5

TRPV1 in Central Cardiovascular Control

Discerning the C-Fiber Afferent Pathway

Michael C. Andresen*, Mark W. Doyle†, Timothy W. Bailey, and Young-Ho Jin

5.1. Introduction

Progress in understanding the central nervous system (CNS) mechanisms regulating cardiovascular function has long been linked to the neurobiology of cranial primary sensory afferents. Activation of visceral afferents with chemical substances provided seminal evidence that particular afferents even within a single organ (e.g., the heart) or sensory modality (e.g., mechanoreceptors) could have fundamentally different characteristics and evoke unique reflex outcomes. In cardiorespiratory afferent studies, early practitioners deployed a range of sometimes rather exotic exogenous compounds to probe the discharge properties of afferent nerves as well as to evoke reflex responses. These chemicals ranged from neurotransmitters, peptides, prostanoids, cytokines, phenylbiguanide, and veratridine to nicotine.1–4 Thus, the pharmacology of primary visceral afferents is intimately interwoven into the fabric of CNS processing and the physiology of autonomic reflexes.

Few substances have enjoyed the longevity or the wide utility of another agent, capsaicin (CAP). Many decades before the cloning and mapping of the vanilloid receptor TRPV1, CAP defined the link of CAP to pain sensation to activation of a particular class of afferents. Early investigations confirmed what every consumer of piquant peppers understands—CAP activates primary nociceptive afferents that convey the painful, burning sensation of CAP application. These CAP-responsive sensory neurons have slowly conducting axons (C-type and thinly myelinated Aδ-type) and cell bodies in the dorsal root ganglia (DRG).5 Similar strategies identified CAP-sensitive afferents within the viscera and an association with cardiovascular regulation.2 Many of these visceral afferents are cardiovascular mechanoreceptors,6 and their reflexes utilize vagal afferent pathways.3 Such visceral afferents constitute a unique cranial

*Department of Physiology and Pharmacology, Oregon Health and Science University, Portland, Oregon USA 97239-3098. andresen@ohsu.edu
†Current address: Dept. of Biology, George Fox University, Newberg, Oregon, USA 97132-2697.
pathway to the CNS because they enter the brain, not through the spinal cord (e.g., 7), but rather through cranial ganglia (e.g., nodose, NG) to directly enter the brainstem. Vagal cranial afferents course directly to neurons within the nucleus tractus solitarius (NTS) to form their first CNS synapses. Thus, NTS is truly the “gateway” through which visceral sensory information must pass to initiate a multitude of reflexes controlling autonomic and homeostatic organ regulation.8,9

Within the brainstem, early neurochemical probing identified multiple potential neurotransmitters using immunocytochemistry and microinjection within NTS.10 These findings often paralleled neurotransmission in the superficial lamina of the spinal cord where visceral and somatic spinal afferents are processed and implicated glutamate, GABA and substance P but many additional neuropeptides were present within NTS.11,12 For example, in the caudal NTS, glutamate agonist microinjection evoked reflex decreases in heart rate and blood pressure from the subnuclei associated with cardiovascular regulation.13 These same regions were abundant in substance P immunoreactivity and introduction of substance P into these regions mimicked the baroreceptor reflex.14,15 Within this context, CAP injected into NTS similarly decreased blood pressure and heart rate consistent with cardiovascular afferent activation. Thus, CAP has long been generally associated with sensory activation and together was part of the evidence supporting this region of NTS as the site of the primary afferent synapses subserving the baroreceptor reflex.14,15

With the cloning of TRPV1 in 1997,16 focus converged on a specific molecular target for CAP and the vanilloid field exploded in new developments. This work has offered new insights to the large body of early observations as well as posing new mysteries about TRPV1 mechanisms of action and their functional significance. The mRNA for TRPV1 is localized to spinal region of the DRG—a region long associated with CAP and pain. TRPV1 and CAP sensitivity are thus selectively expressed in subsets of spinal sensory neurons, typically those with un- or lightly myelinated axons.17−19 Native sensory neurons as well as heterologous expression systems demonstrated that TRPV1 acts as an ion channel with broad selectivity for cations but has a substantial preference for calcium over sodium ions (3:1). The most obvious difference in nodose neurons is in the expression of sodium channels sensitive to TTX20,21—a myelinated/unmyelinated difference that is broadly reminiscent of spinal sensory DRG neurons.22,23 Interestingly, although the broad comparison between somatic afferent neurons and cranial visceral afferent neurons indicates general similarities, it is already clear that important functional differences exist. These critical details of ion channel expression may be responsible for interesting functional differences of these cranial afferents compared to their spinal cousins. CAP selectively binds to TRPV1 and triggers a large cationic flux that depolarizes these cells. A frequently overlooked observation of the initial report noted that TRPV1 mRNA also localized to NG, a group of cranial visceral sensory neurons not associated with nociception or pain pathways.16 As with DRG neurons, CAP-sensitivity of NG neurons was widely reported some decades before the TRPV1 cloning.18,24