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Review

Recent Advances in the Pathophysiology and Treatment of Gastroparesis

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Gastroparesis is a clinical disorder characterized by upper gastrointestinal symptoms related with delayed gastric emptying of solids and liquids in the absence of mechanical obstruction. Diabetes mellitus has been the most common cause of gastroparesis and idiopathic gastroparesis also accounts for a third of all chronic cases. The most important mechanisms of gastroparesis, as understood to date, are loss of expression of neuronal nitric oxide synthase and loss of the interstitial cells of Cajal. However, the pathogenesis of gastroparesis is poorly understood. There have been several studies on specific molecules related to the pathogenesis of gastroparesis. Additionally, the Gastroparesis Clinical Research Consortium of the National Institutes of Health has achieved several promising results regarding the pathophysiology of gastroparesis. As the progress in the pathophysiology of gastroparesis has been made, a promising new drug therapy has been found. The pathophysiology and drug therapy of gastroparesis are focused in this review. Until now, the real-world medication options for treatment of gastroparesis are limited. However, it is expected to be substantially improved as the pathophysiology of gastroparesis is elucidated.
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Key Words
Diabetes mellitus; Etiology; Gastroparesis; Physiopathology; Therapy

Introduction

Gastroparesis is a condition that delays gastric emptying of solids and liquids in cases where there is no mechanical obstruction.[1] A variety of mechanisms, such as vagal nerve dysfunction, sympathetic nerve dysfunction, damage to the enteric nerve system, as well as hyperglycemia itself, impede gastrointestinal (GI) function. The most common disease associated with gastroparesis is diabetes although idiopathic cases are just as frequent if not more so. Rarer associations include postsurgical conditions, collagen vascular diseases, and neurological disorders.[2] Diabetic gastroparesis (DG), first reported in patients with type I diabetes in 1958, has a significantly negative effect on quality of life and is a chronic and often debilitating disorder.[3] Because the symptoms of DG and gastric emptying are as yet poorly correlated, its epidemiology is difficult to assess. Fifty percent of patients with type I diabetes of 10 years' duration had abnormal gastric emptying;[4] 13% of Korean diabetic patients had dyspepsia.[5] A population-based survey of 15,000 adults showed

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that 11 to 18% of gastroparesis patients had upper GI symptoms.[6] A population-based epidemiologic study from Olmsted County, using a combined definition of delayed gastric emptying and symptoms, found a prevalence of 24.2 per 100,000 inhabitants and an incidence of 6.3 per 100,000 persons per year, which indicates that gastroparesis is an uncommon condition in the community compared with tertiary hospital settings.[7] Another population-based cohort study confirmed the relative uncommonness of gastroparesis, showing cumulative proportions, over a 10-year time period, of 5.2% for type 1 DM, 1.0% for type 2 DM and 0.2% among controls.[8] However, a different study estimated that 1.8% of community residents had delayed gastric emptying whereas the prevalence of diagnosed gastroparesis was low (0.02%).[9] On the basis of these reults, the authors suggested that known gastroparesis is likely just the tip of a large hidden iceberg. In other words, the prevalence of gastroparesis undoubtedly is higher than reported, due to the fact that many gastroparesis sufferers remain undiagnosed. In addition, as the incidence rate of diabetes rises, so too will that of gastroparesis. Recently, progress in the pathophysiology of gastroparesis has been made, and a promising new drug therapy has been found. These are the subjects of the present review.

Pathogenesis

The pathogenesis of gastroparesis is poorly understood. Gastric emptying entails interaction among smooth muscle, enteric and extrinsic autonomic nerves, and the interstitial cells of Cajal (ICC).[10] Traditionally, autonomic neuropathy was considered to be the main mechanism of DG, because it was assumed to be a symptom related to diabetic neuropathy. Vagus nerve dysfunction reduces pyloric relaxation and thereby prohibits passage of foods, which are effects similar to the consequences of subdiaphragmatic vagotomy.[11] However, some patients have gastroparesis without evidence of generalized autonomic neuropathy,[12] although these patients may have more subtle and specific disturbances in gastric autonomic innervation. Much recent attention has been focused on intrinsic nerves in the stomach. The most important mechanisms of gastroparesis, as understood to date, are loss of expression of neuronal nitric oxide synthase (nNOS) and loss of ICC.[13]

Inhibitory nitrergic neurons in the gastric wall secret nitric oxide (NO). NO is an important cellular signaling molecule; its various functions include relaxation of smooth muscle and, consequently, accommodation of the fundus and relaxation of pylorus.[14] NO is synthesized by nNOS, which is expressed in the enteric nerve. The major functionality of nNOS is control of the muscle tone of the lower esophageal sphincter, the pylorus, the sphincter of Oddi, and the anus.[15] Additionally, it modulates the accommodative reflex of the fundus and the peristaltic reflex of the small intestine.[16] The molecular change of enteric nervous system effects gastric emptying delay through depletion of nNOS. Animal models showed that there is a loss of function of NOS neurons both in spontaneously diabetic rats and streptozotocin diabetic rats.[17,18] DG was correlated with the loss of nNOS mRNA and protein.[19] Recent studies suggest that hyperlipidemia, shown to impair gastric motility functions in low-density lipoprotein receptor knockout mice and apolipoprotein E knockout mice, is a potential cause of developing gastroparesis.[20,21] Although the expression of nNOS is decreased in DG, the loss of nNOS itself does not predict delayed gastric emptying.[22] In a study on female diabetic rats, gastric relaxation was better correlated with the level of the dimerised form of nNOS than with the absolute nNOS level.[23] This means that the absolute nNOS level is less important than post-translational modification of nNOS. Furthermore, it can explain why the incidence of gastroparesis is significantly higher among young women.[24]

Loss of nNOS, significantly, is related to the loss of ICC in the stomach. ICC generate a slow wave in the stomach and transmit it to smooth muscle, thereby enabling phasic contraction. Loss of ICC in fact is one of the main histological findings in DG. Specifically, ICC were greatly reduced in the distal stomach in diabetic mice manifesting delayed gastric emptying, impaired electrical pacemaking, and reduced motor neurotransmission.[25] Another study found that myenteric-ganglia-related ICC were decreased in 50-70% of all $nNOS^{-/-}$ mice and further, the ICC derived from knockout mice were increased by NO donors.[26] However, the increase of NO by sildenafil did not help humans.[27]

There have been several studies on specific molecules related to the pathogenesis of gastroparesis. One study investigated ultrastructural fibroblast-like cells (FLCs), which are interstitial cells existing near the human small intestine and in close proximity to ICC, but different from them.[28] FLC growth is stimulated by platelet-derived growth factor receptor alpha (PDGFRα) in human gastric smooth muscle. However, a very recent investigation observed no differences in the distribution, morphology, or overall numbers of PDGFRα -immunoreactive FLC relative to ICC in gastroparesis patients.[29] Further studies elucidating the role of

FLC in human GI function are needed. Recent work has emphasized the potential role of immune cells in the pathophysiology of gastroparesis. One such study reported increases in the immunoreactivity of CD45 (a general hematopoietic cell marker) and CD68 (a selective marker for macrophages) for both patients with DG and idiopathic gastroparesis (IG).[30] Another study found that in DG patients, heme oxygenase-2 (HO-2), which, like nNOS, is an endogenous gaseous neuromodulator inhibiting GI motility, was decreased.[31] Choi et al[22] suggested that the decrease of heme oxygenase-1, which is cytoprotective against oxidative injury, increases oxidative stress and induces DG in non-obese diabetic mice. Another study confirmed that increased heme oxygenase-1 expression prevents delayed gastric emptying in diabetic mice.[32] Additionally, it has been reported that the decrease of tetrahydrobiopterin, a major cofactor in nNOS activity and NO synthesis, causes delayed gastric emptying in female rats.[33]

Human studies remain insufficient, though one showed that among 14 patients with refractory gastroparesis, 5 showed an absence of ICC and 9 had an ICC/normal-cell ratio of 20%.[34] Another study found that the ICC density, along with the expression of nNOS and substance P, was decreased in the gastric antrum of diabetic patients, which might explain dysmotility symptoms observed in diabetic patients.[35] Loss of ICC in both human and murine DG, in any case, has been verified.[25,35,36] The Ca^{2+}-activated Cl^- channels are vital for smooth muscle contraction and secretion. ICC selectively express Ano1, which is related to classical Ca^{2+}-activated Cl^- currents.[37] Ano1, for determinations of the ICC distribution in the human and mouse GI tracts, is a better selective marker of ICC than mast cells.[38] A recent investigation involving DG patients and Ano1 splicing showed the changes Ano1 expression brought on DG; Ano1, therefore, could be a new molecular target in terms of both the etiologic and therapeutic aspects.[39]

In diabetic patients, attention also has to be paid to the association between hyperglycemia and gastric emptying. Hyperglycemia stimulates pyloric contraction and inhibits antral contraction, thereby delaying the gastric emptying.[40] Advanced glycation end-products (AGEs), produced during hyperglycemia, can inhibit the expression of intestinal nNOS in vitro.[41] Generation of AGEs in diabetic rat results in loss of intestinal nNOS expression, thereby inhibitors of AGEs might be useful in the treatment of GI complications of diabetes.[42]

The Gastroparesis Clinical Research Consortium (GPCRC) of the National Institutes of Health (NIH) has achieved several promising results regarding the pathophysiology of gastroparesis. An investigation of the cellular changes in patients with DG (n = 20) and IG (n = 20), referencing full-thickness biopsy specimens, discovered that 83% of patients with gastroparesis had histological abnormalities such as loss of ICC and increase in CD45 and CD68 immunoreactivity. There were no differences between the 2 disorders, except that most of the cases of nNOS-expression reduction were found in patients with IG (40%; DG patients: 20%). Connective-tissue stroma was significantly increased in both disorders, according to the results of electron microscopy.[30] However, Faussone-Pellegrini et al[43] suggested that the difference between the 2 disorders lies in the ultrastructural changes in ICC and nerves. They determined that a thickened basal lamina around smooth muscle cells and nerves was the distinguishing feature of DG, whereas in the case of IG, fibrosis around the nerves was dispositive. They also found that damage to ICC and nerves was more severe in IG. They documented the contrasting ultrastructural changes between the disorders, from which results potential target therapies might be developed.[43] Grover et al. reported that ICC and enteric nerves were decreased in both disorders compared with healthy controls; however they did not correlate these findings with symptoms severity. Symptoms severity and nausea are related to myenteric immune infiltration in IG. Loss of ICC delays gastric emptying in DG, whereas in IG, these factors are unrelated.[44]

Treatment

Prokinetic agents are the mainstay of treatment, because they accelerate gastric emptying by increasing antral contractility and improving the effectiveness of gastropyloroduodenal motility. Their other actions include centrally mediated antiemetic effects, proximal gastric relaxation, suppression of visceral sensation, and improvement in gastric dysrhythmias.[45] Metoclopramide, a prokinetic and antinauseant agent approved by the Food and Drug Administration (FDA) for treatment of DG, is a potent central and peripheral dopamine receptor antagonist. The FDA recommends only short-term treatment (4-12 weeks), as metoclopramide crosses the blood/brain barrier, producing CNS side effects such as anxiety, agitation, somnolence, insomnia, and intractable tardive dyskinesia.[46,47] Older people and women should be especially cautious in its use. Domperidone, another dopamine (D2) antagonist, enhances stomach contraction by antagonizing the peripheral receptors in the stomach.[48] Its utility is similar to that of metoclopramide, but without the CNS side effects, and is

Table. Recent Studies on New Prokinetics for Gastroparesis

Agent	Published year	Mechanisms of action	Conclusion
Mitemcinal	McCallum et al,[51] 2007	A motilin agonist	Mitemcinal can induce a statistically significant response to treatment.
GSK962040	Sanger et al,[52] 2009	A selective motilin receptor agonist	GSK962040 selectively activates the motilin receptor.
TZP-101	Ejskjaer et al,[57] 2010	A synthetic, selective ghrelin receptor agonist	TZP-101 is safe, well-tolerated, and effective at acutely addressing several gastroparesis symptoms.
	Wo et al,[58] 2011	A synthetic, selective ghrelin receptor agonist	TZP-101 substantially reduces the frequency and severity of nausea, vomiting and overall gastroparesis symptoms.
TZP-102[a]	-	An orally administered ghrelin agonist	TZP-102 significantly improves in nausea, early satiety, postprandial fullness, and the total Gastroparesis Cardinal Symptom Index.[b]

[a]TZP-102 is under evaluation in a 12-week, phase 2b trial; [b]This result has come from a 4-week double-blind, placebo-controlled study.

widely available in most countries. Although the drug is not approved in the USA, the FDA makes it available for use via an investigational new drug application.[49] A recent study demonstrated that the effect of domperidone is associated with age and genetic polymorphisms in the potassium channel KCNH2 gene and the alpha1D adrenoceptor ADRA1D gene.[50] Erythromycin is a motilin receptor agonist that functions as a potent prokinetic agent. Unfortunately, tachyphlaxis appears to limit its benefits to short-term. The focus therefore has shifted to alternative motilides. Mitemcinal, a motilin agonist, enhanced gastric emptying in a randomized double-blind study on 106 patients with gastroparesis.[51] However, symptomatic improvement was no better than placebo. These and other studies on prokinetics suggests that simply enhancing gastric emptying may not provide the hoped therapeutic outcome and bring into question about the relationship between emptying and symptoms. Nevertheless, the quest for other prokinetics continues. GSK962040 is a small-molecule, selective motilin receptor agonist that stimulates GI motility in humans and rabbits.[52] The results of a phase II study on its single-dose safety, tolerability, and pharmacokinetics are anticipated. The serotonin type 4 (5-HT_4) receptor, with its location on the cholinergic nerve endings of interneurons and motor neurons, is a major target for enhancement of GI motility. However, there is no available data on the use of the serotonin 5-HT_4 receptor agonist prucalopride/TD-5108 and gastroparesis.

Ghrelin, synthesized in the endocrine cells of the gastric mucosa, stimulates growth hormone release, gastric motility and food intake. Ghrelin has antioxidant and anti-inflammatory effects,[53] and enhances gastric emptying in DG patients.[54] Specifically, TZP-101, a selective intravenously administered agonist has been the subject of keen interest. A report on a trial with healthy volunteers documented good safety profile[55] in enhancing gastric emptying and improving symptoms in DG. In 10 symptomatic diabetic patients (type 1, n = 7; type 2, n = 3), solid-meal half emptying was reduced by 20%, and postprandial fullness by 37%, after intravenous TZP-101 administration.[56] A double-blind, randomized and placebo-controlled study on TZP-101 showed that 80 μg/kg is the most effective as well as safe and well-tolerated dose.[57] In patients with severe nausea and vomiting, TZP-101 reduced the severity and frequency of both.[58] Additionally, an oral preparation, TZP-102, has been formulated, and a phase II study is in progress. A 4-week double-blind, placebo-controlled study demonstrated significant improvements in nausea, early satiety, postprandial fullness, and the total Gastroparesis Cardinal Symptom Index.[59] Table summarized the information from new prokinetics under evaluation.

Antiemetic drugs have been used successfully in clinical practice to treat the symptoms of gastroparesis in spite of insufficient scientific evidences. The most commonly used antiemetic drugs are phenothiazines such as prochlorperazine and thiethylperazine. They can be used in combination with prokinetic agents. Most standard antiemetic agents have no effect on gastric motor function.[60] Ondansetron, a 5-HT_3 receptor antagonist, is effective in controlling nausea and vomiting, but has not been shown to improve gastric emptying.[61] Mirtazapine is an antidepressant that is active on the 5-HT_3 receptor; it has been used for the treatment of nausea in patients with gastroparesis refractory to conventional prokinetic therapies.[62,63] Tricyclic antidepressants (TCAs) are efficacious in functional nausea and vomiting and irritable bowel syndrome.[64,65] In a retrospective review of 24 diabetic patients presenting with nausea and vomiting

and unresponsive to prokinetic therapy, 88% reported moderate symptom improvement with TCAs.[66] Tricyclic medications in low doses can reduce pain associated neuropathic pain.[67] This may also account for their beneficial effects in gastroparesis based on the hypothesis that the nausea in this condition results from a vagal sensory neuropathy. However, the actual mechanism is poorly understood. The available studies on TCAs considered only small numbers of patients, and were not randomized.[68] The NIH funded gastroparesis research consortium, GPCRC, has recently conduct a placebo controlled randomized trial of low dose nortriptyline in patients with idiopathic gastroparesis, and the results are eagerly awaited.

Gastric electrical stimulation (GES) is an alternative option for the treatment of medically refractory gastroparesis. The gastric stimulation device is implanted subcutaneously into the abdominal wall, and the electrodes are placed in the serosa. In fact, GES by short pulses and low energy (Enterra Therapy System, Medtronic, Minneapolis, MN, USA) has been approved as a therapeutic option by the US FDA for the treatment of diabetic and idiopathic etiologies of gastroparesis that are refractory to all medical management. Most published data has come from open-label studies, though a double-blind crossover design showed significantly decreased vomiting frequency and GI symptoms as well as improved quality of life in patients with severe gastroparesis.[69] Another crossover prospective study found that six weeks of GES therapy with Enterra significantly reduced vomiting and gastroparetic symptoms, and, after 12 months of GES, the subjective and objective parameters had improved compared with the baseline.[70] Meta-analysis also has suggested that high-frequency GES, on the basis of demonstrated substantial and significant improvement of symptoms and gastric emptying, is an effective and safe method for treating refractory gastroparesis.[71] There is some new research in this field as well. As an alternative to single-channel gastric pacing, which can normalize gastric dysryhthmia and improve gastric emptying in patients with gastroparesis, 2-channel gastric pacing can be used to normalize and enhance gastric slow-wave activity as well as accelerate gastric emptying safely in DG patients.[72] In 2005, a temporary GES technique showed rapid, significant, and sustained symptom improvement.[73] A more recent study showed that endoscopically implanted temporary GES can relieve gastroparesis symptoms and clinically predict a need for permanent GES.[74] Clinical-field use of GES devices should proceed cautiously and in accordance with important considerations, among which is the fact that some patients might develop implantation related infections.[75] Also, it is not a treatment option available for all medically refractory cases of gastroparesis; rather, there are several factors favorable to positive clinical response including (1) diabetic rather than idiopathic gastroparesis, (2) nausea/vomiting rather than abdominal pain as the primary symptom and (3) independence from narcotic analgesics prior to stimulator implantation.[76] Moreover, GES-implantation treatment has not been shown to be clearly superior to placebo for lack of control. Another problem is its high cost.

Conclusion

The real-world treatment options for gastroparesis are limited; however, it is expected that this situation will be substantially improved as the pathophysiology of gastroparesis comes to be better understood.

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