



Review

Putative roles of neuropeptides in vagal afferent signaling



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HIGHLIGHTS

- Role of glutamate in vagal afferent signaling
- Problems with glutamate as the only neurotransmitter in vagal afferent neurons
- Evidence for existence of neuropeptide transmitters in vagal afferent neurons
- Putative role of peptide transmitters in modulating glutamate signaling
- Plasticity provided by vagal peptide transmitters in regulating feeding behavior

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ABSTRACT

The vagus nerve is a major pathway by which information is communicated between the brain and peripheral organs. Sensory neurons of the vagus are located in the nodose ganglia. These vagal afferent neurons innervate the heart, the lung and the gastrointestinal tract, and convey information about peripheral signals to the brain important in the control of cardiovascular tone, respiratory tone, and satiation, respectively. Glutamate is thought to be the primary neurotransmitter involved in conveying all of this information to the brain. It remains unclear how a single neurotransmitter can regulate such an extensive list of physiological functions from a wide range of visceral sites. Many neurotransmitters have been identified in vagal afferent neurons and have been suggested to modulate the physiological functions of glutamate. Specifically, the anorectic peptide transmitters, cocaine and amphetamine regulated transcript (CART) and the orexigenic peptide transmitters, melanin concentrating hormone (MCH) are differentially regulated in vagal afferent neurons and have opposing effects on food intake. Using these two peptides as a model, this review will discuss the potential role of peptide transmitters in providing a more precise and refined modulatory control of the broad physiological functions of glutamate, especially in relation to the control of feeding.

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1. Introduction

The vagus nerve provides a major bidirectional route of communication between the brain and peripheral organs. Afferent fibers of the vagus nerve convey sensory information from the gastrointestinal tract, heart, lung, liver, and pancreas to the central nervous system; while vagal efferent fibers are involved in motor function conveyed from the CNS to visceral organs. The pseudounipolar cell bodies of vagal afferents reside in bilateral nodose ganglia, and are involved in sensing multiple mechanical, chemical, osmotic, thermal, and possibly nociceptive stimuli. The total number of vagal afferent neurons has been found to be roughly similar across a number of different species and ranges from 16,000 to 18,000 perikarya, with the densest distribution of peripherally projecting fibers innervating the proximal GI tract. Tracing experiments demonstrate that the right and left nodose ganglia innervate slightly different peripheral sites [1,2]. Fibers of vagal afferent neurons also project to CNS neurons in the brain stem where they make synaptic connections with individual second order neurons in the nucleus of the solitary tract (NTS).

As a result of the large quantity of information transmitted by vagal afferent fibers it is unsurprising that they outnumber the vagal efferent fibers by approximately 9 to 1 [3]. Vagal efferent neurons carry parasympathetic motor-control fibers that are associated with the autonomic nervous system from the brainstem to visceral organs like the lungs, the heart, and the gastrointestinal tract. Vagal motor neurons are localized in two brain stem nuclei in the nucleus ambiguus (NA) and in the dorsal motor nucleus. They receive afferent inputs predominantly from NTS neurons, either as fiber projections from the NTS neurons or by sending their own dendrites into the NTS [4].

The vast array of information sensed by the vagus nerve from a large number of peripheral organs results in an extensive range of physiological functions, including a role in cardiovascular tone, respiratory tone, satiation, GI motility, digestion and absorption, emesis, and inflammation. The mechanism by which this information is communicated to the brain is not well defined. The release of the neurotransmitter glutamate from vagal afferent neurons has been demonstrated to play a role in a large number of these physiological functions, but the mechanisms by which this single neurotransmitter can regulate such an extensive list of physiological functions from a wide range of visceral sites remain unclear. The mechanisms of glutamate signaling will be addressed in this review. Extensive studies of the late 80s and 90s demonstrated that vagal afferent neurons express a range of peptides that can play a role in mediating some of the functions associated with vagal afferent neurons. Recently two novel putative peptide transmitters have been identified in vagal afferent neurons. These peptides are differentially expressed in vagal afferent neurons and are associated with opposing effects on feeding behavior. Using these two peptides as a model, this review will discuss the potential role of peptide transmitters in providing a more precise and refined modulatory control of the broad physiological functions of glutamate, especially in relation to the control of feeding.

2. Evidence for a role of glutamate in vagal afferent signaling in the NTS

The view that glutamate is the primary neurotransmitter of vagal afferent signaling to the NTS is widely shared [5–10]. This view is grounded in substantial anatomical, electrophysiological, and pharmacological evidence. Glutamate immunoreactivity can be observed in

approximately 60% of neuronal cell bodies in the nodose ganglion [11–13], as well as axons in the tractus solitarius and terminals in the NTS [12]. Nodosectomy, which removes the vagal afferent cell bodies, results in a 40% reduction in the high-affinity uptake of glutamate in the medial NTS of rats [14]. Furthermore, immunohistochemical data suggests that both types of vesicular glutamate transporter, VGLUT1 and VGLUT2, required for packaging cytoplasmic glutamate into vesicles, are present in vagal fibers and terminals in the NTS since they are significantly reduced following nodose ganglionectomy [15]. Interestingly, vagal afferents fibers retrogradely labeled from the stomach are predominantly VGLUT2 positive, while fibers retrogradely labeled from the heart are VGLUT1 positive [16]. In summary, the machinery required for uptake and packaging of glutamate is present in vagal afferent neurons.

Indirect evidence for a signaling role of glutamate in the NTS was demonstrated by intracellular recordings in slices of rat brain. Postsynaptic potentials evoked in NTS neurons were identified as predominantly excitatory [17]. Furthermore, microinjection of [3H]-D-aspartate, a biochemical marker for excitatory amino acid-utilizing neurons, into the NTS of rats, retrogradely labels to cell bodies of nodose ganglia neurons [18]. Direct measurement of glutamate concentration in the NTS by microdialysis demonstrated that glutamate levels increased in the NTS following electrical [19,20], chemical [11,21], and mechanical stimulation of the vagal afferent fibers [22]. Unilateral nodosectomy reduced NTS levels of glutamate on the ipsilateral, but not the contralateral [23,24]. Together these data suggest that many of the vagal afferent fibers projecting to the NTS store and release glutamate, consistent with a transmitter role for glutamate. Although it should be noted that at least one group repeatedly failed to demonstrate changes in glutamate concentration in the NTS by microdialysis in response to vagal afferent electrical stimulation or nodosectomy [25–27].

Importantly, the receptors required for glutamate signaling can be found on postsynaptic NTS neurons. Over the years, molecular cloning of cDNA encoding glutamate receptors has revealed multiple groups of ionotropic glutamate receptor subunits [28]. These included six *N*-methyl-D-aspartate (NMDA) receptor subunits (NR1, NR2A to NR2D, and NR3), four α -amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor subunits (GluR1–GluR4), and five kainate (KA) receptor subunits (GluR5 to GluR7, KA1, and KA2). Multiple G-protein-coupled receptors (GPCR), known as metabotropic glutamate receptors, have also been identified [29]. All of these receptors can be found in the NTS [30–32]. Both microinjection of glutamate into the NTS and vagal afferent stimulation can induce a wide range of physiological responses and these effects can be blocked using glutamate receptor antagonists [22,33–36]. Therefore there is substantial evidence supporting the concept that glutamate is a major neurotransmitter of vagal afferent neurons in the NTS that mediates physiological responses to peripheral sensory information (see Fig. 1).

3. Evidence that glutamate is involved in feeding

Bednar et al. [37] were the first to provide evidence that glutamate release from vagal afferent fibers in the NTS could mediate feeding behavior. They found that in micropunctures of the medial NTS, fasted rats had reduced glutamate concentrations; while intraperitoneal (IP) injections of the gastrointestinal hormone cholecystokinin (CCK) or ingestion of sucrose reinstated glutamate levels. Furthermore they reported that IP injection of the non-competitive NMDA receptor

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