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Basic knowledge

Sphincter of Oddi physiology

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Introduction

The presence of a sphincter at the termination of the common bile and pancreatic duct has been recognized for more than 100 years, but it is the technical progress (endoscopy and manometry) that importantly has resulted in an increased knowledge of the activity pattern and function of the sphincter.

Research in the last two decades has focused on pathophysiology in patients with postcholecystectomy pain and idiopathic recurrent pancreatitis, but has also made major contributions to the understanding of bile tract physiology.

The present paper aims to describe sphincter of Oddi (SO) activity and function as it has become known with this progress.

Anatomy

The first time a ring-like structure at the termination of the common bile duct (CBD) was mentioned was in 1681.[1] This was, however, not noticed in the following years, and it was not until 1879 that Gage described a special muscular arrangement in cats;[2] however, the studies were not sufficiently detailed to conclude that a true sphincter existed.

The important contribution was published in 1887, in which study Oddi histologically investigated the termination of the CBD and the pancreatic duct (PD) in several species.[3] He concluded that there was a true sphincter, and suggested its role in the regulation of bile flow into the duodenum.

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Hendrickson[4] in 1898 confirmed Oddi's findings (Fig. 1) studying histological sections in several directions in humans.

A thorough knowledge of the composition of the sphincteric elements was offered by Boyden.[5] He subdivided the SO into four parts: choledochal sphincter, pancreatic sphincter, ampullar sphincter, and intermediate fibers. The choledochal sphincter and the intermediate fibers were seen in all individuals, whereas the pancreatic and ampullar sphincters were present in only one-third and one-sixth, respectively.[6]

It should be added that although anatomic studies have shown that a pancreatic sphincter segment only is present in one-third of individuals, dynamic investigations have shown that even after manometrically controlled complete bile duct sphincterotomy sphincteric activity is always present in the pancreatic segment.[7]

Function

The function of the SO is to regulate biliary and pancreatic flow into the duodenum, to prevent bile reflux into the pancreas, and vice versa, and to protect against duodenoductal reflux. Only sparse knowledge of the relation between pancreatic flow and SO activity exists. There is, however, no reason not to assume that the pancreatic and biliary system are quite alike, as supported by the fact that the bile and pancreatic secretion to the duodenum has a parallel course.

Bile flow to the duodenum occurs passively when the SO is relaxed. Conversely, total inhibition of bile flow follows maximal stimulation of the SO,[8] as can be seen after the injection of, e.g., morphine (Fig. 2). In addition to this function as a resistor, the SO can also act as a peristaltic pump. In humans, this latter form of action is probably less important, as will be discussed later.

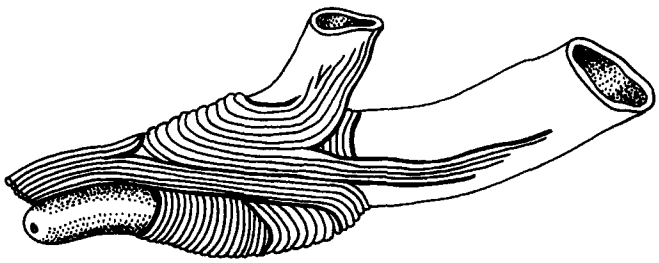

Fig. 1. Anatomy of the choledocho-duodenal junction. For details, see "Anatomy" in text. (Redrawn from [4])

In addition to the control of bile secretion into the duodenum, the SO is also important in the regulation of gallbladder filling. Abolition of SO tone by endoscopic sphincterotomy blocks gallbladder filling on hepatobiliary scintigraphy.[9] Furthermore, studies in human autopsies where the SO had been eliminated and the cystic duct divided at the junction to the gallbladder resulted in no flow through the spiral valves of the cystic duct during water infusion into the common hepatic duct at physiologic flow rates.[10]

The activity pattern of the SO, and thereby its function, is the result of spontaneous myogenic activity, neurohormonal regulation, and local reflexes, and is subject to variation in the fasting state and after food intake.

Basal activity pattern

The activity pattern of the SO has been determined from surgical studies where resistance to flow was measured either perioperatively or through a T-drain in the postoperative period.[11,12] With improved endoscopic and manometric techniques, it became possible to directly measure the pressure variation within the sphincteric segment.[13,14] It has been shown that the SO is a zone with elevated baseline pressure at around 10 mm Hg, and superimposed phasic waves at amplitudes around 100 mm Hg (Fig. 3). The phasic waves normally propagate in an antegrade direction, i.e., toward the duodenum.[15,16] Using a microtransducer technique, Tanaka et al.[17] showed that, compared to the duodenum, there was a basal common bile duct and pancreatic duct pressure of 4 and 8 mm Hg, respectively. Thus, not only is there a positive gradient from the ductal systems toward the duodenum, but the ductal pressure in the pancreas is also higher than that in the common bile duct, preventing bile from entering the pancreas.

The implications of the SO activity pattern in the regulation of bile flow have been briefly mentioned above, and there is general agreement that the SO plays a major role in the regulation of bile and pancreatic flow into the duodenum. There is, however, some controversy as to how this is brought about. The main reason for this controversy is probably that many studies have been carried out in laboratory animals, and there are major differences between species. Cats and dogs seem to behave more like humans, whereas herbivorous animals are different, as can be exemplified by looking at what happens after the injection of the hormone cholecystokinin (CCK): This hormone stimulates bile flow in all species, but in opossums[18] and prairie dogs,[19] CCK stimulates SO phasic wave activity, whereas in cats[20] and humans,[21] it inhibits the SO. Therefore, in the former two species, phasic waves probably are important in promoting bile flow, whereas in humans, the most important action is that of a resistor.[22,23] Variation in tone determines outlet resistance. The phasic waves, in humans, have a dual role: Only at a modest rate do the antegrade contractions allow the SO to act as a peristaltic pump, expelling bile, debris, and microcalculi, when present. The contractions also create a resistance to flow across the sphincter so that major flow can take place only

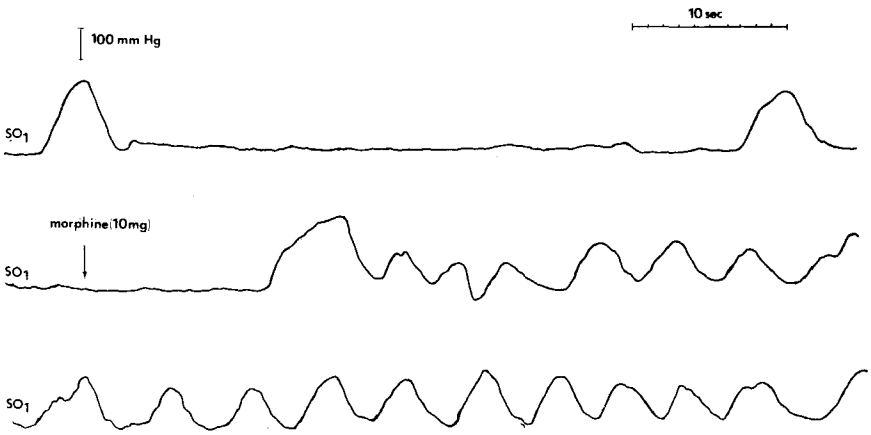

Fig. 2. Effect of i.v. injection of morphine on sphincter of Oddi activity, measured by a single-lumen manometric catheter. (After ref. [48])

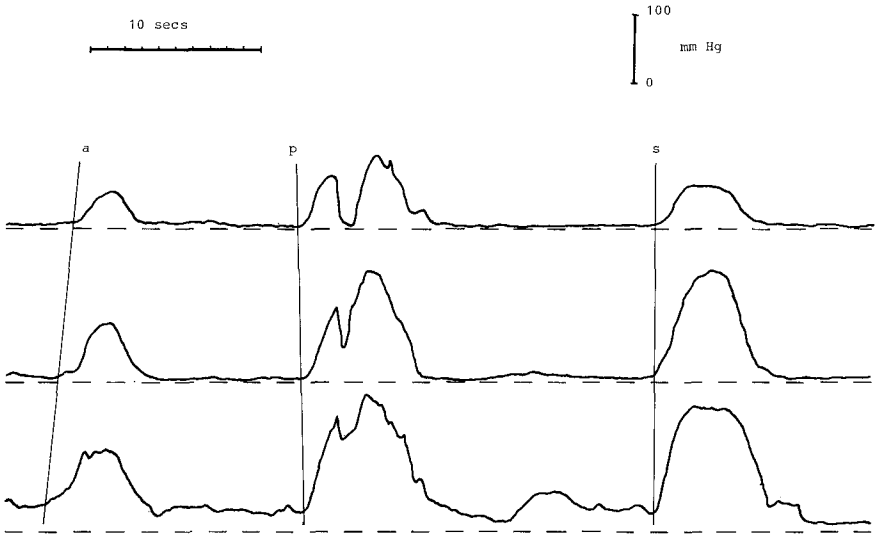

Fig. 3. Sphincter of Oddi contraction modalities measured with a triple-lumen manometric catheter. Anti-peristaltic (*a*), peristaltic (*p*), and simultaneous (*s*) waves are seen. (After ref. [49])

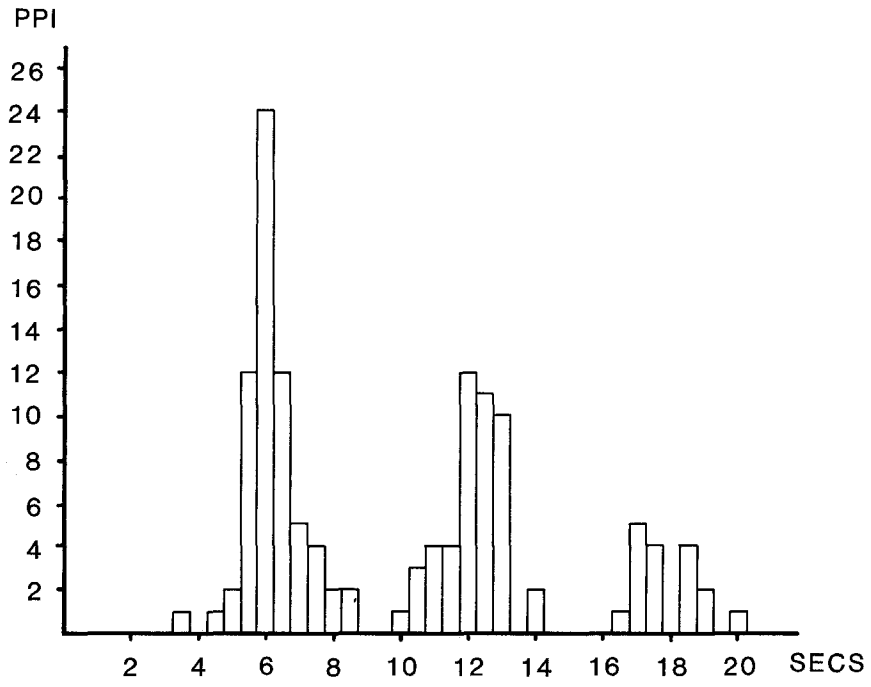

Fig. 4. Sphincter of Oddi pacemaker frequency as calculated from contraction wave peak-to-peak intervals (*PPI*). Maximal interval is 6 s, corresponding to a pacemaker frequency of 10 waves per min. (After ref. [50])

between the contractions. The antegrade direction of the phasic contractions further inhibits duodenoductal reflux.

The SO shows pacemaker activity (Fig. 4) of the same nature as that in the gastric antrum and the small intestine, i.e., phasic variation of membrane potential where the firing level of spike potentials, necessary for contractions, can be reached only at one point of this phasic variation.[15] The pacemaker frequency is rather constant and close to that of the duodenum; this could indicate that pacemaker frequency is determined by the duodenum. However, from experimental studies in the opossum, it is known that the pacemaker frequency is set by the proximal part of the SO.[24]

The SO is subject to the same fasting variation as the upper gastrointestinal tract, which variation can be subdivided into three phases: phase I is characterised by quiescence with little or no activity; phase II consists of irregular contractions of increasing frequency and regularity, culminating in phase III, in which there are propagated contractions of maximal frequency.

Long-term measurements have shown that the phases in the SO follow those of the duodenum; however, the SO is more active than the duodenum in

phase I.[25,26] The activity fronts (phase III) start a little earlier in the SO than in the duodenum, and this indicates that the activity front of the SO is not brought about by contractions from the duodenum around the SO. This idea is also supported in an experimental study in which the SO was autotransplanted into a more distal part of the small intestine. The SO phasic variation still followed the duodenum, albeit the phase III wave frequency was lower.[27]

After food intake, the SO is inhibited in humans.[26] This holds true for the basal pressure as well as for the phasic wave amplitudes. The inhibition is probably brought about by CCK and secretin, facilitating biliary and pancreatic flow.

Neurohormonal regulation

The nervous supply to the SO comprises extrinsic and intrinsic innervation. The sympathetic innervation is supplied from the celiac and superior mesenteric plexuses, and the parasympathetic from the vagus nerve, either directly or via the sympathetic plexuses. The makeup of the pathways involved until the effect is exerted on the SO is complex and not yet clearly understood, a number of different transmitters being involved. The action of the nerves includes both excitatory and inhibitory mechanisms.

The role of the vagus nerve has not been solved. No studies have investigated the influence of vagotomy on the SO in humans. Results of experimental investigations have been contradictory; however, it seems that efferent vagal stimulation inhibits the SO.[28] In vitro studies of the SO in cats have demonstrated adrenergic alfa- and beta-neurones. Alfa-receptor activation stimulated the SO, and beta-receptor activation inhibited it.[29] The importance of this system is controversial, and, under basal conditions, the role of sympathetic and parasympathetic innervation is probably limited.[30]

The intrinsic nervous system is more important, and immunohistochemical studies have shown abundant neurones in the SO segment.[31] Non-adrenergic, non-cholinergic inhibitory innervation is an important feature, and inhibition has been suggested to occur via the transmitters, vasoactive intestinal polypeptide (VIP)[32] and nitric oxide.[33,34]

Although many questions are still unsolved, it is known that neural regulation involves both excitatory and inhibitory pathways. The role of the inhibitory system is probably mediation of CCK-induced and extrinsic neural relaxation of the SO. Cholinergic excitatory neurones may be involved in SO stimulation during phase III of the interdigestive period.

Tetrodotoxin, a drug that blocks neural conduction, increases the phasic activity of the feline SO, indicating that the inhibitory nervous system is most important in the regulation of basal SO activity.[35]

Hormonal influence on the SO has been extensively studied, although most investigations have been carried out in laboratory animals. Species differences have already been mentioned above. This problem may be partly overcome by looking into the mechanism of action of hormones. However, in order to establish the physiological role of hormones in humans, it is necessary to conduct studies with hormones in physiological doses, and this has been done in only a few investigations.

CCK is a potent inhibitor of SO basal and phasic activity, and is probably the most important factor in the inhibition of SO activity after food intake.[36] CCK has a direct stimulatory action on the SO muscle, but it also has a stimulatory action, which is more potent, on intrinsic inhibitory nerves, and therefore gives rise to an overall inhibition of the SO.[37] Furthermore, the stimulatory effect of CCK on the gallbladder, with subsequent reflex relaxation of the SO, further contributes to SO inhibition.[38]

Secretin inhibits the SO, but in physiologic doses only the pancreatic part of the SO is affected.[39] It is hard to understand that such a small sphincter as the SO can have a dual activity pattern in its different ductal segments; however, it is not only in studies on the action of secretin that differences have been observed; differences have also been found in basal recordings in patients suspected to have SO dysfunction.[40]

Glucagon inhibits the SO in pharmacological doses, but has no effect at physiological levels.[41]

Other agents, such as glucagon-(1–21)-peptide,[42] gastrin,[14] and somatostatin,[43] have been studied only in pharmacologic doses.

Reflex regulation

The SO is influenced both by local reflexes and by reflex pathways from more distant organs.

A reflex between the gallbladder and the SO was first described by Wyatt,[44] who found that mechanical stimulation of the gallbladder inhibited resistance to the flow through the SO. More recent studies have shown that increases in gallbladder pressure inhibit the SO.[38,45,46] During periods of low gallbladder pressure, the SO is stimulated. The reflex operates within physiologic ranges of gallbladder pressure, and has been demonstrated in cats, dogs, and humans. The reflex is rational and assures gallbladder filling when empty (low pressure), and diversion of bile to the

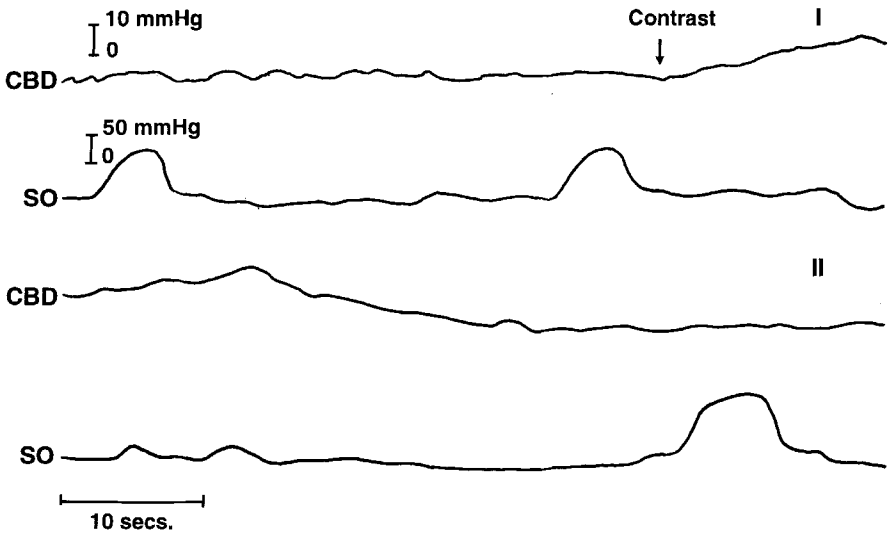

Fig. 5. Influence of increase in common bile duct (*CBD*) pressure on sphincter of Oddi activity. (After ref.[47])

duodenum when the gallbladder is full or is actively contracted.

A similar reflex between the common bile duct and the SO (Fig. 5) has been shown in cats[45] and humans.[47] This reflex is especially important in the post-cholecystectomy state, in that it allows the flow of bile into the duodenum at high secretion rates from the liver. Absence of this reflex would result in periods of high common bile duct pressures at a magnitude able to produce pain.

The reflex is mediated by inhibitory nerves running along the common bile duct, and it is abolished by local infiltration anesthesia at the cystico-choledochal junction.[45]

Nerve damage during cholecystectomy with extensive dissection around the junction of the cystic duct and the common hepatic duct may, through reflex blockade, be a factor in the post-cholecystectomy pain experienced by patients.

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