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Bidirectional gut-brain communication: A role for orexin-A

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ABSTRACT

It is increasingly evident that bidirectional gut-brain signaling provides a communication pathway that uses neural, hormonal, and immunological routes to regulate homeostatic mechanisms such as hunger/satiety as well as emotions and inflammation. Hence, disruption of the gut-brain axis can cause numerous pathophysiologies, including obesity and intestinal inflammatory diseases. One chemical mediator in the gut-brain axis is orexin-A, given that hypothalamic orexin-A affects gastrointestinal motility and secretion, and peripheral orexin in the intestinal mucosa can modulate brain functions, making possible an orexinergic gut-brain network. It has been proposed that orexin-A acts on this axis to regulate nutritional processes, such as short-term intake, gastric acid secretion, and motor activity associated with the cephalic phase of feeding. Orexin-A has also been related to stress systems and stress responses *via* the hypothalamic-pituitary-adrenal axis. Recent studies on the relationship of orexin with immune system-brain communications in an animal model of colitis suggested an immunomodulatory role for orexin-A in signaling and responding to infection by reducing the production of pro-inflammatory cytokines (e.g., tumor necrosis factor α, interleukin-6, and monocyte chemoattractant protein-1). These studies suggested that orexin administration might be of potential therapeutic value in irritable bowel syndrome or chronic intestinal inflammatory diseases, in which gastrointestinal symptoms frequently coexist with behavioral disorders, including loss of appetite, anxiety, depression, and sleeping disorders. Interventions in the orexinergic system have been proposed as a therapeutic approach to these diseases and for the treatment of chemotherapeutic drug-related hyperalgesia and fatigue in cancer patients.

1. Introduction

The reciprocal interaction between gastrointestinal tract and brain and its effects on health and disease have been described since the mid-19th (James, 1884; Cannon, 1929). It has more recently been reported that this gut-brain cross-talk is involved not only in digestive processes and nutrition but also in the regulation of emotions and inflammation, *via* neural, hormonal, and immunological pathways (Bradesi and Mayer, 2007; Coss-Adame and Rao, 2014; Cryan and Dinan, 2012; Mayer, 2011; Roh et al., 2016). Signals from the digestive tract not only reach brain centers that regulate immediate intake, according to the amount and nutritional quality of ingested food, but also brain reward systems that influence eating behaviors, as observed in taste learning and in eating disorders such as overeating and obesity (Han et al., 2018; Volkow et al., 2017). This sensorial information is also related to the hypothalamic-pituitary-adrenal (HPA) axis, affecting stress responses (Stengel and Taché, 2009), and to cognitive processes, including hippocampus-dependent memories that require the transmission of vagal sensory information to the hippocampus *via* a multi-order neural pathway (Suarez et al., 2018).

Chemical mediators that modulate the gut-brain axis include orexins (Gao and Horvath, 2014; Kirchgessner, 2002; Okumura and Nozu, 2011). The neuropeptides orexins A and B (Sakurai et al., 1998), also called hypocretins (De Lecea et al., 1998), derive from *prepro-orexin* and selectively bind to two types of receptors, OX1R and OX2R (HCRTR1 and HCRTR2) (Tsujino and Sakurai, 2009). The distribution of these G protein-coupled receptors differs between the nervous system and the gastrointestinal tract, suggesting that they may play distinct roles in the physiological functions of orexin (Ehrström et al., 2005; Gozzi et al., 2011; Leonard and Kukkonen, 2014; Marcus et al., 2001; Scammell and Winrow, 2011; Tsujino and Sakurai, 2009). Indeed, although *prepro-orexin* and derived neuropeptides are located at central level in cells of the lateral (LH), dorsomedial (DMH), and perifornical (PFH) hypothalamus, orexinergic fibers are distributed over virtually the entire neuroaxis (Nambu et al., 1999; Peyron et al., 1998). This widespread pattern of orexinergic fiber distribution suggests that this peptide system

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may contribute to a large variety of brain functions, mainly related to reward and motivated behaviors (Borgland et al., 2006; Harris et al., 2005; Narita et al., 2006; Risco and Mediavilla, 2018; reviews in Li et al., 2014; Gao and Horvath, 2014; Sakurai, 2014; Tyree and de Lecea, 2017).

Orexin immunoreactivity and orexin mRNA expression have also been observed in neurons and enteroendocrine cells of the gut; thus, orexin is one of the peptides localized in both the central nervous system (CNS) and the enteric nervous system, contributing to energy homeostasis (Ehrström et al., 2005; Kirchgessner, 2002). However, although central orexin has been widely studied, the factors that determine peripheral orexin release have not been fully elucidated (Li et al., 2014; Rani et al., 2018). We describe below the pathways that enable gut-brain dialogue and attempt to define the role of orexin in this relationship.

2. Communication pathways of the gut-brain axis

Parallel information processing pathways have been reported in this bidirectional crosstalk between the CNS and digestive system, both for top-down modulation of gastrointestinal function by the brain and for bottom-up signaling of sensory information from gut to brain.

2.1. Afferent pathways from gut to brain

Sensorial information from the gastrointestinal tract is processed by *primary afferent neurons, enteroendocrine cells,* and *immune cells* (Coss-Adame and Rao, 2014; Kim et al., 2018; Grundy and Brookes, 2012; Mayer, 2011). *Primary afferent neurons* on gastrointestinal tract walls are mechano- and chemo-sensitive to physiological and noxious stimuli (Kim et al., 2018; Grundy and Brookes, 2012). Some of these neurons participate in secretory or peristaltic gut reflexes to maintain gastrointestinal homeostasis, while others establish synapsis with medullary lamina I cells or, *via* vagal afferents, with neurons in the nucleus of the solitary tract (NST) (Barraco et al., 1992; Gieroba and Blessing 1994; Grundy and Brookes, 2012; Han et al., 2018). The NST transmits visceral vagal information to parabrachial pontine nuclei, which in turn connect with forebrain structures such as the hypothalamus (HT), amygdala, and cortex (Ricardo and Koh, 1978; Saper and Loewy, 1980).

Enteroendocrine cells (EECs) are dispersed among epithelial cells of the intestinal wall and act as sensors of mechanical, chemical, and bacterial stimuli in the gastrointestinal tract. A recent study demonstrated that EECs connect with the brainstem *via* a single neuron, linking the intestinal lumen to the brainstem in milliseconds and using glutamate to rapidly transmit sensory signals to vagal neurons (Kaelberer et al., 2018). These gut peptides can also be released into the bloodstream in an endocrine manner, accessing the brain through circumventricular organs and reaching regions such as the area postrema, dorsal vagal complex (NST and dorsal motor nucleus of the vagus -DMV-), and HT. Hence, gastrointestinal information can be transmitted to the brain by multiple pathways (Mediavilla et al., 2005).

The *immune cells* of the gastrointestinal mucosa that do not respond to commensal bacteria maintain their capacity to differentiate and respond to pathogenic organisms through pattern-recognition receptors (PRRs) that favor an inflammatory response, with the release of cytokines such as tumor necrosis factor α (TNFα) and interleukin 1β (IL-1β) (Konsman et al., 2002; McCusker and Kelley, 2013). Although the mechanisms by which the effects of gut inflammation reach the brainstem and HT have not been precisely defined, vagal and humoral pathways may play a role (Konsman et al., 2002). Thus, the vagal signaling system of cytokines reach the NST, lateral parabrachial nucleus, HT, limbic structures, and cortex, affecting different behaviors (Dantzer, 2001; Goehler et al., 2000; Konsman et al., 2002; Larson and Dunn, 2001; Mayer, 2011; McCusker and Kelley, 2013), and immune cells may also pass through the blood-brain barrier and impact on brain regions capable of detecting blood–borne substances (Maier and Watkins, 1998; McCusker and Kelley, 2013; Schwartz and Kipnis, 2011). It has also been suggested that brain endothelial cells may play an important role in the negative affective status observed in inflammatory processes and in the segregation of brain cytokines modulated by gastrointestinal peptides and peripheral cytokines (Fritz et al., 2018; Goehler et al., 2000; Maier and Watkins, 1998). Regardless of the communication pathway involved, analysis of the immune system-brain relationship can assist in understanding how signals from the gastrointestinal tract contribute to brain functioning and how dysfunctions of immune cells in mucosa can be responsible for CNS diseases (Fung et al., 2017; Schwartz and Kipnis, 2011).

2.2. Microbiota-gut-brain axis

The human gastrointestinal tract is colonized by trillions of microorganisms, collectively designated gut microbiota. The microbiota–gut–brain axis was described after observing that intestinal bacteria affect brain neurochemistry and behavior and that behavioral characteristics can be modified by transplanting fecal material between mouse strains with distinct behavioral phenotypes (Collins et al., 2013). Activation of chemo- and mechano-receptors of EECs permits detection in the gut not only of nutrients but also of the presence and activity of microbial organisms (Mayer, 2011), However, the precise manner by which microbes communicate with the CNS to affect neurogenesis, synaptogenesis, myelination, or other brain processes has not yet been established (Cryan and Dinan, 2015, 2019; Heijtz et al., 2011). Some of these effects would be mediated by the vagus nerve (Bercik et al., 2011; Cryan and Dinan, 2015), although other mechanisms have also been proposed, including the influence of microbes on tryptophan metabolism or the direct action of microbial metabolites on the brain (Collins et al., 2013; Cryan and Dinan, 2012; Foster et al., 2017; Fung et al., 2017; Spielman et al., 2018). A list of intestinal microbiota with neuroactive potential has been published, including the intestinal microorganisms that regulate serotonin and GABA production (Valles-Colomer et al., 2019).

The capacity of gut microbiota and probiotic agents to alter cytokine levels and affect brain function illustrates the central role of the gut-brain axis in the pathogenesis of multiple diseases, including Parkinson's disease (Sampson et al., 2016), Alzheimer's disease (Vogt et al., 2017; Spielman et al., 2018), autism (Cryan and Dinan, 2015), irritable bowel syndrome (Coss-Adame and Rao, 2014), depression, stress, and anxiety (Foster et al., 2017; Jiang et al., 2015; Valles-Colomer et al., 2019). Indeed, microbiota immunomodulation is also emerging as an important pathway in gut-brain communication (Foster et al., 2017). Microbiota–gut–brain communications are bidirectional, given that the CNS can induce biochemical changes in the gut, in bacterial composition, and in immune function (Fung et al., 2017; O'Mahony et al., 2009). For instance, neonatal stress produced by maternal separation alters intestinal microbiota and increases levels of the pro-inflammatory cytokines TNF-α and IFN-γ and corticosterone, enhancing visceral hypersensitivity and anxiety (O'Mahony et al., 2009). The effects of social stressor exposure on the structure of microbiota and circulating cytokine levels were not observed in antibiotic-treated animals (Bailey et al., 2011). It has been proposed that stress compromises the integrity of the intestinal epithelial barrier (IEB), allowing bacterial translocation and activation of an immune response *via* the release of cytokines (Foster et al., 2017). Thus, microbiota appear to be essential during the first years of life in bidirectional interactions between microbiota and stress behavior, as observed in germ-free mice with an excessive response (high corticosterone levels) to stress (Foster et al., 2017). These studies point to the possibility of approaching the brain using bacteria such as *Lactobacillus* or *Bifidobacteria*, known to exert positive effects on this organ and on behavior (Foster et al., 2017).

2.3. Efferent pathways from brain to gut

Gastrointestinal tract sensory information to regulate energy

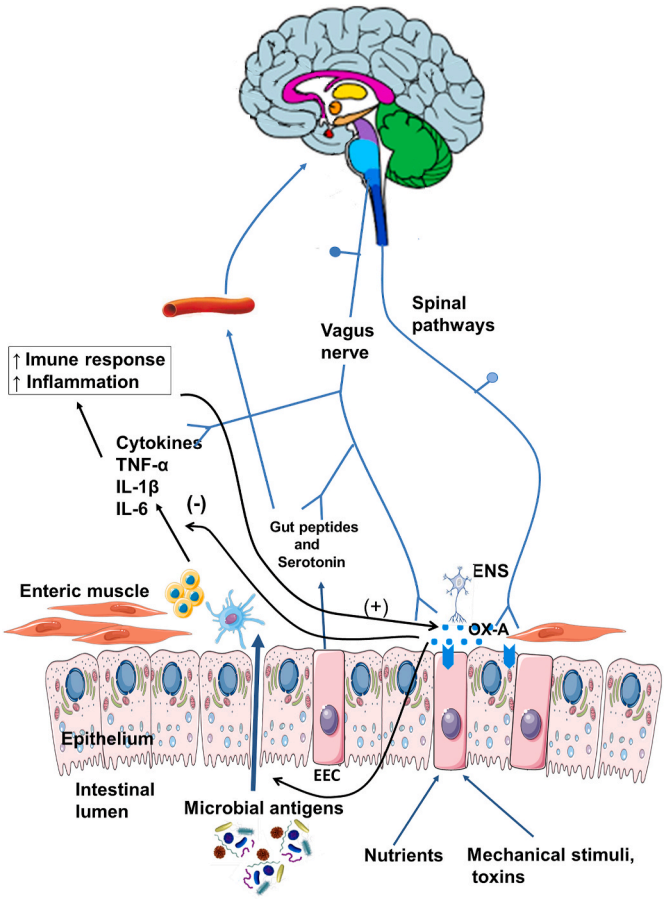

Fig. 1. Peripheral orexin in the gut-brain axis. Different types of enteroendocrine cells (EECs) dispersed among cells of the gut epithelium possess receptors that respond to luminal stimuli. Orexin-A (OX-A) and OX1R have been detected in neurons of the mesenteric plexus and in EECs of the intestinal mucosa. Peripheral orexin indicates the nutritional status of the organism but may also be released in response to inflammation, playing an immunomodulatory role in chronic intestinal inflammatory diseases. OX-A released by myenteric neurons acting on OX1R in enterocytes may regulate intestinal permeability, prevent the activation of immune cells, and protect against systemic and central inflammation. Peripheral orexin released in response to inflammation may also gain access to brain regions, either directly *via* vagal neurons or by modulating the release of peripheral cytokines. The presence of OX1R in vagal afferent neurons suggests that peripheral orexin may transmit signals from the gut to brainstem regions such as the NST and NPB. Orexigenic signals from the gut terminate in the HT, which utilizes this information to regulate peristalsis, gastric emptying, and gastrointestinal secretions *via* descending pathways (see Fig. 2). Orexin-A and OX1R are also localized in dorsal root ganglion neurons. ENS, enteric nervous system; TNF, tumor necrosis factor; IL, interleukin.

homeostasis is integrated in hypothalamic regions such as the arcuate nucleus (ARC) (Berthoud and Morrison, 2008; Duca and Covasa, 2012; Kim et al., 2018). In addition, the LH integrates visceral and gustatory information from the ARC and brainstem (Bernardis and Bellinger, 1996; Dell and Olson, 1951) and from higher-order brain structures associated with emotional, motivational, and acquisitive behaviors (Berthoud and Morrison, 2008; Duca and Covasa, 2012). Hence, the LH not only participates in homeostatic energy regulation but also plays a central role in the neural circuit that associates motivational processes and intake with reward signals, and a dysfunction of this circuit has been related to drug addiction and obesity (Petrovich, 2018; Stuber and Wise, 2016; Volkow et al., 2017).

After processing the information in integration regions, the brain communicates with the gut *via* the autonomous nervous system, HPA axis, and descending monoaminergic pathways. In this way, homeostatic outputs from the HT and amygdala reach pontine and medullar nuclei, including the NST and PBN, in order to modulate primary afferent information and control gastrointestinal function and vago-vagal reflexes (Price, 2003; Saper and Loewy, 1980; Swanson, 2003). The neural circuit includes vago-vagal connections of the NST with the DMV and the ambiguous nucleus, and these nuclei constitute the common final pathway to the gastrointestinal system (Browning et al., 2017). Finally, sympathetic and parasympathetic pathways regulate gastrointestinal contractions, motility, and secretions as well as the immune modulation of gut mucosa (Mayer, 2011).

3. Orexin in the gut-brain axis

The idea of an orexinergic brain-gut network involved in nutrition and homeostatic energy regulation is supported by the presence in the gut of endocrine cells with immunoreactivity to orexin that stimulate colon motility and respond to fasting periods (Kirchgessner, 2002). In addition, neurons immunoreactive to orexin have also been detected in the mucosa of all gut regions, mainly in the duodenum, and in primary afferent neurons of the myenteric plexus in animals and humans (Ehrström et al., 2005; Tunisi et al., 2019). The presence of orexin and orexin receptors in primary afferent neurons is consistent with bidirectional orexinergic gut-brain communication and suggests that peripheral orexin may detect the presence of nutrients and transmit signals on the nutritional status of the organism (Kirchgessner, 2002; Ehrström et al., 2005). Thus, OX1R receptors have been found in vagal afferent neurons that also possess cholecystokinin (CCK) and leptin receptors. Peripheral orexin-A inhibits responses to CCK and reduces leptin levels, indicating a possible role for orexin in the modulation of gut-brain signaling (Burdyga et al., 2003; Ehrström et al., 2005). Orexin immunoreactivity has been observed in nodose ganglion cells; therefore, orexin may transmit gut information to the brain *via* vagal afferent terminals in the NST (Kirchgessner, 2002, Fig. 1). Orexin-A and OX1R have also been localized in dorsal root ganglion neurons and in the spinal cord of mice, confirming the participation of orexin in the transmission of sensorial information to the brain (Kirchgessner, 2002).

The role of peripheral orexin is not clearly defined, and its source and the signal triggering its release are not precisely known. It has been suggested that it may be released from enteric neurons and endocrine cells in response to acute reductions of glucose availability; therefore, given the vagal processing of this peptide, the orexinergic gut-brain axis would be important for short-term intake (the amount of food consumed during a single intake period) and for the acute regulation of energy homeostasis (Kirchgessner, 2002). At any rate, the fact that peripheral orexin-A reduces the gastric emptying rate but has no effect on the appetite in humans allows the effects of peripheral and central orexin to be differentiated (Ehrström et al., 2005; Yamada et al., 2000).

Peripheral orexin-A may intervene in the process that precedes food absorption and inhibit gut motility during a fasting period (Ehrström et al., 2005). Data have been published suggesting that orexin may coordinate the activity of myenteric plexus interstitial cells for intestinal peristalsis and motility (Nakayama, 2011; Squecco et al., 2011). Mouse studies using both mechanical and electrophysiological techniques confirmed a direct effect of orexin-A on the smooth muscle of the duodenum that may reinforce or compensate for orexinergic signals from neurons of the DMV (Squecco et al., 2011). In other words, hypothalamic orexinergic neurons may be regulated by sensory signals from the gastrointestinal system and transmitted *via* brainstem regions involved in autonomic and visceral signal processing (Kirchgessner, 2002; Yoshida et al., 2006; Okumura et al., 2020). Brain orexinergic neurons may use this sensory information to modify vagal reflexes *via* descending pathways to the brainstem, because orexin-immunoreactive fibers have been found in the NST and in the DMV (Yamada et al., 2000). It is therefore possible that central orexin alters the activity of vagal motor neurons and/or modulates the response of the NST to gastrointestinal

Box 1
Key observations about orexin-A in gut-brain axis

- Orexin-A (OX-A) is a chemical mediator in the bidirectional gut-brain dialogue, and orexinergic neurons integrate central and peripheral signals to monitor numerous physiological functions
- Enteric OX-A transmits signals to the brain on nutritional status and inflammation
- Enteric OX-A responds to infection by reducing intestinal epithelial barrier permeability and neuroinflammation. Thus, peripheral orexin may act as an immunomodulator in cases of inflammation, both signaling and responding to infection
- Hypothalamic OX-A plays a role in brain-gut communication by mediating in gut secretions and motility and in the antinociceptive response to gut pain.
- Orexin-A neurons in the lateral hypothalamus detect inner and environmental cues and interact with stress systems. Hence OX-A in the gut-brain axis may contribute to intestinal inflammation-related stress

Hypothesis

- Repeated activation of the orexinergic system in chronic processes may exacerbate gastrointestinal inflammation and contribute to irritable bowel syndrome and chronic intestinal inflammatory diseases

stimuli in order to mediate in cephalic phase reflexes, for example, and affect gastrointestinal motility and secretion (Kirchgessner, 2002; Okumura and Nozu, 2011; Takahashi et al., 1999). In fact, central but not peripheral orexin-A produces gastric secretion, and this effect is suppressed by vagotomy or atropine administration (Okumura and Nozu, 2011; Takahashi et al., 1999). Likewise, only hypothalamic orexin-A processed *via* the vagal pathway has a protective effect against ethanol-induced gastric mucosal damage (Yamada et al., 2007).

4. Orexin and immune diseases

In 1999, animal studies first related the orexinergic system to narcolepsy, characterized by the irresistible need to sleep during the daytime ("sleep attack"), even in inappropriate circumstances (Chemelli et al., 1999; Lin et al., 1999). A relationship between the immune system and orexin was supported by the consideration of NT1 as an autoimmune disease caused by the selective T-cell-mediated death of orexinergic cells (Mahoney et al., 2019). Specifically, it has been proposed that NT1 is associated with antigens of the major histocompatibility complex (HLA) and with T cell receptors (TCRs) and that an autoimmune process in orexinergic cells develops *via* interactions in specific HLA-peptide-TCR pathways (Kornum et al., 2011; Mahoney et al., 2019; Sakurai, 2013).

Immune system modifications induced by LPS reduced hypothalamic orexin levels and caused the rapid production of hypothalamic cytokines in *orexin/ataxin-3* and control mice, which also manifested symptoms similar to sickness behaviors (Tanaka et al., 2016). It was recently reported that peripheral orexin-A protects against the systemic and central inflammation that produces LPS-induced loss of intestinal epithelial barrier integrity (Tunisi et al., 2019). According to the authors, orexin-A avoids the increase in intestinal barrier permeability and the release of LPS observed when the composition of the microbiome is altered. In this way, orexin-A released by myenteric neurons acting on OX1R in enterocytes may regulate intestinal permeability in some types of intestinal dysbiosis and prevent the activation of immune cells and microglia (Tunisi et al., 2019, Fig. 1). Brain orexin-A also improves LPS-induced intestinal hyperpermeability *via* the vagal cholinergic pathway, again demonstrating that orexin mediates in bidirectional gut-brain communication (Okumura et al., 2020).

Peripheral and central orexin may also have analgesic properties. In fact, orexin and orexin receptors have been located in the dorsal root ganglion (Kirchgessner, 2002). Accordingly, and given the abundance of orexinergic fibers in the intestine, the targeting of orexinergic spinal or enteric systems has been proposed for intestinal disorders associated with hyperalgesia (Kirchgessner, 2002). Moreover, alteration of OX1R expression has been observed in inflamed mucosa in colon cancer and also in ulcerous colitis, an inflammatory intestinal disease characterized by ulcers in colonic and rectal mucosa that is a risk factor for colon cancer (Leonard and Kukkonen, 2014; Messal et al., 2018). OX1R expression was found to be aberrant in human colon cancer cell lines, and orexin-A induced apoptosis of tumor cells and reduced their number, leading to a proposal to use OX1R agonists in colon cancer treatment (Voisin et al., 2011). In animal models of colitis, i.p. orexin-A improved colitis symptoms and the histological appearance of colon mucosa and reduced the production of pro-inflammatory cytokines (e.g., TNF-α, IL-6, and MCP-1), suggesting an immunomodulatory role for orexin in chronic inflammation, including inflammatory bowel disease (Messal et al., 2018).

Gastrointestinal disease is frequently associated with stress-related symptoms and sickness behaviors, a set of symptoms associated with an infectious episode (e.g., hyperalgesia, fatigue, fever, adipsia, anorexia, lassitude, hypersomnia, and social isolation) that arise as adaptive behaviors against the infection (Dantzer, 2001; Konsman et al., 2002). Peripheral orexin released in response to inflammation may gain access, either directly *via* vagal neurons or by modulating the release of peripheral cytokines, to brain regions related to stress. Indeed, there are known to be reciprocal connections between orexinergic neurons and stress systems (Grafe et al., 2017; Nambu et al., 1999; Peyron et al., 1998; Scammell and Winrow, 2011), and orexin-containing neurons are sensitive to and regulate corticotropin-releasing factor activity (Winsky-Sommerer et al., 2004). However, orexin does not appear to be related to all types of stressors but rather to those in which the stress draws attention to environmental or inner stimuli (Giardino and de Lecea, 2014; Rodgers et al., 2013; Sakurai, 2014), as in cases of chronic gastrointestinal inflammation. Thus, peripheral orexin has anti-inflammatory and gastroprotective effects and reduces damage to the intestinal mucosa, while brain orexin-A enhances the antinociceptive response to gut signals such as colon distention (Okumura et al., 2015). However, repeated activation of the orexinergic system in chronic processes can increase stress levels and exacerbate gastrointestinal inflammation. In this regard, orexin-mediated excitatory mechanisms in the duodenum have been associated with the irritable bowel syndrome and chronic intestinal inflammatory diseases (Konsman et al., 2002; Nakayama, 2011; O'Mahony et al., 2009), in which gut hypersensitivity frequently coexists with stress, depression, and anxiety (Coss-Adame and Rao, 2014; Foster et al., 2017).

5. Conclusions

There is increasing recognition of the importance of gut-brain

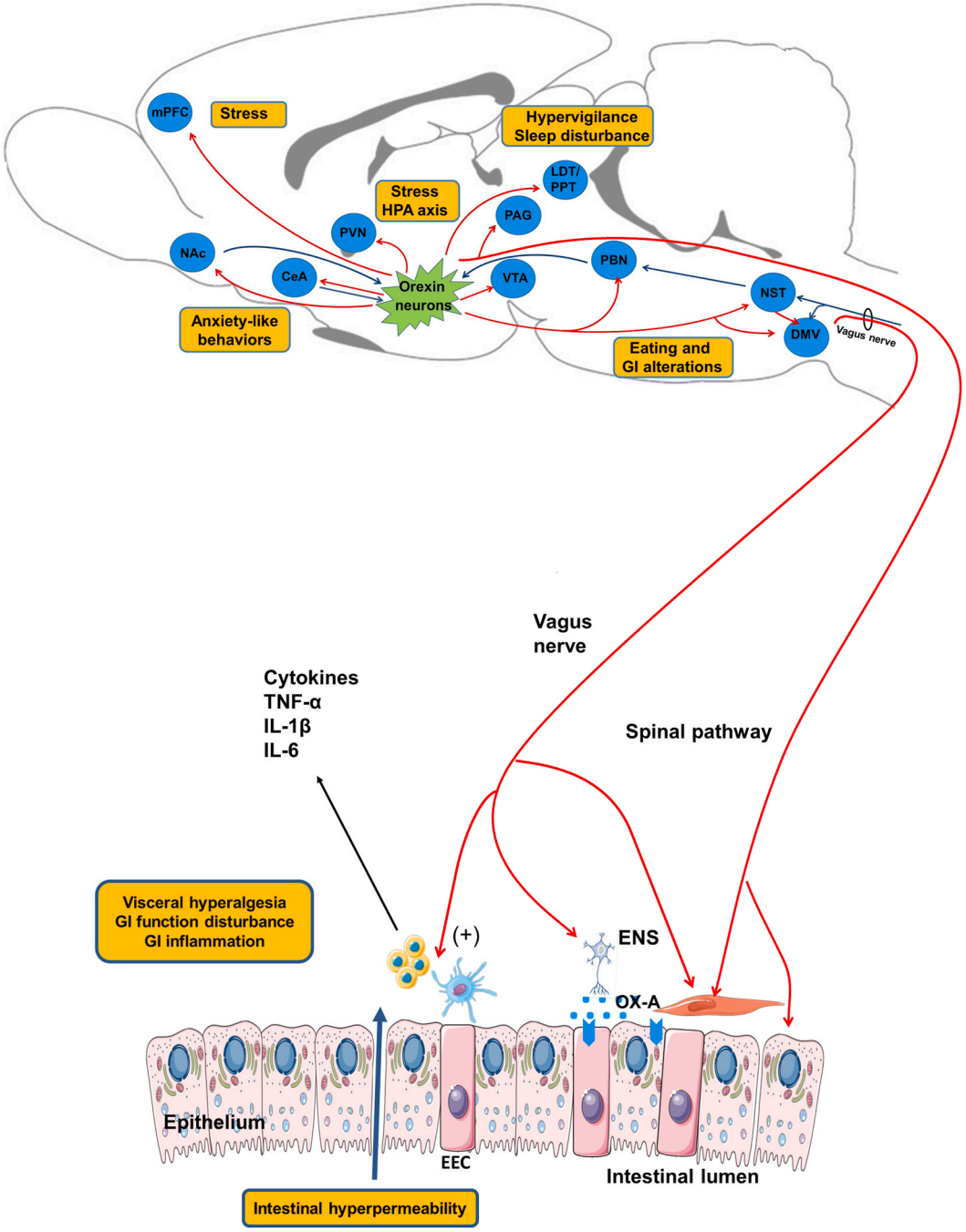

Fig. 2. Orexin brain-gut communication and proposed mechanisms in chronic intestinal diseases. Information from the intestinal environment provided by orexinergic afferents is integrated in the LH with external environmental signals to orchestrate the appropriate autonomic, immune, endocrinal, and behavioral responses to each situation. Projections of hypothalamic orexinergic neurons to such regions as NAc, VTA, NST, and LDT/PPT may help to overcome the sickness behaviors (e.g., lethargy, fatigue, or anorexia) that accompany acute inflammatory processes, increasing appetite and arousal. Hypothalamic orexin-A, *via* the NST and DMV, is processed by efferent vagal fibers that reach the circular smooth muscle and submucosal and myenteric neurons, facilitating intestinal motility, protection of the mucosa, and the release of peripheral orexin. In chronic gastrointestinal diseases, the repeated activation of orexinergic neurons in response to inner salient cues would produce: 1) a state of hypervigilance, with sleep and appetite impairment; 2) anxiety-like behaviors, due to the modification of brain reward circuits and the activation of stress circuits; 3) disturbance of the autonomic regulation and functioning of the gastrointestinal system, affecting vagal tone and intestinal permeability; and 4) increased visceral hyperalgesia due to the alteration of pain-inhibitory orexin pathways. For the purposes of clarity, the figure omits the projections of orexinergic neurons to regions such as the locus coeruleus or dorsal raphe, related to arousal and sleep, and the ARC, related to feeding, among others. CeA, central nucleus of the amygdala; PVN, hypothalamic paraventricular nucleus; NAc, nucleus accumbens; mPFC, medial prefrontal cortex; LDT/PPT, laterodorsal tegmental nucleus/pedunculopontine tegmental nucleus; VTA, ventral tegmental area; PBN, parabrachial nucleus; NST, nucleus of the solitary tract; DMV, dorsal motor nucleus of the vagus. Input (−) and output (−) of orexin neurons.

communication in health and disease, and it is essential to determine the underlying pathways and mechanisms. The orexin/hypocretin system appears to play a major role in this bidirectional crosstalk (Box 1).The physiological role of the gut is not only to digest food and absorb nutrients but also to detect and respond to potentially toxic or noxious signals. In this regard, various researchers have suggested a possible role for peripheral orexin in both signaling and responding to infection, acting as an immunomodulator in cases of inflammation. Central orexin-A also plays a role in brain-gut communication by mediating in the antinociceptive response to gut pain, among other actions (Okumura et al., 2015). Orexin-A neurons in the LH detect inner and environmental cues and interact with systems that regulate emotion, reward, and energy homeostasis (Fig. 2). These connections allow orexinergic neurons to integrate central and peripheral signals and to monitor numerous physiological functions (Haynes et al., 1999; Li et al., 2014; Stuber and Wise, 2016; Tsujino and Sakurai, 2009). Changes in the orexinergic system are therefore implicated in a wide variety of diseases, including obesity, narcolepsy, and gastrointestinal disorders.

Declaration of competing interest

None.

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