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Endocrine regulation of gut function – a role for Glucagon-like peptide-1 in the pathophysiology of Irritable Bowel Syndrome.

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New Findings

Pathophysiological changes linked to Irritable Bowel Syndrome (IBS) include stress and immune activation, changes in gastrointestinal microbial and bile acids profiles and sensitisation of extrinsic and intrinsic gut neurons. This review explores the potential role for L-cells in these pathophysiological changes.
L-cells, which secrete glucagon-like peptide-1 (GLP-1) in response to nutrients, microbial factors, bile acids and short-chain fatty acids, may sense IBS-related changes in the luminal environment. Glucagon-like peptide 1 can act as a hormone, a paracrine factor or a neuromodulatory factor and through its actions on central or peripheral neurons, may play a role in gastrointestinal dysfunction.

Abstract

The prevalent and debilitating functional bowel disorder Irritable Bowel Syndrome (IBS), is characterized by symptoms which include abdominal pain, bloating, diarrhoea and/or constipation. The heterogeneity of IBS underscores a complex multifactorial pathophysiology, which is not completely understood, but involves dysfunction of the bidirectional signalling axis between the brain and the gut. This axis incorporates efferent and afferent branches of the autonomic nervous system, circulating endocrine hormones and immune factors, local paracrine and neurocrine factors and microbial metabolites. L-cells, which are electrically excitable biosensors embedded in the gastrointestinal epithelium, secrete glucagon-like peptide-1 (GLP-1) in response to nutrients in the small intestine. However, they appear to function differently more distally in the gastrointestinal tract, where they are activated by luminal factors including short-chain fatty acids, bile acids and microbial metabolic products, all of which are altered in IBS patients. GLP-1 can also interact with the hypothalamic-pituitary-adrenal stress axis and immune system, both of which are activated in IBS. Given that a GLP-1 mimetic has been found to alleviate acute pain symptoms in IBS patients, GLP-1 may be important in the manifestation of IBS symptoms. This review assessed the current knowledge on the role of GLP-1 in IBS pathophysiology and its potential role as a signal transducer in the microbiome–gut-brain signalling axis.

Irritable Bowel Syndrome.

IBS is a common and debilitating gastrointestinal (GI) disorder characterized by episodic exacerbations of a cluster of symptoms, which include heightened central pain sensitivity, bloating, diarrhoea and/or constipation (Enck *et al.*, 2016). This functional bowel disorder has a high prevalence and may significantly impair the quality of life of sufferers. Diagnosis is symptoms-based, and this is made more difficult by the degree of heterogeneity in the patient population. Risk factors for the development of this multifactorial disorder include being female (Lovell & Ford, 2012), having a family history of IBS (Saito & Talley, 2008), childhood trauma (Dinan *et al.*, 2010) and/or prior GI infection (Thabane *et al.*, 2007; Schwille-Kiuntke *et al.*, 2011). Consistent with a role for immune activation in this disorder, elevated numbers of mucosal T-cells, lymphocytes and mast cells (Chadwick *et al.*, 2002) are noted in IBS patients. Circulating pro-inflammatory cytokine profiles are also different in IBS patients as compared to healthy controls (Dinan *et al.*, 2006; Liebregts *et al.*, 2007). However, pre-morbid psychological conditions increase the likelihood of developing IBS following infectious gastroenteritis (Thabane *et al.*, 2007). Co-morbidity with mood disorders, such as depression and anxiety, is more common in IBS patients (Fond *et al.*, 2014) and a maladaptive stress response, mediated by the hypothalamic-pituitary-adrenal (HPA) axis, is key to the initiation, severity and persistence of IBS-associated symptom flare-ups (Dinan *et al.*, 2006). Indeed, psychosocial and infection-related stresses are additional considerations in comprehending the chronic relapsing pattern that typifies IBS symptoms (O'Malley *et al.*, 2011; O'Malley, 2015). Given that glucagon-like peptide (GLP)-1 mimetics have been found to alleviate acute pain symptoms in IBS patients (Hellstrom *et al.*, 2009; Li *et al.*, 2017), GLP-1 may be important in the manifestation of IBS symptoms. This review has assessed the evidence currently available to support a role for GLP-1 - secreting L-cells in the pathophysiology of Irritable Bowel Syndrome (IBS). Moreover, its potential importance as a signal transducer pivotal to cross-barrier communication, from the luminal microbiome to the gut and on to the brain, was reviewed.

Symptom manifestation in subtypes of IBS patients.

IBS symptoms manifest as bloating, visceral pain and altered bowel habit. Subtypes include diarrhoea-predominant (IBS-D), constipation-predominant (IBS-C) or alternating/mixed phenotypes (IBS-A/IBS-M) (Longstreth *et al.*, 2006). The distribution of these subtypes varies depending on diagnostic criteria used, populations evaluated and the geographical location of the study (Guilera *et al.*, 2005; Hungin *et al.*, 2005; Kibune Nagasako *et al.*, 2016). The Rome symptom-based criteria, which are based on evidence and expert-informed consensus, are used to diagnose functional bowel disorders including IBS. The criteria are subsequently subjected to validation in the field. Miscommunication in the bi-directional brain-gut signalling axis is implicated in bowel dysfunction, however, the enteric nervous system (ENS) has recently been proposed as a potential organic cause of IBS. The submucosal neuronal plexus regulates absorption and secretion from the mucosal epithelium, intramural blood flow and neuroimmune interactions in the GI tract. The myenteric plexus is an important neuronal regulator of contractile activity. Although we are gaining a better understanding of the pathophysiology underlying this disorder, IBS patients continue to be defined according to their predominant stool pattern, as no clear changes in symptom severity or mood disorders can differentiate between subtypes (Rey de Castro *et al.*, 2015). Current treatment is based on targeting of specific bowel symptoms.

Post-prandial exacerbation of IBS symptoms.

A commonly-reported feature of IBS is post-prandial exacerbation of GI symptoms. Many IBS patients experience diarrhoea, flatus, bloating and abdominal pain following ingestion of a meal. Particular food-types, such as milk, pulses, wheat and apples, which are rich sources of poorly absorbed short-chain carbohydrates, are associated with IBS symptom exacerbation (Ragnarsson & Bodemar, 1998; Morcos *et al.*, 2009; Cabre, 2010), an effect that is unrelated to IBS subtype or GI-specific anxiety, depression, body mass index or age (Bohn *et al.*, 2013). Mechanistically, the bacterial fermentation of lactose, fructose and sorbitol, fructo-oligosaccharides, galacto-oligosaccharides and incompletely absorbed sugar polyols such as sorbitol

and mannitol (termed FODMAPs) results in gas build-up, which distends the gut leading to abdominal pain and abnormal motility in patients. Furthermore, unabsorbed food may result in osmotic movement of water into the gut lumen resulting in diarrhoea. Diets which restrict FODMAP-rich foods have had some success in managing IBS symptoms (Staudacher *et al.*, 2012; Halmos *et al.*, 2014; Marsh *et al.*, 2016), although not everyone supports this conclusion (Rao *et al.*, 2015; Peters *et al.*, 2016). A low FODMAP dietary intervention suppresses production of total short-chain fatty acids (SCFAs) (Hustoft *et al.*, 2017), which are increased in IBS patients and linked to symptoms such as visceral hypersensitivity and altered contractile activity (Ford *et al.*, 2014). GLP-1-secreting enteroendocrine L-cells embedded in the epithelium of the distal gut, where the highest density of microbes reside, express receptors for SCFAs (Tolhurst *et al.*, 2012).

Intestinal GLP-1 secreting L-cells.

GLP-1 has a well-characterised role in stimulating pancreatic insulin synthesis, but also has additional functions as a gut regulatory compound (Hellstrom, 2011). GLP-1, a 30 amino-acid peptide derived from the post-translational processing of preproglucagon, is secreted basolaterally by L-cells. L-cells are electrically-excitable biosensors (Chimerel *et al.*, 2014), which sense the arrival of nutrients, such as glucose and amino acids, in the small intestine (Elliott *et al.*, 1993; Drucker *et al.*, 2017). Chemosensory activation of L-cells results in membrane depolarisation, action potential firing and the opening of voltage-gated calcium channels. This subsequently causes enhanced rates of vesicular exocytosis on the basolateral surface of the epithelial barrier (Reimann & Gribble, 2016). This is consistent with a peak in circulating GLP-1 within fifteen minutes of food intake. However, despite the reduced probability of nutrients being present there, the abundance of GLP-1-secreting L-cells increases towards the distal end of the GI tract (Steinert *et al.*, 2017). Moreover, the time it would take for nutrients to reach the distal gut exceeds the circulating GLP-1 peak. This suggests that L-cells in the small intestine and the colon have differing functions in terms of the moieties they sense (Greiner & Backhed, 2016). Glucose and amino acids activate small intestinal L-cells, whereas colonic L-

cells expressing receptors for SCFAs and bile acids (Reimann *et al.*, 2008; Tolhurst *et al.*, 2012). Given its short half-life in the circulation, it is likely that GLP-1, in addition to its classical endocrine function, is also likely to work through paracrine mechanisms.

GLP-1 modulates gastrointestinal function.

IBS is characterised by altered motility and absorpto-secretory functions, which may be centrally or peripherally orchestrated. A placebo-controlled double-blind cross-over clinical trial, which administered a synthetic GLP-1 analogue, ROSE-010 to a mixed group of 99 IBS patients, reported anti-spasmodic and pain-relieving properties (Hellstrom *et al.*, 2009). ROSE-010 appeared to be most effective in IBS-A subtypes in this trial. A more recent study investigated the potential mechanism underlying the beneficial effects of the GLP-1 mimetic on abdominal pain in IBS-C patients. Decreased circulating GLP-1 levels and decreased mucosal expression of GLP-1Rs was associated with constipation-predominant IBS. Moreover, this correlated with the severity of abdominal pain (Li *et al.*, 2017). The authors suggested that lower GLP-1 led to loss of the pro-kinetic effects of GLP-1 in the colon (Camilleri *et al.*, 2012), resulting in constipation and abdominal pain (Li *et al.*, 2017). Consistent with the supposition that decreased GLP-1 contributes to pain-related symptoms, circulating levels of bioactive GLP-1 were also decreased in a rat model of visceral pain sensitivity (Yang *et al.*, 2014).

Biologically active GLP-1 has a high affinity for GLP-1 receptors (Reimann *et al.*, 2008), which are expressed in vagal ganglia (Richards *et al.*, 2014) and in brain regions such as the nucleus tractus solitarius, the ventrolateral medulla (Lim *et al.*, 2009) and the hypothalamus (Richards *et al.*, 2014). GLP-1 receptors have also been detected in both myenteric and submucosal neuronal plexi in the GI tract (Amato *et al.*, 2010; Kedees *et al.*, 2013), the neural regulators of gut contractile activity and absorpto-secretory function, respectively. In the upper part of the GI tract, GLP-1 appears to have a mollifying effect on gut function. Using vagal neural pathways, GLP-1 has been shown to delay gastric emptying (Imeryuz *et al.*, 1997) and small

intestinal secretion (Baldassano *et al.*, 2011) and motility (Nauck *et al.*, 2011). GLP-1 also inhibits post-prandial motility in the antrum, jejunum and duodenum through direct actions on myenteric neurons (Halim *et al.*, 2018). In contrast to the inhibitory effects in the proximal GI tract, central administration of GLP-1 resulted in increased colonic transit, also through vagal signalling (Nakade *et al.*, 2007). Differences in sensory function and the basolateral secretory products of L-cells in the small and large intestine may underlie the contrasting effects of GLP-1 on GI function in proximal and distal regions of the gut (Greiner & Backhed, 2016). Alternatively, the GLP-1 may be important in the divergent symptomology associated with IBS subtypes. Indeed, in a rat model of IBS, intestinal GLP-1 receptor expression and circulating GLP-1 was elevated in IBS-C as compared to IBS-D (Chen *et al.*, 2013).

GLP-1 mediated modification of the stress axis

Crosstalk between GLP-1 and the stress hormone, corticotrophin-releasing factor (CRF), which initiates the HPA signalling axis and is a central tenet in bowel dysfunction in IBS pathology (O'Malley *et al.*, 2010a; o'malley *et al.*, 2010b; Larauche *et al.*, 2012), is an additional consideration in the actions of GLP-1. Sustained activation of the HPA axis in IBS patients (Dinan *et al.*, 2006) is associated with problematic GI symptoms such as abdominal pain and the urge to defecate (Kennedy *et al.*, 2014). GLP-1 can feed into this system through a reciprocal interaction between GLP-1 and the HPA axis. GLP-1 stimulates the HPA axis through CRF neurons (Larsen *et al.*, 1997), and stress-induced defecation is attenuated by antagonists of both CRF (Martinez *et al.*, 2004) and GLP-1 (Gulpinar *et al.*, 2000). Moreover, GLP-1 accelerates stress-induced changes in colonic motility though vagal signalling (Nakade *et al.*, 2007).

L-cells as chemosensors for an altered luminal environment in IBS?

Many studies have demonstrated that changes in the gut microbiome, including reduced bacterial diversity and increased temporal instability, are factors worthy of consideration in understanding IBS pathophysiology (Salem *et al.*, 2018). Evidence supporting the importance of the microbiome in functional bowel disorders comes

from studies demonstrating the benefits of specific commensal strains in alleviating IBS symptoms (Tiequn *et al.*, 2015; Yuan *et al.*, 2017). Moreover, microbial dysbiosis in IBS (Liu *et al.*, 2017) has been implicated in enhanced gut permeability (Simren *et al.*, 2013), visceral hypersensitivity (Crouzet *et al.*, 2013; Valdez-Morales *et al.*, 2013) and altered GI motility (Cani *et al.*, 2013; Gudsoorkar & Quigley, 2014). The GI epithelium is an innate immune barrier isolating the external environment of the gut lumen from the internal milieu. The intestinal barrier is comprised of a mucus coated epithelial monolayer whose integrity is maintained by tight junction proteins, which regulate the paracellular movement of luminal molecules. Beneath the epithelial layer, intrinsic and extrinsic neurons relay neural information both within the GI tract but also between the gut and the central nervous system (CNS). However, evidence that this communication system extends beyond the epithelial barrier to the microbially-dominated environment of the gut lumen, has resulted in it being referred to as the microbiota-gut-brain axis (Forsythe *et al.*, 2014; Bonaz *et al.*, 2018; Martin *et al.*, 2018).

Previous research has demonstrated that luminal bacteria stimulate synthesis of serotonin in colonic enterochromaffin cells, which in turn modulates host GI physiology (Yano *et al.*, 2015), hence we know that inter-kingdom communication across an intact barrier is facilitated by some subtypes of epithelial cells. However, GLP-1-secreting L-cells may similarly act as cellular transducers to convey information about the luminal environment to the host. Evidence to support modification of L-cell signalling by microbial factors include increased secretion of GLP-1 in rodents with a modified microbiome following antibiotic treatment (Hwang *et al.*, 2015) or altered dietary fibre intake (Tolhurst *et al.*, 2012). Furthermore, specific commensal strains increased intestinal and circulating GLP-1 (Stenman *et al.*, 2015; Aoki *et al.*, 2017). Somewhat counter-intuitively, germ-free mice also exhibit increased serum GLP-1 (Selwyn *et al.*, 2015), although another study found that germ-free mice exhibited a strong state of GLP-1 resistance, with impaired GLP-1 evoked gut-brain signalling and enteric nervous system function (Grasset *et al.*, 2017). GLP-1 levels also increase following dietary supplementation

with fermentable fibre (Massimino *et al.*, 1998), which is converted to SCFAs (acetate, propionate and butyrate), molecules known to activate L-cells and induce GLP-1 secretion (Tolhurst *et al.*, 2012; Nohr *et al.*, 2013). L-cells also express receptors for bile acids (Brighton *et al.*, 2015) and the bile acid pool is altered in IBS patients (Mosinska *et al.*, 2018).

The neuromodulatory actions of GLP-1.

Beneath the epithelium lies a complex network of intrinsic and extrinsic neurons, including spinal nerves and the vagus nerve, which innervates most of the GI tract and is comprised of between 70 and 80% afferent nerves (Prechtl & Powley, 1990). The vagus has been implicated in the actions of specific probiotic strains on central cognitive processes (Bercik *et al.*, 2011; Bravo *et al.*, 2011; Perez-Burgos *et al.*, 2013), and some bacterial products are capable of signalling across the mucosal barrier to stimulate vagal nerve firing (Perez-Burgos *et al.*, 2013; Buckley & O'Malley, 2018). Lipophilic molecules, such as SCFAs can directly activate afferent terminals (Lal *et al.*, 2001) but many luminal proteins are large complex protein microbial molecules (Forsythe *et al.*, 2014), which cannot passively cross the barrier. Sensory nerve fibres terminate below the epithelial layer and do not reach through to the lumen. Although infiltration of bacterial products via a leaky epithelium may occur in disorders such as IBS, physiological mechanism of informing the CNS about the luminal environment are also likely to exist. Indeed, as previously mentioned, microbiota can induce modification of gut function through the stimulation of serotonin secretion (Yano *et al.*, 2015). L-cells are also activated by the bacterial metabolite indole, which inhibits voltage-gated K^+ channels, resulting in cellular depolarisation and sustained secretion of GLP-1 (Chimerel *et al.*, 2014). Evidence of direct, physical contact between a pseudopod-like elongation of L-cells and efferent and afferent nerves (Bohorquez *et al.*, 2015) indicates a neurally-mediated mechanism by which L-cell activation could modify GI function. Indeed, GLP-1 has direct neurostimulatory actions on the vagus (McKee & Quigley, 1993), through activation of GLP-1 receptors on vagal afferents (Nakagawa *et al.*, 2004; Ronveaux *et al.*, 2014). Thus, L-cells are appropriately positioned to facilitate cross-barrier

signalling from the gut lumen to the host peripheral nervous system and on to the CNS. Although neuroendocrine signalling has been implicated in IBS (El-Salhy *et al.*, 2012), it has yet to be conclusively demonstrated that the chemosensory actions of L-cells detecting changes in the luminal micro-environment contribute to altered bowel function.

Conclusions

IBS is a prevalent and debilitating functional bowel disorder that is characterised by increased sensitivity to visceral pain and altered bowel habit. In addition to alterations in immune, endocrine and neural signalling, dysfunctional microbiome-gut-brain communication is also implicated in the manifestation of IBS symptoms. GLP-1-secreting L-cells are scattered throughout the GI tract with increasing density towards the distal end of the gut. In addition to its well-characterised incretin effects, GLP-1 is recognised to act as a gut regulatory compound with different effects in the proximal and distal regions of the gut. L-cells basolaterally secrete GLP-1 in response to a variety of molecules including SCFAs, bile acids and bacterial products, which are known to be altered in IBS patients. Moreover, afferent nerves on the basolateral side of the epithelium are sensitive to the neurostimulatory actions of GLP-1 and GLP-1 increases colonic transit and alleviates visceral pain sensitivity in IBS (figure 1).

Whilst clinical studies have been pivotal in revealing the potential therapeutic actions of GLP-1 analogues in IBS-related abdominal pain, further translational studies are needed to determine if this treatment is subtype-specific. Furthermore, the impact of this treatment on bowel habit needs to be determined. The complexity of the luminal environment and the multitude of receptors expressed by L-cells mean that more basic research is needed, both in human tissue and in animal models to unequivocally support a role for GLP-1-secreting L-cells as cross-barrier signal transducers contributing to altered bowel function.

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Competing interests.

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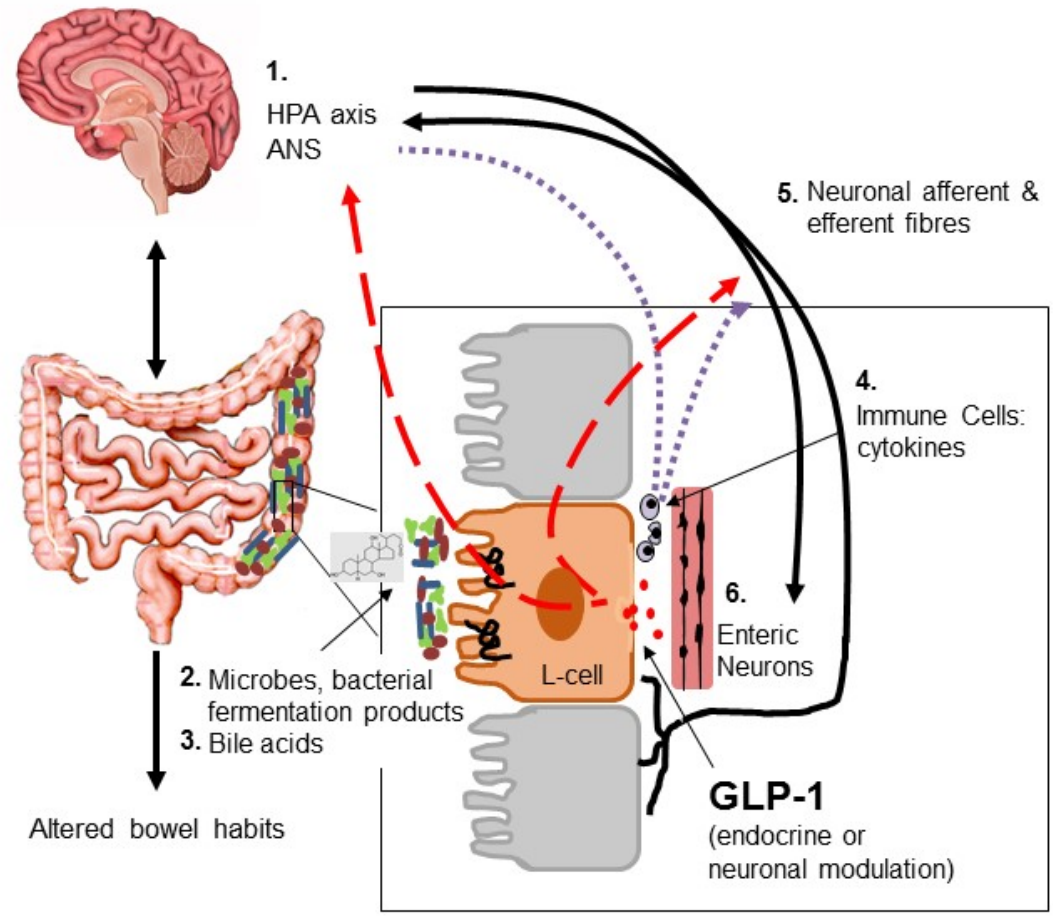
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Figure 1



<u>IBS pathophysiology</u>:

1. **Activation of the HPA stress axis**
2. **Microbial dysbiosis**
3. **Altered bile acid profiles**
4. **Activation of immune response**
5. **Sensitisation of afferent neurons**
6. **Altered enteric neuronal function**

Figure legends

Figure 1: The role of L-cells in IBS pathophysiology

The diagram illustrates the bidirectional brain-gut signalling axis, which is dysfunctional in irritable bowel syndrome (IBS). Pathophysiological changes in IBS that have been linked to Glucagon-like peptide-1 (GLP-1)-secreting L-cells are listed. Potential mechanisms by which GLP-1 may modify gastrointestinal dysfunction are illustrated.