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Review article

Role of glutamatergic neurotransmission in the enteric nervous system and brain-gut axis in health and disease

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ABSTRACT

Several studies have been carried out in the last 30 years in the attempt to clarify the possible role of glutamate as a neurotransmitter/neuromodulator in the gastrointestinal tract. Such effort has provided immunohistochemical, biomolecular and functional data suggesting that the entire glutamatergic neurotransmitter machinery is present in the complex circuitries of the enteric nervous system (ENS), which participates to the local coordination of gastrointestinal functions. Glutamate is also involved in the regulation of the brain-gut axis, a bi-directional connection pathway between the central nervous system (CNS) and the gut. The neurotransmitter contributes to convey information, via afferent fibers, from the gut to the brain, and to send appropriate signals, via efferent fibers, from the brain to control gut secretion and motility. In analogy with the CNS, an increasing number of studies suggest that dysregulation of the enteric glutamatergic neurotransmitter machinery may lead to gastrointestinal dysfunctions. On the whole, this research field has opened the possibility to find new potential targets for development of drugs for the treatment of gastrointestinal diseases. The present review analyzes the more recent literature on enteric glutamatergic neurotransmission both in physiological and pathological conditions, such as gastroesophageal reflux, gastric acid hypersecretory diseases, inflammatory bowel disease, irritable bowel syndrome and intestinal ischemia/reperfusion injury.

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1. Introduction

As a major excitatory neurotransmitter in the central nervous system (CNS), glutamate plays a fundamental role in the modulation of both physiological (e.g. memory, learning) and pathophysiological (e.g. stroke, epilepsy, neurodegenerative diseases such as Alzheimer's and Parkinson's disease, etc.) conditions (Meldrum, 2000; Genoux and Montgomery, 2007). Increasing evidence suggest that glutamate may also have a role in the regulation of a number of functions in the peripheral nervous system, including the gastrointestinal function (Gill and Pulido, 2001). Several studies have been carried out in the last 30 years in the attempt to clarify the possible role of glutamate as a neurotransmitter/neuromodulator in the gut. Such effort has provided immunohistochemical, biomolecular and functional data suggesting that the entire glutamatergic neurotransmitter machinery is present in the complex circuitries of the enteric nervous system (ENS), which participates to the local coordination of gastrointestinal functions, as well as in the brain-gut axis, a bi-directional connection pathway between the central nervous system (CNS) and the gut. This opens an exciting scenario on the possibility to target the enteric glutamatergic neurotransmission for the development of new potential pharmacological tools addressed to the treatment of gastrointestinal disorders. The present review will consider the more recent literature describing the involvement of glutamate as a neurotransmitter in the modulation of the digestive tract under physiological and pathological conditions. In this latter regard, specific paragraphs will be addressed to describe the participation of enteric glutamatergic pathways in gastroesophageal reflux, gastric acid hypersecretory diseases, inflammatory bowel disease (IBD), irritable bowel disease (IBS) and intestinal ischemia/reperfusion (I/R) injury.

2. The enteric nervous system

The ENS is a complex and extensive neuronal network, which extends from the esophagus to the anal sphincter, composed of ganglia, interconnecting fibers and neuronal fibers impinging on effector tissues, including the smooth muscle layer, epithelial lining, intrinsic blood vessels and gastroenteropancreatic endocrine cells (Furness et al., 2014). All aspects of the gastrointestinal function are under control of the ENS including: motility patterns, gastric secretion, transport of fluids across the epithelium, blood flow, nutrient handling, interaction with the immune and endocrine systems of the gut (Furness, 2012; Wood, 2012). A unique property of the ENS with respect to any other section of the peripheral nervous system is that enteric ganglia can maintain integrated functions in the absence of input from the CNS. For instance the bowel can propel intraluminal contents (peristaltic reflex) or generate the migrating myoelectric complex (MMC, whose progression during fasting along the small intestine depends on intrinsic neuronal activity) independent of extrinsic innervations (Furness, 2012). The ENS, however is not autonomous and neuronal control of the gastrointestinal tract depends on an integrated interaction between local reflexes, reflexes that pass through sympathetic ganglia and reflexes that pass from the gut and back to the CNS, via vagal, splanchnic and pelvic nerves (Furness et al., 2014; Veremulen et al., 2014). Large number of neurons, 200–600 millions in human, the same number of neurons that is found in the human spinal cord, give rise to the three major components: the subserous, the myenteric (Auerbach's located between the two smooth muscle layers) and the submucosal (Meissner's located in the submucosal layer) plexuses. This latter is absent in the esophagus and stomach (Furness, 2006; Furness et al., 2014). Approximately 20 distinct types of neurons have been described according to their morphology, neurochemical coding, cell physiology, projections to targets and functional roles. From a functional view point three major classes of neurons have been identified: intrinsic primary afferent neurons, interneurons, excitatory and inhibitory motor neurons (Furness, 2006). Intrinsic primary afferents are sensory neurons which detect mechanical distortion of the mucosa, mechanical forces in the external musculature (tension of the gut wall) or the presence of chemical luminal stimuli and initiate appropriate reflex control of functions including motility, secretion and blood flow (Clerc et al., 2002). Intrinsic primary afferents are multiple-axonal neurons with a large ovoid cell body (type II morphology) and represent the 10–30% of neurons in the submucosal and myenteric ganglia of the small and large intestine of mammals (Wood, 2012). Intrinsic primary afferents connect with each other, with interneurons and with motor neurons, and upon activation display a pronounced after-hyperpolarization that depends on a Ca^{++}-activated K^{+} conductance. Along the whole gastrointestinal tract, the longitudinal and circular smooth muscle layers and the muscolaris mucosae are innervated by uni-axonal excitatory and inhibitory motor neurons (type I morphology), which receive prominent fast excitatory synaptic potentials (Wood, 2012). The primary neurotransmitters for excitatory motor neurons are acetylcholine (ACh) and tachykinins. Several neurotransmitters have been identified in inhibitory motor neurons, including nitric oxide (NO), vasoactive intestinal peptide (VIP) and ATP-like transmitters, although NO is considered the primary transmitter (Furness et al., 2014). Another important class of enteric neurons is represented by secretomotor and secretomotor/vasodilator neurons regulating the electrolyte and water transport across the intestinal mucosa (Vanner and Macnaughton, 2004). Pharmacological and immunohistochemical studies have evidenced ACh-containing as well as VIP-containing neurons which, on their own may or may not express ACh. Submucosal neurons expressing VIP cause sodium and water secretion and, by sending collaterals to submucosal arterioles, increase blood flow (Banks et al., 2005). Several types of interneurons have been identified by means of physiological/structural investigations within the gut wall (Brookes, 2001a, 2001b). In the small intestine myenteric plexus, one type of orally projecting (ascending) and three types of anally projecting (descending) neurons have been described (Neal and Bornstein, 2008). The ascending interneurons are cholinergic and participate to the local motor reflex, as are two types of descending interneurons expressing ACh and either nitric oxide synthase (NOS) or serotonin. Another type of descending interneuron containing ACh and somatostatin participate to the conduction of MMC along the intestine. Some kinds of interneurons are also mechanoceptive and contribute to stretch-initiated reflexes (Mongardi Fantaguzzi et al., 2009). An important non-neuronal component of the ENS is represented by enteric glial