Invited Review

The ileocaecal junction

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Summary. The ilocaecal junction remains a controversial region of the gut. There are still a lot of questions concerning its anatomical structure and function. In this review, a concise overview is given of the recent and older literature on the embryology, anatomy, including the intrinsic and extrinsic innervation, and the pharmacology of this region. Based on the available data from the literature, evidence is accumulating for a sphincteric function.

Key words: Ileocaecal junction, Morphology, Review

Introduction

The ileocaecal junction, the discrete anatomical structure where the ileum enters the caecocolon, present in different form in many species (Wesson, 1937; Pelckmans, 1988; Ouyang, 1992), has been an area of interest for many anatomists and physiologists for more than four centuries. Many properties of this specialized region, located between two ecologically and physiologically distinct regions (Phillips, 1992), are not well understood and even the question whether the ileocaecal junction is a sphincter or a valve or the question whether it should be named ileocaecal junction or pylorus ilealis (DiDio and Anderson, 1968), has not yet been fully answered.

Historical perspective

When Caspar Bauhin in 1579 claimed to be the first to describe the ileocaecal «valvula», he was wrong (Pelckmans, 1988). Variolus beat him to it in 1573, when he described the ileal termination into the colon as the «Operculum ilei» (DiDio and Anderson, 1968). The observations of Bauhin were made on human cadaver material and on dogs and he was really the first to introduce the valvular concept of the ileocaecal junction. During the 16th and 17th century the structure and function of the ileocaecal junction was much debated. Helkiah Crooke, physician to James VI and I of Scotland and England, wrote in 1615 about the «valve which Nature in great wisdom hath set to hinder the refluence or return of excrements and uprofitable humors» (Davenport, 1989). On the mere grounds of comparative anatomy Keith pleaded in 1903 for the existence of a sphincter. This view was further advocated by T.R. Elliott on the basis of physiological experiments.

Using a pressure-sensing apparatus, Elliott could prove the existence of a high pressure zone in the ileocaecal junction of the cat (Elliot, 1904). During the last 90 years, much has been written on the nature of this region, without really adding to fundamental knowledge.

Embryology

The first evidence of a circular muscle coat in this region can be identified in the 30 mm crown-rump (C.R.) stage of embryonic development (Beattie, 1924; Jit, 1956). Both the circular muscle coat of the small intestine and of the large intestine participate in the formation of the junction and they meet at the apex. For the longitudinal muscle evidence exists that from the 99 mm C.R. stage onwards, the outer fibres of the longitudinal muscle of the small gut extend directly into the large gut, the inner fibres extend as a reduplication into the lips of the valve for some distance and then as a single layer even further (Jit, 1956). By synaptogenesis studies it was discovered that the first signs of synaptic contact are found proximally of the ileocaecal junction, to become evident in the ileocaecal junction only by the late foetal period (Lolova and Mikrosk, 1983). These early presynaptic components are considered to be cholinergic, while the adrenergic presynaptic varicosities are formed only after 30-180 days (Ouyang, 1992). The development of the junction can be explained as a process of intussusception, where the small gut progressively projects into the colon. This process comes to an end when the longitudinal muscle coat of the small

intestine continuously extends into the longitudinal muscle layer of the colon. After the intussusception process, interstitial growth of different parts of the junction has to play an important role in the differentiation and formation of a septum of longitudinal muscle.

This intussusception theory explains the clinically common occurrence of intussusception of this region in small children.

Macroscopic anatomy

Macroscopic appearance

The ileocaecal junction is a specialized area that forms the boundary between the small and the large intestine. There are important differences between species; bears, ferrets and hedgehogs have no such structure; dogs have an ileocolonic junction, without a valvular structure, and the mole has a rectilinear transition between the ileum and the colon (Pelckmans, 1988). Due to this species-difference, it seems highly improbable that this region performs the same function in the different animals. The human situation seems to be a more differentiated arrangement, where the oblique entry of the ileum in the caecum can be used as a mechanical barrier. In the terminal ileum, two segments can be distinguished: a precaecocolic portion and a caecocolic portion, situated in the wall of the large intestine and ending in the ileal eminence. The inner mucosal surface of the terminal ileum shows a number of longitudinal folds (DiDio, 1952). In human material two different types of orifices of the ileal eminence in the caecocolon are distinguished in the early literature (DiDio and Anderson, 1968): a bilabial type, with the classical appearance of a valve with two lips, comparable with other valves, e.g. mitral valve; and a papillary type, where a small portion of the small bowel protrudes into the caecum/colon. This papilla is composed of an upper and a lower lip or labium of 0.3 to 0.5 cm thick (Quigley and Phillips, 1983). These labia coalesce at their lateral margins and they continue for a short distance, thus forming an anatomical landmark for the distinction of the caecum and the colon: the frenula coli.

Most of the work on this subject was performed on cadaver material examined 24 hours or more after death, the arbitrary classification probably being a post-mortem artifact. *In vivo* studies and endoscopic views of this region indicate that the structure varies in time between a papillary and a labial configuration.

Blood supply

The arterial blood supply of the ileocaecal region begins with the A. ileocolica. After a relatively long course it mostly continues into one or two caecal arteries. During this long course several vessels branch from the ileocolic artery, from proximal to distal; *ramus*

colicus superior; *arteria appendicularis*; *ramus ilei*; *ramus colicus inferior*; and *ramus caecalis anterior et posterior* (Vandamme and Bonte, 1982).

Near the ramifications of these juxta-intestinal ileal arteries intimal pads, consisting of smooth muscle cells oriented predominantly in a longitudinal direction and of numerous elastic fibres, exist. They probably serve as controlling elements to block in part or totally, the blood flow to certain territories, depending on the functional requirements (Ferraz de Carvalho et al., 1974).

The venous bed of the tela submucosa of the terminal ileum and of the eminentia ilealis is clearly enlarged and this increase of the venous bed reaches a maximum about 2 to 3 cm orally from the orifice. This enlargement of the venous bed is comparable to similar arrangements in other parts of the gastro-intestinal tract, e.g. pharyngoesophageal junction and the esophagogastric junction, and they suggest a closing-mechanism for the control of the ileal outlet (Ferraz de Carvalho et al., 1972).

Extrinsic innervation

The ileocaecal junction has a sympathetic and a parasympathetic extrinsic innervation (Ouyang, 1992). The parasympathetic fibres run through the vagus nerve, though maintenance of the muscle tone in the ileocaecal junction does not depend on this intrinsic innervation (Hinrichsen and Ivy, 1931; Pahlin and Kewenter, 1976). The sympathetic innervation receives input from the superior and the inferior mesenteric ganglia (Hinrichsen and Ivy, 1931; Jarrett and Gazet, 1966). The adrenergic innervation at the ileocaecal junction is more prominent compared with other gastro-intestinal sphincters, suggesting an important pathway in the control of the sphincter (Ouyang, 1992). Different pharmacological experiments have shown that the ileocaecal junction is a high-pressure zone which contracts independently from the adjacent ileum or caecocolon (Rubin et al., 1980). The contractions are mediated through alpha-adrenergic receptors and there also seems to be an inhibitory beta-effect on the ileocaecal sphincter motility (Gazet and Jarret, 1964; Pahlin, 1975).

Distension of a segment of small intestine or large intestine induces a contraction of the ileocaecal region (Pahlin, 1975; Kohler et al., 1991). This excitatory intestino-ileo-caecal sphincteric reflex is a spinal reflex with the main afferent and/or efferent fibres located within the major splanchnic and lumbar colonic nerves (Pahlin and Kewenter, 1975). The excitatory motor response in the sphincter is adrenergic (Pahlin, 1975; Pahlin and Kewenter, 1975).

Microscopic anatomy

Mucosa and submucosa

Ileal mucosa covers the inner part of the ileal eminence, while the outer wall is covered by colonic

mucosa. The transition zone occurs at the free margins of the labia (Quigley and Phillips, 1983).

From personal experiments, a high density of lymphoid tissue and of Peyers patches were detected in this region (Fig. 2).

Muscle coat

Fibres of the longitudinal layer of the ileal

musculature are sent to the ascending colon and to the caecum, in addition to the deep fascicles which run in the ileal eminence, where they are joined by longitudinal muscle fibres of the large intestine (Figs. 1, 3) (Didio and Anderson, 1968; Quigley and Phillips, 1983).

The circular muscle layer of the ileal musculature is surrounded by the circular muscle layer of the large intestine (DiDio and Anderson, 1968). This layer thickens at the base of the ileal eminence and again at
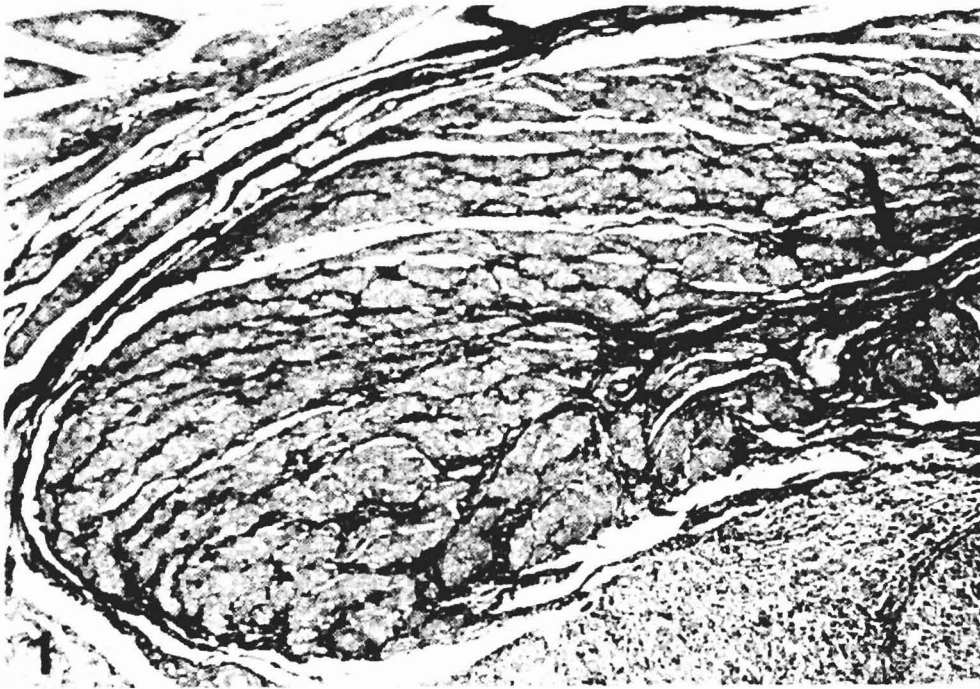
Fig. 1. Micrograph of the circular muscle layer at the tip of the papilla of a porcine ileocaecal junction. Note the longitudinal muscle bundles penetrating the thick circular muscle layer (arrow). x 70

Fig. 2. Micrograph of the papilla of the porcine ileocaecal junction. Note the abundance of lymphoid tissue (arrows). x 30

the free end, where the fibres of the ileal circular muscle layer are in contact with those of the large intestine (Quigley and Phillips, 1983; Phillips, 1992).

Because the circular musculature is far more developed than the longitudinal one (Fig. 1), the normal status of the ileocaecal junction is contraction. A high density of elastic fibres was also noted in the human ileocaecal junction (Ferraz de Carvalho and Faintuch, 1974).

Physiological experiments have shown that the circular muscle coat of the ileocaecal junction differs from the muscle coat of the adjacent colon and ileum. It develops a high tension in response to stretch, i.e. in response to distension of the caecum (Conklin and Christensen, 1975; Cardwell et al., 1981). The reaction to different neurohumoral stimuli (e.g. CCK, gastrin, secretin, glucagon, acetylcholine, adrenoreceptor-blockers) also suggests sphincteric properties (Ouyang et al., 1981; Phillips, 1992).

The frenula are considered to be a remnant of the sphincter between the caecum and the caeco-colon of lower animals.

Intrinsic innervation

Most gastrointestinal sphincters (e.g. pylorus,
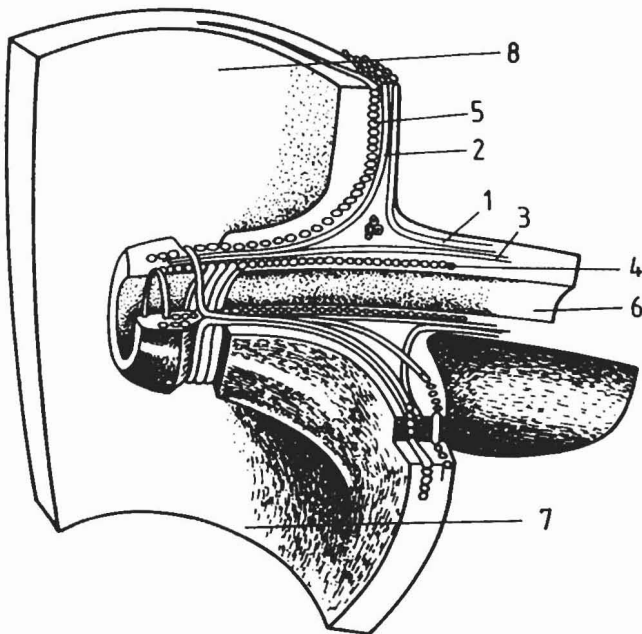
Fig. 3. Schematic representation of the transition zone between the small and the large intestine. The different muscle layers can clearly be traced: 1. Superficial muscle layer of the ileum, directed to the ascending colon; 2. Longitudinal muscle bundle form the ascending colon penetrating the papilla and joining the deep ileal longitudinal muscle bundle; 3. Deep longitudinal muscle layer from the ileum; 4. Circular muscle layer of the ileum; 5. Circular muscle layer of the ascending colon; 6. Ileal lumen; 7. Caecal lumen; 8. Lumen of ascending colon (reprinted with permission of author from DiDio and Anderson, 1968).

sphincter of Oddi, anal sphincter) are known for the obvious increase of the number of neurons and neuronal fibres in the myenteric plexus (Lorenz, 1962). For the ileocaecal region, quantitative data are not available in the literature. Only two references can be found: in a paper by Murakami (1952) where it is vaguely stated that on the level of the ileocaecal junction, there is quite a high number of neurons and neuronal fibres (Murakami, 1952), and in a paper by Hunter (1936) where a higher density of ganglia within the myenteric plexus in the terminal ileum and the ileocaecal junction is mentioned (Hunter, 1936; Phillips, 1992). Murakami also noted the absence of Dogiel type I neurons and the abundance of Dogiel type II neurons in the myenteric plexus of the ileocaecal junction (Murakami, 1952). In the equine myenteric and submucous plexus, nerve cell bodies as well as nerve fibres showing immunoreactivity to substance P, vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP) and peptide histidine isoleucine (PHI) were found. These ramified nerve fibres extended into the mucosa, to the small blood vessels in the submucosa and to the circular muscle layer (SP, VIP and PHI) (Kotze and Van Aswegen, 1990). The presence of CGRP in enteric neurons of the pig was already described as being a specific marker for Dogiel type II neurons (Scheuermann et al., 1987; Timmermans et al., 1992). A possible role and localization for neurotensin remains unclear, as the highest concentration in the gastrointestinal tract is found in the terminal ileum (Rothstein and Ouyang, 1989; Ouyang, 1992). Substance P and met-enkephalin-like immunoreactive nerve fibres were found encircling nerve cell bodies and processes in the myenteric and submucosal plexuses of the cat. The presence of the 5-hydroxytryptamine (serotonin) has been demonstrated in the myenteric plexus (Kotze and Van Aswegen, 1990; Ouyang, 1992). Pharmacological studies have shown that the intrinsic innervation of this region can be triggered by different neurohumoral stimuli (Pelckmans et al., 1989; Boeckxstaens et al., 1990a,b,c). VIP induces an important relaxation of the circular muscle, whereas administration of serotonin causes a non-adrenergic non-cholinergic (NANC) relaxation of the circular muscle, followed by a contraction (Boeckxstaens et al., 1990a). Recent studies were able to identify nitric oxide as the terminal neurotransmitter involved in this NANC relaxation (Bult et al., 1990; Bogers et al., 1991).

Function

The function and relative importance of this specific structure remains the subject of speculation. The only phyllogenetic consistent reflex found across species is the contractile response to colonic distension, pointing towards a role in preventing reflux from colonic content into the ileum (Ouyang, 1992). When removed during surgery it does not always alter the bowel movement, probably due to the redundancy of other mechanisms controlling the forward propulsion of ileal contents

(Ouyang, 1992). Only when a significant portion of the small intestine is removed, does the ileocaecal junction seem to play an important role in the regulation of the transit time and the prevention of malabsorption (Richardson and Griffen, 1972; Cosnes et al., 1978). Viewed in this setting, the junction can be considered as a safety net, only important in cases of pathology of the small bowel or in cases where the resorptive capacity of the colon is severely impaired. The function as anti-reflux barrier for colonic content and bacterial overgrowth was also suggested by some authors (Gazet, 1968; Kumar et al., 1988). Different mechanisms for this reflux-preventing function have been discussed: a pure valvular mechanism (Hunter, 1934; Wakefield and Friedell, 1941; Bellón Caneiro et al., 1986); a sphincteric mechanism (Elliot, 1904); or a combination of both (Ulin et al., 1956). The angulation between the ileum and the colon, maintained by different ligamentous bands, also seems to play a role in the competence of the valve (Hunter, 1934; Wakefield and Friedell, 1941; Buirge, 1943; Borner et al., 1981; Kumar et al., 1988; Phillips, 1992). Serious doubt can be cast on the competence of this valvular structure, which seems to be age-dependent (Scheye et al., 1983), by the easy filling of the ileum with barium during a colonic contrast enema in 90% of normal subjects (Fleischner and Bernstein, 1950; Pahlin, 1975). The functional regression with age may point towards a different role in adulthood, compared with childhood. Thus, normal propulsive activity of the small and the large intestines may be all that is necessary to prevent reflux. The high density of Peyers patches near the orificium in the caeco-colon suggests a role as immunological barrier between the large and the small intestine.

Final remarks

As stated earlier, much has been written on the true nature of this interesting region of the gut. Is it really a sphincter or a valve, or is it just a remnant of the embryological development of the gastrointestinal system? Pharmacologically, it reacts as a sphincter, though the anatomical proof is still very poor. What purpose does it serve? Different animals have different arrangements of this region, without important physiological implications. No really important pathology can be identified which is unique to this structure, although the terminal ileum is the most important focus for Crohn's disease. Is there a specific anatomical reason for this localization? Further fundamental multidisciplinary research is needed in order to understand the possible role of this region in the pathogenesis of clinically important problems.

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