LEADING ARTICLE

Impaired gastric accommodation and its role in dyspepsia

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The accommodation reflex is an important mechanism of normal gastric physiology. In functional dyspepsia, impairment of accommodation has been found in 40% of cases, but it has been described in several other upper gastrointestinal disorders, such as diabetic gastropathy and postfundoplication syndrome. This review focuses on the pathways involved in the normal accommodation reflex, the relevance of impaired gastric accommodation as a cause of morbidity and the methods used to assess gastric accommodation in humans. The available medical and therapeutic strategies based on the actual knowledge of the physiology and pharmacology of the accommodation reflex are outlined, with a focus on the role of nitrergic neurones and serotonergic receptors.

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The stomach performs an important role in digestion, not only by its mechanical action on the chyme or by its secretory products but also by a timed release of the ingested nutrients into the duodenum. The accommodation reflex provides a way to temporarily store ingested food before controlled release into the intestine occurs. It consists of a reduction in gastric tone and an increase in compliance in response to food intake, allowing for an increased fundic volume without accompanying rise in intragastric pressure.[1] Under physiological conditions, this adaptive relaxation is not perceived.

Functional dyspepsia is defined as persistent or recurrent upper abdominal pain or discomfort in the absence of evidence of organic disease that is likely to explain the symptoms.[2] Recent studies have reported the occurrence of impaired gastric accommodation in patients with functional dyspepsia and several related disorders, and it has been suggested that this might contribute to the pathogenesis of symptoms. In view of the high prevalence of dyspepsia in the general population, the considerable healthcare costs associated with functional dyspepsia, and the lack of effective therapeutic approaches,[2 3] impaired gastric accommodation is an attractive target for further pathophysiological and therapeutic studies. In this review, we summarise the current knowledge on the physiological and pathophysiological role of gastric accommodation and potential therapeutic approaches for impaired accommodation.

ASSESSING GASTRIC ACCOMMODATION

Several different tools have been developed for the assessment of the accommodation reflex in humans, in health and disease. As each of these methods has its specific advantages and disadvantages, some knowledge about their functioning is essential.

Measurement of pressure and volume relationships: gastric barostat

Of all existing methods, the barostat was the first to be developed, and still remains the gold standard, with proved reproducibility.[4 5] It allows the evaluation of pressure changes under isovolumetric or volume changes under isobaric conditions. A highly compliant polyethylene balloon is introduced through the mouth into the gastric fundus and connected to an electronic barostat device. Thereafter, the balloon is gradually inflated to overcome the intra-abdominal pressure, which is usually defined as the lowest pressure needed to induce a minimal volume of 30 ml, or the occurrence of respiratory variation on the volume measurement. The pressure at this level is called the minimal distending pressure. A minimal distending pressure with an additional 2 mm Hg is generally accepted as the optimal baseline pressure for the measurement of changes in volume, including meal-induced gastric accommodation.[6] Under isobaric conditions, the volume increase in the balloon after meal ingestion directly reflects gastric relaxation and provides a measure for meal-induced accommodation. By using the same device, information can be acquired about gastric sensitivity and compliance in the same session.[7] However, the invasive nature of the barostat procedure has limited its use to research facilities and has prompted the development of more patient-friendly instruments. Also, some concern about possible bias in the measurements owing to the presence of the bag in the stomach and the complex geometry of the stomach have been expressed.[8 9]

Measurement of gastric volumes

Gastric emptying scintigraphy is a standardised technique to measure the emptying rate of a radiolabelled meal. This involves the assessment of radiographic counts over the whole stomach area as a function of time. It has been proposed to divide the area of interest into a distal and proximal gastric segment, to assess regional gastric emptying. Studies on patients with functional dyspepsia using this technique showed redistribution of the meal to the distal

Abbreviations: CCK, cholecystokinin; cGMP, guanosine 3′,5′-cyclic monophosphate; 5-HT, 5-hydroxytryptamine; MRI, magnetic resonance imaging; SPECT, single-photon emission computed tomography

stomach, at the expense of the usual accumulation in the proximal stomach.[10 11] It has been suggested that this redistribution reflects, and is a consequence of, impaired accommodation of the proximal stomach.[10 11]

Single-photon emission computed tomography (SPECT) takes advantage of the selective uptake and excretion of technetium 99m pertechnetate by the gastric mucosa.[12] On the basis of tomographic images obtained by a gamma camera, computer software produces a three-dimensional image of the stomach from which the volume can be determined. By comparing fasting and postprandial volumes, gastric accommodation is quantified.[12 13] An initial validation study in healthy volunteers showed a good relationship between preprandial and postprandial volumes determined by SPECT and simultaneous intragastric barostat measurement.[14] However, another study that measured the effects of meal ingestion and administration of glucagon on gastric volumes determined by SPECT or intragastric barostat measurement on separate days failed to confirm such a good correlation.[15] Instead, these authors suggested that SPECT imaging, which lacks the distending force of an intragastric barostat, may be able to detect changes in postprandial volume, largely driven by the meal volume, but may not adequately reflect changes in gastric tone.[15] However, subsequent studies on simultaneous measurements of SPECT gastric volumes and scintigraphic emptying showed that postprandial proximal stomach volume measured with SPECT exceeds meal volume.[16 17] To our knowledge, no studies have directly compared accommodation measured with the barostat and SPECT in patients with functional dyspepsia.

Although it has already been used for the measurement of gastric emptying[18] and transpyloric flow,[19] transabdominal ultrasound of the stomach has also been proposed as a non-invasive and largely available alternative to the barostat for the measurement of gastric accommodation. For this purpose, consecutive ultrasound sections at two levels of the stomach are obtained, both during fasting and postprandially.[20] However, this method is highly user dependent and correct measurements can be precluded by anatomical structures (eg, ribs) and the intragastric air bubble. To overcome this last issue, a three-dimensional ultrasound has been proposed, during which consecutive moving ultrasound image scans of the whole stomach area are obtained, both during fasting and postprandially.[21] Computerised software then allows the translation of these images to gastric volumes, and a recent pilot study reported a good correlation with barostat volumes.[21] Further validation studies are still required. Although it has been used for assessing gastric emptying, magnetic resonance imaging (MRI) after a gadolinium-labelled meal is theoretically also able to assess gastric volumes.[22 23] A marked correlation was reported between gastric volumes assessed by MRI and a simultaneous barostat study.[24] However, additional validation studies are still required for three-dimensional ultrasound and MRI estimations of gastric accommodation.

Challenge tests of gastric volume capacity

Impaired accommodation results in a limited postprandial gastric volume capacity. Drinking challenge tests therefore have the potential to provide a more physiological and non-invasive way of assessing gastric accommodation. Drinking tests essentially consist of the gradation of satiety while the subject is drinking at a constant rate. When maximal satiety is reached, the volume that has been ingested is recorded and is considered as a surrogate marker for gastric accommodation. Both nutrient or water challenge tests have been used, and several studies have established that patients with functional dyspepsia ingest considerably less volumes of liquid and that their symptom scores increase faster.[7 25–27] No correlation of water drinking tests and gastric accommodation assessed by the gastric barostat could be shown,[27] but the lack of calories and the rapid emptying of water from the stomach may impair the ability of water to serve in a gastric volume challenge test.[28] When nutrient drinking tests are used within a certain range, the caloric density of the meal does not seem to be a major determinant of the maximum tolerated volume.[25] Literature reports on the correlation between gastric accommodation and the outcome of nutrient drinking tests in functional dyspepsia have been inconsistent. One study failed to find a correlation between a rapid caloric drinking test (150 kcal/min) and gastric accommodation measured with a barostat.[27] It has been proposed that a slower drinking rate is necessary to allow a full accommodation reflex,[28] and two studies reported good correlations between a slow nutrient drinking test (22.5 kcal/min) and accommodation measured with a barostat.[7 25] Finally, a study that used SPECT imaging to estimate gastric accommodation failed to find a correlation with a 45 kcal/min nutrient challenge test.[29]

Physiology of gastric accommodation

Pathways involved in the accommodation reflex

The control of gastric accommodation has been studied in several animal models. The accommodation reflex consists of a vagovagal reflex pathway, resulting in activation of non-adrenergic, non-cholinergic nerves, including an important nitrergic component.[30–34] Nitric oxide produced by the neuronal nitric oxide synthase in nitrergic neurones, diffuses passively into the smooth muscle cell and increases the activity of soluble guanylate cyclase, thereby promoting guanosine 3′,5′-cyclic monophosphate (cGMP) synthesis, which has an inhibitory effect on smooth muscle tone (fig 1). Barostat and SPECT studies on humans have confirmed the involvement of a nitrergic component. In healthy volunteers, inhibitors of nitric oxide synthase decreased fundic relaxation after a meal,[33 34] and barostat studies showed that administration of nitrates increases postprandial gastric volume.[35] By contrast, a SPECT study found only increased fasting, but not postprandial gastric volumes.[36]

Besides activation of nitrergic pathways, inhibition of cholinergic pathways may also contribute to meal-induced gastric accommodation. Animal studies suggested the presence of presynaptic inhibitory α_2-adrenoceptors and 5-hydroxytryptamine (5-HT_{1A}) receptors on cholinergic nerve endings in the stomach.[37 38] In keeping with this hypothesis, administration of the α_2-adrenoceptor agonist clonidine and the 5-HT_{1A} receptor agonist buspirone enhanced gastric accommodation to a meal.[35 39] On the other hand, administration of the cholinesterase inhibitor prostigmine enhanced postprandial phasic contractions, but did not inhibit meal-induced accommodation in healthy people.[40]

Animal studies from the 1960s had already suggested the involvement of serotonin in vagally mediated gastric relaxation in mice and rats,[41] and this was confirmed in more recent studies in the guinea pig.[42] The observation that administration of the selective serotonin reuptake inhibitor paroxetine enhances the gastric accommodation reflex is highly suggestive of involvement of 5-HT in meal-induced relaxation in humans too.[43] By contrast, a SPECT study failed to show a marked effect of paroxetine on gastric volumes.[44] The site of release of 5-HT and the nature of the 5-HT receptor involved have been incompletely elucidated. Studies on humans,[6] as well as on dogs and cats,[31 45] where the 5-HT_{1D} receptor agonist sumatriptan relaxes the proximal stomach, often in a nitric oxide-dependent fashion, are suggestive of a 5-HT_1-like receptor. The full identification of the type of 5-HT_1-like

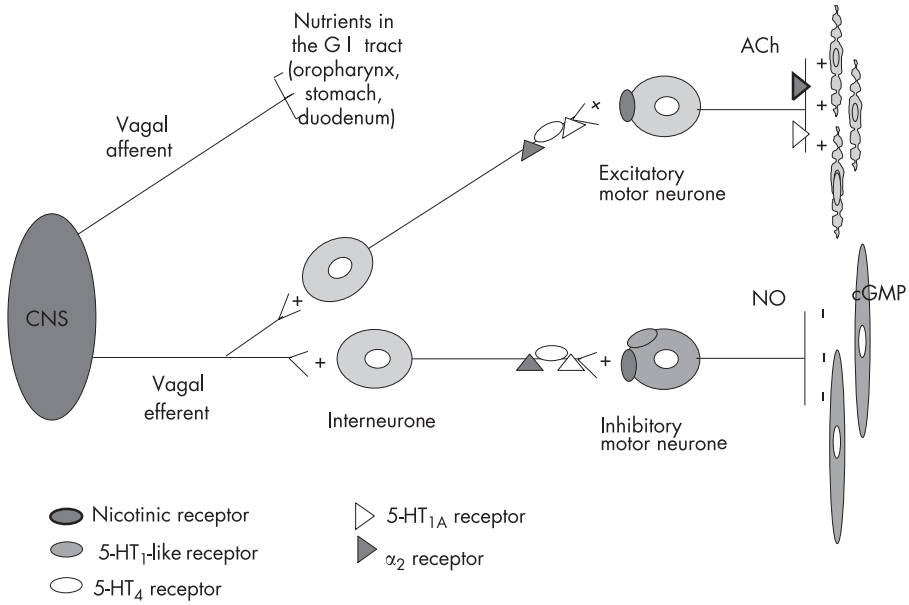

Figure 1 Pathways and receptors involved in the control and the pharmacotherapy of the gastric accommodation reflex. Activating receptors are shown as ovals and inhibiting receptors are shown as triangles. 5-HT receptors hydroxytryptamine; NO,nitric oxide; cGMP, guanosine 3′,5′-cyclic monophosphate; CNS, central nervous system.

receptor awaits further studies, as a role for 5-HT_{1D}, 5-HT_{1F} and 5-HT_{1P} subtypes has been suggested.[45–47] However, a role for other 5-HT receptors cannot be totally excluded, as agonists at 5-HT_4[48 49] or 5-HT_3[50] receptors were also shown to promote gastric relaxation in humans.

Initiation of the accommodation reflex

Several factors may contribute to initiating and maintaining gastric accommodation in response to meal ingestion. Studies on healthy volunteers found no evidence of a cephalic phase, but showed that oropharyngeal and gastric exposure to an ingested meal contribute to triggering of the gastric accommodation reflex.[51] Dual intragastric balloon studies identified antral distension-induced relaxation of the proximal stomach as a likely contributor to the gastric phase of the accommodation reflex.[52] Several studies have shown that duodenal stimulation, including balloon distension, lipid infusion or acid infusion, is able to induce relaxation of the proximal stomach.[53–57] This has been interpreted as reflecting a duodenal phase of the accommodation reflex, and studies using duodenal lipid infusion have been used to study the control of the gastric accommodation reflex. Lipid digestion and the subsequent release of cholecystokinin (CCK) and activation of CCK B receptors are key factors in these events.[54–56] However, studies using an orally ingested meal could not confirm the importance of lipid digestion and CCK release.[56 58] These data suggest that the main factors contributing to the triggering of the gastric accommodation reflex do not necessarily involve CCK-mediated duodenal feedback. It is therefore conceivable that activation of CCK-dependent pathways during duodenal lipid infusion exert a negative feedback on gastric emptying of lipids only, without interfering with gastric accommodation after an orally ingested meal.

DISEASES AND CONDITIONS ASSOCIATED WITH IMPAIRED GASTRIC ACCOMMODATION

Functional dyspepsia

Prevalence of impaired accommodation

Gastric imaging studies with ultrasound or scintigraphy provided the first observations suggestive of impairment of accommodation in patients with functional dyspepsia.[10 20] Gastric barostat studies confirmed the occurrence of impaired gastric accommodation in tertiary care patients with functional dyspepsia.[6 59–61] Meanwhile, several studies have investigated gastric accommodation in functional dyspepsia with varying techniques, and most of these confirmed the occurrence of impaired accommodation in at least a subset of patients (table 1).[6 10 11 13 20 59–62 64]

Role of impaired accommodation in symptom generation

The role of impaired accommodation in the pathogenesis of functional dyspepsia is still a matter of controversy. Not all studies deal with the symptom pattern in patients with functional dyspepsia with impaired accommodation. For their scintigraphy study, Troncon *et al*[10] selected patients with severe postprandial bloating. Our group reported a 40% prevalence of impaired accommodation measured by barostat in functional dyspepsia, and we found that this was associated with more prevalent symptoms of relevant or severe early satiety and weight loss.[6] A similar barostat study from Amsterdam found no association between gastric accommodation and the symptom pattern in functional dyspepsia, but this study was the only one that failed to find a difference in accommodation between health and functional dyspepsia.[61] In a scintigraphic study, early redistribution of the meal to the distal stomach, suggestive of impaired accommodation, was associated with symptoms of early satiety.[11] A SPECT imaging study from the Mayo group reported an association between impaired accommodation and weight loss in functional dyspepsia; early satiety was not assessed.[13] However, a later study from the same group confirmed the prevalence of impaired accommodation in patients with functional dyspepsia, but did not find an association with the presence or absence of symptoms based on a medical chart review.[62] In addition, a SPECT study on gastric volumes in a community of patients with dyspepsia did not show a marked difference in preprandial and postprandial gastric volumes compared with healthy controls.[63]

To clarify some of the controversy, several studies investigated the effects of inducing impaired accommodation in healthy people on food tolerance and postprandial

Table 1 Overview of studies that reported on the prevalence and symptom associations of impaired gastric accommodation in patients with functional dyspepsia

Author	Patients	n	Technique	Difference from health	Assocation with symptom pattern
Coffin [59]	Functional dyspepsia	10	Gastric barostat	Impaired accommodation as a group	Evocation of clinical symptoms
Troncon [10]	Functional dyspepsia	11	Scintigraphic distribution	Altered intragastric distribution as a group	Not done*
Gilja [20]	Functional dyspepsia	20	Ultrasound	Impaired accommodation as a group	Temporal association with meal-induced symptoms
Tack [48]	Functional dyspepsia	40	Gastric barostat	Impaired accommodation as a group; abnormal in 40%	Early satiety and weight loss more prevalent
Salet [60]	Functional dyspepsia	12	Gastric barostat	Impaired accommodation as a group	No correlation†
Thumshirn [35]	Functional dyspepsia	17	Gastric barostat	Impaired accommodation in 70%	Not done
Kim [13]	Functional dyspepsia	33	SPECT imaging	Impaired accommodation as a group; abnormal in 41%	Weight loss associated with impaired accommodation‡
Boeckxstaens [27]	Functional dyspepsia	44	Gastric barostat	No difference	NA§
Caldarella [52]	Functional dyspepsia	30	Gastric barostat	Impaired accommodation as a group	Not done
Piessevaux [11]	Functional dyspepsia	40	Scintigraphic distribution	No difference as a group; distal redistribution in up to 50%	Early satiety associated with early distal redistribution
Bredenoord [62]	Functional dyspepsia	151	SPECT imaging	Impaired accommodation in 43%	None
Castillo [63]	Dyspeptic subjects in the community	35	SPECT imaging	None	NA

SPECT, single-photon emission computed tomography; NA, not applicable.
*Patients were selected on the basis of symptoms of severe postprandial bloating.
†Only nausea, bloating and pain were assessed.
‡Early satiety was not assessed in this study.
§When the cut-off for normality of a study at another centre was used, no correlation was found between symptoms and ''impaired accommodation''.

symptoms. Administration of motilin or the motilin agonist erythromycin induces a proximal stomach contraction, thereby significantly inhibiting meal-induced accommodation,[65 66] and this is associated with the induction of early satiation.[25 66] Inhibition of meal-induced accommodation by the administration of a nitric oxide synthase inhibitor was associated with increased meal-induced satiety in one study.[34] In another study, however, administration of a nitric oxide synthase inhibitor was associated with decreased sensations during measurement of postprandial volumes with a gastric barostat.[33] It is unclear to what extent these sensation scores were driven by distending intragastric balloon (smaller after nitric oxide synthase inhibition) or by genuine meal-related perceptions.

Mechanism of symptom generation in impaired accommodation

Although observations in patients with functional dyspepsia and studies in healthy volunteers suggest that impaired accommodation can be a cause of symptoms, especially early satiation, there is still discussion about the sites and mechanisms involved. Impaired accommodation has the potential to induce symptoms that arise from the non-relaxing proximal stomach. On the basis of barostat and tensostat studies, it was suggested that wall tension, rather than elongation, is involved in generating perceptions from the proximal stomach.[67 68] Furthermore, in healthy volunteers, administration of erythromycin increases the tone of the proximal stomach, and this is accompanied by enhanced perception of phasic isovolumetric contractions, probably through activation of tension-sensitive mechanoreceptors.[69] However, further studies are clearly needed, as the accuracy of estimation of tension by the barostat or tensostat has been questioned, and as other mechanisms such as strain have not been sufficiently considered in human studies.[9]

It is also conceivable that insufficient proximal stomach relaxation could cause an antral redistribution of a meal. In this case, symptoms would result from antral overdistension. Indeed, antral area measured by ultrasonography has been related to fullness in healthy volunteers.[70 71] In double antral and fundic barostat studies on healthy volunteers, the proximal and distal stomach were found to have similar mechanosensitivity, and there was no evidence of spatial summation of symptom intensity by distension at two sites. Barostat and SPECT studies confirmed that meal ingestion also elicited antral relaxation.[16 72] However, the antrum was much less compliant than the fundus and this could result in earlier activation of tension receptors with an equivalent degree of distension,[72] which could be potentiated in case of impaired fundic relaxation. In functional dyspepsia, studies using water-filled balloon distension and positional changes suggested that both antral and fundic hypersensitivity, as well as impaired duodenofundic and antrofundic reflex activity, were involved in symptom generation, and that overdistension in the antrum was the most important site for symptom generation.[52]

In healthy volunteers, increasing intragastric pressure causes fundic relaxation and accelerates gastric emptying for liquids, whereas gastric emptying for solids remains unaffected.[73] In patients, several observations suggest that impaired accommodation may be associated with more rapid gastric emptying in patients.[11 20 74 75] The rapid gastric emptying observed in these studies might be a consequence of impaired proximal stomach volume capacity and might contribute to symptom generation by the induction of dumping-like symptoms.

Pathogenesis of impaired accommodation

The cause of impaired accommodation in functional dyspepsia has not been established. In theory, impaired accommodation can result from a disorder at the level of the sensory apparatus, the vagovagal reflex pathway, the intrinsic inhibitory innervation or the smooth muscle in the proximal stomach. Studies on patients with acute-onset, presumably post-infective, functional dyspepsia suggest that impaired accommodation occurs more often in these patients, where it is attributable to impaired function of nitrergic nerves in the stomach.[75] On the other hand, psychological factors, mainly anxiety, may also negatively affect the accommodation reflex, as has recently been shown.[76]

Other disorders

Several other motility and postsurgical upper gastrointestinal disorders may also be associated with impaired accommodation (tables 2, 3). As a group, patients with diabetic gastropathy and patients who have undergone Nissen

Table 2 Overview of studies that reported on the prevalence and symptom associations of impaired gastric accommodation in patients with other upper gastrointestinal disorders

Author	Patients	n	Technique	Difference from health	Assocation with symptom pattern
Penning [77]	Slow transit constipation	17	Gastric barostat	Impaired accommodation as a group	Not done
Thumshirn [35]	Rumination	12	Gastric barostat	No difference as a group; impaired accommodation in 50%	Not done
Bredenoord [62]	Rumination	15	SPECT imaging	No difference as a group	NA
Samsom [78]	Diabetic dyspepsia	8	Gastric barostat	Impaired accommodation as a group	Associated with bloating severity
Bredenoord [62]	Diabetic dyspepsia	11	SPECT imaging	Impaired accommodation in 33%	None

NA, not applicable; SPECT, single-photon emission computed tomography.

fundoplication have decreased gastric accommodation.[74 78–80 82] In a SPECT study for investigation of unexplained upper gastrointestinal symptoms, impaired accommodation was found in 44% of patients with post-fundoplication dyspepsia, and 33% of patients with diabetes with dyspeptic symptoms.[62] Impaired accommodation was also reported in subsets of patients with severe slow transit constipation,[77] and in patients with symptoms after distal gastrectomy.[81] A barostat study suggested impaired accommodation in rumination,[83] but a SPECT study from the same centre failed to confirm such a finding.[62]

Treatment options for impaired gastric accommodation

It seems logical to advise patients to eat small-sized meals more often, although the efficacy of this measure has never been formally discussed. No pharmacological treatment of established efficacy is currently available for patients with impaired gastric accommodation. Several pharmacotherapeutic studies in small numbers of patients are discussed below. These strategies remain restricted to specialised centres after careful evaluation of the underlying pathophysiology and are not suitable for routine use.

Because of the central role of nitric oxide, nitric oxide donors have been used to enhance gastric relaxation and to reduce dyspeptic symptoms.[84] However, the effect of nitrates was short, and major side effects such as hypotension and headache are to be expected from this approach. At least in theory, another approach might be to aim at increasing nitric oxide-induced cGMP levels to promote smooth-muscle cell relaxation. Sildenafil is an inhibitor of phosphodiesterase type 5, an enzyme involved in the inactivation of cGMP, causing smooth-muscle cell relaxation. In a cross-over placebo-controlled barostat study involving 10 healthy volunteers, pretreatment with 50 mg of sildenafil considerably increased postprandial gastric volume.[85] So far, no studies on patients with functional dyspepsia have been reported, but several case reports claimed favourable responses in patients with diabetic gastropathy, although it remains unclear whether the effect involved an influence on impaired accommodation.[86]

As 5-HT receptors are involved in the accommodation reflex, different strategies to act on this pathway have been tested. Short-term pretreatment with paroxetine, a selective serotonin reuptake inhibitor, enhanced gastric accommodation to a meal in healthy volunteers,[43] but has not been formally evaluated in patients with functional dyspepsia. A SPECT study could not demonstrate an effect of the selective serotonin reuptake inhibitor escitalopram on accommodation.[87] In line with animal studies that suggest involvement of a 5-HT_1-like receptor, sumatriptan, a 5-$HT_{1B/1D}$ receptor agonist used as a treatment in migraine, was shown to relax the stomach in the fasting state and postprandially in healthy patients.[88] In acute studies, similar effects were obtained in patients with functional dyspepsia with impaired accommodation, where this was associated with a decrease in meal-induced satiety.[7] However, subsequent studies showed that the drug fails to relax the stomach in patients with acute-onset functional dyspepsia,[75] and that intranasal administration of the drug only produced a slight increase in fundic volume in healthy volunteers lasting for a short time, probably owing to a different bioavailability.[89] Because of the costs related to its use, the subcutaneous route of administration, the risk of vascular side effects and the lack of appropriate safety studies for long-term use, this class of drugs cannot be used in the treatment of functional dyspepsia at present.

5-HT_4 receptor agonists may enhance gastric accommodation through the activation of presynaptic receptors. Cisapride was shown to enhance gastric accommodation in healthy volunteers.[48] Cisapride was withdrawn from the market because of issues of cardiac safety.[90] Tegaserod is a 5-HT_4 agonist without cardiac safety issues, used in the treatment of constipation-predominant irritable bowel syndrome. A 1-week pretreatment with tegaserod 6 mg twice daily enhanced preprandial and postprandial gastric volumes in healthy volunteers.[49] As mentioned before, the 5-HT_3 agonist MKC-733 induced gastric relaxation in healthy

Table 3 Overview of studies that reported on the prevalence and symptom associations of impaired gastric accommodation in patients with post-surgical upper gastrointestinal disorders

Author	Patients	n	Technique	Difference from health	Assocation with symptom pattern
Vu [77]	Post-fundoplication dyspepsia	12	Gastric barostat	Impaired accommodation as a group	Not done
Vu [74]	Pre-fundoplication and post-fundoplication	12	Gastric barostat	Impaired accommodation compared with pre-fundoplication	Associated with postprandial fullness
Lindeboom [79]	Post-fundoplication dyspepsia	28	Gastric barostat	Impaired accommodation in partial and complete fundoplication	Associated with postprandial fullness
Bouras [14]	Post-fundoplication dyspepsia	15	SPECT imaging	Impaired accommodation as a group	Not done
Bredenoord [62]	Post-fundoplication dyspepsia	37	SPECT imaging	Impaired accommodation in 44%	None
Scheffer [80]	Post-fundoplication dyspepsia	18	Ultrasound	Impaired accommodation in a subgroup	Associated with dyspeptic symptoms
Le Blanc-Louvry [81]	Distal gastrectomy	16	Gastric barostat	Impaired accommodation in a subgroup	Associated with dyspeptic symptoms

SPECT, single-photon emission computed tomography.

volunteers, but it is unclear whether this was partly mediated through the occurrence of nausea.[50]

An alternative way to promote gastric accommodation is to inhibit the action of excitatory motor neurones, which are mainly cholinergic. Besides the use of muscarinic antagonism, this can be achieved by activation of presynaptic inhibitory α_2 or 5-HT_{1A} receptors. In a small placebo-controlled cross-over study, buspirone, a 5-HT_{1A} receptor agonist with anxiolytic properties, at doses of 10 mg thrice daily, considerably enhanced gastric accommodation to a meal in functional dyspepsia and this was accompanied by considerable improvement in dyspepsia symptom severity scores.[91] The most frequent side effects of buspirone include headache, dizziness, insomnia and nervousness. A newly developed 5-HT_{1A} receptor agonist R-137696 was shown to dose-dependently induce relaxation of the proximal stomach in humans.[92] A subsequent small placebo-controlled 4-week multicentre study failed to show any effect of the drug on gastric compliance and accommodation, suggesting that desensitisation to the drug effect had occurred within this time frame.[93] Presynaptic α_2 receptors are present on intrinsic cholinergic nerve endings in the stomach.[37] Acute studies showed that activation by the α_2 agonist clonidine resulted in considerable gastric relaxation and enhanced gastric accommodation after meal ingestion. Additionally, clonidine also has some visceral antinociceptive properties, with decreased perception of gastric distension occurring at doses that do not affect gastric tone.[35] Hypotension and rebound hypertension are possible.

CONCLUSION

Several observations suggest that impaired gastric accommodation is involved in symptom generation in functional dyspepsia and potentially in other disorders such as diabetic gastropathy or post-fundoplication dyspepsia. The symptom most closely associated with impaired gastric accommodation is early satiety, and weight loss may be a long-term consequence. The cause of impaired accommodation remains to be established, but studies on functional dyspepsia suggest a role for post-infectious nitrergic nerve dysfunction. Although the gastric barostat remains the gold standard, less invasive approaches to assess postprandial relaxation, including volumetric methods and drink tests, are under additional evaluation. A progressive unravelling of the physiology of the gastric accommodation reflex has identified several targets for pharmacotherapeutic correction of impaired accommodation. Presently, clinically convincing studies are still lacking and controlled trials in patients with impaired accommodation are eagerly awaited.

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