Gonadotropin-Releasing Hormone and Its Physiological and Pathophysiological Roles in Relation to the Structure and Function of the Gastrointestinal Tract

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Key Words
Diabetes · Functional bowel disorders · Gonadotropin-releasing hormone · Gastrointestinal dysmotility · Irritable bowel syndrome · Luteinizing hormone · Progonadoliberin-2

Abstract

Background: Gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) are involved in the reproductive cycle and regulate the secretion of sex steroids from the gonads. In mammals, GnRH1 is secreted as a hormone from the hypothalamus, whereas both GnRH1 and GnRH2 are present as neuropeptides in a variety of tissues. This review describes the role of GnRH in the gastrointestinal tract. Summary: GnRH1, GnRH2, and LH receptors in humans and rats, and GnRH receptors in rats, have been described in the gastrointestinal tract, where they affect motility, gastric and hormone secretion, and cell proliferation. GnRH analogs are clinically used in the treatment of sex hormone-dependent diseases, i.e., endometriosis and malignancies, and as pretreatments for in vitro fertilization. Severe gastrointestinal dysmotility has been shown to develop in some women after such treatment, along with a reduction in the number of enteric neurons and autoantibodies against GnRH. Consequently, a rat model of enteric neurodegeneration has been developed based on the administration of the GnRH analog buserelin. Serum IgM antibodies against GnRH1, the GnRH2 precursor progonadoliberin-2, and the GnRH receptor have also been described in patients with irritable bowel syndrome and dysmotility, as well as in patients with gastrointestinal disorders associated with diabetes mellitus, posterior laryngitis, and primary Sjögren’s syndrome, although no treatments using GnRH analogs have been administered.

Conclusion: GnRH and receptors for GnRH and LH are present in the human and rat gastrointestinal tract. Treatment with GnRH analogs may induce severe dysmotility, and a rat mod-
el of enteric neurodegeneration has been developed based on stimulation by the GnRH analog buserelin. Autoantibodies against GnRH and its receptor are found in a subgroup of patients with functional bowel disorders and dysmotility, independent of treatment with GnRH analogs.

Introduction

Gonadotropin-releasing hormone (GnRH) is secreted in a pulsatile fashion from hypothalamic neurons into the hypophyseal portal circulation, where GnRH receptors on the anterior pituitary are activated, resulting in a subsequent secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [1, 2]. FSH and LH target the gonads and regulate the secretion of steroid hormones [3]. As GnRH has a half-life of a few minutes and is secreted into the hypophyseal portal circulation, the levels of this hormone are not measurable in peripheral blood [2]. In vertebrates, 23 native decapeptides of GnRH exist. Changes in the amino acids at molecular positions 5–8 differentiate the decapeptides from each other [4]. In mammals, two types of GnRH have been found: GnRH1 and GnRH2. GnRH1 is the peptide secreted from the hypothalamus, whereas both types have neuroendocrine, paracrine, and autocrine functions in a wide range of organs, as well as neurotransmitter/neuromodulatory roles in the central and peripheral nervous systems [4]. The GnRH receptor is a G-protein-coupled receptor with 7 transmembrane domains [5]. Several different receptors have been described, but only the GnRH1 receptor is expressed in mammals [3], and both GnRH1 and GnRH2 are able to stimulate the GnRH1 receptor [4]. A variety of different GnRH analogs are used in clinical settings. Initially, GnRH analogs stimulate the release of FSH and LH, but after approximately 10 days of chronic treatment, the receptor is desensitized and the secretion of FSH and LH declines [6]. This leads to chemical castration and makes GnRH agonists useful in the treatment of sex hormone-dependent neoplasms in clinical settings, where sex hormones are considered to exacerbate medical conditions [2]. In recent years, there has been a growing interest for the role of GnRH in the regulation of the gastrointestinal tract.

Search Methods

The term ‘GnRH and gastrointestinal tract’ was used to search for research publications in PubMed during October 2015. All English language papers were reviewed, independent of publication year. In addition, to describe the mechanisms of LH effects on the ovaries, the terms ‘LH and apoptosis’ and ‘LH and cell death’ were used.

Expression of GnRH and Gonadotropins in the Gastrointestinal Tract

mRNA for both GnRH1 and GnRH2 can be detected via polymerase chain reaction analysis in the human gastrointestinal tract [7]. The cellular localization of GnRH has been described in about half of the submucosal and myenteric neurons along the human gastrointestinal tract [8, 9] (table 1). In one study, GnRH was not detected via immunocytochemistry in the rat gastrointestinal tract in vivo [10], and neither the GnRH receptor, FSH, the FSH receptor, or LH were detected via polymerase chain reaction or immunocytochemistry in rat or human gastrointestinal tracts [7]. In contrast, other groups have observed GnRH and GnRH receptor immunoreactivity in rat enteric neurons, smooth muscle cells, and epithelial parietal cells.
and still more have found GnRH receptor mRNA in enteric neurons [15]. LH receptors have been described on enteric neurons in both rats and humans [7, 10, 16, 17] (table 1). The LH receptor belongs to the rhodopsin/β2-adrenergic receptor-like family A of the G-protein-coupled receptor group and is predominantly expressed in the gonads [18]. The receptor binds both LH and human chorionic gonadotropin (hCG) with a high affinity and has been found to also be expressed outside the gonads, e.g., in the brain, urinary bladder, and retina [19].

### Effects of GnRH on Normal Gastrointestinal Tissue

GnRH and its analog, alarelin, have been shown to inhibit gastric secretion and gastrin release in rats and dogs [14, 20]. These same peptides, as well as GnRH antagonists, have been shown to inhibit cell proliferation in the gastric epithelium and in gastric smooth muscle cells [13, 21]. Another in vitro study failed to show any effects of the GnRH analog, buserelin, or of continuous LH stimulation on rat enteric neuron survival. However, intermittent stimulation with LH led to reduced neuronal survival [17]. When studying jejunal motility in rats, migrating myoelectric complexes (MMCs) were frequently found during fasted states and were found less frequently postprandially. After ovariectomy, rats administered low-dose treatments of the GnRH agonist, leuprolide, had typical fasted-state patterns of jejunal motility, without MMCs. When given leuprolide at higher doses, the fed-state pattern was inhibited, and MMCs occurred at a frequency similar to that observed in fasted control rats. Thus, reproductive hormones have a significant effect on gastrointestinal motility [22].

### Effects of GnRH in Gastrointestinal Diseases

Knowledge about the antiproliferative effects of GnRH has led to the use of GnRH analogs in cancer cell survival, and these analogs induce apoptosis and inhibit cell proliferation in several cancer cell lines, e.g., colon cancer [23]. No dichotomy exists for GnRH agonists and antagonists in gastric epithelial cells or tumor cells, and both are used to inhibit cell proliferation [13, 21, 23, 24]. Furthermore, antibodies against GnRH have also been widely used to inhibit cancer cell proliferation [25].

### Table 1. The expression of GnRH, GnRH receptor, and LH receptor in the gastrointestinal tract in rats and humans

<table>
<thead>
<tr>
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<th>GnRH1 mRNA</th>
<th>GnRH2 mRNA</th>
<th>GnRH mRNA</th>
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<td>Huang [15], 1996</td>
<td>Huang [12], 2001</td>
<td>Sand [7], 2013</td>
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<td>Smooth muscle</td>
<td>Chen [13], 2004</td>
<td>Chen [13], 2004</td>
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<td>Epithelial cells</td>
<td>Huang [12], 2001</td>
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<td>Ohlsson [8], 2007</td>
<td>Sand [7], 2013</td>
<td>Hammar [16], 2012</td>
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Numbers in brackets are the related references that describe the expression of the protein. Immunocytochem. = Immunocytochemistry.
Leuprolide has been considered for several years in the treatment of irritable bowel syndrome (IBS). In a randomized, double-blind, placebo-controlled study of patients with moderate to severe functional bowel disease, three intramuscular injections of leuprolide over 12 weeks, which each delivered a continuous low dose of leuprolide that lasted for 1 month, led to improved scores in symptoms including nausea, vomiting, bloating, abdominal pain, early satiety, and overall symptoms [26]. Continued treatment for an additional 40 weeks led to even more striking and significant improvements of the symptoms [27]. When expanding these studies to include a multicenter study, a significant improvement in nausea and abdominal pain was still found [28]. A similar study in women with menstrual cycle-related IBS was performed, in which leuprolide treatment improved all gastrointestinal symptoms and the subjects’ overall quality of life [29].

Two hypotheses to explain the observed effects of leuprolide in IBS have been proposed [26–29]. The first is that GnRH binds to specific receptors on the pituitary and controls the secretion of gonadotropins [1]. Laboratory studies have shown that LH and ovarian products, such as progesterone and hCG, are neural antagonists of gastrointestinal motility [30, 31]. Because of the continuous stimulation by leuprolide, the hypothalamic-pituitary-gonadal axis is downregulated and the secretion of gonadotropins and gonadal products is inhibited [3, 32]. The second hypothesis states that by acting on GnRH receptors on myenteric neurons [15], leuprolide is an effective neural modulator that can act by regulating voltage-gated calcium channels and the endoplasmic reticulum calcium pump, resulting in the movement and control of intracellular and extracellular calcium [33]. This assumption is supported by the fact that the peripheral administration of leuprolide has been shown to restore gastrointestinal motor function both in a woman receiving a transplant who developed chronic intestinal pseudoobstruction after a viral infection [34] and in female ovariectomized rats [22], whereas the administration of the same drug into the intraventricular system of the rat brain had little effect, if any [35]. GnRH analogs have so far not been used in clinical settings due to the risks of long-term treatment, which include menopausal symptoms and the development of osteoporosis as the most serious side effects [36].

**Antibody Formation against GnRH and Gonadotropins**

An enzyme-linked immunosorbent assay (ELISA) was developed to measure GnRH antibodies in 1 patient with severe gastrointestinal dysmotility secondary to repeated treatment with buserelin during in vitro fertilization (IVF). Several measurements over time showed that the serum antibody titer was elevated after each administration of buserelin and then declined over time [8]. This ELISA has since then been further developed, and cut-off levels have been adjusted [37–40] (table 2). Elevated levels of IgM antibodies against GnRH1 have been found in patients with diabetes mellitus, gastrointestinal dysmotility, IBS, posterior laryngitis, and primary Sjögren’s syndrome, independent of treatment with GnRH analogs. This is in contrast to patients with celiac disease, inflammatory bowel disease (IBD), microscopic colitis, and scleroderma, who express antibodies to the same extent as control subjects [37–39, 41–44]. Furthermore, IgM antibodies against GnRH receptors have been found in patients with dysmotility, IBS, and primary Sjögren’s syndrome [43, 44], and IgM antibodies against progonadoliberin-2, the precursor of GnRH2 [45], have been found in patients with diabetes mellitus, dysmotility, and IBS [44]. When considering all dysmotility patients who were examined via full-thickness biopsies of the bowel wall, those with a reduced number of GnRH-containing neurons were found to have IgM antibodies against GnRH1 in their serum, independent of GnRH treatment [9] (table 2). No autoantibodies against GnRH or its receptor have been found in patients with functional dyspepsia (unpublished data).
IgA antibodies against GnRH or its receptor have only rarely been found [39, 40]. IgG antibodies were found to be expressed at the same level in patients with gastrointestinal disorders, diabetes, or primary Sjögren’s syndrome as in control subjects when the ELISA methods were further developed [9, 38, 43, 44]. Patients with diabetes or primary Sjögren’s syndrome did not express antibodies against either LH or the LH receptor [43, 44].

Gastrointestinal Dysmotility and Antibody Formation after GnRH Treatment

Severe gastrointestinal dysmotility has been described in some women after treatment with GnRH analogs [8, 9, 46]. Histopathological examinations of these patients have revealed a reduction in the total number of enteric neurons and a reduced percentage of GnRH-expressing enteric neurons, along with the presence of serum IgM antibodies against GnRH1 and/or progonadoliberin-2 [8, 9, 46]. In a previous study, LH receptor-containing neurons were downregulated in the single patient examined for LH receptor expression, but no antibodies against LH or the LH receptor were found in any patients [46].

Consecutive patients (124 women) at an infertility clinic were examined in relation to gastrointestinal symptoms before and after buserelin treatment. Prior to the start of IVF, nausea and vomiting was more common in patients than in control subjects. Treatment with buserelin led to a significantly greater occurrence of intestinal symptoms, including constipation, nausea, and vomiting, which resulted in an impaired psychological well-being and had a negative influence on daily life. These patients also had an increased tendency for abdominal pain and bloating compared to before the treatment [40]. Five years later, the patients had increased abdominal pain but improved psychological well-being compared with that before the IVF treatment. Fifteen percent of the patients had developed IBS or had exacerbated symptoms, but none had developed severe dysmotility [40]. The patients had already expressed IgM antibodies against the GnRH receptor and IgG antibodies against LH and its receptor prior to treatment. Their serum antibody levels were unaffected by the buserelin treatment, and no antibodies against buserelin were identified [40].
In a cohort of women with endometriosis (n = 109), patients with a history of GnRH treatment had more severe abdominal pain than patients who had never been treated with GnRH analogs [47]. Antibody development does not appear to be obligatory after GnRH treatment, but it does appear to occur more frequently in patients who develop complications in relation to the treatment [48, 49]. Although no specific pathophysiological mechanisms have been confirmed, polymorphisms of the LH receptor gene and concomitant endometriosis have been suggested as triggering factors for developing gastrointestinal dysmotility in response to GnRH analogs [46].

**Rat Model of Buserelin-Induced Enteric Neurodegeneration**

An experimental model of GnRH-induced enteric neuropathy has been developed [10]. It involves 4 repeated sessions of buserelin treatment, with 1 session consisting of 5 days of daily 20-μg subcutaneous injections, with 3 weeks of recovery between each session. This treatment resulted in a 50% reduction in the number of enteric neurons throughout the gastrointestinal tract [10]. This effect was observed in both submucosal and myenteric neurons, although it was most evident in the myenteric neurons and was more pronounced in the distal regions than in the proximal regions of the gastrointestinal tract. Elevated serum levels of estradiol after buserelin treatment along with the secondary synchronization of the hormonal cycle and thickened uterine muscle layers suggest that elevated FSH and LH secretion may be involved in the observed neurotoxic effects [10, 50]. In addition, a reduction in the relative number of LH receptor-containing neurons was observed, which was proceeded by an increased expression of activated caspase-3 [10].

In the colon, a subclassification of neuronal populations showed an increase in the relative number of neurons expressing corticotropin-releasing factor (CRF) in the submucosal neurons and an absolute increase in the amount of CRF-containing myenteric neurons [51]. Apart from a tendency for an increase in the relative number of somatostatin-expressing neurons, the relative numbers of neurons expressing calcitonin gene-related peptides, cocaine- and amphetamine-related transcripts, galanin, gastrin-releasing peptides, neuropeptide Y, nitric oxide synthase, substance P, vasoactive intestinal peptide (VIP), and the vesicular acetylcholine transporter were unaffected [50].

Lower levels of Enterobacteriaceae in the colon were observed after buserelin treatment, whereas the amount and diversity of gut microbiota were unaffected [51]. Although severe neuropathic effects were observed with this treatment, no effects on body weight or the morphological characteristics of the bowel wall were observed [10, 50, 51]. The mucosal, submucosal, and muscular layers showed no signs of inflammation when the rats were euthanized after 4 buserelin treatment sessions. However, signs of ganglioneuritis were apparent and became more pronounced after 4 treatment sessions than they were after 3 sessions [52]. No inflammatory or permeability biomarkers were detected in the serum or plasma after treatment [10, 50]. When examining the functional consequences, the gastrointestinal transit time, galactose absorption, basal intestinal permeability, and stress response behaviors were unaffected. The only measurable, objective findings were decreased fecal weight, increased fecal fat content, and an inability to increase small intestinal permeability in response to carbachol stimulation [50, 51].
Discussion

The main effects of GnRH on the gastrointestinal tract are the modulation of gastrointestinal motility and gastric secretion and the inhibition of cell proliferation. GnRH treatment may lead to severe dysmotility in a subgroup of women, and intermittent treatment with GnRH analogs in rat results in a model of enteric neuropathy. Elevated LH secretion along with the ensuing overstimulation of the LH receptors and increased apoptosis is hypothesized to be a cause of enteric neurodegeneration. IgM antibodies against GnRH1, progonadoliberin-2, and GnRH receptors may be present in a subgroup of patients with functional bowel disorders and dysmotility, both in idiopathic forms and when associated with diabetes mellitus, posterior laryngitis, primary Sjögren’s syndrome, or GnRH treatment.

The mode of action by GnRH or its analogs on the gastrointestinal tract are mostly unknown. Although GnRH receptors have not been found in the gastrointestinal tract in all studies [7], they may still be present, as has been described by others [11–15]. GnRH analogs stimulate the anterior pituitary, resulting in elevated LH secretion along with the stimulation of LH receptors and elevated steroidal sex hormone secretion [1–3, 50]. The harmful effects evoked in the gastrointestinal tract could be mediated by this route because LH receptors are found in the gastrointestinal tract in humans and rats [7, 10, 16, 17], and they are downregulated following GnRH stimulation [10]. Elevated serum levels of estradiol following buserelin treatment along with the secondary synchronization of hormonal cycles and a thickened uterine muscle layer [50] confirm the presence of elevated FSH and LH secretion in a rat model [10].

LH receptors are present in both the genital organs and the gastrointestinal tract [7, 10, 16–18], and this could be a plausible explanation for the observed association between digestive tract dysfunction and genital organ diseases in women [47, 53–55]. The high prevalence of LH receptor polymorphism in patients who develop severe dysmotility after GnRH treatment further points to a central role of the LH receptor in gastrointestinal function [46]. Future research should focus on explaining the interaction between GnRH and LH receptors in the bowel wall and the mechanisms underlying GnRH-induced neurodegeneration. Intermittent stimulation with GnRH in vivo is harmful to the gastrointestinal tract [8–10, 46, 50, 51], whereas continuous GnRH treatment has the opposite effect [26–29]. These contradictory results may be due to very different hormonal effects in response to the hyperstimulation of FSH and LH secretion after intermittent GnRH stimulation and the downregulation of hormonal levels after continuous GnRH stimulation [1, 2, 6, 50]. In support of this idea, intermittent LH stimulation in vitro reduced rat neuronal survival when compared to GnRH and continuous LH stimulation [17]. This strengthens the hypothesis that intermittent LH stimulation is a pathophysiological factor responsible for GnRH-induced enteric neuropathy.

Differences in cell proliferation may be explained by different experimental study designs that used varying exposure times to ligands and varying ligand concentrations. Furthermore, because cell cultures have been performed without the ability to test both agonists and antagonists in the same trial, the mechanisms are not fully explained. The absence of a dichotomy between GnRH agonists and antagonists suggests that mechanisms other than the postulated effect on GnRH receptors may be involved, e.g., some receptors may be expressed in cancer cells but not found in normal cells [13, 21, 23, 24]. For comparison, stimulation of the LH receptors on human ovarian granulosa cells lead to the secretion of several peptides, e.g., estradiol, progesterone, pituitary adenylate cyclase-activating peptide, VIP, and amphiregulin [56, 57]. Both pituitary adenylate cyclase-activating peptide and VIP influence apoptosis and caspase-3 activation [56]. hCG stimulation of granulosa cells increases the concentration of cAMP, which induces apoptosis in a variety of cell types and may explain the 50% increase in apoptosis observed in human granulosa cells [57]. Most of the effects evoked via LH receptor
stimulation seem to be mediated through cAMP/protein kinase A, although a dramatic change was also observed in gene transcripts coding for steroidogenic enzymes, cytoskeletal proteins, and several signaling molecules coding for pro- and antiapoptotic processes [58].

In addition, a downregulation of LH receptors has been shown to be accompanied by decreased levels of apoptosis [59]. Similarly, the relative number of activated caspase-3 immunoreactive enteric neurons has been shown to be increased prior to neuronal loss in a GnRH-induced rat model of neuropathy [10].

The histopathological findings related to buserelin administration are similar in humans and rats, showing neuronal loss and/or ganglionitis with an intact mucosa and submucosa [8–10, 46, 52]. Still, functional studies in rats have not revealed overt dysfunction, although as much as 50% of the enteric neurons have been shown to be lost [50, 51]. The increased fecal fat content is likely to be related to maldigestion/malabsorption of fat, which requires intact neuronal circuits [60], because the epithelia and mucosa were intact [10, 50, 52] and body weight was unaffected, which excludes differences in food intake as the cause [50, 51].

In addition, the gut microbiota content was unaffected [51]. Carbachol stimulation has been used in experimental trials to mimic the conditions that exist during a meal. The inability of the small intestine to increase its permeability in response to carbachol may be one mechanism that impairs the absorption capacity of the bowel [51].

The gut microbiota release lipopolysaccharides, which affect the enteric neurons via Toll-like receptor-4 [61]. The Enterobacteriaceae family is associated with inflammation, which is also the case for CRF. The inflammatory process associated with IBD is thought to be modulated by peripheral CRF receptors [62]. The expression of Toll-like receptor-4 on epithelial cells is increased by CRF receptor stimulation in vitro and after sham stress, which decreases the established tolerance of the epithelial barrier to Gram-negative bacteria and their products [63].

The decrease in Enterobacteriaceae in the colon associated with enteric neuropathy may be an effort to counteract the effects of concomitant increases in the levels of CRF [51] and other proinflammatory factors as a way to maintain normal levels of intestinal permeability [61–63].

The observation of increased abdominal pain in endometriosis patients in association with GnRH treatment suggests that more severe cases of endometriosis should be treated with GnRH analogs [47]. However, whether the use of analogs in this type of treatment would induce another type of abdominal pain, apart from endometriosis pain, must be further examined. In one study, 15% of the patients who underwent IVF exhibited a newly debuted case of IBS or an exacerbation of an already present case of IBS, and the IVF cohort experienced more abdominal pain 5 years after the treatment [40]. These patients were not examined by full-thickness biopsies, but theoretically, they could have developed some degree of neuronal loss, as was observed in the rat model. The preserved function in the rats, albeit with severe neuronal damage [50, 51], indicates a huge reserve capacity of the enteric nervous system.

Patients with functional bowel disorders may have enteric neuropathy, although it may not be detectable in routine clinical analyses and investigations. A moderate enteric neuropathy induced by IVF may make the patient more vulnerable to develop dysmotility when complications from diseases such as diabetes mellitus or neurological disorders occur later in life. The increased prevalence of gastroesophageal reflux in the long-term follow-up of IVF-induced pregnancies may represent similar occurrences of neuropathy [64].

The expression of serum antibodies against progonadoliberin-2, GnRH, or its receptor in some patients with idiopathic IBS may reflect enteric neuropathy in a subgroup of IBS patients [38, 44]. A recent study in IBS patients showed signs of neuroplasticity, with increased nerve fiber density and sprouting, which could reflect secondary changes in response to prior neurotoxicity [65]. The presence or absence of serum antibodies in patients may depend on the specific time at which blood samples are collected and the extent of neuronal damage. It
is possible that the antibodies are only measurable within a limited time period [8], which may explain the lack of an observed association between clinical findings and the presence of antibodies. Alternatively, antibody-positive IBS patients may constitute a separate etiological subgroup.

Treatment with GnRH analogs per se has not been shown to induce serum antibody expression in humans or rats [10, 40, 50]. Based on all of the studies in this field [8–10, 37, 38, 40–44, 46], our hypothesis is that antibodies reflect neuronal damage in a subgroup of patients and are not causal. Several antibodies against neuronal tissue have previously been described to occur subsequent to gut dysmotility [66]. IgM antibodies against GnRH1 and progonadoliberin-2 are the most interesting because they are expressed at some point in all patients with GnRH-induced dysmotility [8, 9, 46] and in a subgroup of patients with diabetes mellitus, dysmotility, and functional bowel diseases [37, 38, 41–44]. IgA and IgG antibodies or antibodies against LH or the LH receptor are of no clinical interest in patients with diabetes or in those with gastrointestinal complaints [9, 38, 39, 43, 44, 46]. The absence of GnRH antibodies in rats may depend on the absence of GnRH expression in rat enteric neurons [10, 50].

GnRH1 and GnRH2 are present in both the central and peripheral nervous system [3, 7, 45]. Autonomic neuropathy and gastrointestinal complaints are common in patients with diabetes mellitus and primary Sjögren’s syndrome [41, 43], and depression and affective disorders are common in patients with functional bowel diseases [67]. Future studies are needed to determine whether the measurable serum antibodies are related to central neuronal damage or to peripheral neuronal damage [37, 38, 41, 43, 44]. A moderate enteric neuropathy per se does not appear to induce anxiety or depression-like behavior in rats [51]. Thus, the affective disorders associated with functional bowel diseases [67] most likely depend on interactions between the gut and the brain.

Conclusion

GnRH is expressed in the small and large intestine in humans, and LH receptors are present in both human and rat gastrointestinal tracts. GnRH and GnRH receptors have also been found in the rat gastrointestinal tract in some studies, although their expression has not been verified by other studies.

The effect of GnRH on the gastrointestinal tract has not been well studied. However, GnRH analogs have been shown to modulate gastrointestinal motility in humans and rats and to influence gastrointestinal secretion in other animals. Cell proliferation is inhibited by GnRH, which has led to the treatment of malignancies using GnRH agonists and antagonists. Continuous treatment with GnRH analogs has been shown to be efficient in the treatment of functional bowel disorders, although the underlying mechanisms are still unknown. However, these compounds are not in clinical use as they are associated with severe side effects.

Intermittent treatment with GnRH analogs in women occasionally results in severe gastrointestinal dysmotility associated with enteric neuropathy, and intermittent treatment with the GnRH analog buserelin in rats has led to the development of a model of enteric neuropathy. The mechanism behind this enteric neuronal loss is assumed to depend on high LH levels along with an overstimulation of the LH receptor and the induction of apoptosis.

IgM antibodies against GnRH1, progonadoliberin-2, and GnRH receptor seem to be of importance in patients with diabetes mellitus, dysmotility, and functional bowel diseases, independent of GnRH treatment. This raises the question of whether enteric neuropathy may be the common etiology in these conditions. IgA and IgG antibodies and antibodies against LH or the LH receptor are currently of no clinical interest in relation to these gastrointestinal disorders.
Disclosure Statement

The author declares no financial or competing interests.

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