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Histological changes in diabetic gastroparesis

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Summary

Our understanding of the cellular abnormalities that lead to diabetic gastroparesis has evolved in concert with our increased understanding of the key cell types that regulate gastric physiology. We now know that several key cell types are affected by diabetes, leading to gastroparesis. These changes include abnormalities in the extrinsic innervation to the stomach, loss of key neurotransmitters at the level of the enteric nervous system, smooth muscle abnormalities, loss of interstitial cells of Cajal (ICC) and most recently changes in the macrophage population resident in the muscle wall. This chapter will review our current understanding with a focus on data from human studies when available.

Keywords

Interstitial cells of Cajal; gastric emptying; macrophages; enteric nerves; vagus; smooth muscle

Introduction

Our understanding of the cellular abnormalities that lead to diabetic gastroparesis has evolved in concert with our increased understanding of the key cell types that regulate gastric physiology. We now know that several key cell types are affected by diabetes, leading to gastroparesis. These changes include abnormalities in the extrinsic innervation to the stomach, loss of key neurotransmitters at the level of the enteric nervous system, smooth muscle abnormalities, loss of interstitial cells of Cajal (ICC) and most recently changes in the macrophage population resident in the muscle wall. This chapter will review our current understanding with a focus on data from human studies when available.

Extrinsic innervation in diabetic gastroparesis

Diabetic gastroparesis was first described by Dr. Kassander in 1958. After the initial description, investigations centered on the role of abnormalities in the extrinsic innervation

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to the stomach in the causation of diabetic gastroparesis. Both sympathetic and parasympathetic abnormalities were described with increasing evidence over the years for a defect in the vagal innervation to the stomach and indeed the upper gastrointestinal tract[1]. Damage to the vagal innervation of the stomach was shown by a sham feeding test which takes advantage of the innervation of the pancreas by the vagus. During the cephalic phase of food digestion, stimulation of the vagus results in release of pancreatic polypeptide. Patients with advanced diabetic gastroparesis have a blunted pancreatic polypeptide response as well as reduced gastric secretion in response to sham feeding suggesting vagus nerve dysfunction[2, 3]. Abnormalities in vagal innervation of the stomach may contribute to the motor abnormalities seen, including abnormal relaxation of the pylorus. However the initial histological report in 1988[4] in 16 diabetic patients of which 5 had gastroparesis failed to show any histological defects. In retrospect this was likely due to the small n value and the limited techniques available at that time (hematoxylin and eosin, Gomori trichrome, luxol-fast blue, and Holmes' silver stains). In subsequent animal and human studies abnormalities have been described. These include abnormalities at a histological level both in myelinated and unmyelinated nerve fibers of the vagus nerve[1, 5] which were also reported to be smaller in the Bio Breeding (BB) rat model of spontaneous diabetes. Sympathetic nervous system abnormalities have also been described with changes in the axons and dendrites within the prevertebral sympathetic ganglia.

Smooth muscle

In the past, relatively rarely, patients with severe symptoms of diabetic gastroparesis, often unremitting nausea and vomiting, had gastrectomies as a treatment of their symptoms with variable results. An examination of the resected tissue showed evidence of smooth muscle degeneration and fibrosis, with eosinophilic inclusion bodies[6]. In a study of 2 patients with severe diabetic gastroparesis one had no fibrosis while the other showed fibrosis with the use of a trichrome stain[7]. A more recent study from full thickness biopsies at the time of gastric stimulation implantation did not show significant fibrosis[8] suggesting that the fibrosis seen in the earlier studies may represent a more end stage aspect of the disease.

Non obese diabetic (NOD) mice are an often used model of diabetic gastroparesis. NOD mice develop a leukocytic infiltrate of the pancreatic islets resulting in a type 1 type of diabetes. Studies on organotypic cultures from the stomachs of these mice has shown a loss of smooth muscle derived IGF-1[9] suggesting that smooth muscle function may be impaired before the onset of overt fibrosis.

Enteric nerves

After the initial discovery that extrinsic nervous system defects are present in diabetic gastroparesis, work on animal models found that the intrinsic nervous system was also affected. Initial work was carried out in rats. Rats made diabetic with streptozotocin[10] showed an increase in VIP-like immunoreactivity in nerve cell bodies and nerve fibers with no change in substance P. These changes were reversible with insulin administration[11]. The same rat model also showed evidence for altered enteric nerve ion transport[12]. A study using[13] spontaneously non-insulin-dependent diabetic rats demonstrated depolarization of

the smooth muscle membrane potential, an attenuation of non-adrenergic non-cholinergic inhibitory neurotransmission and a reduction in reactivity of adrenoceptors to noradrenaline. Work carried out using spontaneously diabetic biobreeding/Worcester (BB/W) rats showed that number of nitric oxide synthase (NOS) containing neurons in the gastric myenteric plexus and NOS activity were significantly reduced in diabetic BB/W rats, suggesting a nitrergic defect[14]. Similar findings were found in streptozotocin-induced diabetes in rats. Of note, gastric relaxation correlates better with the dimerized form of nNOS rather than absolute nNOS levels suggesting post-translational modification is important and in fact may be more relevant than overall quantification of nNOS[15]. Work in mice has similarly shown loss of nNOS expression in diabetes, both in the stomach[16] as well as other regions of the gastrointestinal tract[17].

Studies in humans have also highlighted the role of nNOS in diabetic gastroenteropathy. Work using human colon showed that enteric nerves cells with enhanced apoptosis and loss of peripherin, nNOS, NPY, and ChAT neurons with evidence for increased oxidative stress[18]. A study on male patients with gastric cancer, with and without type 2 diabetes showed reduced interstitial cells of Cajal (ICC), nNOS, and SP in the antrum of patients with diabetes[4]. In a study on 16 patients with diabetic gastroparesis 6 had reduced myenteric nerve cell bodies[19]. The study from the gastroparesis clinical research consortium (GpCRC) funded by the NIH examined tissue from the gastric body of20 patients with diabetic gastroparesis. Interestingly, overall there was no statistical difference in PGP9.5 (a marker of neurons) or nNOS containing neurons between patients with diabetic gastroparesis and controls although 4 patients did have a greater than25% decrease in nNOS containing neurons. At the electron microscopy level several patients had empty secretory vesicles in nerve terminals suggesting altered neurotransmission[20]. These data suggest that, given the relative sparing of enteric neurons, the enteric neuronal abnormalities seen, such as loss of nNOS expression may be more reversible than initially thought. We need to understand the regulation of the expression of nNOS and other key proteins in order to target their expression.

Interstitial cells of Cajal

In the early 1990s several studies reported on the requirement for an intact ICC network for normal gastrointestinal motility. Loss of ICC has been associated with several diseases including chronic intestinal pseudo-obstruction and slow transit constipation[21]. ICC generate an electric event known as the slow wave that sets the smooth muscle membrane potential and thereby regulating contractility. ICC are also involved in cholinergic and nitrergic neurotransmission with enteric nerves innervating both ICC and smooth muscle[22] and in mechanotransduction. Loss of ICC is the most common abnormality seen in diabetic gastroparesis. First reported in mouse models of diabetic gastroparesis[23], it soon became apparent that loss of ICC is also seen in humans[24]. The GpCRC study that reported on enteric nerve changes also looked at numbers of ICC and found that 50% of patients with diabetic gastroparesis had a significant decrease in the number of ICC[8]. At an ultrastructural level it was apparent that even when the number of ICC was not reduced there were significant changes to ICC and the surrounding stroma with 95% (19/20) of patient tissue examined showing ICC abnormalities and a thick stroma separating ICC from smooth

muscle cells[20] and nerves. A protein key to the electrical function of ICC is Ano-1, a calcium-activated chloride channel. Ano1 expression is altered in diabetic gastroparesis[25] and patients with diabetic gastroparesis have different variants of Ano-1 compared to diabetic patients without gastroparesis. These variants were associated with altered electrical activity of the ion channel suggesting that even when structurally normal, the function of ICC may be impaired in diabetic gastroparesis[26].

Loss of ICC impairs gastric function. Loss of ICC in diabetic gastroparesis is associated with disruption of the generation and propagation of electrical slow waves resulting in gastric dysrhythmias[27]. A decrease in frequency of the slow wave is referred to as bradygastria, with tachygastria referring to an increase in frequency. These changes are often transient and both have been reported in diabetic gastroparesis with symptoms related to meals[28, 29]. Refractory diabetic gastroparesis was found to correlate with both loss of ICC and an abnormal electrogastrogram. Animal studies have shown that it is not only the absolute number of ICC that leads to electrical dysrhythmias as a patchy disruption of ICC networks may also result in reentrant tachy-arrhythmias as well as loss of generation of the slow waves resulting in brady-arrhythmias. A recent study reported severe ICC loss in 12 out of 34 patients with refractory diabetic gastroparesis and correlated loss of ICC with an abnormal electrogastrogram showing tachygastria[30]. Loss of ICC is correlated with development of delayed gastric emptying with a more severe loss of ICC associated with a more severe delay in gastric emptying[31].

Fibroblast-like cells

A recent addition to our understanding of the cell types required for normal gastric motor function are a type of interstitial cell with fibroblast-like ultrastructure that is referred to as “fibroblast-like cells (FLC)”[32, 33]. These cells were shown to have gap junctions with smooth muscle cells and to be close to but distinct from ICC[34, 35]. A distinct feature of this cell type is the high expression of SK3 (small conductance calcium-activated potassium channels type 3) channels and of PDGFRα[36–38]. FLC are involved in enteric neurotransmission, specifically purinergic neurotransmission[39–41]. Given that FLC, like ICC are involved in enteric neurotransmission and ICC are decreased in diabetic gastroparesis the question was soon raised on whether FLC are also altered in diabetic gastroparesis. The one study that addressed this question did not find any difference in the number or distribution of FLC in diabetic gastroparesis[42] suggesting that diabetic gastroparesis is not due to structural changes to this cell type.

Immune cells

Type 1 diabetes is associated with an immune related destruction of pancreatic islets. This has led to the suggestion that diabetic gastroparesis may have an inflammatory component. Indeed in a study on antral biopsies from 14 patients with diabetic gastroparesis a mild lymphocytic infiltrate was found in the myenteric plexus in 6 of the 14 patients[19]. These findings were not borne out in a subsequent study comparing gastric body tissue from patients with diabetes and diabetic gastroparesis. Immune cells in the circular muscle layer were studied using antibodies to CD45, CD206, iNOS, and the putative human macrophage

markers HAM56, CD68, and EMR1. Overall no difference in CD45 positive cells was found between the 2 groups but an association was found between CD206 positive cells and ICC numbers[43]. These data suggest that the type of infiltrate may be more relevant than the absolute number of immune cells (see below).

Macrophages

Mouse models of diabetes have strongly suggested a critical role for macrophages in the development of delayed gastric emptying. Diabetes is associated with increased oxidative stress. In NOD mice, development of diabetes was accompanied by up regulation of heme oxygenase 1 (HO1) in macrophages[16]. The muscle wall of the stomach is populated with resident macrophages that have recently been described to play a role in neuronally mediated regulation of contractility[44]. In response to various stimuli, mouse macrophages polarize to either the classically activated proinflammatory M1 macrophage or the anti-inflammatory alternatively activated M2 (CD206 positive) macrophage. Development of diabetes was associated with up-regulation of HO1 in CD206 positive M2 macrophages. Onset of delayed gastric emptying did not alter the number of macrophages, but there was selective loss of CD206 positive/HO1 positive M2 macrophages and an increase in M1 macrophages[45]. Treatment of diabetic mice with delayed gastric emptying with hemin or IL10 to upregulate HO1 resulted in repopulation of the stomach wall with M2 macrophages and normalization of gastric emptying. These data suggest that HO1 positive M2 macrophages are required for prevention of diabetes-induced delayed gastric emptying and that M1 macrophages are associated with development of delayed gastric emptying. HO1 breaks down heme into iron, biliverdin and carbon monoxide. Diabetic NOD mice with delayed gastric emptying treated with carbon monoxide inhalation at low levels (100 ppm) showed reduced oxidative stress, restored Kit (a marker of ICC) expression and normalized the delayed gastric emptying suggesting that carbon monoxide mediates, at least in part, the effects of HO1[46].

A role for macrophages in the development of diabetic macrophages appears to also hold true for humans. In a study from the GpCRC, full thickness gastric body biopsies were studied from non-diabetic controls, diabetic controls, and patients with diabetic gastroparesis. The number of CD206 positive cells correlated with the number of ICC suggesting that in humans, like mice, CD206 positive macrophages may play a cytoprotective role in diabetes[43].

Summary/Discussion

A major issue with our current therapies for diabetic gastroparesis is that they are all symptom-based, including use of prokinetics[47–49]. While a prokinetic helps restore the synchronicity between delivery of food and hormone and peptide release, it does not target the underlying defects. To truly treat diabetic gastroparesis we need to develop disease modifying agents and to do so, we need to understand the mechanisms of disease better. We now know that there are several cell types affected in diabetic gastroparesis. These include extrinsic nerves, the enteric nervous system and ICC, with ICC loss being the most common cellular defect seen. Recent advances in our understanding of the role macrophages play in

the stomach wall and the role of activated macrophages in diabetic gastroparesis suggests that gastric macrophages may be central to the development of the diverse cellular damage that leads to gastroparesis. Sustained expression of HO1 by CD206 positive macrophages protects against the injurious effect of mediators released by M1 macrophages. Not every diabetic develops gastroparesis and the duration between the onset of diabetes and the onset of gastroparesis varies widely, with some patients developing the disease after only 3–4 years. This strongly suggests other factors, including genetics and epigenetics, may play a significant role in the polarization of macrophages and the increase in expression of HO1 and this is an area of high interest that will need further study. Understanding the role macrophages play in diabetic gastroparesis as the key cell type that underlies injury to other cell types would allow the development of a disease modifying strategy for treating diabetic gastroparesis with potential to markedly change how we currently manage diabetic gastroparesis.

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Key Points

Several key cell types are affected by diabetes leading to gastroparesis.

Diabetic gastroparesis is associated with damage to the extrinsic innervation to the stomach, loss of key neurotransmitters at the level of the enteric nervous system, smooth muscle abnormalities, loss of interstitial cells of Cajal (ICC) and changes in the macrophage population resident in the muscle wall

Macrophages appear to be a key cell type underlying injury to other cell types

Targeting macrophages may allow for the development of a disease modifying strategy for treating diabetic gastroparesis with the potential to markedly change how we currently manage diabetic gastroparesis.