A dense network of extrinsic and intrinsic sensory neurons supplies the gastrointestinal tract. Intrinsic sensory neurons provide the enteric nervous system with the kind of information that this brain of the gut requires for its autonomic control of digestion, whereas extrinsic afferents notify the brain about processes that are relevant to energy and fluid homeostasis and the sensation of discomfort and pain. The sensory repertoire of afferent neurons is extended by their responsiveness to mediators released from enteroendocrine and immune cells, which act like “taste buds” of the gut and serve as interface between the gastrointestinal lumen and the sensory nerve terminals in the lamina propria of the mucosa. Functional bowel disorders such as non-ulcer dyspepsia and irritable bowel syndrome are characterized by abdominal discomfort or pain in the absence of an identifiable organic cause. It is hypothesized with good reason that infection, inflammation or trauma causes sensory pathways to undergo profound phenotypic and functional alterations that outlast the acute insult. The pertinent changes involve an exaggerated sensitivity of the peripheral afferent nerve fibres as well as a distorted processing and representation of the incoming information in the brain. This concept identifies a number of receptors and ion channels that are selectively expressed by primary afferent neurons as important molecular targets at which to aim novel therapies for functional bowel disorders.

Key words: Sensory innervation of the gastrointestinal tract, enteroendocrine cells, gastrointestinal immune system, peripheral mechanisms of visceral hyperalgesia, functional bowel disorders

INTRODUCTION

The two major functions of the gastrointestinal (GI) tract are, on the one hand, to take up and digest food, absorb nutrients and water, eliminate useless material and, on the other hand, to recognize harmful food constituents, antigens and pathogens as well as neutralize or expel them via emesis and diarrhoea. These seemingly conflicting tasks of the alimentary canal require a
careful analysis of the luminal contents and the functional status of the GI tract so that the appropriate effector programmes can be selected. It is therefore not surprising that the digestive system is endowed with an elaborate network of surveillance systems that comprise intrinsic sensory neurons, extrinsic sensory neurons, enteroendocrine cells (EECCs) and immune cells. This article focusses on the major characteristics of these multiple monitoring systems of the GI tract and discusses their reciprocal interactions, their relevance to mucosal integrity and their implications in functional bowel disorders (FBDs).

*Sensory innervation of the GI tract*

The alimentary canal is innervated by 4 populations of sensory neurons (*Fig. 1*). Intrinsic primary afferent neurons (IPANs) have their cell bodies either in the myenteric plexus (Auerbach plexus) or in the submucosal plexus (Meissner plexus) and innervate both mucosal and muscular layers of the gut (1, 2). Being part of the *enteric* nervous system (ENS), they comprise mucosal chemosensors, mucosal mechanosensors and muscular tension receptors. In addition, IPANs

![Fig. 1. Innervation of the GI tract by intrinsic and extrinsic sensory neurons. The two populations of intrinsic primary afferent neurons originate in the submucosal plexus (SMP) and myenteric plexus (MP), respectively. The two populations of extrinsic sensory neurons are vagal afferents originating from the nodose ganglia (NG) and spinal afferents originating from the dorsal root ganglia (DRG). CM, circular muscle; LM, longitudinal muscle.](image-url)
synapse with each other and in this way form self-reinforcing networks that issue outputs to interneurons, motor neurons, secretomotor neurons and vasodilator neurons (1—3). IPANs thus provide the ENS with the kind of information that this “brain of the gut” requires for its autonomic control of digestion.

The IPANs are complemented by two groups of extrinsic sensory neurons, vagal and spinal afferents, which convey information from the gut to the brain. In addition, some of them serve an efferent-like function by releasing neuropeptide transmitters such as calcitonin gene-related peptide and tachykinins (substance P, neurokinin A) from their peripheral endings, these transmitters in turn influencing the activity of enteric neurons and GI effector systems (4). The vagal and spinal afferents originate from somata in the nodose and dorsal root ganglia (Fig. 1), respectively, and differ in a number of neurochemical and functional properties (5, 6). Importantly, 80—90% of the axons in the vagus nerves are afferent nerve fibres that project to the nucleus tractus solitarii and area postrema of the brainstem (7—9). The spinal afferents supplying the gut terminate predominantly in distinct laminae of the dorsal spinal cord where they are organized in a segmental manner but, unlike those of somatic afferents, distributed over several spinal segments (10, 11).

Except for particular spatial arrangements in the myenteric plexus and muscle (9, 12), the visceral endings of the vagal and spinal afferents have no end organs or morphological specializations. Associated mostly with nonmyelinated and some thinly myelinated axons, the extrinsic sensory nerve fibres supply mucosa, submucosa (particularly arterioles), muscle, myenteric plexus and serosa (4, 7, 8, 9, 12, 13). With these projections and their sensory modalities, they can respond to changes of the chemical environment in the lumen, interstitial space and vasculature and to mechanical distortion of the gut wall, typically distension, but also to contraction or relaxation of the muscle (4, 7—9, 12, 13).

The major task of extrinsic afferents is to notify the central nervous system about processes and conditions that are relevant to energy and fluid homeostasis of the body. Therefore, they participate in autonomic and neuroendocrine reflex circuits, but the information which they convey to the brain is rarely perceived as a conscious sensation, at least under physiological conditions (14). In a number of FBDs, however, patients suffer from GI pain and discomfort, and there is now ample evidence that hypersensitivity of the extrinsic afferent system is an important factor in the complaints of these patients (15).

Sensory neuron interactions with enteroendocrine cells

Dispersed among the epithelial cells, EECCs of the GI mucosa produce a variety of digestive hormones. Many of these cells are in close proximity to nerve fibres which, on the one hand, may regulate the activity of EECCs and,
on the other hand, be targets of the hormones released from EECCs (16—18). Experimental evidence indicates that EECCs function as detectors that analyze the luminal contents, survey the mucosal status and hence act like “taste buds” of the gut. By releasing hormones they not only contribute to the endocrine regulation of digestion but also serve as interface between the GI lumen and sensory neurons in the lamina propria of the mucosa.

The enterochromaffin cells are the major source of 5-hydroxytryptamine (5-HT) in the body, contributing more than 80% to the total amine content (19). These cells release 5-HT in response to certain constituents of food, mechanical distortion of the mucosal villi (16), bacterial products such as cholera toxin (20), cytostatic drugs such as cisplatin (19) and mucosal injury (21). 5-HT in turn activates intrinsic and extrinsic sensory nerve fibres via interaction with distinct 5-HT receptors. The 5-HT receptors on intrinsic sensory neurons of the submucosal plexus are predominantly of the 5-HT\(_{1P}\) and 5-HT\(_{4}\) type (22), while those on intrinsic sensory neurons of the myenteric plexus (23) and on extrinsic afferents are preferentially of the 5-HT\(_{3}\) type (19, 24).

Stimulation of 5-HT\(_{3}\) receptors on vagal afferents elicits emesis, which explains why vomiting, caused by cytostatic drugs that release 5-HT from EECCs, is prevented by 5-HT\(_{3}\) receptor antagonists such as ondansetron (19). 5-HT\(_{3}\) receptors on spinal sensory neurons are involved in the afferent signalling of colorectal distension (25), but the use of 5-HT\(_{3}\) receptor antagonists in controlling GI sensitivity is limited because 5-HT\(_{3}\) receptors are also present on various neurons of the ENS (23, 26). Accordingly, 5-HT\(_{3}\) receptor antagonists inhibit peristalsis in the guinea-pig intestine (27) and cause constipation in humans (28).

Cholecystokinin (CCK) is released from the duodenum in response to products of fat and protein digestion (17). The peptide, in turn, stimulates extrinsic vagal afferents involved in satiation, reflex inhibition of gastric motility and emptying, reflex increase in gastric blood flow and mucosal protection (29—34). CCK-evoked excitation of vagal sensory neurons is mediated by CCK\(_{1}\) (CCK\(_{A}\) receptors, which is consistent with the expression of this receptor type on nodose ganglion afferents of the rat (35, 36). CCK\(_{1}\) receptor antagonists hold some potential in the treatment of gastro-oesophageal reflux disease and functional dyspepsia (37), given that CCK\(_{1}\) receptors appear to be involved in the transient lower oesophageal sphincter relaxations induced by gastric distension (38) and in the meal-like fullness and nausea associated with intraduodenal lipid and gastric distension (39).

Gastric acid entering the duodenum releases secretin from endocrine S cells in the proximal small intestine to enhance pancreatic exocrine secretion and bile flow. In addition, secretin leads to stimulation of vagal afferent neurons and subsequent inhibition of gastric contractility and emptying via a vago-vagal reflex (40). Accordingly, the neural reflex inhibition of gastric motility in
response to duodenal acidification seems to be initiated, in part, by secretin (41). Somatostatin, a peptide released from endocrine D cells may exert an inhibitory effect on extrinsic afferents because octreotide, a long-acting analogue of somatostatin, has been found to reduce perception of gastric and rectal distension (37). Furthermore, corticotropin-releasing factor released in the GI mucosa from EECCs or immune cells may increase extrinsic afferent nerve activity, as has been suggested by a study of the perception of rectal distension in human volunteers (42).

**Sensory neuron interactions with GI immune cells**

Besides sensory neurons and EECCs, immune cells constitute another major defence system that oversees the integrity of the digestive tract. As the human GI mucosa extends for an area of 200—300 m² and is home to some $10^{13}$ bacteria and other microorganisms which may threaten to invade and translocate the gut wall (43), the alimentary canal possesses a highly specialized immune system that contains organized and nonorganized cellular elements (18, 44). The gut-associated lymphoid tissue comprises antigen-sampling M cells, lymphocytes that may either occur in aggregates (such as in Peyer’s patches) or lie loosely scattered in the epithelium and lamina propria, and immune-associated cells including macrophages, eosinophils, neutrophils, and mast cells. In addition, many epithelial cells are able to secrete chemokines (e.g., interleukin-8) and thus to recruit immune cells (45). The GI immune system is called into operation whenever the mucosa is affected by microbial infection, allergen exposure, inflammation or other types of injury. Following their release from activated immune cells, cytokines, prostaglandins (PGs), leukotrienes, bradykinin, histamine, 5-HT and proteases can either acutely excite sensory nerve fibres or alter their sensitivity in the long term.

Vagal afferent neurons play a role in the communication between the peripheral immune system and the central nervous system. Thus, intravenous injection of interleukin-1β (IL-1β) causes increased firing in vagal afferents (46) and activation of neurons in the brainstem (47). Since IL-1 receptors are expressed by nodose ganglion cells, IL-1β may excite vagal afferents by a direct action on the axons although PG formation and activation of PG receptors on vagal sensory neurons could also contribute (48). In addition, IL-1β increases the sensitivity of gastric vagal afferents to fire in response to CCK, and there is information that CCK acting via CCK$_1$ receptors mediates part of the excitatory action of IL-1β on vagal afferents (46).

Consistent with these effects of peripheral IL-1 is the concept that vagal afferents participate in the behavioural responses to infection and inflammation, which in the rat comprise fever, anorexia, somnolence, decrease in locomotor
activity, decrease in social exploration and hyperalgesia (49, 50). This “sickness behaviour” is initiated by cytokines and can be reproduced by peripheral administration of IL-1β, IL-6, tumour necrosis factor-α or bacterial endotoxin which induces IL-1β. Although proinflammatory cytokines can access the brain via circumventricular organs that are devoid of a blood-brain barrier, experiments involving subdiaphragmatic vagotomy have shown that the cytokine-evoked decrease in locomotor activity, decrease in social exploration and hyperalgesia depend in part on afferent signalling by vagal sensory neurons (49—51).

IL-1β also sensitizes splanchnic afferents to the excitatory effects of mesenteric ischaemia and histamine and, at high dosage, excites them via stimulation of IL-1 receptors (52). These cytokine effects on extrinsic afferents may be of relevance to a number of GI diseases in which there is an activation of the immune system with subsequent release of cytokines. In addition, it needs to be considered that IL-1β, IL-6 and/or tumour necrosis factor-α are formed in response to ischaemia (52), acid-induced gastric mucosal injury (53, 54) and surgical trauma (55). Thus, it may be in a wide range of pathological circumstances that cytokines come into play and modify the activity of afferent neurons.

Following intestinal anaphylaxis, vagal and spinal afferents in the rat are stimulated via histamine acting at H₁ receptors and 5-HT acting at 5-HT₃ receptors (56—58). It can be anticipated that histamine and 5-HT are released from mast cells under these conditions and that, by stimulating extrinsic afferents, they contribute to anaphylaxis-evoked disturbances of intestinal motor activity (59) and cardiovascular reflex responses (60). Apart from anaphylaxis, ischaemia is another condition that causes release of 5-HT and histamine, these amines contributing to the ischaemia-evoked discharge of sensory neurons (56, 61). Further mediators that influence afferent nerve activity include serine proteases such as mast cell tryptase, trypsin and thrombin. These proteases activate a particular group of cell surface receptors termed proteinase-activated receptors (PARs) through proteolytic cleavage of the extracellular N-terminal domain of the receptors and exposure of a new N-terminal domain that acts as “tethered ligand” and thus causes self-activation of the receptors (62). Of the 4 PARs identified thus far, PAR-1 and PAR-2 are expressed by dorsal root ganglion neurons, and a PAR-2 agonist elicits excitation of afferent axons in jejunal mesenteric nerves (62).

PGs are key mediators of inflammatory hyperalgesia, which is in keeping with the expression of prostaglandin EP and IP receptors on primary sensory neurons. PGE₂ excites mesenteric afferent nerve fibres supplying the rat jejunum through direct activation of EP₁ receptors on the axons and through prostanoid-mediated contraction of the bowel (63). In addition, PGs sensitize visceral afferents to other algesic substances such as bradykinin which per se
increases the discharge of serosal afferents from the rat jejunum by activation of bradykinin B₂ receptors (64).

**Sensory neuron activation by contraction and distension**

The GI tract with its interstitial cells of Cajal as pacemaker cells is continuously moving, and the associated changes in the mechanical status of the gut are recorded by both intrinsic and extrinsic afferent neurons. The mechanosensitivity of IPANs enables the ENS to react to distortion of the mucosal villi and to distension of the gut wall and thus to regulate GI motility, secretory activity and vascular perfusion according to the digestive needs. Both intrinsic enteric and vagal mechanosensors contribute to the adaptive relaxation of the gastric fundus in response to distension by food intake (65, 66).

Distension of the stomach or the colorectal region beyond a certain level gives rise to pain which is thought to be mediated by spinal afferents (7, 8, 13). Although some of the mechanosensitive visceral afferents are high-threshold sensors, as is typical of somatic nociceptors, most of them are low-threshold sensors which, however, encode distension or other mechanical stimuli over a wide range of innocuous and noxious intensities (11, 67). Both populations of visceral mechanosensors can sensitize under conditions of inflammation (11), in which case normal distension levels may be encoded at an intensity that causes visceral discomfort. Alternatively, if there is pseudo-obstruction of the bowel, postoperative or mechanical ileus, distension intensities may quickly turn into the noxious range and hence give rise to autonomic reflexes, neuroendocrine responses and pain.

**Sensory neuron activation by GI mucosal injury**

Among the bacterial toxins that are most injurious to the GI mucosa are those produced by *Clostridium difficile*. The diarrhoea, inflammation and necrosis caused by Clostridium toxin A involve, at an early stage, spinal afferents that release tachykinins which, via tachykinin NK₁ receptors, stimulate enteric secretomotor neurons but also contribute to mast cell degranulation, macrophage activation and neutrophil infiltration (68—70). Although the mechanism whereby Clostridium toxin A activates sensory neurons remains to be disclosed, it is known that the toxin induces epithelial cells to release macrophage-inflammatory protein-2 and other chemokines which may not only induce an inflammatory reaction on their own but, via unknown links, also lead to stimulation of sensory neurons (71). Cholera toxin, to the contrary, acts on enterochromaffin cells to release 5-HT which subsequently stimulates electrolyte and fluid secretion mostly by an enteric secretomotor reflex (72).
There is a body of evidence that experimental damage of the GI mucosa leads to activation of spinal afferent neurons which through their efferent-like function signal for local protective measures in the mucosa or through their afferent function activate autonomic and neuroendocrine mechanisms of homeostasis (4). Hydrochloric acid and pepsin are highly aggressive secretions of the stomach which attack the mucosal tissue if they can overwhelm the epithelial barrier. This is thought to take place when the mucosal barrier is focally disrupted by the mechanical forces of digestion, by ingested alcohol, nonsteroidal anti-inflammatory drugs or irritant food, or by reflux of bile. The surge of acid intruding the lamina propria stimulates spinal afferents which via a peripheral mechanism of action increase blood flow through the gastroduodenal mucosa and initiate other mechanisms of defence (4). Acid-sensitive extrinsic afferents thus represent a neural emergency system that can be activated by a variety of injurious chemicals (4). This alarm system also operates in the human gastric mucosa (73) and in the mucosa of the small and large intestine of experimental animals (74).

While local protective measures in the rat gastric mucosa are initiated by spinal afferents (4), it is vagal afferents that signal an acute acid challenge of the rat gastric mucosa to the central nervous system (75, 76). It would hence seem that vagal and spinal afferents are specialized to mediate completely different homeostatic reactions to a noxious acid insult of the gastric mucosa (77). Although vagal afferents in the stomach have long been known to discharge action potentials when their peripheral terminals are exposed to acid (78), their molecular detector of H+ ions remains unknown. Since the acid-evoked afferent signalling is not altered by pretreatment with the vanilloid capsaicin (75), it appears improbable that acid transduction is accomplished by the vanilloid receptor of type 1, which is a polymodal detector of a variety of stimuli including H+ (79). Whether acid-sensing ion channels (80) are involved has not yet been explored. It likewise awaits to be examined whether the homomeric P2X2 and heteromeric P2X2/3 purinoceptor cation channels expressed by afferent neurons (81) are transducers of GI mucosal damage. Vagal afferents expressing these receptors are activated or sensitized by adenosine triphosphate which in the injured gut may be released from damaged mucosal cells, immune cells, endothelial cells as well as sensory, enteric and sympathetic nerve endings (81, 82). Although 5-HT is released from the acid-injured mucosa (21), this amine has been ruled out to contribute to the acid-evoked excitation of vagal afferents (57).

The involvement of vagal afferents in the central signalling of a gastric mucosal acid challenge (75, 76) and peripheral immune challenge (49, 50) is of obvious relevance to understanding visceral sensation in health and disease. After it has long been held that vagal sensory neurons do not play any role in visceral pain, there is now growing awareness that these neurons make a distinct
contribution to the emotional-affective, neuroendocrine and behavioural aspects of GI nociception (11, 83). This view is corroborated by the central processing of a gastric mucosal acid challenge. After the information from the acid-threatened stomach has been communicated to the brainstem, it is passed on to subcortical brain nuclei (Fig. 2) involved in emotional, behavioural, autonomic and neuroendocrine reactions to a noxious stimulus (76). There is, however, no activation of the insular cortex, the major cerebral representation area of afferent input from the stomach (Fig. 2), which suggests that vagal afferent signalling of an acute acid insult to the gastric mucosa does not give rise to perception of pain (76).

**GI surveillance systems in concert**

The conflicting needs of the digestive system in the selective absorption of nutrients and rejection of harmful materials require that the mucosal compartment is closely surveyed. For this purpose, EECCs and immune cells are strategically positioned in the mucosa of the GI tract to analyze the luminal contents (Fig. 3). Following stimulation by food constituents and gastric secretions, EECCs release their messengers in order to coordinate various
digestive processes according to need. EECCs and epithelial cells also have the capacity to react to toxins, foreign macromolecules and infectious microorganisms. This task, though, is the particular domain of the GI immune system which in anticipation of the continuous threats from the lumen is the largest in the body.

Afferent neurons, of intrinsic and extrinsic origin, that send their axon terminals into the lamina propria of the GI mucosa receive information from the adjacent epithelial and immune surveillance systems (Fig. 3). Their messages are transduced by sensory neurons through receptors for enteroendocrine, immune and mast cell mediators and signalled to the ENS and central nervous systems. Since EECCs and immune cells are specialized to monitor cell-specific stimuli, the input from these cells enables afferent neurons to detect luminal stimuli that otherwise could not be encoded by their peripheral axons. These interactions between the non-neural surveillance systems and afferent neurons have now been recognized as important factors in the appropriate regulation of digestion, gut defence and gut sensation.

**Fig. 3.** GI surveillance systems in concert. Epithelial cells, enteroendocrine cells, immune cells as well as intrinsic and extrinsic sensory neurons interact with each other and issue outputs to the enteric and central nervous system, respectively.
Common to FBDs such as non-ulcer dyspepsia and irritable bowel syndrome is that the patients complain of sensory discomfort and pain. Although multiple pathogenic mechanisms underlie the symptoms of FBDs (15), it is ultimately extrinsic sensory neurons which signal to the brain that something abnormal happens in the GI tract. There is now good reason to hypothesize that, in patients with FBDs, events in the GI tract are represented in the brain in a distorted fashion, be it because there are pathological alterations in the environment of gut sensors, in the sensory gain of afferent neurons or in the central processing of afferent information from the GI tract. How are these changes brought about? It is now recognized that gastroenteritis, which may have subsided long ago, is a major risk factor for irritable bowel syndrome and the associated discomfort and pain (84, 85). GI hypersensitivity (Fig. 4) involves peripheral and central mechanisms of sensitization (86), which underlie the phenomena of GI allodynia (sensation of pain in response to stimulus strengths that normally are innocuous) and hyperalgesia (exaggerated sensation of pain in response to noxious stimulus strengths).

In analogy with somatic states of hyperalgesia it is hypothesized that immunological and inflammatory processes initiate long-lasting changes in the function and phenotype of the GI afferent nervous system (11, 14, 84). A recent study has convincingly shown that mechanical or chemical irritation of the colon in newborn rats leads to chronic visceral hypersensitivity in the adult animals, although no pathology in the colon is discernible (87). Such a permanent modification of the sensory gain is most probably related to changes in the expression of receptors, ion channels and transmitters, changes in the biophysical properties of receptors and ion channels (Fig. 4), and changes in the structure, connectivity and survival of afferent neurons (11, 88). The peripheral messengers for these persistent adaptations include nerve growth factor acting on spinal afferents, brain-derived neurotrophic factor acting on vagal afferents and, conceivably, cytokines such as leukaemia inhibitory factor (11, 18, 37, 88). Produced in inflamed tissue, these mediators induce afferent neurons to increase the expression of neurotransmitters, receptors and ion channels such as the sensory neuron-specific voltage-gated Na+ channel Na1.8 (88) which when transported into the periphery may contribute to persistent hypersensitivity of the nerve terminals.

Sensory neurons as targets for the therapy of functional bowel disorders

The concept that hypersensitivity of primary afferent neurons contributes to the pain and discomfort associated with FBDs (15) implies that extrinsic afferents of the gut are prime targets at which novel therapies may be aimed
Drugs that act on nociceptive neurons have some advantages over other analgesics, not the least because they hit the first element in the pain pathways. In addition, these drugs may be manufactured such that they cannot enter the brain and hence are free of unwanted adverse effects on brain functions. Ideally, sensory neuron-targeting drugs should block the exaggerated signalling of hypersensitive afferents, which implies that they aim at molecular targets that are upregulated (Fig. 4) in FBDs (89). The complex innervation of the GI tract, though, complicates the search for specific traits on extrinsic sensory neurons, and the development of efficacious and safe GI analgesics needs to address several key questions:

(a) Which noxious/innocuous stimuli in the gut are relevant to the pain in FBDs?
(b) Which receptors/ion channels on extrinsic afferents do these FBD-relevant stimuli act on?
(c) Do the FBD-relevant extrinsic afferents express receptors, ion channels or other molecular targets in a cell-specific manner?
(d) Is the expression of pain-relevant targets on extrinsic afferents changed in FBDs?

Excitatory ion channels such as vanilloid receptors of type 1, acid-sensing ion channels, P2X3 purinoceptors and tetrodotoxin-resistant Na+ channels are of particular relevance because they are selectively expressed by extrinsic
afferents (89) and, when activated, increase the intracellular Ca\(^{2+}\) concentration and thereby stimulate Ca\(^{2+}\)-dependent kinases, regulate gene expression and alter the cellular phenotype. For assessing the significance of these targets in GI hyperalgesia it is important to know whether number, subunit composition and biophysical properties of sensory neuron-specific ion channels and receptors are persistently altered after a visceral insult (11). In addition, targets such as 5-HT receptors, CCK receptors, glutamate receptors, tachykinin receptors, calcitonin gene-related peptide receptors, \(\gamma\)-aminobutyric acid receptors, opioid receptors, cannabinoid receptors, PG receptors and PARs are also worth exploring. In developing drugs along these lines it will be important to assess which quantitative contribution sensory neuron-specific targets make to the induction of hyperalgesia and whether modulation of a single target is therapeutically efficacious and safe (89).

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