Brain Research 1693 (2018) 146–150

Contents lists available at ScienceDirect

Brain Research

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

Review

Mechanisms of vagal plasticity influencing feeding behavior

Guillaume de Lartigue [a,*], Chelsea Xu [b]

[a] The John B. Pierce Laboratory, New Haven, CT, USA
[b] Department Cellular and Molecular Physiology, Yale University School of Medicine, New Haven, CT, USA

ARTICLE INFO

Article history:
Received 3 November 2017
Received in revised form 21 March 2018
Accepted 26 March 2018

Keywords:
Plasticity
Vagus nerve
Obesity
Feeding
Neuropeptide
Conductance

ABSTRACT

Sensory neurons of the vagus nerve receive many different peripheral signals that can change rapidly and frequently throughout the day. The ability of these neurons to convey the vast array of nuanced information to the brain requires neuronal adaptability. In this review we discuss evidence for neural plasticity in vagal afferent neurons as a mechanism for conveying nuanced information to the brain important for the control of feeding behavior. We provide evidence that synaptic plasticity, changes in membrane conductance, and neuropeptide specification are mechanisms that allow flexibility in response to metabolic cues that can be disrupted by chronic intake of energy dense diets.

Contents

1. Introduction

Vagal afferent neurons peripherally innervate cardiovascular, respiratory, and gastrointestinal organs (de Lartigue, 2014). Their pseudounipolar cell bodies reside in the nodose ganglia with central axons that terminate in the nucleus of the solitary tract (NTS) and convey information on a range of diverse stimuli, including heart rate, blood pressure, lung stretch and irritation, as well as gastrointestinal stretch and nutrient detection (de Lartigue, 2014). Thus, neurons of the nodose ganglia respond to a vast number of stimuli. While individual neurons will only be exposed to stimuli in their milieu, the local environment changes rapidly and frequently throughout the day. For example, vagal afferent neurons innervating the gut are exposed to gastrointestinal stretch, transmitters from enteric neurons, gastrointestinal hormones, the products of digestion and absorption, and bacterial products that all change throughout the day depending on nutrient availability. The response to these signals can be altered depending on the metabolic state, as well as local and systemic immune and inflammatory state. Therefore, vagal afferents display a remarkable degree of adaptability in response to a variety of signals and must be able to convey this information centrally.

Neural plasticity refers to the ability of neurons to change in form and function in response to alterations in their environment. This is essential for the normal development of circuits necessary to learn and to respond appropriately to our internal and external

* Corresponding author at: The John B. Pierce Laboratory, 290 Congress Ave, New Haven, CT 06519, USA.
E-mail address: gdelartigue@jbbierce.org (G. de Lartigue).

https://doi.org/10.1016/j.brainres.2018.03.030
0006-8993/

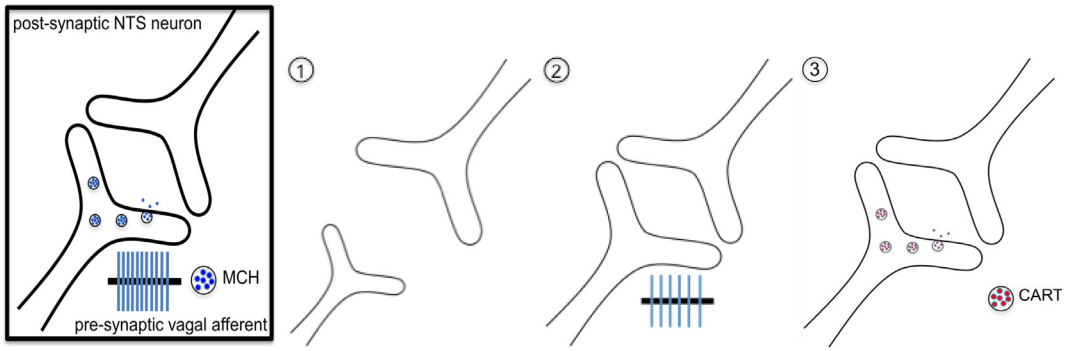

Fig. 1. Pre-synaptic mechanisms of plasticity in the vagus nerve. (1) Synaptic plasticity. Prolonged intake of high-fat or high-sugar diets leads to withdrawal of the central vagal afferent fibers. (2) Membrane conductance. Obese animals experience decreased excitability of vagal afferent neurons, leading to reduced firing in response to metabolic signals from the gut. (3) Neuropeptide switching. In a fasted state, MCH (melanin concentrating hormone) is released and motivates food intake. Upon food entering the gut, CCK signals nutrient availability and promotes neurotransmitter switching from MCH to CART (cocaine and amphetamine regulated transcript), which to signals satiety to the hindbrain.

environments. Importantly, neuronal plasticity continues throughout life in order to improve performance and learn to adapt in response to experience both centrally (Ho et al., 2011) and in primary mature sensory neurons (Hubel, 1962). At the cellular level there are three forms of plasticity that have been identified to impact neuronal signaling in the central nervous system, including structural changes in dendritic and axonal anatomy, changes in membrane excitability, and neuropeptide respecification (Fig. 1). There is evidence for these different types of plasticity all occurring in peripheral vagal afferent neurons. In this review we will discuss this evidence focusing on the impact of vagal gut-brain plasticity on feeding.

2. Synaptic remodeling

Changes in neuronal connectivity occur constantly in the adult brain in an experience-dependent manner. These occur both pre-synaptically and post-synaptically, including effects on synaptic vesicle release and recycling, transmitter receptor trafficking, cell adhesion, and changes in gene expression (Ho et al., 2011). Under pathologic conditions there can also be changes in synapse number caused by retraction of pre-synaptic processes or neuronal atrophy. For example, in depression, there is evidence for atrophy of pyramidal neurons in the hippocampus and medial prefrontal cortex (Iwata et al., 2013). Further, Alzheimer's disease is characterized by reorganization of connectivity and loss of synapses (Sw and Da, 2006). Thus, synaptic remodeling is associated with pathologic states and behavioral phenotypes.

Changes in the number of central vagal afferent fibers in mature animals have also been observed under pathologic conditions. Damage to peripheral axons of the vagus nerve is associated with remodeling of central vagal fibers. In response to the vanilloid receptor (TRPV1) channel agonist, capsaicin, the density of lectin IB4, which binds to unmyelinated c-fibers, initially decreases in the NTS, presumably reflecting capsaicin induced neuronal death. Over time, IB4 density in the NTS increases, possibly indicative of neuronal regeneration and sprouting of new fibers (Ballsmide, 2015; Peters et al., 2014). A similar response has been observed in response to chronic consumption of palatable energy-dense diets. After 21 days of either high-fat or high-sugar diet IB4-labeledc-fibers withdraw from the hindbrain, and this is followed by pronounced increase in IB4 density after 8 weeks (Vaughn et al., 2017; Sen et al., 2017). The mechanism for this apparent remodeling and the extent to which it causes changes in feeding behavior and/or leads to obesity require further study.

3. Changes in excitability

The intrinsic excitability of neurons determines their activation in response to an electrical or chemical signal. Regulation of intrinsic excitability can therefore control the dynamic range of stimulus response at the cellular level (Marder et al., 1996). Voltage-gated conductance can change neuronal firing properties such as the threshold (ie. ranging from spontaneously active to inactive until high concentrations of stimulus), frequency (ie. single firing to bursts), or rate of repolarization (ie. how quickly a cell can fire after activation). These properties can change rapidly on the timescale of hours (Aizenman et al., 2003) to days (Desai et al., 1999). Similarly, changing expression of receptors at the terminals would impact the strength of the response. Therefore changing the excitability of a neuron either by altering conductance or receptor expression under physiological conditions can quickly impact behavior.

The threshold of gastric vagal afferents to mechanical stimuli is dynamic and dependent on the combination of GI hormones, feeding state and metabolic state. Gastric vagal afferent fibers can be characterized into two sub-types based on their response to tension or touch, with tension-sensitive fibers terminating predominantly in the muscular layer, and touch-sensitive fibers terminating in the mucosa (de Lartigue et al., 2014a). In lean mice fed ad libitum, leptin increases the threshold of gastric mucosal vagal afferent neurons to tactile stimuli, an effect that is lost in lean fasted mice and HF diet fed obese mice (Kentish et al., 2012). Conversely tension sensitive fibers are depressed by leptin in lean fed mice, an effect that is absent in fasted mice or HF diet fed obese mice. Therefore the threshold is largely determined by the availability and sensitivity to circulating hormones which is shaped by the feeding and metabolic state.

Under fasting conditions, leptin release is reduced (Sinha et al., 1996) while ghrelin levels will increase (Muller et al., 2002). Ghrelin reduces the excitability of mucosal and tension gastric vagal afferents (Kentish et al., 2012) and is also associated with reduced leptin signaling in vagal afferent neurons (de Lartigue et al., 2010). In obesity, ghrelin may not play an important role in reducing gastric vagal afferent sensitivity to leptin since ghrelin levels are reduced (Shiiya et al., 2002; Tschop et al., 2001), instead reduced vagal afferent neurons have been associated with the development of leptin resistance (de Lartigue, 2014; de Lartigue et al., 2012). Importantly loss of leptin receptor the threshold potential of gastric vagal afferents in obesity. In duodenal vagal afferent neurons the resting membrane potential is not significantly different between neurons in lean and obese animals, nor are characteristics of action potentials such as the duration, threshold, maximum rise