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Neurotrophic factors in enteric physiology and pathophysiology

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Abstract

Neurotrophic factors are traditionally recognized for their roles in differentiation, growth, and survival of specific neurons in the central and peripheral nervous system. Some neurotrophic factors are essential for the development and migration of the enteric nervous system along the fetal and post-natal gut. Over the last two decades, several non-developmental functions of neurotrophic factors have been characterized. In the adult gastrointestinal tract, neurotrophic factors regulate gut sensation, motility, epithelial barrier function, and protect enteric neurons and glial cells from damaging insults in the microenvironment of the gut. In this issue of *Neurogastroenterology and Motility*, Fu et al. demonstrate that brain-derived neurotrophic factor plays a role in the pathogenesis of distention-induced abdominal pain in bowel obstruction. In light of this interesting finding, this mini-review highlights some of the recent advances in understanding of the physiological and pathophysiological roles of neurotrophic factors in the adult gut.

Abbreviated abstract:

Neurotrophic factors play essential roles for the development and migration of the enteric nervous system along the gut during the early stage of life. Recent research suggests that neurotrophic factors are involved in regulation of gut function beyond the developmental stage, including visceral sensation, motility, epithelial barrier, neuroprotection, and neuroplasticity. These newly recognized functions may have therapeutic implications in bowel disorders and diseases.

Keywords

visceral sensitivity; motility; intestinal barrier; neuroprotection; neuroplasticity

1. INTRODUCTION

Neurotrophic factors include a wide variety of polypeptides that are essential for the development and survival of neurons in the central and peripheral nervous system. These

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COMPETING INTERESTS

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neurotrophic factors can be classified into three families based on their structures, receptors, and signaling pathways: the neurotrophin family, the glial cell-derived neurotrophic factor (GDNF) family, and the neuropoetic cytokines.¹ The neurotrophin family is the most fully characterized group, which includes nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5). Neurotrophins bind to two classes of transmembrane receptors to evoke distinct cellular responses, the neurotrophin receptor p75 for cell death and the tropomyosin receptor kinase (Trk) receptors for cell survival. These two classes of receptors also interact with each other for fine tuning and cross talk. All neurotrophins bind to p75 with relatively equal affinity; however, affinities to Trk receptors are different among neurotrophins. NGF is the preferred ligand for TrkA. BDNF and NT-4/5 bind to TrkB. NT-3 preferentially binds to TrkC, but can also bind to TrkA and TrkB under certain circumstances.¹ Three main intracellular signaling pathways could be activated by the Trk receptors, i.e. the mitogen-activated protein kinases (MAPK)/extracellular signal-regulated kinases (ERK) pathway, the phosphoinositide 3-kinase (PI3K)/Akt pathway, and the phospholipase C (PLC)- γ pathway. Each of the pathways mediates different but overlapping cellular responses.¹

Several neurotrophic factors are critical for the development of the enteric nervous system (ENS), such as GDNF, NT-3, ciliary neurotrophic factor (a neuropoetic cytokine), and leukemia inhibitory factor (a neuropoetic cytokine).² These neurotrophic factors and their cognate receptors exist not only in the fetal and post-natal gut, but also in the adult gut (Table 1).³⁻⁶ In addition to their roles in ENS development, neurotrophic factors have been recently recognized to influence many important functions in the adult gut, such as sensation, motility, epithelial barrier, neuroprotection, and neuroplasticity. In the current issue of *Neurogastroenterology and Motility*, Fu et al. demonstrated that BDNF played an important role in abdominal pain associated with bowel obstruction.⁷ Using a rat partial colon obstruction model, the authors showed that mechanical distention induced BDNF expression in the gut smooth muscle cells. BDNF acted on colon-projecting neurons in the dorsal root ganglia (DRG) to suppress the transient A-type K⁺ channel activity, which in turn increased membrane excitability of primary afferent neurons and resulted in visceral hypersensitivity.⁷ This mini-review put the findings by Fu's group in a broader perspective by providing an overview of recent discoveries on the roles of neurotrophic factors in enteric physiology and pathophysiology beyond the developmental stage.

2. NEUROTROPHIC FACTORS AND VISCERAL SENSITIVITY

Visceral hypersensitivity is present in many gastrointestinal disorders, such as functional dyspepsia, irritable bowel syndrome (IBS), and inflammatory bowel disease (IBD). There is an increasing body of evidence suggesting that neurotrophins, particularly NGF and BDNF, are involved in abdominal pain. NGF, by interacting with the primary afferent nerves, contributes to the development of visceral hypersensitivity in several animal models, such as trinitrobenzene sulfonic acid (TNBS),^{8,9} butyrate,^{10,11} neonatal maternal deprivation,¹² chronic stress,¹³ and bowel obstruction.¹⁴ Several cell types in the digestive tract are known to produce and release NGF, such as intestinal epithelial cells, mast cells, enteric neurons, enteric glial cells, and smooth muscle cells (Table 1).^{10,12,15,16} NGF level is elevated in the

colonic mucosa of patients with IBS,^{17,18} and increased expression of NGF is correlated with visceral hypersensitivity in these patients.¹⁸

The mechanisms of NGF action on visceral sensation are not completely understood. Enhancing the activity of pronociceptive receptors and/or ion channels on primary afferent neurons can result in sensory hypersensitivity. NGF increases the transient receptor potential cation channel subfamily V1 (TRPV1) expression in DRG.¹⁹ TRPV1 is a nonselective cation channel that mediates scalding heat and pain. Upregulation of TRPV1 by NGF via the PI3K/Akt pathway may contribute to visceral hypersensitivity following TNBS-induced colitis.¹⁹ Mechanical stretch in bowel obstruction causes upregulation of NGF in gut smooth muscle cells.¹⁴ High levels of NGF increase tetrodotoxin-resistant Na⁺ currents in colon-projecting DRG neurons and augment neuronal excitability, which may contribute to visceral hypersensitivity in bowel obstruction.¹⁴ NGF-dependent upregulation of acid-sensing ion channels in colon-projecting DRG neurons is suggested to be involved in butyrate-induced colonic hypersensitivity.¹¹

DeLafoey et al. were the first group of researchers to report the involvement of BDNF in visceral hypersensitivity.⁸ Intraperitoneal injection (i.p.) of BDNF decreased sensory threshold to colonic distension in healthy rats. Anti-BDNF antibody (i.p.) blocked TNBS-induced visceral hypersensitivity.⁸ The role of BDNF in visceral hypersensitivity is further supported by the observation that TNBS-induced colonic hypersensitivity was significantly reduced in BDNF heterozygote knock-out (BDNF^{+/-}) mice than that in BDNF^{+/+} mice.²⁰ BDNF was mainly present in TRPV1-expressing nociceptive DRG neurons and released into the dorsal horn of the spinal cord to modulate neurotransmission.²¹ The expression of BDNF in sensory neurons was kept low in adults at physiological state, but greatly increased after colonic inflammation.²¹ BDNF acted on the TrkB receptors on DRG neurons to activate the PLC- γ , but not the MAPK/ERK or PI3K/Akt pathway, to increase calcitonin-gene related peptide (CGRP) expression during colitis.²² CGRP is a well-recognized pain mediator. Increased CGRP expression in the DRG by BDNF may contribute to the activation of visceral nociceptive pathways in colitis.

Besides gut inflammation, early life adverse events may also upregulate BDNF expression in the visceral sensory pathways and contribute to hypersensitivity in adulthood. Winston et al. reported that chronic prenatal stress induced visceral hypersensitivity in adult male and female offspring in rats.²³ Chronic prenatal stress also exacerbated visceral hypersensitivity following another episode of chronic stress experienced in adulthood, and the female rats demonstrated a greater and prolonged visceral hypersensitivity than the male rats. Chronic stress in adulthood upregulated BDNF expression in the dorsal horn of the spinal cord of female rats through an epigenetic mechanism of histone acetylation. The increase of BDNF expression was greater in prenatally stressed female rats, which might contribute to the sex specificity of visceral hypersensitivity.²³ Early life colon immune challenge followed by adult colon immune challenge induced similar epigenetic upregulation of BDNF in the DRG and spinal cord and might contribute to the exacerbation of visceral hypersensitivity.²⁴

The article by Fu et al. in this issue adds an additional piece of evidence for the role of BDNF in visceral hypersensitivity and proves that non-neuronal tissue can produce BDNF.⁷

Bowel obstruction is associated with cramping pain in the acute phase and persistent abdominal pain in the chronic phase.²⁵ Fu et al. demonstrated that mechanical stretch induced BDNF expression in gut smooth muscle cells. Elevation of BDNF in the local gut microenvironment caused visceral hypersensitivity by increasing neuronal excitability of primary afferent neurons.⁷ Notably, intestinal epithelial cells also secrete BDNF. Elevated BDNF levels in colonic mucosa may contribute to visceral hypersensitivity in IBS patients.²⁶

3. NEUROTROPHIC FACTORS AND GUT MOTILITY

Effects of neurotrophic factors on gut motility were first recognized as an adverse effect in a clinical trial testing if BDNF would increase survival of amyotrophic lateral sclerosis (ALS) patients.²⁷ Although the study failed to show benefit of BDNF treatment for ALS, an increased stool frequency occurred in patients treated with a higher dose of BDNF.²⁷ In addition, exogenous BDNF accelerated gastrointestinal and colonic transit in healthy human volunteers and in patients with constipation.²⁸ In fasting rats, exogenous BDNF increased myoelectric activity in the gastrointestinal tract.²⁹ BDNF enhanced peristalsis in the rat colon,³⁰ and BDNF^{+/−} mice had delayed gastrointestinal transit, slow velocity of fecal pellet propulsion, and decreased stool frequency.^{30,31} BDNF levels were significantly reduced in colonic biopsies from patients with slow transit constipation.³¹ All the evidence mentioned above indicates that BDNF has prokinetic effects on gut motility.

The mechanisms underlying the stimulatory effect of BDNF on gut motility are not fully understood and conflicting results have been reported. Gut motility is regulated by the ENS, but BDNF does not directly activate enteric neurons. Instead, it causes a TrkB-mediated enhancement of Ca²⁺ transients induced by serotonin and substance P (SP), suggesting its modulatory role in ENS neural circuits.³² The neural blocker tetrodotoxin failed to block BDNF-induced enhancement of cholinergic contraction in isolated longitudinal muscle-myenteric plexus strips from the rabbit jejunum.³³ However, tetrodotoxin attenuated BDNF-induced augmentation of contraction in the longitudinal muscle-myenteric plexus strips from the mouse colon.³¹ Interestingly, exogenous BDNF had no effect on the basal tone or spontaneous phasic contraction in isolated smooth muscle strips from the rabbit jejunum and mouse ileum and colon,^{31,33} but increased spontaneous phasic contraction in the isolated longitudinal muscle-myenteric plexus strips from the mouse colon.³¹ Thus, it is unclear whether BDNF can initiate smooth muscle contraction by itself or it merely augments contraction elicited by other excitatory neurotransmitters. Nevertheless, evidence suggests that BDNF enhanced SP and CGRP-induced smooth muscle contraction in mouse ileum and distal colon,³⁴ and cholinergic contraction in rabbit jejunum.³³ BDNF-induced enhancement of cholinergic contraction in the rabbit jejunum was mediated through activation of TrkB on smooth muscle cells and subsequent phosphorylation of PLC.³³

NGF is also involved in regulation of gut motility. Exogenous NGF increased the gastrointestinal myoelectric activity in fasting rats.²⁹ NGF overexpression occurred in the rat small intestine after *Trichinella spiralis* infection.³⁵ Treatment with anti-NGF antibody *in vivo* improved the altered gut motility caused by *Trichinella spiralis* infection, suggesting that NGF plays a role in the development of abnormal gut motility.³⁵

The role of NT-3 in gut motility was only investigated by exogenous administration. Exogenous NT-3 accelerated gastrointestinal transit in healthy human volunteers.²⁸ NT-3 also accelerated colonic transit, increased stool frequency, and facilitated passage of stool in constipated patients.²⁸ In fasting rats, exogenous application of NT-3 increased myoelectric activity in the gastric antrum, duodenum, jejunum, and colon.²⁹ The role of endogenous NT-3 in adult gut motility remains to be investigated.

4. NEUROTROPHIC FACTORS AND INTESTINAL BARRIER

The intestinal mucosa serves as a barrier to control uptake across the intestinal epithelium and prevent invasion of harmful substances, such as antigens, bacteria, or viruses into the internal environment of the body. There are only a few studies investigating the effects of neurotrophic factors on intestinal barrier function. Barreau et al. showed that neonatal maternal deprivation increased gut paracellular permeability in adult rats, which was suppressed by the anti-NGF antibodies and mimicked by neonatal NGF treatment (i.p.).¹² Neonatal maternal deprivation increased NGF and TrkA expression in colonic tissue. NGF increased mast cell numbers and degranulated mast cells in the rat colon, suggesting that mast cells may be involved in neonatal maternal deprivation-induced disruption of mucosal barrier function.¹² NGF expression was elevated in the colonic mucosa of diarrhea-predominant IBS patients, and high level of mucosal NGF was correlated with impaired gut barrier function in these patients.¹⁸

Unlike the detrimental effects of NGF on gut barrier function, BDNF seems to help maintain intestinal epithelial integrity. It has been shown that the BDNF^{+/-} mice had lower trans-epithelial resistance, decreased expression of tight junction proteins, such as occludin, zonula occludens-1 (ZO-1), and claudin-1, and increased expression of claudin-2 in the colon,³⁶ suggesting that endogenous BDNF is essential for the maintenance of intestinal mucosa integrity. BDNF treatment in cultured ht-29 cells from the human colon adenocarcinoma cell line induced upregulation of occludin, ZO-1, claudin-1, and downregulation of claudin-2,³⁷ further suggesting that BDNF modulates intestinal barrier function through regulating the expression of tight junction proteins. Paradoxically, high level of BDNF was found in the colonic mucosa of post-infectious IBS mice, which was associated with decreased occludin, ZO-1, and claudin-1 expression and impaired intestinal barrier function.³⁷ Thus, the role of BDNF in regulating intestinal barrier function needs to be further elucidated.

GDNF is recently recognized to play a protective role in intestinal barrier function. Both enteric glial cells and enterocytes can secrete GDNF under physiological condition.^{5,38} GDNF overexpression in transgenic mice reduced dextran sulfate sodium-induced colonic inflammation and loss of intestinal barrier functions.³⁹ The restoration of intestinal epithelial barrier function by GDNF can be attributed to its anti-apoptotic effects and upregulation of ZO-1 expression in colonic epithelial cells.³⁹ GDNF also plays a protective role in intestinal barrier integrity against intestinal ischemia-reperfusion injury by upregulating the expression of occludin and ZO-1.³⁸ In an *in vitro* study using cultured intestinal epithelial cells, Meir et al. found that GDNF exerted no additional barrier-stabilizing effects in the mature barrier formed in differentiated enterocytes, but augmented maturation of epithelial barrier

functions in immature intestinal epithelial cells through the cAMP/protein kinase A and p38 MAPK signaling pathways.⁵ Therefore, when considering these findings together with the *in vivo* observations, it is possible that GDNF might act on the immature epithelial cells in the intestinal crypts.

5. ROLE OF NEUROTROPHIC FACTORS IN NEUROPROTECTION AND NEUROPLASTICITY IN THE ENS

Recent literature suggests that neurotrophic factors promote the survival and maintenance of neurons and glial cells not only in the developing but also in the adult ENS. One of the earliest articles to report the protective role of GDNF on enteric neuropathy was a study by Anitha et al.⁴⁰ Using both *in vitro* culture system of enteric neurons as well as an *in vivo* streptozotocin-induced diabetic mouse model, Anitha et al. demonstrated that hyperglycemia induced neuronal apoptosis and loss of nitrergic inhibitory neurons in the ENS, and GDNF overexpression in transgenic mice prevented hyperglycemia-induced changes in the ENS.⁴⁰ Interestingly, in the current issue, Luo et al. demonstrated that GDNF levels, along with NGF and NT-3, increased in varying degrees in the gut during the acute stage of diabetes before loss of enteric neurons occurs.⁴¹ Expression of GDNF was significantly decreased in the colon of diabetic rats eight and twelve weeks after disease onset, which was coincident with the loss of enteric neurons, specifically the nitrergic inhibitory neurons and cholinergic excitatory neurons.⁴² These results suggest that a degenerative process in the ENS is initiated eight weeks after the induction of diabetes but not in the early stage. Elevated GDNF, NGF, and NT-3 levels in the gut in the early stage of diabetes may protect enteric neurons from hyperglycemia-induced cellular damage, whereas decreased expression of GDNF in the later stage may contribute to diabetic enteric neuropathy. GDNF stimulates the Ret receptor tyrosine kinase and activates several intracellular signaling pathways, such as the MAPK pathway, the PI3K/Akt pathway, and the PLC pathway. The PI3K/Akt pathway is important for cell survival. The level of phosphorylated Akt (p-Akt) was reduced in the diabetic rat colon eight and twelve weeks after disease onset.⁴² Thus, diabetes-induced enteric neuropathy may be mediated by a reduction of GDNF and its main downstream signaling pathway PI3K/Akt in the gut. Exogenous GDNF or elevation of endogenous GDNF may have therapeutic potential to prevent or ameliorate enteric neuropathy. In fact, electroacupuncture at acupoint ST-36 increased GDNF and p-Akt levels in the colon, which partially rescued the lost enteric neurons in diabetic rats.⁴³ Similarly, gastric electrical stimulation prevented vagotomy-induced apoptosis of enteric neurons in the stomach, which was mediated by enhanced release of GDNF and activation of its downstream pathway PI3K/Akt.⁴⁴ GDNF was also found to protect enteric glial cells from apoptosis induced by gut inflammation through an autocrine mechanism in enteric glial cells.⁴⁵

Although BDNF has been known to have neuroprotective effects in the central nervous system, the evidence for neuroprotection in the ENS is scarce. BDNF was shown to inhibit inflammation-induced apoptosis in enteric glial cells.⁴⁶ A recent study suggested that BDNF might be able to protect enteric neurons from accumulating misfolded α -synuclein in enteric neurons in a Parkinson's disease (PD) animal model.⁴⁷ Patients with PD often have aggregated α -synuclein in enteric neurons, which is associated with loss of enteric neurons

and the development of constipation. Transgenic mice overexpressing mutant human α -synuclein developed PD-like enteric neuropathology. FTY720, a sphingosine analog, reduced ENS α -synuclein aggregation and constipation in the α -synuclein transgenic mice. The neuroprotective effect of FTY720 was mediated by upregulation of BDNF expression and activation of TrkB receptors in the gut, which reduced ENS synucleinopathy and improved gut motility.⁴⁷

There are conflicting results regarding the potential for neuroprotection by NGF in the ENS. In TNBS-induced colitis rats, selective loss of NGF-sensitive neurons was observed in the colon, which was associated with upregulation of NGF in the intestine.⁴⁸ Thus, high level of NGF may activate the p75 receptors on enteric neurons to induce cell death in the ENS during gut inflammation. On the contrary, under physiological conditions, NGF produced by the intestinal epithelial cells may have protective effects on the enteric neurons via activating the TrkA receptors in the ENS.⁴⁹

In addition to its effects on cell survival, NGF regulated the neurochemical phenotype of enteric neurons and selectively reduced the proportion of vasoactive intestinal peptide-immunoreactive enteric neurons.⁴⁹ NGF is also implicated in neuronal sprouting in the colonic mucosa of IBS patients. Døthel et al. reported that increased expression of NGF and TrkA receptors in the colonic mucosa of IBS patients was associated with a higher nerve fiber density in the lamina propria.¹⁷ Mucosal tissue supernatants from IBS patients stimulated neuritogenesis in an NGF-dependent manner.¹⁷ However, functional consequences of these neuroplastic changes induced by NGF remain unknown.

6. CONCLUSIONS AND FUTURE PERSPECTIVES

The role of neurotrophic factors in development and maturation of the nervous system has been exclusively investigated and well recognized. Increasing evidence suggests that neurotrophic factors continue to regulate functions of both neuronal and non-neuronal cells beyond the developmental stage. Although our understanding of the participation of neurotrophic factors in the regulation of gastrointestinal functions has advanced considerably during the past decade, much work remains to be done in clarifying the sources for neurotrophic factors, locations of their cognate receptors, downstream signaling pathways, and factors regulating the expression of neurotrophic factors and their receptors. It is possible that involvement of neurotrophic factors in enteric physiology and pathophysiology is greater than currently apparent. In this respect, it is mandatory to thoroughly investigate the role of neurotrophic factors in enteric physiology and pathophysiology before therapeutic approaches can be administered.

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KEY POINTS

- Neurotrophic factors and their receptors are expressed in both fetal and mature gastrointestinal tract.
- Neurotrophic factors play essential roles for the development and migration of the enteric nervous system along the gut during the early stage of life.
- In adult gut, neurotrophic factors are involved in regulation of visceral sensation, motility, epithelial barrier function, and have neuroprotective and neuroplastic effects in the enteric nervous system. These newly recognized functions may have therapeutic implications in bowel disorders and diseases.

TABLE 1.

Distribution of neurotrophic factors and their receptors in the adult gut

Neurotrophic factor/ neurotrophic factor receptors	Animal	Region of the gut	Layer and/or cell type	Functional implication and/or regulation of expression	Reference
BDNF	Rat	Colon	Smooth muscle cells	Colon distension increases BDNF expression in the smooth muscle cells. BDNF plays a role in distention-associated abdominal pain in bowel obstruction.	7
	Mouse	Esophagus, stomach, duodenum, ileum, and colon	Epithelial cells, smooth muscle cells, enteric neurons	BDNF expression in the colonic epithelial cells is increased following IBS-D fecal supernatant treatment, which may contribute to visceral hypersensitivity.	4, 26
	Human	Colon	Epithelial cells, lamina propria cells, enteric neurons, human colonic epithelial cell line Caco-2	BDNF level is low in the colonic mucosa of patients with slow transit constipation. BDNF expression in the Caco-2 cell culture is increased following IBS-D fecal supernatant treatment.	3, 26, 31
GDNF	Rat	Ileum	Enteric glial cells	Ischemia reperfusion upregulates GDNF expression by the enteric glial cells in the rat ileum, which helps to maintain intestinal barrier function. GDNF level is elevated in the rat ileum during the early stage of diabetes, which protects enteric neurons from hyperglycemia-induced cellular damage.	38, 41
	Human	Ileum	Enteric glial cells and enterocytes, HT29B6 and Caco-2 cell lines	GDNF activates the Ret/GFR α receptor complex and contributes to epithelial barrier stabilization.	5
NGF	Rat	Jejunum, ileum, and colon	Epithelial cells, mast cells, smooth muscle cells, enteric neurons and glial cells	Many factors can increase NGF expression and release in the gut, including but not limited to: gut infection, gut inflammation, mechanical distension of the gut wall, neonatal maternal separation, diabetes.	6, 10, 12, 14-16, 35, 41
	Human	Colon	Immune cells in the lamina propria	NGF expression is elevated in the colonic mucosa from IBS patients, which may contribute to visceral hypersensitivity and impaired gut barrier function in these patients.	17, 18
NT-3	Rat	Ileum	N/A	NT-3 protein level is increased during the early stage of diabetes.	41
	Human	Intestine	Enteric plexuses, intermuscular basal lamina, and along or between circular and longitudinal smooth muscle cells.	N/A	3
p75	Rat	Colon	Myenteric neurons	Neonatal maternal separation upregulates p75 mRNA expression in the rat colon of neonates but not adults.	12, 15
	Mouse	Esophagus, stomach, duodenum, ileum, and colon	Enteric neurons	N/A	4
TrkA	Rat	Colon	Myenteric neurons	Neonatal maternal separation upregulates TrkA mRNA expression in the rat colon of neonates but not adults.	12, 15

Neurotrophic factor/ neurotrophic factor receptors	Animal	Region of the gut	Layer and/or cell type	Functional implication and/or regulation of expression	Reference
	Human	Intestine	Enteric neurons and glial cells	N/A	3
TrkB	Mouse	Esophagus, stomach, duodenum, ileum, colon	Myenteric neurons	N/A	4
	Human	Intestine	Enteric neurons and glial cells	N/A	3
TrkC	Human	Intestine	Enteric neurons	N/A	3
Ret/GFRα.1/GFRα.2	Human	N/A	HT29B6 cell line and Caco-2 cell line	GDNF activates the Ret/GFRα receptor complex and contributes to epithelial barrier stabilization.	5

Abbreviations: BDNF, brain-derived neurotrophic factor; GDNF, glial cell line-derived neurotrophic factor; GFR, GDNF family receptor; IBS-D, diarrhea predominant irritable bowel syndrome; N/A, not available; NGF, nerve growth factor; Trk, tropomyosin receptor kinase receptor; NT-3, neurotrophin-3.