Physiology & Behavior 105 (2011) 94–99

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

A tale of two endings: Modulation of satiation by NMDA receptors on or near central and peripheral vagal afferent terminals

Robert C. Ritter *

Dept of VCAPP and Programs in Neuroscience, Washington State University, Pullman, WA 99164-6520, United States

ARTICLE INFO

Article history:
Received 31 January 2011
Accepted 28 February 2011

Keywords:
Vagus
Control of food intake
Gastrointestinal
Satiety

ABSTRACT

Glutamate is the neurotransmitter responsible for fast excitatory transmission from vagal afferents to second order neurons in the NTS. Antagonism of NMDA-type glutamate receptors in the NTS increases food intake and attenuates reduction of food intake by vagally mediated satiation signals, such as cholecystokinin. Although, the cellular location(s) of NMDA receptors that participate in satiation is uncertain, recent findings suggest that attenuation of satiation by NMDA receptor antagonists is due, at least in part, to their action on primary vagal afferents themselves. While evidence is accumulating that NMDA receptors located on vagal afferent endings in the hindbrain are involved in control of food intake, there also is preliminary evidence that peripheral NMDA receptors also may influence vagal control of food intake. Hence, NMDA receptor expression on central and perhaps peripheral vagal afferent endings could provide a parsimonious mechanism for modulation of satiation signals by endogenously released glutamate.

In rats, the right and left nodose ganglia contain cell bodies of roughly 17,000 pseudounipolar neurons — the primary vagal afferents [1]. The distal axon endings of these neurons innervate internal organs, while the proximal endings synapse in the nucleus of the solitary tract of the hindbrain (NTS), functionally tying the viscera to the brain. An estimated 70% of vagal afferents innervate the abdominal viscera, especially the stomach and intestines (for review see [2]). One of the functions of abdominal vagal afferents is to participate in the control of food intake by responding to gastrointestinal stimuli [3]. Although information has accumulated steadily regarding the sensitivity of vagal afferents to specific gastrointestinal stimuli, much less is known about the mechanisms by which gastrointestinal signals are transmitted to higher order neurons or modulated by transmitter receptors on central and/or peripheral vagal afferent endings.

Vagal afferents synthesize and apparently release a variety of neuroactive substances, including purines, amines, amino acids and peptides. Nevertheless, several types of evidence indicate that the excitatory amino acid anion, glutamate, is a major neurotransmitter for vagal afferent neurons. For example, vagal afferent terminals express immunoreactivity for vesicular glutamate transporters [4–8], which is indicative of glutamatergic neurotransmission. In addition, electrophysiological experiments reveal that glutamate is released from central vagal afferent terminals during electrical or chemical stimulation [9–11] triggering glutamate-mediated postsynaptic currents in NTS neurons. Finally, glutamate receptor antagonists applied to the NTS are reported to attenuate a number of physiological responses evoked by vagal afferent stimulation [12–16]. Clearly, glutamate and its cognate receptors play a pivotal role in vagal sensory function.

Neuronal responses to glutamate are mediated by three families of ionotropic glutamate receptors, (AMPA-, kainate- and NMDA-type) [17–20] and by several groups of G-protein coupled, metabotropic receptors [21]. Most electrophysiological observations indicate that vagal afferent terminals excite NTS postsynaptic neurons by activating AMPA-/kainate-type receptors, and to a lesser extent by actions at NMDA-type receptors. Although the traditional view of ionotropic glutamate receptors, including NMDA receptors, is that they are located on postsynaptic cell bodies and dendrites, NMDA receptor subunit immunoreactivity has been localized to axon terminals at a variety of sites in the brain [22,23], including on vagal afferent terminals in the NTS [24]. Furthermore, electrophysiological data indicate that NMDA receptors located on axon terminals modulate transmitter release in many areas of the central nervous system, including the visual cortex [25], entorhinal cortex [26], and primary somatosensory afferent terminals in the spinal dorsal horn [27–29]. Thus, it now appears that NMDA-type glutamate receptors, located on axon terminals, play an important role in determining the amount and types of chemical transmitters released onto postsynaptic receptors.

Intriguingly, mRNA coding for NMDA receptor subunit has been detected in the nodose ganglia by in situ hybridization (ISH) [30] and polymerase chain reaction (PCR) [31]. In addition, reports by Czaja et al. (Fig. 1) indicate that NMDA NR1 subunit immunoreactivity is present in more than 90% of vagal afferent cell bodies in the nodose ganglia [1], while expression of NMDA NR2 subtypes reveals that vagal afferents comprise several apparently distinct phenotypes, with regard to the

* Tel.: +1 509 335 8114; fax: +1 509 335 4650.
E-mail address: britter@vetmed.wsu.edu.

0031-9384/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.physbeh.2011.02.042

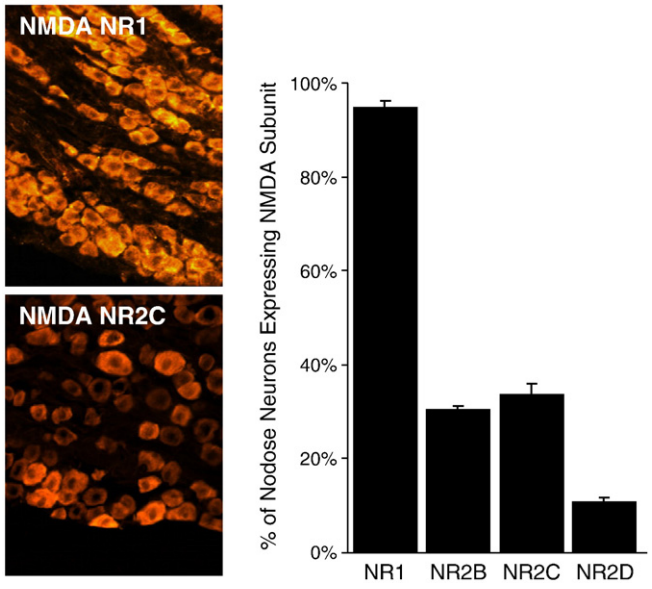

Fig. 1. Left panels: Photomicrographs of 10 micron sections from rat nodose ganglia illustrating vagal afferent neurons labeled with affinity-purified polyclonal primary antisera raised in goat against the NR1 or NR2C NMDA channel subunits. Right panel: Histogram depicting the proportion of the total vagal afferent population immunopositive for various NMDA channel subunits. Data replotted from Czaja et al. [1]. Note that more than 95% of vagal afferents express NR1 immunoreactivity. The NMDA channel is heteromeric containing both NR1 and NR2 subunits. However, NR1 is obligatory for all NMDA receptors. The fact that it is expressed in most, if not all, vagal afferents suggests that all vagal afferents express NMDA receptors.

composition of their NMDA receptors [32]. Finally, using ultrastructural methods, others have demonstrated the presence NMDA NR1 immunoreactivity on vagal afferent terminals in the NTS [24].

Because of the evidence that NMDA receptors are expressed by vagal afferents, and are localized both presynaptically on central vagal afferent terminals and postsynaptically on some hindbrain neurons innervated by vagal afferents, we postulated that NMDA receptors might participate in control of food intake by the vagus. Accordingly, in 1997 we published our first report demonstrating that rats increased their food intake following intraperitoneal injection of MK-801, a non-competitive, open channel blocker of NMDA receptor ion channels [33]. The results of these initial experiments revealed several interesting aspects of food intake associated with NMDA receptor blockade. First, MK-801 increased intake of either solid rodent diet or 15% sucrose solution (Fig. 2) following overnight food deprivation. The antagonist did not increase water intake following

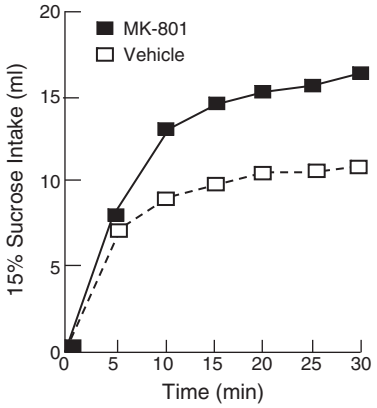

Fig. 2. Sucrose intake by 16 h food deprived rats offered 15% sucrose solution. The non-competitive NMDA channel blocker, MK-801 (100 μg/kg, IP), significantly increased sucrose intake.
Redrawn from Burns and Ritter [33].

water deprivation. These results suggested that the effects of MK-801 were selective for food intake. In addition, we observed that when rats were not food deprived, MK-801 failed to trigger initiation of food intake. However, if MK-801 was administered to non-fasted rats that then were offered cookies, a highly palatable preferred food, intake was dramatically enhanced. These results suggested to us that the net effect of systemic NMDA ion channel blockade was to delay termination of food intake once it started. This hypothesis was subsequently supported by the results from our lab, which demonstrated that if fasted rats were allowed to eat for 10 to 15 min prior to injection of MK-801 (Fig. 3), the antagonist did not further increase intake [34]. In order to be effective the drug had to be on board before or soon after feeding commenced. It was ineffective once the process of satiation was complete. Subsequently, additional results were reported by Jahng and Houpt [35], who examined the effect of MK-801 on the first and second nighttime meals in rats. They found that IP injection of MK-801 just prior to the start of nighttime feeding increased meal duration, but did not shorten the interval between meals, supporting the hypothesis that MK-801 interfered with meal termination or the process of satiation.

Lesions of the caudal NTS abolish increased food intake in response to IP MK-801 injections [36]. This finding suggested that the dorsal hindbrain was a site that is necessary for MK-801 to increase food intake, but does not actually indicate the relevant receptors are located there. However, we also found that MK-801 injected via the fourth ventricle or directly into the NTS increased food intake in a manner similar to systemic MK-801 injection, but at much lower doses [37,38]. In addition, Covasa and coworkers subsequently demonstrated that a variety of competitive NMDA receptor antagonists also increased food intake when injected via the fourth ventricle or into the NTS [39–41]. These results support the conclusion that NMDA receptors in the dorsal hindbrain participate in control of food intake. In addition, the fact that chemically diverse, competitive NMDA receptor antagonists, injected into the hindbrain, produce effects on food intake that are comparable to those produced by MK-801 suggest that the effect is indeed due to NMDA receptor-specific antagonism, as opposed to a chemical effect that is unrelated to NMDA receptor function.

The fact that the dorsal hindbrain, where vagal afferents terminate, is a site where NMDA receptors participate in control of food intake prompts the question of whether NMDA receptor activation is necessary for the processing vagally mediated satiation signals. In this regard it is very well documented that the gut peptide, cholecystokinin (CCK) reduces food intake by activating vagal afferents innervating the gastrointestinal tract [42], and we were encouraged by a prior report that MK-801 attenuated reduction of liquid diet consumption by rats fed through a chronically implanted cheek fistula [43]. In our own initial test for NMDA receptor participation in CCK-induced reduction of food intake we found that IP injection of MK-801 attenuated reduction of food intake by IP CCK-8 in freely feeding rats [44]. More recently, Guard et al. [40] have reported that systemic injection of the competitive NMDA antagonist D-CPPene not only attenuates CCK-induced reduction of food intake, but also attenuates CCK-induced increases of NTS Fos immunoreactivty, indicating that somewhere between the gut and the NTS NMDA receptors are necessary for CCK's vagally mediated effect on feeding and neuronal activation. Finally in experiments completed very recently we found that injection of MK-801 directly into the NTS prevented reduction of food intake by IP CCK (Fig. 4). Moreover, when D-CPPene was injected into the fourth ventricle we were able to prevent CCK-induced reduction of food intake and attenuate CCK-induced increase in NTS Fos expression [45]. These results strongly support the hypothesis that activation of NMDA receptors within the hindbrain itself is required in order for CCK to reduce food intake.

As noted earlier NMDA receptors are expressed by vagal afferents as well as by neurons in the NTS. Consequently, it is possible that