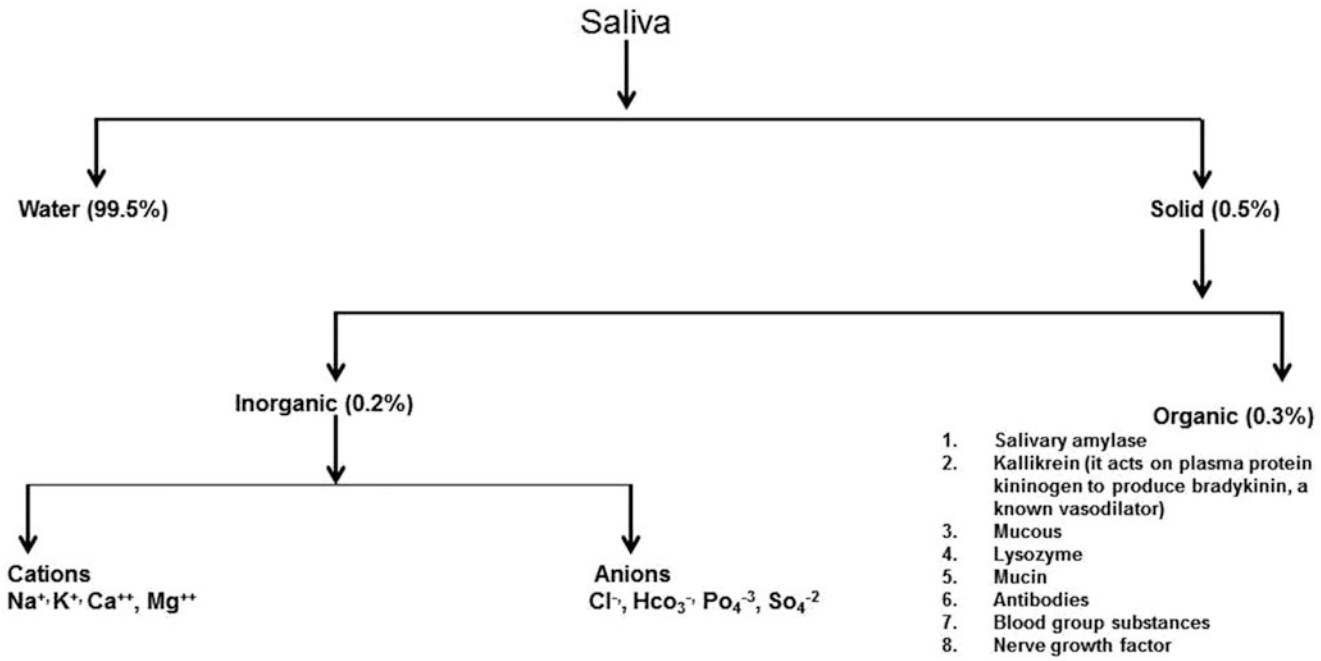


Fig. 13.1 Composition of saliva

copious salivary secretion rich in water and HCO_3, but low content of protein.

The main stimulus for salivary secretion is the feed intake that activates a number of taste receptors, olfactory receptors, mechanoreceptors, and nociceptors. All forms of taste sensations (sour, salt, sweet, and bitter) are able to stimulate salivary secretion, but sour has more pronounced effect. The movement of teeth during mastication stimulates mechanoreceptors present in periodontal ligaments. Olfactory receptors at the roof of the nasal cavity stimulate salivary secretion. The sensation is perceived through sniffing that increases airflow to the receptor area. Olfactory salivary reflex is common for submandibular salivary gland but absent in parotid glands. Spicy food activates nociceptors for salivary secretion. Dryness of the oral cavity also stimulates salivary secretion. Growth hormone, sex steroids, and thyroid hormones affect salivary gland metabolism and secretory property. Decreased level of sex steroids leads to hyposalivation in postmenopausal women. In sheep, aldosterone induces sodium uptake (without water) by salivary ductal cells and leads to decreased sodium concentration in the saliva. But aldosterone has little effect on ductal sodium reabsorption in human. Gastrin induces salivary secretion during gastric phase of salivary secretion whereas cholecystokinin and melatonin stimulate salivary secretion during intestinal phase. Ageing results atrophy of salivary glands and decreased saliva secretion. The loss of teeth, olfactory, and noci receptors during ageing also cause hyposalivation. Secretory pattern of saliva also follows circadian and circannual rhythm. Salivary secretion is lower in the morning and gradually increases till afternoon to reach highest around late afternoon. Flow of saliva is higher during winter than summer. Circadian pattern of salivary secretion is regulated by peripheral clock mechanism (clock gene) as in other organs. Secretion of salivary substances also follow circadian pattern. Salivary IgA concentrations show circadian rhythmicity and reaches peak during sleep.

Phase of Salivary Secretion

Secretion of saliva occurs in two phase basal and reflex action. Secretion of saliva without any stimulation is called basal salivary secretion. The reflex action is of two types. In unconditioned reflex, salivary secretion occurs due to the presence of food in mouth. Oesophago-salivary reflex and gastro-salivary reflex are seen when the food is present at oesophagus and stomach. The salivary secretion through conditioned reflex is brought about by thinking of food, sight, or smell. This reflex can be elicited even by non-physiological stimuli like ringing of a bell if properly conditioned.

13.1.2.1.4 Functions of Saliva

Taste: Saliva helps in dissolution of feed particles and helps in the perception of taste. The hypotonic nature of saliva helps in dissolution of nutrient particles. Further, saliva contains a protein named gustin required for the growth and maturation of these buds.

Protection and Lubrication: Saliva protects the oral tissue against irritating agents by forming a seromucosal layer. Mucins of salivary secretions facilitate lubrication and maintenance of salivary viscosity. They also prevent the adhesion of pathogens to the oral mucosa and prevent colonization. In addition, they protect against proteolytic attacks by microorganisms. The lubricating action of saliva also helps in mastication and deglutition.

Dilution and Cleaning: Saliva helps in mechanical cleaning of oral cavity and clears the residues such as nonadherent bacteria and cellular and food debris. Saliva limits the sugars utilization by biofilm microorganisms after eliminating excess carbohydrates.

Buffering Action: The bicarbonate and phosphate present in the saliva act as buffering agents. The bicarbonate is the major buffering agent of the saliva and phosphate contributes a little. Buffering action of saliva helps to maintain a stable oral pH and protect the mouth from pathogenic microorganisms. Further, saliva neutralizes the acids produced by acid forming microorganisms, thus, preventing demineralization of tooth enamel.

Integrity of Tooth Enamel: Saliva plays a key role in maintaining the physical-chemical integrity of tooth enamel through various ways. Firstly, salivary glycoproteins help to form acquired dental pellicle (a thin protein film over the surface enamel and dentin). Secondly, it neutralizes acid by dilution and buffering action and protects the enamel from erosion. Saliva contains calcium, phosphate, and fluoride necessary for remineralization of enamel.

Digestion: In omnivores such as rats and pigs, saliva contains a starch-digesting enzyme α-amylase (ptyalin). This enzyme is usually absent from saliva of carnivores such as cats and dogs. Lingual lipase present in young animals helps to digest lipids during milk diet and disappears as the animals mature.

Absorption of Vit-B12: Salivary glands produce a glycoprotein called "Haptocorrin" or "Cobalophilin" that binds with Vit-B12 and protects it from acid digestion in stomach. However, in duodenum, the Vit-B12 once again becomes free to bind, this time to another molecule called "Intrinsic Factor" forming a B12–IF that is absorbed in the ileum.

Tissue Repair: Epidermal growth factor produced by the submandibular glands has a role in wound contraction.

Antibacterial Properties: Secretory immunoglobulin A (IgA) of saliva neutralizes viruses, bacterial, and enzyme toxins. Among the non-immunologic salivary protein components, there are enzymes (lactoferrin, lysozyme, and peroxidase), proline-rich proteins, histatins, mucins, statherins, and cystatins. Lysozyme hydrolyses the cellular wall of some bacteria. The histatins, a family of histidine-rich peptides, have antimicrobial activity against some strains of

Streptococcus spp. They neutralize the lipopolysaccharides of the external membranes of Gram-negative bacteria and are potent inhibitors of *Candida albicans* growth and development.

Thermoregulation: Some animals such as rats spread their saliva on their body so that it evaporates and provides a cooling effect on the body. The parotid glands of dogs are capable of secreting at ten times of the rate of parotid glands in human during panting.

Special Functions in Ruminants: In ruminants, saliva provides a proper media for the bacterial growth and activity in the rumen. Further, bicarbonates and other contents of alkaline saliva (pH 8.1) neutralize the volatile fatty acids produced during microbial fermentation and maintain a stable rumen pH. Apart from buffering action, saliva acts as anti-foaming agent due to its mucin content. Urea is nonprotein source supplies nitrogen for the bacterial growth and microbial protein synthesis. Phosphates are utilized for nucleoprotein and phospholipid synthesis.

13.1.2.1.5 Pathophysiology of Salivary Gland

Ptyalism: Hyper secretion of salivary glands lead to a condition called ptyalism characterized by drooling of saliva. Ptyalism is secondary to swallowing disorders in animals. The causes of ptyalism are toxins, drugs, poison such as organophosphorus compounds, glossitis, stomatitis, convulsive disorders, nervousness, motion sickness, linear foreign body ingestion, and oral tumour. The conformational defects like pendulous lips may also result ptyalism. In rabies, ptyalism is very characteristics hence care should be taken to examine patient with ptyalism.

Sialadenitis: The inflammation of the salivary gland is called sialadenitis. It rarely occurs in dogs and cats.

Xerostomia (dry mouth): Xerostomia or dry mouth is a clinical condition develops due to hyposalivation. It is uncommon in dogs and cats but can occur in animals under frequent radiation exposure. Xerostomia causes discomfort during eating and oral infections. Administration of drugs like atropine, severe dehydration, fever, and anaesthesia may also cause hypo salivation. Immune-mediated keratoconjunctivitis sicca in canines can also lead to xerostomia.

13.1.2.2 Gastric Secretion

The stomach lies between the oesophagus and duodenum at the left side of the abdominal cavity. Stomach stores food which is then mixed with acid, mucus, and pepsin; and released at a controlled and steady rate into the duodenum. Gastric juice contains hydrochloric acid (HCl), lipase, and pepsin that help in the digestion of proteins and fats. Gastric acid also helps to inactivate microorganisms thus acts as first line of defence against infection.

13.1.2.2.1 Functional Anatomy of Stomach

The stomach can be divided into four distinct functional compartments based on the distribution of gastric mucosa however, not all species have all four compartments.

Oesophageal stomach: The portion of stomach that lies just below the oesophagus is called oesophageal stomach. It is lined by stratified squamous epithelium. This portion of stomach is non-glandular in nature as no mucus, acid, or proteolytic enzymes are produced from this area. The horse has a rather large oesophageal stomach compartment, but it is very smaller than the dog, pig, and cow.

Cardia stomach: It is situated just below the oesophageal stomach. Here, the gastric mucosa changes from stratified squamous to simple columnar epithelium. It is considered a glandular stomach that produces thick mucus and buffer. The mucous and buffer protect the epithelium from corrosive actions of gastric acid the proteolytic enzymes. The portion of cardia is very large in pigs, very small in dogs. Cardia is almost absent in horse and cow.

Fundic stomach: This portion is the largest compartment, and all the animals have fundic stomach. It is glandular in nature and mucosal lining of this area has very deep invaginations lined by a variety of cells that produce acid, proteolytic enzymes, hormones, and mucus.

Pyloric stomach: It is the terminal portion of the stomach joined with duodenum and guarded by pyloric sphincter. Pyloric stomach is glandular with moderately deep glands lined by epithelial cells. These glands produce only mucus and buffer without acid or proteolytic enzymes. The G cells present at the pyloric region produce the hormone gastrin in response to gastric distension or in increased stomach pH. All mammals have a pyloric stomach.

13.1.2.2.2 Gastric Mucosa

The fundic stomach contains gastric pits lined with mucus-secreting cells at the luminal surface. The mucous protects the gastric mucosa from acid and proteolytic enzymes by forming a gel. The mucous gel also entraps bicarbonate ions for neutralization of gastric HCl. Each gastric pit has deep gastric gland that extends to reach the submucosal layer. There are about 35 millions of gastric glands in human stomach. Each gastric gland has three parts namely neck, body, and base. The junction of glands and gastric pits is called Isthmus. The cells have rapid regenerating property to mature within 2–3 days. About 0.5 million cells are desquamated per hour and replaced by new cells. There are different types of cells in the gastric pits.

Chief cells (peptic cells or zymogenic cells): Chief cells are predominant at the base of glands throughout the fundus of the stomach. They contain plenty of rough endoplasmic reticulum and dense zymogen granules. They secret

pepsinogen, a proteolytic enzyme precursor into the lumen of the gastric gland. The zymogen granules move towards the apical surface to fuse with plasma membrane and release pepsinogen. Pepsinogen is converted to its active from pepsin by the hydrochloric acid. Chief cells also produce rennin, a proteolytic enzyme required to curdle milk. Renin is important in neonates to digest milk proteins.

Parietal cells (Oxyntic cells): These cells are pyramidal in shape with plenty of mitochondria, lysosomes, and tubulovesicles. The canaliculi are projected from the apical surface and lined by actin filaments and microvilli. The cells are tubulovesicular in nature under resting (non-secretary) condition. Upon excitation, the microcanalicular system extends up to the interior of the cells. These cells produce gastric HCl that facilitates hydrolytic breakdown of proteins and also kills many of the bacteria ingested through food. In most species, parietal cells also produce a protein known as intrinsic factor that helps in absorption of Vit-B12. Intrinsic factor tightly binds with Vit-B12 and facilitates absorption of the intrinsic factor–vitamin B12 complex through endocytosis in ileum.

Enterochromaffin (Enteroendocrine cells): These are small polygonal cells found predominantly in the small intestine and appendix, but also scattered in the colon, rectum, and stomach. In gastric mucosa, these cells are found among the parietal and chief cells. They are the predominant neuroendocrine cells of GI tract and produce serotonin which controls gastric acid and proteolytic enzyme secretion in endocrine and paracrine fashion.

Mast cells: They are found in the lamina propria of GI tract and comprise 2–5% of mononuclear cells. Mast cells are activated by substance P and release inflammatory mediators like serotonin, histamine, proteases, prostaglandin D, and other pro-inflammatory cytokines.

Delta cells (δ-cells or D cells): These are somatostatin-producing cells of the stomach, intestine, and pancreatic islets. D cells have close connection with gastrin-producing G cells and somatostatin inhibits gastrin release.

Gastrin cells (G cells): These are flask-shaped cells with microvilli at the apical surface found in the pyloric mucosa. G cells secret gastrin in response to peptides and amino acids. The neurotransmitters help in gastrin release are gastrin-releasing peptide (GRP) and bombesin.

13.1.2.2.3 Composition of Gastric Juice

Gastric secretion has two components. Basal secretion is the continuous secretion produced from epithelial cells and other mucus-producing cells. The electrolyte composition of basal secretion is similar to plasma ultrafiltrate which is neutral or slightly alkaline in nature. The basal secretion also has mucous that protects the gastric epithelium. Upon stimulation, cells of gastric glands secret HCl and pepsinogen. The flow rate of gastric secretion under resting or basal condition is about 5 mL/h which can go maximum up to 80 mL/h under stimulated secretion. The composition of gastric juice is depicted in Fig. 13.2.

13.1.2.2.4 Gastric Acid Secretion

HCl is actively secreted by the parietal/oxyntic cells of the fundic glands (Fig. 13.3). H^+ and Cl^- are secreted separately. The CO_2 diffuses from plasma into parietal cells and combines with cellular water to form carbonic acid

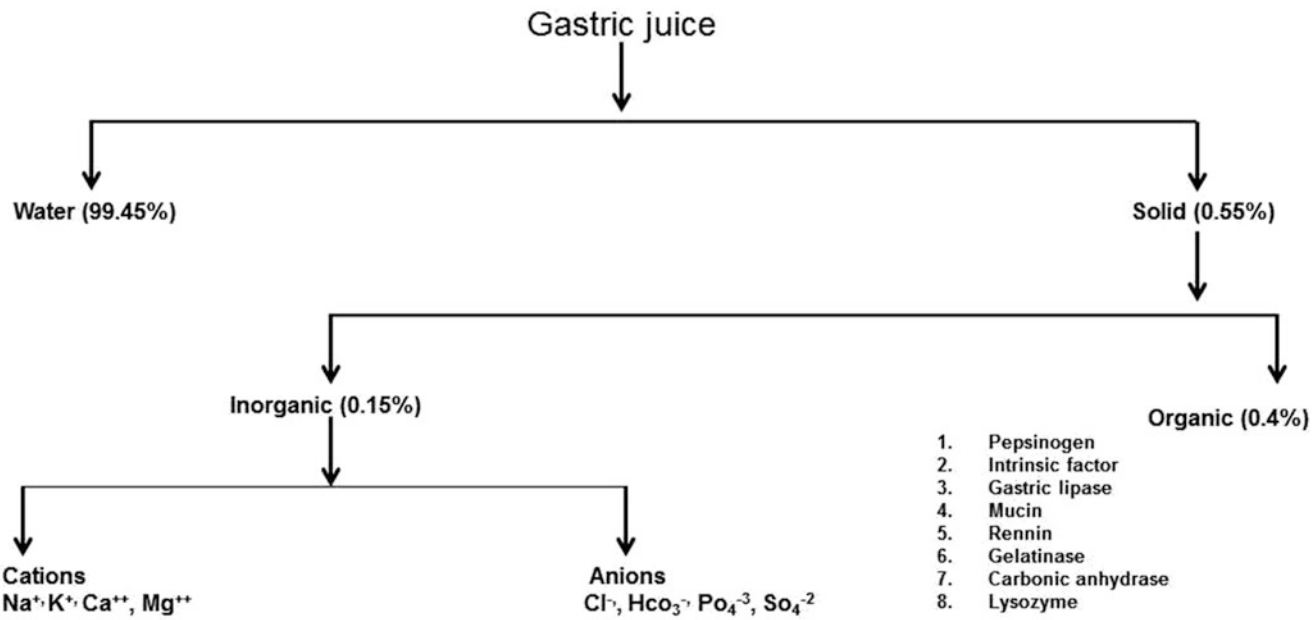


Fig. 13.2 The composition of gastric juice

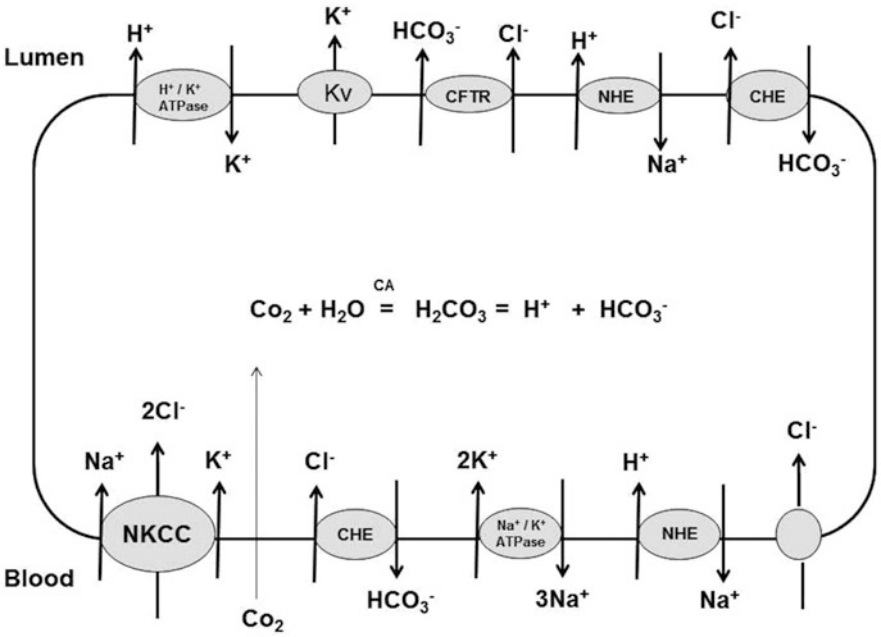


Fig. 13.3 Mechanism of gastric acid secretion. [The CO_2 diffuses from plasma into parietal cells and combines with cellular water to form carbonic acid (H_2CO_3) under the influence of carbonic anhydrase (CA). Carbonic acid then dissociates into HCO_3^- and H^+. The H^+ is extruded from oxyntic cells by K^+-stimulated ATPase that acts as an H^+/K^+ exchange pump. The transport of Cl^- into the lumen of stomach is mediated by Cl^-/HCO_3^- exchange (CHE)-transporter and cystic fibrosis transmembrane conductance regulator (CFTR). Recycling of K^+ is mediated by voltage-gated K^+ channel (Kv) and Na^+-K^+-Cl^- cotransporter (NKCC)

Table 13.5 Ion transporter systems and their roles in gastric HCl secretion

	Transporter/exchange system	Location	Function
Extrusion of H^+	ATP-dependent H^+/K^+ exchange	Apical membrane	Extrudes H^+ in exchange for K^+
	Na^+/H^+ exchange (NHE)	Apical membrane	Transport Na^+ against concentration gradient in exchange for H^+
Extrusion of Cl^-	Cl^-/HCO_3^- exchange (CHE) transporter	Basolateral and apical membrane	Extrudes Cl^- in exchange for HCO_3-
	Cystic fibrosis transmembrane conductance regulator (CFTR)	Apical membrane	Transport Cl^- against its electrochemical gradient into the gastric lumen
K^+ recycling	Voltage-gated K^+ channel	Apical membrane	Sustains the activity of H^+/K^+ exchange ATPase
	Na^+-K^+-Cl^- cotransporter (NKCC)	Basolateral membrane	Helps in the inward transport of one N^+, one K^+, and two Cl^-

(H_2CO_3) under the influence of carbonic anhydrase. Carbonic acid then dissociates into HCO_3^- and H^+. The H^+ is extruded from oxyntic cells by K^+-stimulated ATPase acts as an H^+/K^+ exchange pump. The transport of Cl^- into the lumen of stomach is mediated by Cl^-/HCO_3^- exchange (CHE)-transporter and cystic fibrosis transmembrane conductance regulator (CFTR). The key features of HCl secretion are extrusion of H^+ and Cl^- together with K^+ recycling mediated through a numbers of ion transporter systems (Table 13.5).

Alkaline tide: It is a state of metabolic alkalosis develops after heavy meal due to the diffusion of HCO_3^- into the venous blood. During every hydrogen ion secretion, one bicarbonate ion enters into the blood in exchange for chloride by Cl^-/HCO_3^- exchange (CHE) transporter.

13.1.2.2.5 Pepsinogen Secretion

Pepsinogen exists as zymogen granules in association with divalent cations like Ca^{+2} within the cells and secrets by exocytosis. The granules are fused together and also with the plasma membrane. Fusion results in a small pore formation through which Ca^{+2} is released and leads to vesicular swelling. A large pore is formed and pepsinogen is released through this pore.

13.1.2.2.6 Gastric Mucosal Barrier

The concentration of gastric HCl (150 mM) is three to four million times greater than plasma. Therefore, some protective mechanisms are required to prevent the back diffusion of the HCl that may damage the surrounding tissue. Gastric

Table 13.6 Components of gastric mucosal barrier

Pre-epithelial protection (first line of defence)	Mucus gel	Protects the gastric mucosa by forming a visco elastic gel
	Bicarbonate ion	Bicarbonate ions are entrapped within the mucous gel and neutralize hydrogen ions. It creates a pH gradient in the mucus gel and maintains the pH of epithelial surface near neutral
Epithelial protection	Luminal cell hydrophobicity	Amphoteric phospholipids in the luminal cell membrane increases the hydrophobicity and prevent the water-soluble agents to reach at the epithelium
	Sulphydryl compounds (reduced glutathione)	Neutralizes reactive-free radicals like superoxide, hydrogen peroxide, and hydroxyl radicals
	Rapid cell turnover	The proliferation rate of epithelium is very high and steady state. Human gastric epithelial cells can divide once in every 36 and matured within 48 and 96 h. This allows rapid renewal of damaged epithelial surface
	Restitution	It is the process of migration of new cells from the gastric pits to replace the damaged cells within a very short period of time
Sub-epithelial protection	Mucosal blood flow	The disposal of hydrogen ions and other deleterious agents are achieved by mucosal blood flow

mucosal barrier protects the stomach mucosa against gastric acid and other noxious agents. There are three levels of protective mechanism, pre-epithelial, epithelial, and sub-epithelial (Table 13.6).

Role of prostaglandin in gastric mucosal defence: Prostaglandin stimulates the secretion of mucus and bicarbonate to promote pre-epithelial protection against gastric injury. Endogenous prostaglandins increase mucosal blood flow and help in the disposal of hydrogen ions and harmful agents. They also increase the hydrophobicity of epical cell membranes and prevent the exfoliation of mucosal cells. Therefore, decreased prostaglandin secretion may result in gastric damage. Hence, antacids are prescribed along with non-steroidal anti-inflammatory (NSAID) drugs that primarily act by inhibiting prostaglandin synthesis.

13.1.2.2.7 Control of Gastric Secretion

Gastric functions are controlled by an integrated mechanism involving neural, endocrine, and paracrine pathways. The neural control is brought about by the enteric nervous system (ENS) with cholinergic and vagal inputs. Hormones are released into blood and control the secretion by classical endocrine pathways. Paracrine factors like histamine and somatostatin diffuse into the target cells to control their functions.

Neural control: The neural control of gastric functions can be divided into cephalic, gastric, and intestinal phases.

Cephalic Phase: It is stimulated by three reflexes, unconditioned, conditioned, and vagal. Cephalic phase accounts for 1/3 to 1/2 of total gastric acid secretion through cholinergic and vagal mechanisms. The unconditioned reflexes are brought about by sight, smell, taste, and swallowing of food. The conditioned reflex results from thought of food. The cephalic phase is entirely. The response is mediated by the vagus nerve which involves three mechanisms that stimulate gastric acid secretion.

1. The vagal efferent fibres synapse with postganglionic cholinergic neurons that innervate the parietal cell. Acetylcholine (ACh) released from postganglionic cholinergic neurons increases gastric acid secretion via M3 muscarinic receptors.
2. Vagal efferent fibres synapse with enteric neurons which secret gastrin-releasing peptide (GRP) or bombesin. GRP stimulates G cell to secret gastrin which reaches the oxyntic cells via circulation to stimulate acid secretion.
3. Somatostatin is the main inhibitor of HCl secretion. Vagal efferent fibres synapse with inhibitory neurons innervating the somatostatin cell and somatostatin release in inhibited.

The cephalic phase of gastric secretion is absent in ruminants.

Gastric Phase: It begins with the presence of food in the stomach and involves both vagal and local neurone reflexes (due to gastric distension). The vagal efferent pathway is mediated by postganglionic cholinergic neurons release acetyl choline and bombesin to stimulate G cells for gastrin release. Gastrin in turn stimulates acid secretion. Acetylcholine (ACh) also acts directly over the parietal cell by muscarinic M3 receptors to release gastric acid. The distension of stomach stimulates stretch receptors that cause the release of gastrin from G cells and histamine from enterochromaffin cells (ECLs). Both gastrin and histamine stimulate parietal cells to release HCl.

Intestinal phase: It starts after the food leaves the stomach and enters into the duodenum. It is mediated by duodenal cholecystokinin (CCK) and gastrin. CCK is a full agonist of gastrin and stimulates H^+ secretion in cats but partial agonist and competitive inhibitor in dogs. The intestinal phase also contains a cholinergic component to stimulate gastric secretion. However, most of intestinal responses are inhibitory to gastric secretion.

Endocrine and Paracrine Control: In addition to neural reflexes, some endocrine and paracrine factors involved in regulation of gastric acid secretion (Table 13.7).

Inhibitors of Gastric Acid Secretion

Several drugs are used to inhibit gastric acid secretion as therapeutic interventions in acid reflux disorders. They are classified on the basis of their mode of actions (Table 13.8).

Table 13.7 Endocrine and paracrine factors involved in regulation of gastric secretion

Endocrine and paracrine factors	Source	Mechanism of action	Functions
Gastrin	G cells of gastric mucosa, duodenum, jejunum, ileum, and pancreas in response to proteins, peptides, and amino acids	Gastrin acts via CCK-2 receptor (G-protein-coupled receptor) in parietal and enterochromaffin-like cells (ECL cells) to release histamine from ECL cells	Gastrin stimulates histamine release that causes acid secretion from stomach (role of histamine on acid secretion is discussed later) Gastrin promotes growth of gastric oxyntic cells by increasing the expression of fibroblast growth factor, epidermal growth factor receptors, and mitogen-activated protein kinase
Histamine	Enterochromaffin-like cells (ECL cells)	Histamine acts via H2 receptors to generate cAMP. It causes translocation and activation of H^+/K^+-ATPase (proton pump). Inhibits somatostatin release via H3 receptors	Efflux of H^+ into the lumen of gastric lumen Inhibition of somatostatin indirectly stimulates gastric acid secretion
Somatostatin	D cells of gastric mucosa. The primary stimuli for somatostatin release are gastric acid and gastrin. Gastric HCl activates calcitonin gene-related peptide (CGRP) neurons to release somatostatin	It acts through somatostatin receptor subtype 2 (sst2) with multiple signalling molecules	Somatostatin inhibits acid secretion directly acting on the parietal cells. Indirect actions of somatostatin include inhibition of histamine and gastrin secretion
Acetylcholine	Postganglionic neurons in Meissner's plexus	Acts over ECL cells through M1 receptors Activation of proton pump by M3 muscarinic receptors on parietal with increased intracellular calcium Inhibition of somatostatin via of M2 and M4 receptors on D cells	Stimulates histamine release Increases acid secretion Inhibits somatostatin release
Prostaglandins (PGE_2)	Endothelial cells and macrophages	Acts through surface receptors in parietal and gastric mucosal cells	Decreases histamine release and reduces acid secretion
Transforming growth factor-alpha (TGF-alpha)	Epithelial cells		Inhibits gastric acid and mucous secretion
Peptide YY	Ileum and colon	Inhibits gastrin stimulated histamine release	Inhibits gastric acid secretion
Cholecystokinin (CCK)	I cells in the duodenum and jejunum	Stimulates acid secretion via CCKb receptors on parietal cells Increases serotonin secretion via CCKa receptors on mucosal D cells	It performs dual role. It stimulates acid secretion through CCKa receptors and inhibits acid secretion via CCKb. But inhibition is the predominate effect
Secretin	S cells in the duodenum	Inhibits gastrin release	Decreases acid secretion
Neurotensin	Ileum and nerve terminals in the myenteric plexus in response to fat diet		Inhibits acid secretion
Glucagon-like peptide 1 (GLP-1)	L cells of duodenum		Stimulates somatostatin release hence decreases acid secretion
Oxyntomodulin	L cells of duodenum		Stimulates gastric acid secretion
Ghrelin	Entero-endocrine cells of gastric mucosa	Acts via growth hormone receptors in the oxyntic cells	Stimulates acid secretion
Orexin	Hypothalamus and gastric mucosa	Acts through orexin-1 receptors (OX1R) at anterior hypothalamus and ventromedial nucleus	Stimulates gastric acid secretion
Adrenomedullin	ECLs of the gastric mucosa	Stimulates gastric somatostatin release and decreases serotonin level	Inhibits gastric acid secretion

Table 13.8 Drugs used to inhibit gastric acid secretion

Class		Examples
Inhibitors of H^+/K^+-ATPase (Proton pump)		Verapamil, omeprazole, vanadate
Inhibitors of carbonic anhydrase		Acetazolamide
Inhibitors of cell activation	Calcium channel blockers	Verapamil, lanthanum
	Prostaglandin E2	
Receptor antagonists	H_2 receptor antagonists	Ranitidine, cimetidine
	Gastrin receptor antagonists	Proglumide, benzotript
	Anticholinergic drugs	Atropine
Calmodulin inhibitor		Trifluoperazine

13.1.2.2.8 Functions of Gastric Juice

Functions of HCl: Gastric HCl converts pepsinogen to its active form pepsin and facilitates the digestion of protein. It also promotes optimum environment (pH) for the action of pepsin. It can also slightly hydrolyse sucrose. It helps to destroy pathogens and acts as physiological barrier against infection.

Gastric mucin: Gastric mucin forms a gel (95% water, 5% mucin, and electrolytes) over the gastric mucosa to protect it from the corrosive action of gastric acid and other harmful agents. It also entraps bicarbonate to neutralize HCl and maintains a pH gradient to protect gastric mucosa.

Functions of gastric enzymes: Pepsinogen is a proteolytic enzyme secreted from chief cells and mucus neck cells. It is converted to its active form pepsin by HCl. Secretion of pepsinogen is enhanced by ACh, CCK, and gastrin. The optimal pH for the action of pepsin is between 1.6 and 2.5. Pepsin cleaves the proteolytic bonds involving amino acids such as tyrosine, phenylalanine, and leucine.

Gastric lipase is a lipid digesting enzyme secreted by chief cells. It is capable of hydrolysing 20% of triglycerides in the feed. In dogs, gastric lipase is secreted under the influence of histamine, prostaglandin E2, pentagastrin, and secretin. The activity of gastric lipase is independent of gastric pH.

Rennin is a proteolytic enzyme secreted from gastric mucosa. It is usually seen in newborn calves under milk diet. Rennin converts casein into paracasein which in turn combines with calcium to form an insoluble coagulum.

Function of Intrinsic Factor (IF): It is secreted from parietal cells and helps in Vit-B12 absorption. IF forms a complex with Vit-B12. The complex then binds with cubilin receptor in the ileal mucosa and absorbed by the enterocytes through endocytosis. In the enterocytes, Vit-B12 is released from IF.

13.1.2.2.9 Pathophysiology of Gastric Acid Secretion

Achlorhydria: It is a clinical condition in which the stomach is unable to produce hydrochloric acid. It is caused due to a variety of reasons such as pernicious anaemia, *Helicobacter pylori* infection, gastric bypass, hypothyroidism, radiation exposure of gastric mucosa, and gastric cancer.

Hypochlorhydria (HCH): It is characterized by reduced secretion of gastric acid. The predominant causes of HCH are chronic atrophic gastritis, *Helicobacter pylori* infection, or autoimmune disorders.

Hyperchlorhydria (sour stomach/acid stomach): It is a clinical condition in which the gastric HCl production is more than normal. It usually occurs due to higher gastrin production.

13.1.2.3 Pancreatic Exocrine Secretion

Pancreas is a lobulated gland comprises two distinct components exocrine and endocrine. Both exocrine and endocrine components are distinct structurally and functionally. The pancreas is appeared as discrete organ containing a right (proximal to the duodenum) and left limb in species like dogs and cats. Pancreas in large animals like cattle and horse is appeared diffused within the mesentery close to duodenum. The exocrine part of the pancreas constitutes more than 90% of the total pancreatic mass. The exocrine pancreas is an acinus gland structurally similar with salivary glands. The pancreatic enzymes are stored in the acinar cells in the form of zymogen granules and released upon activation. Pancreas also secrets HCO_3^- ions that neutralizes acid chime entering into the duodenum.

13.1.2.3.1 Structure of Exocrine Pancreas

The exocrine pancreas is structurally similar with salivary gland. The secretory units are called acini along with ductules for drainage. Each pancreatic acinus is composed of pyramidal glandular cells. There are centro-acinar cells situated at the junction between acini and duct. Acinar cells synthesize and store digestive enzymes at the apical region of acinar cells. The acinar cells contain nucleus and plenty of rough endoplasmic reticulum. There are numerous microvilli at the apical surface of the cells. The acinar cells are connected through tight junctions and act as a barrier for the large molecules but allow paracellular transport of water and ions. The secretions are poured into the lumen of the acinus and drained through duct system. The duct system comprises ductules and interlobular (intercalated) ducts. The ductules carry acinar secretion into the intercalated ducts. The intercalated ducts drain into main pancreatic duct called duct of Wirsung. The accessory pancreatic duct is called duct of Santorini. Both the main and accessory pancreatic

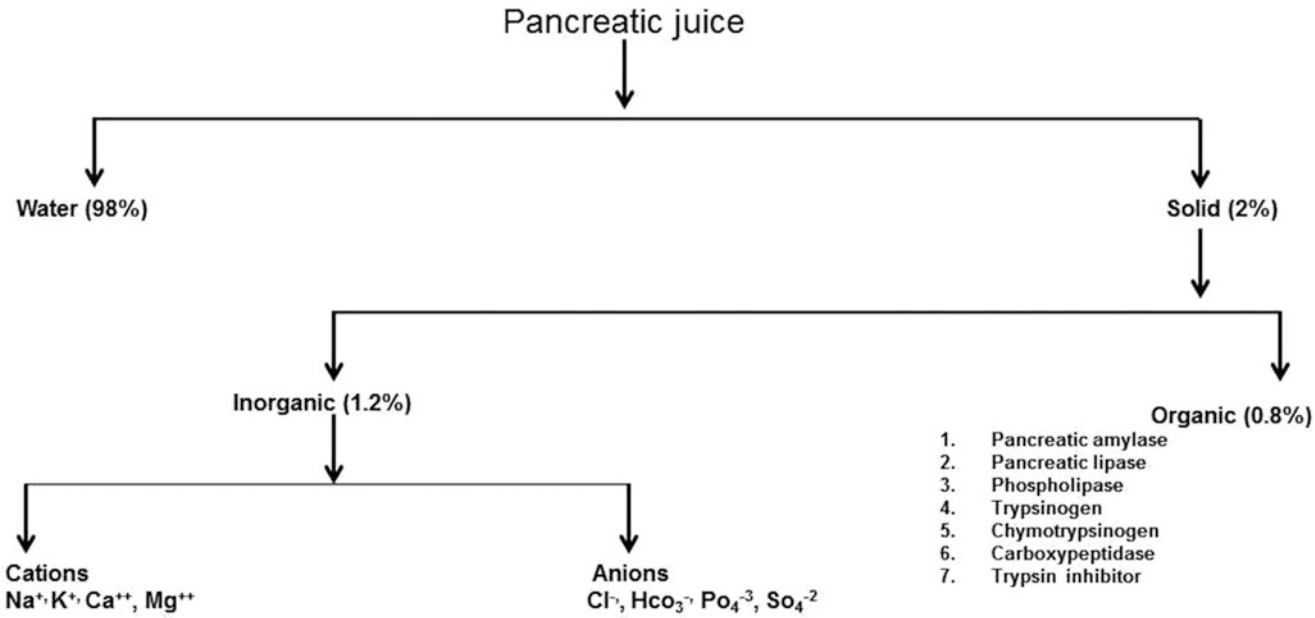


Fig. 13.4 Composition of pancreatic juice

Table 13.9 Transporters involved in pancreatic bicarbonate secretion

Transporter	Location	Function
Electrogenic Cl^-/HCO_3^- exchanger	Luminal surface of pancreatic duct cells	Extrudes HCO_3^- in exchange for Cl^-
Na^+/H^+ exchanger	Basolateral surface of pancreatic duct cells	Extrudes H^+ in exchange for Na^+
Na^+-HCO_3^- cotransporter	Basolateral surface of pancreatic duct cells	Entry of HCO_3^- at basolateral side
Na^+, K^+-ATPase	Basolateral surface of pancreatic duct cells	Maintains inward Na^+ and outward K^+ gradient
K^+ channel	Basolateral surface of pancreatic duct cells	Maintains membrane potential
Cystic fibrosis transmembrane conductance regulator (CFTR)	Luminal surface of pancreatic duct cells	Transport Cl^- into the lumen against its electrochemical gradient
Water channels (Aquaporin) AQP1, AQP5	Both basolateral and luminal surface	Water transport

ducts drain separately into the duodenum along with common bile duct guarded by sphincter of Oddi.

13.1.2.3.2 Composition of Pancreatic Juice

The pancreatic juice is alkaline in nature due to high HCO_3^- content (113 mEq/L). About 1.500 L pancreatic juice is secreted per day in human, 3–5 L/100 kg/day in cow, 0.5–1 L/100 kg/day in sheep, and 2–3 mL/min dog. The composition of pancreatic juice is depicted in Fig. 13.4.

13.1.2.3.3 Mechanism of Pancreatic Bicarbonate Secretion

Carbonic anhydrase catalyses the reaction between cellular water and diffused carbon-di-oxide to form carbonic acid. The dissociation of carbonic acid yields HCO_3^-. It extrudes from the cells into the lumen in exchange for Cl^- by electrogenic Cl-/HCO_3− exchanger. Continuous supply of Cl^- in the lumen is maintained by secretin-regulated Cl^- channel. The H^+ is removed from the cell by Na^+/H^+ exchanger at the basolateral membrane. The Na^+ gradient is achieved through Na^+, K^+-ATPase system. There are several transporters involved in the pancreatic secretory process (Table 13.9 and Fig. 13.5).

13.1.2.3.4 Mechanism of Pancreatic Enzyme Secretion

The enzymes are stored as zymogen granules in the acinar cells and secreted via exocytosis. All the enzymes are secreted as inactive form to avoid tissue digestion. Proteasomes are involved in the pancreatic enzyme secretion.

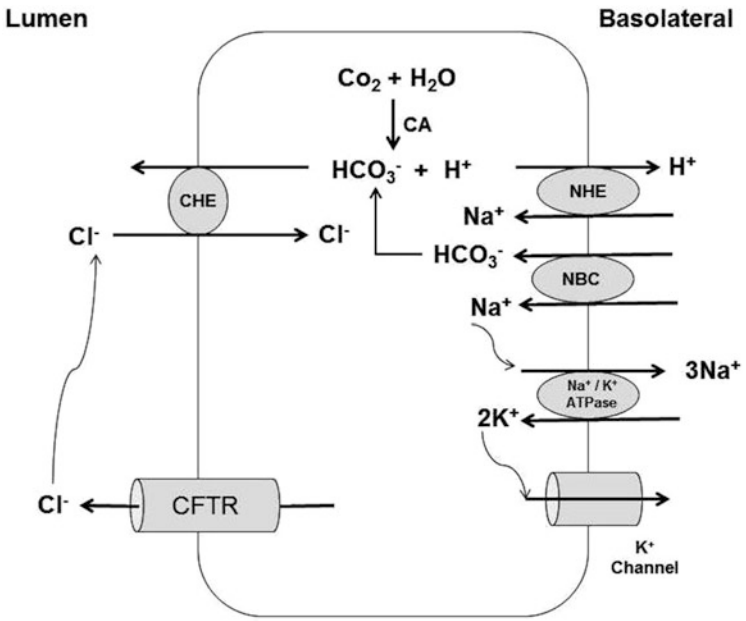


Fig. 13.5 Mechanism of pancreatic bicarbonate secretion. [Carbonic anhydrase (CA) catalyses the reaction between cellular water and diffused carbon-di-oxide to form carbonic acid. The dissociation of carbonic acid yields HCO_3^-, which extrudes from the cells into the lumen in exchange for Cl^- by electrogenic Cl^-/HCO_3^- exchanger (CHE). Continuous supply of Cl^- in the lumen is maintained by CFTR. The H^+ is removed from the cell by Na^+/H^+ exchanger (NHE) at the basolateral membrane. The Na^+ gradient is achieved through Na^+, K^+-ATPase system. The membrane potential is maintained by K^+ channel]

In mouse pancreas, anti-factor 4 of the 26S proteasome regulates the secretion of digestive enzymes. In cows, high leucine concentration decreases pancreatic amylase secretion by inhibiting proteasomes. The protein synthesis in the acinar cells is induced by mammalian target of rapamycin complex (mTOR), phosphatidylinositol-3 kinase (PI3K)-RAC alpha serine/threonine-protein kinase (Akt), and the general amino acid control repressor 2 (GCN2) signalling mechanism. The initiation of translation is occurred through the activation of AktmTOR and ribosomal protein S6 kinase beta-1 (S6K1) induced by leucine and phenylalanine. The exocytosis of zymogen granules is mediated by calcium ions. CCK and acetylcholine stimulate the acinar cells to release zymogen granules through two second messengers namely inositol-triphosphate (IP3) and nicotinic acid adenine dinucleotide phosphate (NAADP). Both of these two compounds induce the release of calcium from the sarcoplasmic reticulum via inositol 1,4,5-trisphosphate and ryanodine receptors, respectively.

13.1.2.3.5 Control of Pancreatic Secretion

Pancreatic secretion occurs in three phases viz. cephalic phase, gastric phase, and intestinal phase. The cephalic phase of pancreatic secretion is under the control of ANS. The gastric and intestinal phase is controlled by hormones and enteropancreatic reflex.

Cephalic phase: It is induced by sight, taste, and smell of food. Acetylcholine is released from vagal nerve endings and acts through muscarinic receptors to increase intracellular calcium and granular exocytosis (see Sect. 13.1.2.3.4 Mechanism of pancreatic enzyme secretion). Cephalic phase constitutes 20% of the total pancreatic enzyme secretion. But little of the secretion can reach to the intestine as little amount of water and electrolytes are secreted along with the enzymes.

Gastric phase: Gastric phase is initiated after the presence of food in stomach. Gastric distension stimulates stretch receptors and to initiate vago-vagal reflex or gastro-pancreatic reflex. Gastric phase is accounting for another 5–10% of pancreatic enzymes secretion but like cephalic phase; little can be reached to duodenum due to unavailability of water.

Intestinal phase: The copious secretion of pancreatic enzymes along with water and electrolytes occurs during the intestinal phase. The enzyme secretion is mediated through CCK under the influence of proteoses and peptones and constitute around 70–80% of total enzyme secretion. CCK has two receptor subtypes CCK1 and CCK2. In calf, both the receptors are expressed in the pancreas, but CCK 2 is the main receptor in adulthood. CCK increases intracellular calcium to release zymogen granules of the acinar cells (see Sect. 13.1.2.3.4 Mechanism of pancreatic enzyme secretion).

The secretion of water and bicarbonate is mediated by secretin. It acts through secretin receptor (SR) located basolaterally in the acinar cells. Secretin activates cAMP-dependent anion Cl/HCO_3^- exchanger and CFTR at the apical membrane of pancreatic acinar cells.

There are several factors affecting exocrine pancreas secretion in animals. In ruminants, age is the primary factors to affect pancreatic exocrine functions. The amount of pancreatic juice secretion increases with age. In calf, the amount of pancreatic juice is 150 mL/day on fourth day after birth compared to 1000 mL/day at 3 months of age. The flow rate is also increased with age. It is about 7.9 mL/kg bwt in 3-week-old calves compared to 14.2 mL/kg bwt at 3 months of age. Types of feed also affect the pancreatic enzyme

secretion. The nature of dietary carbohydrates affects the secretion of pancreatic amylase. In sheep, corn feeding stimulates more amylase production compared to hay. In goats, the amylase secretion is increased with dietary starch content. The starch entering the intestine after bypassing the rumen has tremendous influence over pancreatic amylase secretion. Leucine, isoleucine, and phenylalanine stimulate the secretion of amylase, trypsin, chymotrypsin, and lipase.

13.1.2.3.6 Functions of Pancreatic Juice

Neutralization of acid chyme: The pH of the pancreatic juice is alkaline due to high HCO_3^- concentration. The pH of pancreatic juice in dogs ranges from 7.4 to 8.3. Pancreatic juice neutralizes the acid chime entering into the duodenum to raise the pH 6.0 to 7.0.

Role in digestion: Pancreatic juice contains enzymes responsible for digestion of carbohydrates, proteins, and lipids.

Pancreatic α-amylase causes hydrolysis of α-1,4-glucosidic bonds present in starch and glycogen. Pancreatic amylase is activated by Cl^-. The optimum pH for α-amylase action is 6.7–7.2. Newborn calves and pigs have lower amylase than mature animals.

Pancreatic juice contains proteolytic enzymes for protein hydrolysis. There are two classes of proteolytic enzymes. Endopeptidases cleave peptide bonds along the peptide chains whereas exopeptidases act at the amino terminal or carboxyterminal ends of polypeptide chains. The proteolytic enzymes of pancreatic juice and their functions are depicted in Table 13.10.

Pancreatic lipase hydrolyses dietary triglycerides into glycerol, monoglycerides, and fatty acids. But lipase requires emulsified fat as dietary substrate. Bile salts help in the emulsification of fats. In addition to lipase, pancreatic juice also contains phospholipase A that converts lecithin to lysolecithin. The detergent action of lysolecithin favours emulsification of fats.

13.1.2.4 Hepatobiliary Secretion

The hepatobiliary system comprises liver, gall bladder, and bile ducts. Liver is the largest gland in the body that performs wide ranges of physiological functions including metabolism of macro- and micronutrients, blood volume regulation, lipid and cholesterol homeostasis, immunity, endocrine control of growth signalling pathways, and detoxification of xenobiotic compounds, drugs, and hormones. The hepatocytes of the liver produce bile that transports through bile ducts into the gall bladder. The bile is concentrated and stored at the gall bladder. Bile helps in emulsification of dietary lipids for enzymatic actions.

13.1.2.4.1 Structure of Hepatobiliary System

Hepatobiliary system comprises two components. The intrahepatic components lie within the liver, whereas extrahepatic components are situated outside of the liver. Hepatic cords comprising hepatocytes are arranged radially around the central vein. In between the hepatic cords, there are endothelial lined spaces called sinusoids. The portal triads viz. portal vein, hepatic artery, and bile ducts are situated at the periphery of hepatic lobules. Portal arteries and veins carries allow the blood to flow centrally and bile duct facilitates to drain bile peripherally into ductules and finally to bile duct in portal triads. The liver sinusoids contain Kupffer cells (Littoral cells) having phagocytic activity. They are the components of mononuclear phagocytic system or reticuloendothelial system. The space between sinusoidal endothelium and hepatocytes is called space of Disse. The ions and nutrients have to cross this place before entering into hepatocytes. The stellate cells are also situated at the space of Disse and help to form fibrous scar tissue to prevent the spreading on infections. Thus, it protects the hepatocytes from toxins. The large pores along the sinusoidal epithelium allow unrestricted passage of albumin from sinusoid into the extravascular fluid.

Bile is synthesized in the hepatocytes and secreted into the bile canaliculi. Bile canaliculi exist as a groove of plasma membrane between two hepatocytes. Bile canalicular membrane represents about 13% of the total hepatocyte plasma membrane. It has numerous microvilli to increase the surface area. The bile canaliculi empty into the canals of Hering which gives rise to the biliary tress comprising intra- and interlobular ducts. The intralobular ducts join to form interlobular bile ducts which ultimately give rise to right and left hepatic ducts. The right and left hepatic ducts give rise to common hepatic duct. The cystic duct arising from the gall bladder communicates with common hepatic duct to form common bile duct that opens into the duodenum. The opening of duodenum and common bile duct is guarded by the

Table 13.10 Proteolytic enzymes of pancreas

Class	Enzymes	Functions
Endopeptidase	Trypsin	Cleaves peptide bonds on carboxyl side of basic amino acids (arginine or lysine)
	Chymotrypsin	Cleaves peptide bonds on carboxyl side of aromatic amino acids
	Elastase	Cleaves the peptide bonds of aliphatic amino acids at carboxyl side
Exopeptidase	Carboxypeptidase A	Cleaves carboxyl terminal amino acids that have aromatic or branched aliphatic side chains
	Carboxypeptidase B	Cleaves carboxyl terminal amino acids that have basic side chains

sphincter of Oddi. Common bile duct unites with the main pancreatic duct before entering the duodenum. Sphincter of Boyden is situated in the common bile duct just before the joining of pancreatic duct. Sphincter of Oddi is closed during inter-digestive period but, when the gastric chyme enters into the duodenum, the sphincter is relaxed under the influence of cholecystokinin (CCK).

There are a population of epithelial cells that forms a three-dimensional network of bile ducts called cholangiocytes. The hepatic bile is modified at the biliary tract through the secretion and reabsorption by the cholangiocytes.

The sphincter of Oddi is less developed in ruminants and pigs and bile flow is continuous into the duodenum. Similar mechanism occurs in horse due to lack of gall bladder. In dogs and cats, continuous secretion of bile is unnecessary as they feed only once or twice a day so the bile is stored in gall bladder.

Gall Bladder

It is a pear-shaped organ that helps to store bile until the body needs it for digestion. It is the component of extrahepatic biliary system. Gall bladder is connected with liver and duodenum by biliary tract. The wall of the gallbladder is made of several layers. The innermost mucosal layer is composed of columnar epithelium with microvilli. The epithelial lining is characterized by recesses called Aschoff's recesses, which form pouches inside the lining. Under epithelium there is a layer of connective tissue followed by a muscular wall that contracts in response to cholecystokinin, a peptide hormone by the duodenum. The main function of the gall bladder is to store and concentrate bile. The hormone cholecystokinin (CCK) mediates the contraction of gall bladder. CCK is released from I cells of duodenum and jejunum under the influence of fatty acids and amino acids. Beside gall bladder contraction, CCK also relaxes the sphincter of Oddi to release bile into the duodenum. Agents increase the bile flow by contracting the gall bladder is called chalogogues such as CCK.

13.1.2.4.2 Bile

Bile is a complex lipid-rich hepatic secretion. It is synthesized in the hepatocytes and modifications occur at the bile duct epithelium through secretory and absorptive mechanism. Gall bladder acts as the temporary storage site of the bile and bile is released into the duodenum after the contraction of gall bladder.

Formation of Bile

Bile is produced in the hepatocytes and subsequently modified in bile ductules by cholangiocytes. The secretion requires active transport systems in the biliary tree.

Synthesis of bile acids: Bile acids are synthesized in the pericentral hepatocytes from its cholesterol precursor. Bile acids derived from hepatocyte are called primary bile. The secondary bile acids are formed by gut microbes through dehydroxylation, dehydrogenation, oxidation, epimerization, and esterification. Formation of bile acids is a complex process that involves 17 different reactions catalysed by 16 enzymes. The hydrophobic cholesterol is converted to an amphipathic hydrophilic compound through hydroxylation of sterol ring and side chain oxidation. There are two pathways of bile acid synthesis. In the classical pathway, modification of the steroid nucleus occurs before the side chain. Whereas in the alternative pathway side chain modifications occur prior to changes in the steroid nucleus. The rate limiting enzyme of classical pathway is cholesterol 7α-hydroxylase (CYP7A1). In human and rodents, the classical pathway is predominant pathway of bile synthesis accounts for 90% and 70% bile formation, respectively. The alternative pathway is mostly seen in human neonates due to lack of CYP7A1 expression. After the synthesis, bile acids are conjugated with glycine and taurine. It is a two-step process. Firstly, bile acids are converted to bile acid-COA by bile acid-CoA synthase followed by amidation with taurine or glycine with the help of enzyme bile acid-CoA: amino acid N-acyltransferase (BAAT). The amino acid conjugation makes bile acids more resistant to hydrolysis by pancreatic carboxypeptidases so, taurine and glycine-conjugated bile acids escape the cleavage in the intestinal lumen.

Sinusoidal uptake of bile acids: Conjugated bile acids are taken up by the hepatocyte through an active process. The process involves both Na^+-dependent and Na^+-independent mechanisms. There are different ion channels involved in this process. Sodium taurocholate cotransporting polypeptide (Ntcp) facilitates entry of conjugated bile salts after utilizing transmembrane sodium gradient maintained by Na+, K+-ATPase at the plasma membrane. The Na^+-independent mechanism is brought about by organic anion transporting polypeptide 1 and 2 (oatp1 and oatp 2) also helps in the uptake of conjugated bile salts along with other organic anions.

Intracellular transport: The intracellular transport of bile salts to the canalicular pole of the hepatocyte is mediated by intracellular binding proteins. Two cytosolic bile acid binding proteins namely 3-hydroxysteroid dehydrogenase and dihydrodiol dehydrogenase are identified in rat and human liver cells.

Transport of bile salts into canaliculi: The secretion of bile acids from the hepatocytes into the canaliculus requires an active transport system due to high osmotic and chemical gradient between hepatocytes (5 μM) and canalicular space (1000 μM). There is a linear relationship between bile acid secretion rate and bile flow. When the flow of bile depends upon the osmotic force of bile acids, it is called bile acid-dependent flow which accounts for 30–60% of spontaneous basal bile flow. When the secretion of bile occurs via the osmotic force generated by other than bile acids, it is called

bile acid-independent flow accounts 30–60% of basal bile flow. In bile acid-dependent flow, bile salts enter into the canaliculus by two transporter system namely bile salt export pump (BSEP) and multi-drug resistance protein 2 (MRP2). BSEP facilitates apical excretion of taurine and glycine amidated bile salts and MRP2 mediates the transport of sulphated and glucuronidated bile salts along with non-bile-salt organic anions (bilirubin glucuronides). After entering into the bile canaliculus, bile salts create an osmotic gradient to allow influx of water and electrolytes. In bile acid-independent flow, the osmotic gradient is created by HCO_3^- and reduced glutathione. HCO_3^- enters into the canalicular space by anion exchanger 2 (AE2) and MRP2 mediates the transport of reduced glutathione. The osmotic gradient created by HCO_3^- and reduced glutathione allows the influx of sodium and water.

Modifications to bile in the biliary tree: Biliary epithelial cells modify bile by adding fluid and electrolytes into the canalicular bile. The secretion of epithelium is stimulated by secretin and accounts 30% of basal bile flow. Somatostatin decreases epithelial secretion. Both secretin and somatostatin act through their receptors at basolateral surface of cholangiocytes. Secretin stimulates intracellular cAMP production which in turn activates low conductance chloride channel like cystic fibrosis transmembrane conductance regulator (CFTR). The efflux of chloride depolarizes cholangiocyte and allows the entry of bicarbonate via electrogenic sodium-bicarbonate cotransporter. Increased intracellular bicarbonate stimulates apical chloride/bicarbonate exchanger which facilitates the secretion of bicarbonate in exchange with chlorides. The water movement across the canalicular membrane is mediated by water channel aquaporin at the apical and basolateral membrane. Bile ductules have reabsorptive function and water reabsorption occurs at the distal to the canaliculi under the influence of prostaglandin.

Regulation of Bile Acid Synthesis

The synthesis of bile acids is mainly regulated by bile acids through farnesoid X-receptor (FXR) pathway. In this mechanism, bile acids activate FXR in the enterocytes followed by synthesis of fibroblast growth factor (FGF15/19). EGF15/19 then transport to the hepatocytes by portal circulation and binds with fibroblast growth factor receptor-4 (FGFR4) and Klotho protein complex to inhibit the rate limiting enzyme of bile acid secretion (CYP7A1). There are several proteins involved in the regulation of bile acid synthesis (Table 13.11).

Composition of Bile

Bile comprises nearly 95% water with dissolved solids like bile salts, lipids, pigments, enzymes, vitamins, heavy metals along with exogenous drugs, xenobiotics, and environmental toxins (Fig. 13.6). There are two forms of bile, hepatic bile and gall bladder bile. The gall bladder bile is more concentrated (Table 13.12). The solutes that are pumped actively in the bile canaliculus are called primary solutes. Apart from bile salts, glutathione, conjugated bilirubin, bicarbonate, glucuronide, or sulphate conjugates of xenobiotics are called primary solutes. Water, electrolytes, glucose, low-molecular weight solutes are called secondary solutes as they flow passively into the canaliculi by the osmotic force generated by primary solutes. The predominant compound of bile is bile acids (67%) followed by phospholipids (22%), proteins (4.5%), cholesterol (4%), and bilirubin (0.3%). Flow rate and electrolyte concentrations of hepatic bile varies with species (Table 13.13).

Bile acids: The primary bile acids synthesized in the hepatocytes includes cholic acid (CA) and chenodeoxycholic acid (CDCA). These two are the primary bile acids in most of the animal species. In pigs, hyocholic acid (HCA) is the primary bile acid derived from chenodeoxycholic acid after hydroxylation at 6α position. Secondary bile acids are produced by the intestinal bacteria by removing the α-hydroxyl group at the position 7 of CA or CDCA. The secondary bile acid includes deoxycholic acid (DCA), lithocholic acid (LCA), and ursodeoxycholic acid (UDCA) or ursodiol.

Bile phospholipids: Lecithin is the sole phospholipid in the bile. Lecithin is secreted as vesicles into bile. The translocation of vesicles is mediated by a transmembrane protein called MDR3 P-glycoprotein.

Bile cholesterol: The main route of cholesterol excretion is the through bile. The bile salts and lecithin solubilize hydrophobic cholesterol in the form of micelles. Under abnormal conditions, the cholesterol may precipitate in the

Table 13.11 Regulatory proteins of bile acid synthesis

Protein	Tissue	Functions
Farnesoid X-receptor (FXR)	Intestine, liver, kidney	Inhibits the rate limiting enzyme of bile acid secretion (CYP7A1)
Hepatocyte nuclear factor 4α (HNF4α)	Intestine, liver	Increases hepatic bile acid synthesis by stimulating the expression of CYP7A1
Small heterodimer partner (SHP)	Liver, intestine	Negative feedback regulation of bile synthesis
Pregnane X-receptor (PXR)	Liver, intestine	Detoxification of bile acids
Vitamin D receptor (VDR)	Intestine	Detoxification of bile acids
Fibroblast growth factor (FGF15/19)	Intestine	Inhibits the rate limiting enzyme of bile acid secretion (CYP7A1)

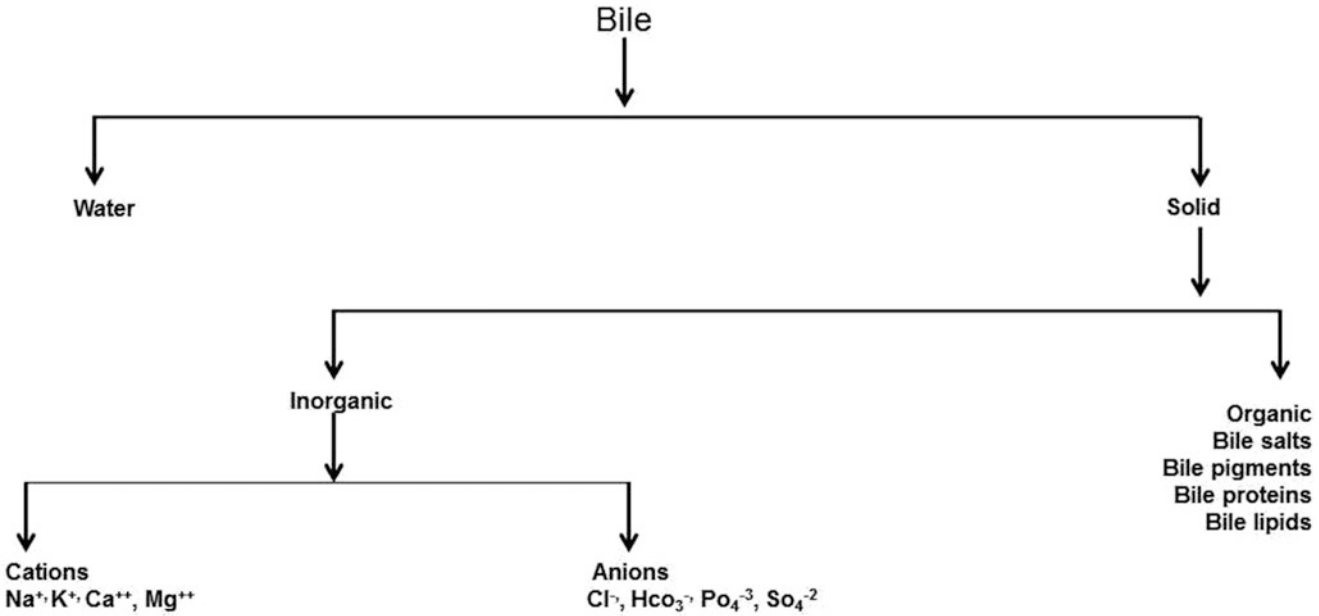


Fig. 13.6 Composition of bile

Table 13.12 The composition of hepatic and gall bladder bile

Constituents	Hepatic bile	Gall bladder bile
Water	97.5 gm%	92 gm%
Bile salts	1.1 gm%	6 gm%
Bilirubin	0.04 gm%	0.3 gm%
Cholesterol	0.1 gm%	0.3–0.9 gm%
Fatty acids	0.12 gm%	0.3–1.2 gm %
Lecithin	0.04 gm%	0.3 gm %
Na^+	145 mEq/L	130 mEq/L
K^+	5 mEq/L	12 mEq/L
Ca^+	5 mEq/L	23 mEq/L
CI	100 mEq/L	25 mEq/L
HCO_3	28 mEq/L	10 mEq/L
pH	7.1–7.3	6.9–7.7

Table 13.13 Flow rate and electrolyte concentrations of hepatic bile varies in different species

Species	Flow (μL/min/kg)	Concentration (mmol/L)						
		Na^+	K^+	Ca^{++}	Mg^{++}	Cl^-	HCO_3^-	Bile acids
Man	15–15.4	132–165	4.2–5.6	0.6–2.4	0.7–1.5	96–126	77–55	3–45
Dog	10	141–230	4.5–11.9	1.5–6.9	1.1–2.7	31–107	14–61	16–187
Sheep	9.4	159.6	5.3	–	–	95	21.2	42.5
Rabbit	90	148–156	3.6–6.7	1.3–3.3	0.15–0.35	77–99	40–63	6–24
Rat	30–150	157–166	5.8–6.4	–	–	94–98	22–26	8–25
Guinea pig	115.9	175	6.3	–	–	69	49–65	–

Erlinger (1992)

gallbladder, resulting in the formation of cholesterol gallstones.

Bile proteins: Plasma proteins are transported into bile by two routes viz. trans-hepatocyte or paracellular pathways. The bile proteins can be classified into several groups like transport proteins (albumin, ceruloplasmin, transferrin, haptoglobin, apolipoprotein), enzymes (lysosomal enzymes, alkaline phosphatase, amylase), hormones (insulin, CCK, epidermal growth factor), and immunoglobulins (IgG, IgA, and IgM).

Bile pigments: Bilirubin and biliverdin are the two main bile pigments. Bilirubin is derived from the metabolism of haemoglobin. Bilirubin is carried to the hepatocytes albumin and stored in the hepatocytes by binding to the Y protein. In hepatocytes, bilirubin is conjugated with glucuronic acid to form bilirubin diglucuronide which is excreted into the canaliculi. The green colour of bile is chiefly due to conjugated bilirubin. Intestinal bacteria convert conjugated bilirubin into urobilinogen and stercobilinogen to excrete through faeces. A portion of intestinal urobilinogen is reabsorbed into the blood and removed by the kidney. The urobilinogen gives urine a distinct yellow colour.

Functions of Bile

Digestion and absorption of dietary lipids: Bile promotes the digestion and absorption of dietary lipids such as cholesterol and long-chain fatty acids. Bile increases the solubility of lipids for better enzymatic actions. The micelle also helps in the absorption of lipid digestion end products by increasing their diffusion across the intestinal epithelium. Bile also helps in the absorption of fat-soluble vitamins (A, D, E, K).

Bile also facilitates intestinal absorption of dietary proteins by causing denaturation and hydrolysis of proteins by pancreatic proteolytic enzymes.

Cholesterol homeostasis: Bile acid increases absorption of biliary and dietary cholesterol in the intestine together with elimination of cholesterol from the body. The hepatic secretion of cholesterol is enhanced by bile acids which enable the removal of cholesterol from liver to intestine.

Gut antimicrobial defence: The bacteriostatic actions of bile acid-fatty acid mixed micelles prevent bacterial infection in the GI tract. Bile causes membrane-damaging effects over the microbes. Further, bile induces some antimicrobial peptides such as cathelicidin to regulate intestinal inflammation.

Prevention of calcium gallstone formation: Bile prevents the formation of calcium gallstone and calcium oxalate kidney stones after binding calcium.

Signalling molecules: Bile activates farnesoid X receptor alpha (FXR), vitamin D receptors (VDR), G-protein-coupled receptors, pregnane X receptor (PXR), and epidermal growth factor receptor (EGFR) to regulate gut motility, hepatic functions, and energy homeostasis.

13.1.2.4.3 Control of Bile Secretion

Agents that increase the secretion of bile are called choleretics. The synthesis and secretion of bile are not under direct control of ANS. However, the hepatic duct system, sphincter of Oddi, and gall bladder are innervated by ANS. Catecholamines increase bile flow through beta receptors. CCK is the only known hormone that contracts the gallbladder along with relaxation of the sphincter of Oddi. The parasympathetic nervous system regulates gallbladder muscle tone. Vagotomy (disruption of the parasympathetic system) decreases bile flow by decreasing cAMP production. Blocking of the sympathetic nervous system also results in decreased bile flow. The secretion of bile can be inhibited by α2-adrenergic receptor agonist whereas α-1 adrenergic receptor agonists increase bile secretion. Secretin has stimulatory role in bicarbonate secretion by activating cAMP synthesis followed by phosphorylation of protein kinase A (PKA). Protein phosphorylation results in activation of Cl^-/HCO_3^- exchanger and opening of CFTR. Several endocrine factors are involved in the regulation of bile secretion (Table 13.14).

13.1.2.4.4 Enterohepatic Circulation of Bile Acids

The bile salts secreted in the duodenum are absorbed in the ileum and return back to the liver again by portal veins for reutilization. This effective recycling of bile salts is called enterohepatic circulation. The anatomical components of enterohepatic circulation comprise liver, gallbladder, biliary tract, small intestine, and portal venous circulation. The absorption of bile acids in the intestine is facilitated by both active (ileum) and passive (down the intestinal length) transport mechanism. Around 95% of intestinal bile acids are absorbed by the enterocytes of the ileum through apical sodium-dependent bile acid transporter (ASBT). From the enterocytes, bile acids are refluxed into the sinusoids by organic solute transporter and heterodimer (OST/OST) transports. From the sinusoids, bile acids are taken up by the hepatocytes by Na^+-dependent taurocholate cotransport peptide (Ntcp).

13.1.2.5 Secretory Functions of the Intestine

Intestinal secretion is necessary to dilute and solubilize nutrients for better digestive and absorptive functions. In the intestine, continuous water and electrolyte recirculation

Table 13.14 Endocrine factors regulating bile secretion

Name	Effect on bile secretion	Mechanism
Somatostatin	Inhibitory	Inhibits cAMP through somatostatin receptor 2 (SSTR2)
Gastrin	Inhibitory	Decreases the expression of secretin receptor (SR) It also interacts with CCK-B receptors and activates protein kinase C (PKCα)
Endothelin-1	Inhibitory	Inhibits cAMP production via endothelin (ETA) receptors
Insulin	Inhibitory	Decreases cAMP level by stimulating PKCα and inhibiting PKA
D2 dopamine agonists	Inhibitory	Decreases cAMP level by stimulating PKC γ and inhibiting PKA by D2 receptors
Acetylcholine	Stimulatory	Activation of the Cl^-/HCO_3^- exchanger

Table 13.15 The length of intestine in different species

	Species						
Average length (m)	Horse	Cattle	Sheep/goat	Pig	Dog	Cat	Rabbit
Small intestine	22.44	46.00	26.20	18.29	4.14	1.72	3.56
Caecum	4.39	0.88	0.36	0.23	0.08	0.35 (large intestine)	0.61
Colon	3.08	10.18	6.17	4.99	0.60		1.65
Total	29.91	57.06	32.73	23.51	4.82	2.07	5.82

Stevens (1977)

occur from the lumen of the intestine to the enterocytes. The osmotic gradient generated by Na^+-H^+ exchange and solutes entering into the absorptive cells facilitate water influx by diffusion. The fluid movement allows the intestinal content to become isotonic for efficient absorption.

13.1.2.5.1 Anatomical Considerations

The intestine of domestic animals has variability among species (Table 13.15). The small intestine comprises duodenum, jejunum, and ileum. Duodenum is the first portion of small intestine extends from pyloric sphincter to the ligament of Treitz, a fibrous band that demarcates duodenum and jejunum. The portion of small intestine between Treitz and the ileocecal sphincter are jejunum (first one third segments) and ileum (remainder segments). Like other components of GI tract, intestine also have four distinct layers namely mucosa, submucosa, muscularis, and serosa. The mucosa provides physical defence against microorganism and digestive enzymes. The small intestine has a single mucosal layer, whereas colon consists of an inner more viscous and outer less viscous mucosal layer. The mucosal layer is renewed through by the secretion of mucous from the goblet cells. The functional activity of the intestinal lumen depends upon the intestinal epithelial cells (IECs). There are different intercellular junctions made of gap junctions, desmosomes, and adherent junctions comprising different proteins like occludins, claudins, and zonula occludens (ZO-1, ZO-2). They maintain the integrity of intestinal epithelial layer and facilitate the paracellular transport of ions and macromolecules. The epithelial cell lining is rapidly regenerated by $Lgr5^+$ stem cells. These stem cells are differentiated into varies epithelial cell subsets via progenitor cells or transit amplifying cells. Different classes of epithelial cells possess different functions in relation to digestion, neuroendocrine, and immunity. The cell types include enterocytes, enteroendocrine cells, M cells, Paneth cells, and tuft cells.

Surface area of the small intestine is characterized by large folds called plica circularis that increases the surface area. There are finger-like epithelial projections called as villi to increase the further increase surface area by about 10 to 14-fold. The villi are covered with microvilli to form brush border which further increases the surface area. Crypts of Lieberkühn are the glandular structure at the vase of villi. Glycocalyx, a jelly-like layer of glycoproteins covers the microvilli which contains digestive enzymes that project into glycocalyx. The part of enterocytes towards the lumen is called apex and the part opposite to lumen is called basolateral membrane. Nutrients are absorbed into enterocytes through apex and exit through basolateral membrane before entering into blood.

The large intestine is divided into caecum, colon, rectum, and anus from proximal to distal end. The colonic enterocytes are morphologically identical with intestinal enterocytes. Unlike small intestinal mucosa, the villi are absent in large intestine but contains deep tubular pits extends up to muscularis layer. The colonic mucosal cells include absorptive colonocytes, goblet cells, M cells, and Paneth cells.

Goblet cells are situated between enterocytes. They secret mucins that provide physical protective barrier against intestinal pathogens. The mucous entraps secretory IgA that further helps to destroy intestinal pathogens.

Microfold (M) cells specialized epithelial cells found in the intestinal lymphoid tissue (Peyer's patches). M cells help in antigen transport across the epithelial cells. M cells engulf luminal pathogens and their antigens by phagocytosis and presented to dendritic cells at lamina propria.

Paneth cells are situated at the base of the intestinal crypt responsible for the secretion of antimicrobial peptides (AMPs) like alpha defensins, secretory phospholipase A2 (sPLA2), lysozyme, cathelicidins, C-type lectin regenerating islet-derived protein IIIγ (RegIIIγ) and angiogenin4. These AMPs help to protect the epithelial barrier.

13.1.2.5.1.1 Blood and Lymph Supply to the Intestine

Numerous small arteries enter the base of the villus to form a capillary network under its epithelium. Veins arise at the tip of the villus from a capillary network that runs downward. The venules and veins, empty into the portal vein which enters into the liver and venous blood is mixed with that of hepatic arterial blood. The hepatic vein conveys the blood from the liver to the posterior vena cava. Monosaccharides, amino acids, free glycerol, short-chain fatty acids, water and inorganic salts and are absorbed through this route.

The lymph capillaries originate as lacteals near the villus tip and enter into a lymph plexus inner side of the muscular coat. The branches of these plexus enter into the submucosa to form a loose plexus of large lymphatics and pass into

mesentery. The lymph capillaries drain their content into large lymph vessels, which empty into the mesenteric vessels. The mesenteric connect with mesenteric lymph nodes. The contents of the mesenteric vessels empty into the cisterna chyli which is continued as thoracic duct and finally empties into the venous system anterior to heart. Glycerides, long-chain fatty acids, cholesterol, and the immunoglobulins are absorbed by the lymphatic system. The rate of lymph flow increases after a meal.

13.1.2.5.2 Intestinal Secretion

Water and Electrolytes

During the digestive process, large quantities of water are secreted into the small intestinal lumen. But all the water is also reabsorbed simultaneously in the small intestine. The movement of water is facilitated by osmotic gradients by two distinct processes.

Osmotic gradient due to digested feed materials: The feed that enters into the intestinal lumen are not so hypertonic. But upon digestion their osmolality increases rapidly. The starch into the intestinal lumen has limited osmolality but, when it is digested into maltose, its osmolality increases tremendously. So, as the digestion continues, the osmolality of intestinal lumen gradually increases and pulls the water. But the digested end products such as glucose, maltose, and amino acids are absorbed, the osmolality decreases and leads to water absorption.

Osmotic gradient due to ion channels: The bicarbonate enters into the duodenal epithelium by paracellular mechanism via leaky tight junctions. Apart from this, duodenal epithelium contains different ion channels to regulation electrolyte movement across the duodenal epithelium. The movement of HCO_3^- is mediated via sodium-bicarbonate cotransporters (NBC), anion exchanger (AE), Na^+/H^+ exchange (NHE) transporter, Na^+-K^+-Cl^- (NKCC) channels, Na^+-K^+-ATPase pump, and Na^+/HCO_3^- cotransporter (NBC). The movement of Cl^- ion is facilitated by cystic fibrosis transmembrane conductance regulator (CFTR). The secretagogues (agents which increase the intestinal secretion) activate adenylyl cyclase and generation of cyclic AMP. Increased cAMP activates CFTR to increase the secretion of chloride ions into the lumen. The accumulation of Cl^- into the lumen generates an electrical gradient that pulls sodium into the lumen. As a result, NaCl is secreted and osmotic gradient is created to draw water.

Know More...
Cholera toxins cause abnormal activation of (CFTR) in crypt cells that results in massive secretion of water to manifest severe diarrhoea.

Neuroendocrine Factors

Intestinal glands secret a variety of neuroendocrine factors that regulate GI tract functions (Table 13.2).

13.1.2.5.3 Regulation of Intestinal Secretion

The factors that stimulate intestinal secretion are wall distension, luminal acidity, glucose, and bile salts. Stretch reflexes act via parasympathetic and enteric nervous system. The Ach released from cholinergic nerve endings increases bicarbonate secretion by increasing intracellular Ca^{++}. The sympathetic neurotransmitters like noradrenaline (NA) and neuropeptide Y (NPY) inhibit secretion. The enteric nervous system releases somatostatin which inhibits duodenal secretion by decreasing cAMP via somatostatin receptor (SSTR1).

One of the most important secretory agents of the intestine is serotonin (5-hydroxytryptamine, 5-HT). The receptors of serotonin are distributed from duodenum to the colon. It inhibits sodium Na^+/H^+ exchanger and prevents influx of Na^+ into the enterocyte.

Both vasoactive intestinal polypeptide (VIP) and prostaglandin E2 (PGE2) increase HCO_3^- secretion via G-protein-coupled receptor by increasing cAMP production. The secretion of mucin is associated with HCO_3^- secretion through CFTR.

Substance P (SP) alters water exchanges in the intestinal epithelium together with increased blood flow and intestinal motility.

Kinins act on the Na^+-K^+-ATPase pump and transmembrane conductance regulator (CFRT) to regulate duodenal bicarbonate secretion.

Some dietary bioactive peptides also regulate intestinal secretion. They can escape the hydrolysis and return to GI tract through circulation. One of such substance is carnosine (β alanyl-L-histidine) exerts vasodilatory function by cGMP production.

13.1.3 Digestion and Absorption of Nutrients

The digestion of nutrients in monogastric species is predominantly enzymatic with a minor microbial digestion in the large intestine. The characteristics features of enzymatic digestion is the hydrolysis of glycosidic bonds (carbohydrates), peptide bonds (proteins), ester bonds (lipids), and phosphodiester (nucleic acids) by the insertion of water molecule. The enzymatic digestion occurs in two phases namely luminal and membranous phase. The luminal phase of digestion is occurred in the lumen of GI tract and facilitates incomplete hydrolysis of nutrients leads to the production of short-chain polymers of original macromolecule by salivary, gastric, and pancreas glands. The membranous phase of digestion is catalysed by the enzymes situated at the apical surface of enterocytes. These enzymes help in

Table 13.16 Carbohydrate splitting enzymes of brush border and their functions

Enzyme	Substrate	Product
Maltase	Maltose, maltotriose, α-dextrins	Glucose
Lactase	Lactose	Glucose and galactose
Sucrase	Sucrose; also maltotriose and maltose	Fructose and glucose
α-Dextrinase	α-Dextrins, maltose maltotriose	Glucose
Trehalase	Trehalose	Glucose

the final breakdown of the substrates derived from luminal phase of digestion followed by absorption of end products of nutrients across the intestinal epithelium.

13.1.3.1 Digestion and Absorption of Carbohydrates

13.1.3.1.1 Dietary Substrate

The principal dietary carbohydrates are polysaccharides, disaccharides, and monosaccharides. The predominant dietary polysaccharides are starch, glycogen, and cellulose. Glycogen and starch are composed of glucose chains connected by α-1,4-glucosidic linkage and branching chains are joined by α-1,6-glucosidic linkage. Sucrose and lactose are main dietary disaccharides composed of glucose and fructose or glucose and galactose, respectively.

Fibrous like hemicellulose and cellulose consists of β-1,4 glucose unit. Ruminants can effectively utilize cellulose by hydrolysing them with ruminant microbes. The monogastric herbivores are unable to utilize cellulose as efficient nutrient source except horse. The large intestine of equines is well developed and microbial digestion of cellulose takes place in their large intestine.

13.1.3.1.2 Digestion of Carbohydrates in the Mouth and Stomach

Saliva contains salivary α-amylase or ptyalin (where present) which mixes with the feed during chewing. Salivary amylase hydrolyses starch into maltose and other small glucose polymers containing 3–9 glucose residues. However, only 5% of starch is digested in the mouth as the feed remain in the oral cavity for a very short period of time.

The action of salivary amylase that continues till the feed enter into the gastric body and fundus. The gastric acidity decreases the activity of salivary amylase as the optimum pH for α-amylase is 6.8 in comparison to gastric pH of 4.0. But, before complete blockade of salivary amylase, 30–40% of the starches will have been hydrolysed to form maltose.

13.1.3.1.3 Digestion of Carbohydrates by Pancreatic Amylase

Pancreatic α-amylase is identical with the salivary α-amylase of saliva, but its potency is several times more than salivary amylase. It causes the hydrolysis of almost all the starches within 15–30 min. The enzyme has specificity for α-1, 4 linkage and results in the combination of disaccharides and trisaccharides and α-limit dextrin.

13.1.3.1.4 Digestion of Carbohydrates by Intestinal Enzymes

The enterocytes of the small intestine contain brush boarder enzymes such as maltase, lactase, sucrase, and dextrinase specific for dietary disaccharides (e.g. maltose, lactose, sucrose) and limit dextrins (Table 13.16). They convert disaccharides and limit dextrins into hexose (glucose and galactose) or pentose (fructose) molecules ready for the absorption. Sucrase and isomaltase exist as an enzyme complex responsible for the hydrolysis of the products of amylase digestion. The enzyme lactase has two forms. The primary lactase involved in the digestion is associated with the brush border of the enterocytes with strong lactase activity. Another nonspecific β-galactosidase associated with cell lysosome hydrolyses lactose slowly at an optimal pH of 3. Maltase, sucrase, and isomaltase are rarely found in the intestine in newborn calves and pigs and their activity increases with the age. In contrast, lactase activity is highest during neonatal period and gradually decreases with age.

13.1.3.1.5 Absorption of Carbohydrate

The end products of the carbohydrate digestion (monosaccharides) are absorbed through the enterocytes and transported to the portal circulation. The absorption of glucose is occurred through specific transporters called sodium-linked glucose transporter (SGLT-1) at the brush border of the enterocytes of the duodenum and jejunum. Galactose is also absorbed through SGLT-1. SGLT uses sodium gradient for transport of glucose. The sodium gradient is created by Na^+, K^+-ATPase pump. This pump maintains a low intracellular sodium concentration by expelling 3 Na^+ in exchange for 2 K^+ entering inside the cell. The binding of two sodium ions with SGLT-1 facilitates conformational changes to allow glucose binding. Glucose together with two sodium ions then enter into the enterocytes. SGLT-1 then undergoes another conformation change to release glucose followed by sodium. The sodium ion then expelled through Na^+, K^+-ATPase pump. The glucose then leaves the enterocytes via glucose transporter (GLUT-2). A small amount of glucose is utilized by the enterocytes. Phlorizin

blocks SGLT1 and inhibits sodium-dependent glucose transport into the enterocytes.

The fructose is absorbed by facilitated diffusion utilizing glucose transporter (GLUT-5) on the apical membrane independent of concentration gradient. GLUT-2 and GLUT-5 present at the basolateral membrane transfer fructose to portal circulation.

The rate of absorption of glucose and galactose are highest among the monosaccharides. The rate of absorption of fructose is almost half of the glucose. The rate of absorption of mannose is lowest (one-tenth of glucose).

13.1.3.1.6 Regulation of Carbohydrate Digestion

The levels of disaccharidases particularly sucrase-isomaltase (SI) and maltase-glucoamylase are increased in response to high carbohydrate diet. There is a transcriptional regulatory mechanism involving different transcriptional proteins. Three are several transcriptional regulatory proteins involved in the regulation of SI protein transcription. Hepatocyte nuclear factor (HNF-1), caudal-related homeodomain proteins (Cdx) and GATA type zinc finger transcription factors are involved in the upregulation of SI protein transcription by binding at the DNA regulatory regions at the 5′ flanking region of SI gene located at chromosome 3. The down regulation of SI protein transcription is mediated by the presence of glucose.

Epidermal growth factor (EGF) increases glucose transport by promoting insertion SGLT into the luminal membrane.

Peptide YY (PYY) increases glucose absorption by increasing energetic efficiency of glucose transport.

Somatotropin increases glucose absorption from the intestinal epithelium.

The genetic factors also influence the glucose absorption. Studies in broilers reported that birds genetically selected for higher growth had less intestinal absorptive epithelium.

13.1.3.2 Digestion and Absorption of Proteins

13.1.3.2.1 Dietary Substrate

The protein substrates available for digestion are of two types, exogenous and endogenous proteins. The exogenous or dietary proteins are long chains of amino acids bound together by peptide linkages. The characteristics of each protein are determined by the types of amino acids and their sequence of arrangements. The majorities of dietary proteins are easily digestible by the proteolytic enzymes (Table 13.17). However, the proteins conjugated with

Table 13.17 Principal proteolytic enzymes and their functions

Source	Enzymes (proenzymes)	Activator	Substrate	Product
Stomach	Pepsin (pepsinogen)	HCl	Proteins and peptides	Cleaves peptide bonds adjacent to aromatic amino acids
Exocrine Pancreas	Trypsin (trypsinogen)	Enterokinase	Proteins and peptides	Cleaves peptide bonds on carboxyl side of basic amino acids (arginine or lysine)
	Chymotrypsins (chymotrypsinogens)	Trypsin	Proteins and polypeptides	Cleaves peptide bonds on carboxyl side of aromatic amino acids
	Elastase (proelastase)	Trypsin	Elastin, some other proteins	Cleaves peptide bonds on carboxyl side of aliphatic amino acids
	Carboxypeptidase A (procarboxypeptidase A)	Trypsin	Proteins and polypeptides	Cleaves carboxyl terminal amino acids that have aromatic or branched aliphatic side chains
	Carboxypeptidase B (procarboxypeptidase B)	Trypsin	Proteins and polypeptides	Cleaves carboxyl terminal amino acids that have basic side chains
	Ribonuclease		RNA	Nucleotides
	Deoxyribonuclease		DNA	Nucleotides
Intestinal mucosa	Enterokinase		Trypsinogen	Trypsin
	Aminopeptidases		Polypeptides	Cleaves amino terminal amino acid from peptide
	Dipeptidases		Dipeptides	Amino acids
	Carboxypeptidases		Polypeptides	Cleaves amino terminal amino acid from peptide
	Endopeptidases		Polypeptides	Cleaves between residues in midportion of peptide
	Nuclease and related enzymes		Nucleic acids	Pentoses and purine and pyrimidine bases
Cytoplasm of mucosal cells			Di-, tri-, and tetrapeptides	Amino acids

carbohydrates may restrict effective proteolysis. The dietary proteins can also be damaged by heating during processing. Endogenous proteins include digestive gland secretions, desquamated cells, and small amounts of plasma proteins.

13.1.3.2.2 Digestion of Proteins in the Stomach

The digestion of dietary proteins begins at the stomach as saliva lacks proteolytic enzymes. The predominant proteolytic enzyme of the stomach is pepsin. It is secreted as inactive pepsinogen and activates under the influence of gastric HCl. In human gastric mucosa, two different forms of pepsinogen are available. Pepsinogen I is secreted from acid-secreting regions, whereas pepsinogen II is also found in acid secreting as well as pyloric region. Maximal acid secretion correlates with pepsinogen I levels. Pepsinogen hydrolyses peptide bonds adjacent to aromatic amino acids (phenylalanine or tyrosine) and yields polypeptides of different sizes. The optimum activity of pepsinogen is achieved at the pH range of 2.0–3.0. The gastric HCl provides favourable environment form pepsinogen activity. The enzyme is inactive at a pH above 5.0.

13.1.3.2.3 Digestion of Proteins in Intestine

Most protein digestion occurs at the duodenum and jejunum, under the influence of proteolytic enzymes from pancreatic secretion and peptidases from brush border.

Digestion of Proteins by Pancreatic Enzymes: In the small intestine, the partial protein breakdown products of gastric digestion are hydrolysed by major proteolytic enzymes of pancreas like trypsin, chymotrypsin, carboxypolypeptidase, and proelastase. Trypsinogen is activated by enterokinase and trypsin in turn activates chymotrypsin, elastase, and carboxypeptidase. The endopeptidases (like trypsin, chymotrypsin) yield peptides with C-terminal amino acids which are subsequently hydrolysed by exopeptidases (carboxypolypeptidase). The end products of trypsin hydrolysis contain C-terminal amino acids having basic side chains, which become the substrates for carboxypeptidase B. The chymotrypsin produces peptides with aromatic or branched aliphatic side chains which are further hydrolysed by carboxypeptidase A. Elastase hydrolyses elastin fibres. The proteins digested by the pancreatic juices are mostly dipeptides and tripeptides.

Digestion of Peptides by Peptidases of Mucosal Epithelial Cells: The last stage of protein digestion is mediated by the peptidases of mucosal epithelial cells. The epithelial cells contain aminopeptidases at cytosol and brush border. The brush border proteolytic enzymes show more tripeptidase activity (50%) compared to dipeptidase activity (less than 10%) compared to cytosolic enzymes. The tetrapeptidases are present in the brush border. The cytosolic peptidases are also capable of hydrolysing proline-rich peptides. But the leucine-rich peptides are hydrolysed by brush border aminopeptidase. Initially, long-chain peptides are hydrolysed to di- and tripeptides which then enter into the enterocytes for further hydrolysis by intracellular peptidases to form free amino acids.

13.1.3.2.4 Absorption of Amino Acids

Amino acids are absorbed active transport processes against concentration and electrochemical gradients and transported to the portal circulation. There are separate transport mechanisms for different groups of amino acids. The mechanisms are classified into Na-dependent and sodium independent. In sodium-dependent mechanism, Na^+ is required for absorption of amino acids. There is a different sodium-dependent transport mechanism for different amino acids (Table 13.18).

The sodium-independent amino acid transport mechanism involves ϑ-glutamyl cycle with the involvement of glutathione. The extracellular amino acids form a non-covalent binding with the plasma membrane and interact with ϑ-glutamyl moiety to form ϑ-glutamyl-amino acid complex to enter the cell. Inside the cytosol, the ϑ-glutamyl-amino acid complex is split by ϑ-glutamyl cyclotransferase to release amino acids.

13.1.3.2.5 Absorption of Immunoglobulins in Neonates

The maternal immunoglobulins are absorbed from the small intestine in animals like cattle, horse, sheep, goat, dog, and cat through colostrum maternal immunity transfer. Protein enters in the enterocytes by pinocytosis and transports to the lymphatics. The ability to absorb immunoglobulins diminishes soon after birth. In piglets, the ability decreases within 1–2 days. However, in rodents the absorption continues up to 3 weeks.

Absorption of antigens, bacterial and viral proteins is mediated through large microfold cells or M cells in conjugation with lymphoid tissue (Peyer's patches). M cells transfer the antigens to the lymphoid cells to active them. The activated lymphoblasts are entered into the circulation and later migrated to the intestinal epithelium to secret igA in response to the same antigenic exposure.

13.1.3.3 Digestion and Absorption of Lipids

13.1.3.3.1 Dietary Substrate

The dietary lipids include triglycerides (TG), phospholipids (PL), and sterols. Triglycerides are the predominant dietary lipid component chiefly found in the lipids of animal origin. TG provides 90–95% of the total energy derived from dietary lipids. The main phospholipid is in the diet is phosphatidylcholine (PC) derived from diet and the bile as well. Bile is the main source of PC in the intestinal lumen. The plant and animal origin dietary cholesterol include β-sitosterol and cholesterol, respectively. Other form of dietary lipids includes fat-soluble vitamins.

Table 13.18 Amino acid transport system in the intestine

Amino acid transport system	Transported amino acids	Mechanism	Rate of transport
Neutral (monoamino, monocarboxylic)	**Aromatic** (tyrosine, phenylalanine tryptophan) **Aliphatic** (glycine, serine, alanine, leucine, isoleucine, valine, threonine, histidine, methionine, cysteine, asparagine, glutamine)	Na-dependent active transport	Very rapid
Dibasic (diamino)	Arginine, lysine, cystine, ornithine	Na-dependent (partial) active transport	10% of neutral transporters (rapid)
Dicarboxylic (acidic)	Aspartic acid, glutamic acid	Carrier-dependent active transport. Partially Na dependent	Rapid
Amino acids and glycine	Proline, hydroxyproline, and glycine	Na-dependent active transport	Slow

13.1.3.3.2 Digestion of Lipids

Oral Cavity and Stomach The lipid digestion starts at oral cavity by the enzyme lingual lipases secreted from Ebner's glands. Before enzymatic hydrolysis, lipid droplets are broken down into smaller particles by mechanical force exerted by chewing. It increases the surface area for better enzymatic action. Lingual lipase cleaves TG into fatty acids and glycerol.

Hydrophobic lipids are clustered together in large droplets hence required special machinery called emulsification to facilitate digestion in aqueous medium. The stomach performs emulsification of lipids by the mechanical force generated by contraction. The grinding action is performed by the antrum of the stomach followed by the retropulsion of the content back to corpus. The process continues for several times for generating fine lipid droplets. The emulsification is further reinforced in the duodenum by the bile salts. The detergent-like action of bile salts reduces the surface tension and prevents the aggregation of lipids particles to form droplets. Gastric lipase causes hydrolysis of TG into glycerol and fatty acids.

The abundance of gastric and lingual lipase shows species specificity. In rats, lingual lipase predominates gastric lipase, but reverse is true for primates and human. In stomach, the activity of lipase is restricted in the fundus region. The optimum pH for both lingual and gastric lipase is 4 (hence called acid lipase) but the enzymes may remain active at pH 6–6.5. Both lingual and gastric lipase is unable to hydrolyse PL and cholesterol esters.

In neonates, both gastric and lingual lipase play important role in digesting milk for two reasons. Firstly, milk fat contains considerable proportion of medium chain TG compared to long-chain TG and the acid lipases are specific for medium-chain TG. Secondly, the pancreatic lipase is not developed during the neonatal period.

Small Intestine

In the jejunum, TGs are digested by pancreatic lipase. Phospholipids are hydrolysed by pancreatic phospholipase A2 (pPLA2) to yield free fatty acids and lysophosphatidylcholine. Most of the cholesterol in the diet are free cholesterol and can be absorbed through micelles. Only the esterified cholesterol (10–15%) requires enzyme hydrolysis by cholesterol esterase to release free cholesterol.

Pancreas also secrets a colipase which protects lipase from inactivation and facilitates the interaction of lipase with its substrate.

13.1.3.3.3 Absorption of Lipids

The enterocyte brush border membrane is separated from the lumen by an unstirred aqueous layer. The fatty acids and monoacylglycerol generated by the enzymatic hydrolysis of lipids are unable to reach in the intestinal brush border membrane due to their poor solubility in the aqueous membrane. Micelle formation is required to bring the lipid molecules close to the microvilli.

Micelle Formation: Micelles are the aggregation of phospholipids and cholesterol together with bile salts in such a manner that the hydrophobic ends of the lipid molecules are inside and hydrophilic ends are outside the aggregate to keep the lipids in aqueous solution. The micelles are further combined with monoacylglycerol, free fatty acids, and fat-soluble vitamins to form mixed micelles. Mixed micelles then move to intestinal mucosal cells and release contents near the brush border. The bile salts are recycled for emulsification and micelle formation.

Lipid Uptake by the Enterocytes: The uptake of lipids by the enterocytes is mediated through different transport proteins. Niemann-Pick C1 like 1 (NPC1L1), a glycosylated protein, is involved in the cholesterol uptake. It is located in the enterocyte brush border membrane. Ezetimibe blocks

Table 13.19 Transporters for water-soluble vitamins in the intestine

Vitamin	Transporter	Regulatory mechanism
Thiamine (vitamin B1)	Thiamine transporters (THTR-1 and THTR-2)	Transcriptionally regulated mechanism and intracellular Ca^{++}/calmodulin regulatory pathway
Riboflavin	RF transporters (RFVT-1 and RFVT-3)	Transcriptional regulated mechanism
Niacin and nicotinic acid	Monocarboxylate transporters (MCTs). pH-dependent	Ca^{++}/calmodulin regulatory pathway
Biotin (vitamin B7) and pantothenic acid	Na-dependent multivitamin transporter (SMVT) and accessory protein PDZ domain-containing protein 11 (PDZD11)	Intracellular protein kinase C (PKC)-mediated pathway
Folic acid (Vitamin B9)	Reduced folate carrier (RFC) and the proton-coupled folate transporter (PCFT)	Intracellular cAMP-mediated pathway and protein tyrosine kinase-mediated pathway

NPC1L1 and used in hypercholesterolaemia. Fatty acid (FA) transport protein (FATP) and cluster-determinant 36 (CD36) are involved in the transport of fatty acids into the enterocytes. Inside the cytosol of enterocytes, FA-binding protein (FABP) facilitates the transport of fatty acids.

Esterification and Chylomicron Formation: Glycerol and fatty acids (short- and medium chain) are directly absorbed into the blood stream. But, long-chain fatty acids, monoglycerides, cholesterol and fat-soluble vitamins are esterified within the prior to their delivery into the blood stream. In the enterocytes, the cholesterol and monoacylglycerols (MAG) undergo esterification by Acyl-CoA: cholesterol acyltransferase (ACAT) and diacylglycerol acyltransferase (DGAT) situated at the membrane of endoplasmic reticulum.

The esterified products are conjugated with apolipoproteins to form chylomicron. The chylomicrons are the large molecules composed of cholesterol and triglycerides at the core covered by a phospholipid membrane interspersed with apolipoprotein. The outer hydrophilic membrane allows the chylomicron molecules to travel in the aqueous medium.

The chylomicrons are transported to the Golgi vesicle in cis-Golgi in prechylomicron transport vesicles (PCTVs). These PCTVs are released into lymph vessels to reach into the blood stream. Hepatic fatty acid binding proteins (FABP) are required for this process.

The basolateral membrane of the enterocytes also contains ATP-binding cassette (ABC) transporter A1 to facilitate cholesterol efflux.

13.1.3.4 Absorption Vitamins

Water-Soluble Vitamins

The water-soluble vitamins can be obtained by two sources. The water-soluble vitamins of dietary origin (ascorbic acid) are absorbed in the small intestine. The vitamins synthesized by intestinal microbes (Vitamin B7) are absorbed at large intestine. There are some dual origin vitamins (niacin, thiamine, riboflavin, folic acid, biotin, and pantothenic acid) absorbed at both small and large intestine. Niacin is synthesized in the body from tryptophan except cat. Most of the water-soluble vitamins like thiamin, niacin, riboflavin, pyridoxine, biotin, ascorbic acid, and pantothenic are absorbed at the upper small by specific carriers (Table 13.19). In contrast, Vit-B12 and folate absorption are Na^+-independent and major site of absorption is ileum.

Vit-B12 requires two different glycoproteins namely haptocorrin and intrinsic factor (IF) secreted in saliva and gastric juice, respectively. Vit-B12 first binds with haptocorrin which protects it from stomach environment. In the duodenum, haptocorrin is cleaved by pancreatic protease to release free Vit-B12 which then binds with IF. The complex of vitamin B12–IF binds with cubilin receptors at the ileum and taken up by the enterocytes through endocytosis.

Fat-Soluble Vitamins

Absorption of vit E: Vitamin E remains in two forms viz. tocopherols and tocotrienols. Both these forms vary in their bioavailability and antioxidant property. Like the absorption of other lipid molecules, vit E absorption is also required micelle formation. The entry of vit E into the enterocytes is mediated by scavenger receptor class B type I (SR-BI). The vit E is carried to the lymphatic system via chylomicron. ABC transporters (ABCA1) are also involved in the absorption of vit E.

Absorption of vit A: Dietary vit A consists of retinyl esters (animal origin) or carotenoids (fruits and vegetables). The retinyl esters require luminal hydrolysis by lipase to release retinol. The carotenoids can be absorbed intact or cleaved to retinol by β-carotene-15,15′-dioxygenase in the liver or intestine. The free retinol is transported to enterocytes by the enterocytes and binds with cellular retinol-binding protein (CRBP). The esterification of retinol is catalysed by lecithin: retinol acyltransferase (LRAT). Retinyl esters are then secreted as chylomicrons.

Absorption of vit K: Two forms of vit K are available namely K1 (phylloquinone) and K2 (menaquinones). The dietary sources of vit K1 are green leafy vegetables and vegetable oils. Vitamin K2 is found in fermented products. Gut microbes are also able to produce menaquinones. NPC1L1, SR-BI, and CD36 are involved in the uptake of vit K by the enterocytes.

Absorption of vit D: Vitamin D exists in two physiological forms namely vit D3 (cholecalciferol) and vit D2 (ergocalciferol). The major dietary form of vit D is cholecalciferol. The absorption of vit D follows similar mechanism as other lipophilic compounds. The carrier mediated transport of vit D into the enterocytes are mediated by SR-BI, CD 36, and NPC1L1.

13.1.3.5 Absorption of Minerals

The dietary minerals exist as complex structures with major nutrients like proteins, carbohydrates, and fats. The digestion of minerals includes the hydrolysis to release minerals from the modular units. The absorption of minerals occurs via transcellular (uptake of minerals by the enterocytes, intracellular transport, and efflux through basolateral membrane into the circulation) and paracellular (applicable only for metals in aqueous phase). The solubility of some minerals is pH independent (Solubility does not depend on pH, for example, Na^+, K^+, Mg^{+2}, Ca^{+2}), and they are soluble throughout the gastrointestinal pH range (1–8) while some minerals (Cu^{+2}, Fe^{+2}, Mn^{+2}, Zn^{+2}) requires acidic medium for their solubility and remain insoluble hydroxy-polymers at neutral or alkaline pH.

Calcium: Calcium is absorbed from the intestinal lumen by two distinct mechanisms. In the duodenum, calcium is absorbed through active transcellular mechanism under low calcium intake. The calcium uptake by the enterocytes is mediated by voltage-gated transient receptor potential (TRP) channels. The transport of calcium across the cells is facilitated by a carrier protein called calbindin. The calcium is pumped out from the enterocytes by calcium-ATPase. The transport of calcium is enhanced by vit D which stimulates calbindin synthesis. The hormone-induced stimulation of calcium absorption in the gut is called transcaltachia. In the ileum, jejunum, and colon the calcium absorption occurs through passive paracellular mechanism at moderate to high calcium level. The ionized calcium diffuses through tight junctions at the basolateral membrane into the blood. The paracellular route of calcium absorption is predominating in ruminant (50% of total dietary calcium). Less soluble calcium complexes such as calcium carbonate ($CaCO_3$) are mixed with HCl in the abomasum and their solubility increases. Thus, the concentration of ionized calcium is more at the duodenum. Further the absorption of water duodenum and jejunum increases calcium concentration to facilitate paracellular absorption of calcium. The chelating agents decrease calcium absorption.

Phosphate: The absorption of phosphate occurs at all sections of small and large intestine. In ruminants, phosphate absorption occurs in the rumen also. There are two distinct mechanisms of phosphate absorption. Under low phosphate concentration, the absorption is mediated by active transcellular transport system. The uptake of calcium by intestinal and ruminal epithelium occurs via type II Na^+-coupled phosphate cotransporter proteins (NaPi-II) situated at the apical membrane. NaPi-II utilizes Na^+ ions to transport an HPO_4^{-2} anion. The phosphate efflux occurs at the basolateral membrane by facilitated diffusion with the help of phosphate channel. The Na^+ ions enter inside the cells are pumped out by Na^+/K^+ ATPase pump at the basolateral membrane. Vit D helps in the absorption of phosphate by stimulating the production of NaPi-II. Passive paracellular transport of phosphate occurs when soluble HPO_4^{-2} or $H_2PO_4^-$ are more in the intestinal lumen.

Copper: The first step of copper absorption is the reduction of dietary copper to cuprous form by apical metalloreductases called 6-transmembrane epithelial antigen of prostate (STEAP) family of proteins. The cuprous form is taken up by the gut epithelium through *Saccharomyces cerevisiae* copper transport protein (Ctr1p). The intracellular copper trafficking is mediated by Cu chaperone proteins (Atox1). The efflux of copper from the cells into the blood stream is facilitated by copper transporting ATPases (ATP7A or ATP7B).

Zinc: The intestinal absorption of zinc occurs at duodenum and ileum. The zinc is imported to the epithelium from the intestinal lumen through Zrt-, Irt-like protein (ZIP4) at the apical site. The zinc is exported from enterocytes into the portal blood by Zinc transporter 1 (ZnT-1). Animal proteins stimulate zinc absorption. Phytates chelate zinc and inhibit its absorption.

The absorption iron is discussed in haematology section.

13.1.3.6 Absorption of Water, Sodium, Potassium, and Chloride

Bi-directional movement of water across the mucosa of the small and large intestines occurs in response to osmotic gradients. About 98% water is reabsorbed in the intestine to reduce the faecal water loss (only 2%). The osmotic gradient is created by absorption of solutes and that promote the water uptake in the intestine.

The uptake of sodium is mediated by secondary active transport together with glucose, amino acids, and other compounds. Both Na^+ and Cl^- enter into the enterocytes by Na^+-K^+-$2Cl^-$ cotransporters. The sodium is exported from the enterocytes by via sodium pumps. The secretion of Cl^- is facilitated by chloride channels.

The movement of K+ across the gastrointestinal mucosa is due to diffusion. K+ moves actively down its electrochemical gradient by H^+-K^+ ATPase in the luminal membrane. The K^+ is secreted at the basolateral membrane by K^+ channels. Loss of ileal or colonic fluids in chronic diarrhoea leads to severe hypokalaemia.

13.1.4 Avian Digestion

On the basis of feed habits, birds can be classified into granivorous or seed eating birds (e.g. domestic pigeons, budgerigar, zebra finch, canary), omnivores but tending to be granivorous (e.g. sulphur-crested cockatoo, rosella, African grey parrot, macaw, chicken), omnivorous, but tending to be frugivorous or fruit eating birds (e.g. mynah, toucan, barbets), omnivores, but tending to be nectarivorous and frugivorous (e.g. lorikeets, lories), and carnivorous (e.g. owls, falcons, eagles, vultures). The avian digestive system has some striking differences in comparison to mammals. Most of these modifications are intended to reduce the weight to fly. The teeth are absent in birds. The jaw muscles are lighter in weight. In most of the species, the soft palate is absent and a cleft at the hard palate communicates with the nasal cavity. The muscular stomach or gizzard is located at the body's centre of gravity for balancing during flight. The intestine is shorter in length compared to mammals. Some additional features of avian digestive system compared to mammals are paired caecum and shorter colon which links the ileum and cloaca. The avian species is unique for its common passage for excretory and digestive waste products.

13.1.4.1 Anatomical Consideration

The avian digestive system begins at the mouth and ends at the cloaca and has several intervening organs in between.

Beak/Mouth

Birds obtain their feed by the beak and received in the mouth. There is huge variability in the shape and size of beak in different avian species according to food habits. In general, the beak covered with keratin. The birds don't have teeth to chew its feed. Instead, the tongue is used to push feed to the back of the mouth so that it can be swallowed. The palate forms the roof of the mouth cavity containing two clefts. The long median cleft or choana connects with the nasal cavity followed by a short infundibular cleft opens at the auditory tubes. The numbers of salivary glands are less in birds and secret only mucous type saliva which helps in lubricating the feed bolus. Oral sacs are seen in certain species of birds. They help to carry food and act as sexual display apparatus. The laryngeal mound is an elevation behind the tongue. It has papillae that help in deglutition. It connects with glottis with a narrow slit like opening.

Oesophagus and Crop

Oesophagus is a flexible tube that connects pharynx with the stomach. The flexibility of the oesophagus is due to longitudinal folds. The wall of the oesophagus consists of mucosal, submucosal, muscularis, and serosal layers. In the muscular layers, circular smooth muscles are predominant. The epithelium is keratinized stratified squamous in nature. Unlike mammals the upper and lower oesophageal sphincters are absent in birds. The oesophagus in birds can be divided into cervical and thoracic parts. Oesophageal sacs, bilateral diverticulum of cervical oesophagus is a characteristic feature of cervical oesophagus in certain species of male birds. It is used during breeding season for sexual display. The thoracic oesophagus is characterized by numerous mucous glands that provide lubrication for food for swallowing. The innervation of cervical oesophagus is parasympathetic whereas vagus and the coeliac plexus innervate thoracic oesophagus. The crop is a pouch-like structure originates as a dilatation of the cervical oesophagus with food storage function. The crops are well developed in omnivores and herbivores/granivorous birds compared to carnivorous birds. The crop is absent in ostriches, gulls, owls, geese, and penguins. In chicken, the crop has single pouch whereas pigeon's crop has two pouches. The crop is lined by keratinized stratified squamous epithelium. The feed is stored in the crop till the ventriculus becomes empty to receive it and it is controlled by a sphincter. The empty crop also sends hunger signals to the brain so that more feed is consumed. Apart from the storage functions, the crop secrets "crop milk" to feed newly hatched chicks in doves and pigeons. Crop also provides favourable environment for probiotic microbes.

Know More

In hoatzin (*Opisthocomus hoazin*), an obligate folivorous (eating leaves) crop is the largest part of its digestive tract.

Stomach

The stomach in avian species consists of two parts viz. proventriculus (pars glandularis) and gizzard or ventriculus (pars muscularis). The proventriculus resembles mammalian stomach, but ventriculus is unique to bird that facilitates mechanical grinding of feed. The size of proventriculus depends upon the feed habits of the birds. It is larger in aquatic carnivorous birds compared to granivorous species. The birds that lack crop (ostrich) have large proventriculus to store feed. The proventriculus contains oxyntic cells that secrete HCl, pepsin, and mucous.

Ventriculus or gizzard is the muscular stomach composed of thick and thin smooth muscles. The gizzard is covered by a sandpaper-like membrane called koilin membrane. The sandpaper-like appearance of the koilin membrane is due to solidification of mucous. Koilin membrane protects the gizzard from acid and enzymes secreted in proventriculus. The sandpaper-like appearance of koilin membrane also facilitates the mechanical grinding of feed. The bile pigments are refluxed from the duodenums that give characteristics greenish brown colour of the koilin membrane.

Small stone particles (grit) are ingested by some birds (mostly granivores) along with feed. These stones are used to grind feed in the gizzard.

Proventriculus is innervated by vagus and perivascular nerves from mesenteric and coeliac plexus. The muscles and blood vessels are innervated by cholinergic and noradrenergic fibres, respectively.

Small Intestine

The small intestine is divided into duodenum, jejunum, and ileum. The length of intestine is shorter in carnivores, frugivorous compared to herbivorous and granivorous. The division between duodenum and jejunum is demarcated by Meckel's diverticulum or vitelline diverticulum, a remnants of vestigial yolk sac. The intestinal mucosa is appeared progressively thinner from the duodenum to the ileum. The intestinal villi become shorter at the jejunum. The villi are covered by enterocytes with microvilli.

Large Intestine

The large intestine is composed of the caecum and the rectum (colon). The caecum has wide variability in their structures between different species of birds. The caecum is single in the birds of Ardeidae family (herons), paired in herbivores, granivores, and owls and double paired in secretary birds (*Sagittarius serpentarius*). The caecum is rudimentary in birds of Columbiformes and Piciformes order. The birds under Psittaciformes, Apodiformes, and Piciformes order do not have caecum. The right and left caecum (in birds with paired ceca) originate at the junction of the small and large intestines called ileocecal junction. The caecum is divided into three distinct portions namely basis ceci near ileocecal junction, corpus ceci at the medial region, and apex ceci at distal position. The caecum performs several functions. It helps in the microbial digestion of cellulose and reabsorption of water. The efflux of urine from colon into the caecum is mediated by antiperistatical movement. The urine acts as the source of nitrogen for cellulolytic microorganisms.

The rectum (colon) is joined with the cloaca which is the common passage for digestive, reproductive, and urinary systems. Unlike mammals, the colon in avian species contains numerous villi and goblet cells. The cloaca is divided into three compartments viz. into coprodeum, urodeum, and proctodeum. The cranial most coprodeum compartment stores faecal materials. Coprodeum is separated from urodeum by the coprourodeal fold. The middle compartment or urodeum stores urine. The ductus deferens open into the urodeum. There is antiperistaltic movement of urine from urodeum into the coprodeum and large intestine to facilitate reabsorption of water. The urodeum and proctodeum is separated by uroproctodeal fold. The caudal most portion is the proctodeum where cloacal bursa opens. The proctodeum opens outside through vent.

The cloaca bursa, a fabricius structure projecting dorsally from proctodeum. It is the lymphoid organ of birds and involved in B lymphocytes preprocessing.

Liver and Pancreas

The liver is usually bi-lobed. The right and left liver lobes are joined cranially at the midline. The right liver lobe is larger than left lobe. In domestic fowl and turkey, the left lobe has dorsal and ventral portions. Gallbladders are present in most of the species except ostrich, pigeon, and parrots. The bile drains into the duodenum by two ducts, hepatocystic and cysticoenteric duct.

The pancreas is situated between duodenal loop and divided into dorsal, ventral, and splenic parts. Pancreas is shorter in carnivores and granivores compared to piscivores (eating fish). Pancreas secrets amylase, lipase, proteolytic enzymes, and bicarbonate.

13.1.4.2 Gastrointestinal Motility

The prehensile organ of birds is beak. The processing of feed after ingestion is facilitated together by beak and tongue. Saliva lubricates the feed for swallowing. Rapid posterior movements of the tongue propel the feed bolus into the pharynx. Primary peristalsis within the oesophagus moves the feed into stomach. Oesophago ingluvial fissure controls the movement of feed inside the crop. During fasting, it is closed and restricts the entry of feed into the crop. But when the proventriculus is filled, it relaxes and allows the feed to enter inside the crop for temporary storage. The contraction of crop wall allows the feed to enter into the stomach. Motility of stomach is characterized by slow waves of circular smooth muscle (most birds lack birds lack longitudinal smooth muscles) generated from interstitial cells of Cajal. The peristaltic waves of the stomach move aborally into the gizzard and small intestine. Egestion, the oral expulsion of undigested materials, is seen in carnivorous birds. It is different from regurgitation or vomiting. The gastric emptying is controlled by enterogastric reflexes. The migrating myoelectric complex (MMC) is characteristics feature of small intestine similar to mammals. The filling of ceca is mediated by rectal antiperistaltic and ileal peristaltic waves. Continuous antiperistaltic movements of the help to carry urine from the urodeum into the ceca.

13.1.4.3 Secretary Functions of Digestive System

The primary role of the saliva is the lubrication of feed. The species that eat dry food have large numbers of salivary glands. Different types of salivary glands in birds are maxillary (roof of the mouth), palatine (either side of nasal opening at roof of the mouth), spheno-pteryoid glands (roof of pharynx on each side of eustachian tube), anterior and posterior submandible glands (inter-mandibular space), lingual glands (tongue), and crico-arytenoid glands (glottis). The salivary

glands secret mostly mucous in majority of the species but, in poultry, saliva also secret amylase. The flow rate of saliva is 7–30 mL per day in chicken.

Crop milk that contains 50–60% protein, 32–45% fat (cholesterol, phospholipids, triglycerides, free fatty acids), and 1–3% carbohydrate. The ash content of crop milk is 4.4–4.8% which comprises mostly calcium, phosphorus, sodium, and potassium.

Proventriculus contains two types of glands. The simple mucosal glands are responsible for the mucous secretion and the compound submucosal glands resemble chief and the parietal cells of mammalian gastric mucosa secrets HCl and pepsinogen in addition to mucous. The pH range of gastric juice is about 0.5–2.5. The pH is higher in herbivores than carnivores. The flow rate of gastric juice is higher in birds compared to dogs, human, and monkeys. It ranges from 8 to 10 mL/kg body weight/h in chicken. The pepsin secretion rate (2400–2500 IU/kg body weight/h) is higher in avian species compared to mammals. The main stimulus for gastric secretion is histamine.

The pancreas juice contains digestive enzymes and bicarbonate ions. The predominant pancreatic enzymes are pancreatic amylase (28–30%) followed by chymotrypsin (20%) and trypsin (10%). Other pancreatic enzymes include procarboxypeptidases (A and B), proelastase, lipase, and trypsin inhibitor (prevent the autolysis of epithelium). The buffering action of pancreatic juice helps to neutralize the acidic chime to bring the pH around 6–8. The flow rate of pancreatic juice is more in birds compared to dogs, rats, and sheep.

Biliary secretion rate in chicken is about 24.2 μL per minute. Predominant bile salts in the chicken and turkey are chenodeoxycholyltaurine and cholyltaurine. Whereas, in ducks, chenodeoxycholyltaurine and phocaecholyltaurine are predominant. Some species of birds contain amylase in their bile. The avian species also exhibit enterohepatic circulation of bile.

13.1.4.4 Digestion and Absorption of Nutrients

Carbohydrate

The digestion of starch takes place in the upper jejunum by pancreatic α-amylase into maltose, maltotriose, and α-limit dextrins. In the unstirred water layer, the maltose, maltotriose, and α-limit dextrins are hydrolysed by maltase, isomaltase, and α-limit dextrinase into hexose (glucose and galactose) or pentose (fructose). The brush border enzymes (Table 13.16) split disaccharides into monosaccharides that are ready for absorption. The majority of monosaccharides are absorbed through active transport mechanism by utilizing the sodium gradient.

Protein

Protein digestion begins at the ventriculus (gizzard) pepsin secreted from proventriculus. The second stage of protein digestion occurs at intestinal lumen by trypsin, chymotrypsin, and elastase secreted from pancreas. These pancreatic enzymes hydrolyse large protein molecules into small oligopeptides and dipeptides. Final stage of protein digestion is facilitated by pancreatic (carboxypeptidases A and B) and brush (aminopeptidases and dipeptidases) enzymes. The absorption of amino acids in birds is similar to mammals. Different amino acid transporters are used to transport amino acids.

Lipids

The digestion of lipids begins with the emulsification at the gizzard as the upper GI tract doesn't secret lipase. The process of emulsification is accelerated in the duodenum when the diet is mixed with bile. The enzymatic hydrolysis of dietary lipids is initiated with the activation of lipase by pancreatic colipase. The hydrolysis of phospholipids is mediated by pancreatic phospholipase A. The products of lipid hydrolysis undergo micelle formation for solubilization. The mechanism of incorporation of micelle into the mucosal cells is not known. However, some theories suggest disruption of micelle before their entry to the mucosal cells. Jejunum is the principal site for lipid absorption in chicken and turkey. But the linoleic acid, stearic acid, and palmitic acid are absorbed in the ileum. The uptake of lipids by the brush border membrane is passive and the rate of absorption depends upon the saturation. The transport of lipids in the cytosol is mediated by fatty acid binding proteins. These proteins have high affinity for unsaturated fatty acids than saturated fatty acids. The medium- or short-chain fatty acids are unable to bind with these proteins. The fatty acids undergo esterification within the enterocytes and incorporated into portomicrons to secret into the hepatic portal blood supply in contrast to mammals where the lipids are entered into the lymphatic circulation.

Utilization of Yolk

Yolk contains 50% lipids that are major source of energy in the newly hatched fowl. The digestion of yolk lipids is mediated by lipase secreted from internal surface of the yolk sac. The yolk lipids are absorbed by three routes viz. yolk sac membrane, yolk stalk epithelium, and the intestinal mucosa. During early embryogenesis, the endodermal cells the yolk sac membrane absorbed and packaged the yolk lipids to release it into the blood. This process is accelerated during last week of incubation and may continue after hatching. The yolk assimilation through yolk stalk is started few

hours after hatching and may continue up to 5 days in turkeys. Yolk lipids reach into the intestine through yolk stalk are hydrolysed and absorbed. The yolk stalk is occluded by the lymphocyte aggregation 4 days after hatching and the yolk stalk converts to lymphopoietic tissue after 14 days and acts as a site for extra medullary haematopoiesis. The remnant of yolk sac is called Meckel's diverticulum.

Learning Outcomes

- **Overview of monogastric digestion:** The digestion is a complex process of feed intake, conversion of the complex feed into their simplest form by mechanical and biochemical processes, absorption of the nutrients and their assimilation together with the removal of undigested feed materials. The process of digestion starts at the oral cavity where mastication reduces particle size of the ingested feed and incorporates saliva into ingesta for swallowing. The stomach facilitates grinding and mixing of the food along with digestion of proteins with the help of acid and enzymes. Once the chime passes into the small intestine, it is mixed with pancreatic enzymes and membrane bound enzymes in the enterocytes to convert the complex feed materials into their simplest form for absorption. The gastrointestinal system is the portal through which nutritive substances, vitamins, minerals, and fluids enter the body. The functions of digestive system are under neural and endocrine control.
- **Secretory functions of GI tract:** Different parts of GI system secrete a wide range of chemical substances to assist digestive and regulatory processes of GI function. Salivary glands, stomach, pancreas, gall bladder, and intestine are the predominant organs that contribute GI secretions. The salivary glands and the pancreas are complex acinar glands situated outside of the elementary canal, but their acinar secretions are poured into the GI tract. The glandular part of stomach contains deep tubular cells (oxyntic gland) that secret acid and pepsinogen. Small intestine is equipped with specialized secretory cells at the epithelial invaginations called Crypts of Lieberkühn. Single cell mucous glands like goblet cells contribute to mucous secretion in response to irritation. The glands of GI system are stimulated by direct contact of food. The tactile, chemical, and wall distension activates ENS that stimulates the glands for secretion. Parasympathetic stimulation increases the secretions of glands of upper GI tract. The GI secretions are also influenced by endocrine factors. The hepatobiliary system secrets bile that helps in digestion and absorption of lipids.
- **Digestion and absorption of nutrients:** The digestion of nutrients in monogastric species is predominantly enzymatic with a minor microbial digestion in the large intestine. The characteristics features enzymatic digestion is the hydrolysis of glycosidic bonds (carbohydrates), peptide bonds (proteins), ester bonds (lipids), and phosphodiester (nucleic acids) by the insertion of water molecule. The enzymatic digestion occurs in two phases namely luminal and membranous phase. The luminal phase of digestion is occurred in the lumen of GI tract and facilitates incomplete hydrolysis of nutrients leads to the production of short-chain polymers of original macromolecule by salivary, gastric, and pancreas glands. The membranous phase of digestion is catalysed by the enzymes situated at the apical surface of enterocytes. These enzymes help in the final breakdown of the substrates derived from luminal phase of digestion followed by absorption of end products of nutrients across the intestinal epithelium.
- **Avian digestion:** The avian digestive system has some striking differences in comparison to mammals. Most of these modifications are intended to reduce the weight to fly. The teeth are absent in birds. The jaw muscles are lighter in weight. In most of the species, the soft palate is absent and a cleft at the hard palate communicates with the nasal cavity. The muscular stomach or gizzard is located at the body's centre of gravity for balancing during flight. The intestine is shorter in length compared to mammals. Some additional features of avian digestive system compared to mammals are paired caecum and shorter colon which links the ileum and cloaca. The avian species is unique for its common passage for excretory and digestive waste products.

Exercises

Objective Questions

1. Deglutition centre is situated at _____.
2. MMC is generally occurs during _____ period.
3. Pacemakers of the guts is _____.
4. Somatostatin inhibits the motility of stomach and the gut. (True/False).

5. Zygomatic salivary gland is present in _____ species.
6. The inflammation of the salivary gland is called _____.
7. The cephalic phase of gastric secretion is absent in _____.
8. The rate limiting enzyme of classical pathway of bile acid synthesis is _____.
9. Arrange these monosaccharides on the ascending order of their rate of absorption. Glucose, fructose, mannose. _____.
10. Predominant bile salts in the chicken and turkey are _____ and _____.
11. Agents increase the bile flow by contracting the gall bladder are called _____.
12. The conversion of trypsinogen to trypsin is accelerated by enzyme _____.

Subjective Questions

1. Why motion sickness leads to nausea?
2. How saliva helps in vitamin B12 absorption?
3. Antacids are prescribed along with non-steroidal anti-inflammatory (NSAID) drugs. Justify the statement.
4. Achlorhydria is associated with pernicious anaemia. Justify the statement.
5. Why metabolic acidosis occurs after heavy meal?
6. Gall bladder bile is more concentrated than hepatic bile. Justify the statement.
7. Why emulsification is required prior to lipid digestion.

Answers to Objective Questions

1. Medulla
2. Inter-digestive
3. Interstitial cells of Cajal (ICC)
4. True
5. Canine
6. Sialadenitis
7. Ruminants
8. Cholesterol 7α-hydroxylase (CYP7A1)
9. Glucose > Fructose > Mannose
10. Chenodeoxycholyltaurine and cholyltaurine
11. Chalogogue
12. Enterokinase

Keywords for Answer to Subjective Questions

1. Motion sickness, vestibular apparatus, vomiting centre
2. Saliva, Haptocorrin
3. Prostaglandin, mucosal blood flow, gastric mucosal barrier
4. Parietal cell, hydrochloric acid, intrinsic factor
5. HCl secretion, alkaline tide
6. Gall bladder, reabsorption of water
7. Lipid droplet, hydrophobic, surface area

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