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Review

Differential distribution of voltage-gated channels in myelinated and unmyelinated baroreceptor afferents

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ABSTRACT

Voltage gated ion channels (VGC) make possible the frequency coding of arterial pressure and the neurotransmission of this information along myelinated and unmyelinated fiber pathways. Although many of the same VGC isoforms are expressed in both fiber types, it is the relative expression of each that defines the unique discharge properties of myelinated A-type and unmyelinated C-type baroreceptors. For example, the fast inward Na^+ current is a major determinant of the action potential threshold and the regenerative transmembrane current needed to sustain repetitive discharge. In A-type baroreceptors the TTX-sensitive $Na_v1.7$ VGC contributes to the whole cell Na^+ current. $Na_v1.7$ is expressed at a lower density in C-type neurons and in conjunction with TTX-insensitive $Na_v1.8$ and $Na_v1.9$ VGC. As a result, action potentials of A-type neurons have firing thresholds that are 15–20 mV more negative and upstroke velocities that are 5–10 times faster than unmyelinated C-type neurons. A more depolarized threshold in conjunction with a broader complement of non-inactivating K_V VGC subtypes produces C-type action potentials that are 3–4 times longer in duration than A-type neurons and at markedly lower levels of cell excitability. Unmyelinated baroreceptors also express KCa1.1 which provides approximately 25% of the total outward K^+ current. KCa1.1 plays a critically important role in shaping the action potential profile of C-type neurons and strongly impacts neuronal excitability. A-type neurons do not functionally express the KCa1.1 channel despite having a whole cell Ca_V current quite similar to that of C-type neurons. As a result, A-type neurons do not have the frequency-dependent braking forces of KCa1.1. Lack of a KCa current and only a limited complement of non-inactivating K_V VGC in addition to a hyperpolarization activated HCN1 current that is nearly 10 times larger than in C-type neurons leads to elevated levels of discharge in A-type neurons, a hallmark of myelinated baroreceptors. Interestingly, HCN2 and HCN4 expression levels are comparable in both fiber types. Collectively, such apportion of VGC constrains the neural coding of myelinated A-type baroreceptors to low threshold, high frequency, high fidelity discharge but with a limited capacity for neuromodulation of afferent bandwidth. Unmyelinated C-type baroreceptors require greater depolarizing forces for spike initiation and have a low frequency discharge profile that is often poorly correlated with the physiological stimulus. But the complement of VGC in C-type neurons provides far greater capacity for neuromodulation of cell excitability than can be obtained from A-type baroreceptors.

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1. Introduction

Arterial baroreceptors are stretch sensitive nerve endings that encode the magnitude and time course of blood pressure into a compact neural code. This stream of afferent information continuously influences the reflexive processes of neurocirculatory control (Hainsworth et al., 1970; Longhurst, 1984; Loewy, 1990; Hainsworth, 1991). The physiological and neuroanatomical characteristics of the arterial baroreflex (BRx) are provided by other contributors to this compendium of reviews. Here, we provide a summary of the voltage gated ion channels (VGC) associated with the afferent limb of the BRx, but from a perspective of the markedly contrasting neural discharge patterns and reflexogenic hemodynamics of myelinated and unmyelinated baroreceptor afferent fibers. The discharge characteristics of individual myelinated and unmyelinated baroreceptor fibers responding to the arterial pressure pulse have been studied in a variety of species and present quite similar fiber dependent dynamics (Katona et al., 1968; Thoren and Jones, 1977; Coleridge et al., 1987). Myelinated baroreceptor afferents generally exhibit lower thresholds for discharge and higher frequencies of spike activity that are markedly less variable and produce a more faithful neural encoding of the arterial pressure pulse than can be observed in unmyelinated baroreceptor afferents. Unmyelinated baroreceptor afferents generally have discharge thresholds at pressures near or above typical mean arterial pressures with sparse and irregular patterns of discharge that rarely exceed 10's of Hz, often responding with very few or only a single spike per cardiac cycle. Interestingly, such contrasting neurophysiological characteristics are not without functional impact on the reflexes they elicit. Myelinated baroreceptor afferents require substantially higher neural discharge frequencies (>50 Hz) to elicit a reflex bradycardic effect comparable in magnitude to low frequency (<5 Hz) discharge of unmyelinated baroreceptor afferents (Kunze and Andresen, 1991; Fan and Andresen, 1998; Fan et al., 1999). This review will show that similarly clear lines of distinction can be drawn all the way down to the level of voltage gated ion channels (VGC) which, in some instances, are uniquely expressed in either myelinated or unmyelinated baroreceptors but not both.

The VGC that shape afferent discharge dynamics are driven to threshold by a neural transduction process that converts mechanical stretch of the arterial wall, and presumably the baroreceptor afferent terminal, into a membrane depolarization, i.e. the generator potential. The molecular components of the mechanotransduction process(es) at the peripheral terminal of baroreceptor afferents are not yet clear. The most recent evidence implicates involvement of the acid-sensing ion channel (ASIC) subfamily of the DEG/ENaC super family of amiloride-sensitive Na^+ channels (Lu et al., 2009). Presumably, channel activation underlies the formation of a pressure dependent generator potentials and subsequent fiber discharge. In this review we focus on the VGC involved in establishing the resting membrane potential, the threshold for action potential discharge, the profile of the somatic action potential and the capacity for sustained repetitive discharge in baroreceptor afferents. Of particular interest is the relative contribution these VGC make in defining the differential discharge characteristics of myelinated and unmyelinated baroreceptor fibers. Although preliminary evidence is building for a gender biased functional subtype that is a mixed modality myelinated A-type afferent with decidedly C-type action potential dynamics and chemical sensitivities (Li et al., 2008; Qiao et al., 2009), in this review we treat these neurophysiologically distinct sensory afferents as two, mutually exclusive functional subtypes one with (A-type) and one without (C-type) myelination of the axonal fiber.

The majority of the data reviewed here were obtained using electrophysiological and immunohistochemical methodologies in conjunction with an adult male rat model, unless otherwise noted. The selection of this species is particularly important as the aortic depressor nerve (ADN) in rat contains baroreceptor fibers that solely elicit the BRx responses of hypotension and respiratory suppression (Sapru et al., 1981; Kobayashi et al., 1999). There is limited evidence, in rat, that chemoreceptors may be present at the aortic arch but these studies have neither been replicated nor confirmed through demonstration of integrated chemoreflexive function (Cheng et al., 1997; Kobayashi et al., 1999). Furthermore, the rat ADN is readily accessible for surgical isolation and therefore amenable to fiber labeling techniques using lipophilic dyes (Mendelowitz et al., 1992). This unique neuroanatomical feature makes possible the reliable identification of baroreceptor afferent neurons for cellular electrophysiological study and confocal reconstruction of the presumed mechanosensitive peripheral terminal ending.

2. Cell body as a surrogate

The physiological relevance of using the cell body as a model system is markedly enhanced through the use of fluorescent lipophilic tracers applied to the ADN or baroreceptor nerve terminals (Sapru et al., 1981; Li et al., 1998). In this manner the molecular profile and current dynamics of VGC involved in the neural processes of pressure transduction and spike encoding can be studied in vitro using cell bodies unequivocally identified as baroreceptor afferents and studied apart from the general population of visceral afferents of unknown sensory modality. Much of what is known concerning the identity and properties of VGC in labeled aortic baroreceptor neurons arises from patch clamp electrophysiological study using enzymatically isolated neurons in short term culture or neurons from an acutely dissected intact ganglion preparation (Mendelowitz and Kunze, 1992; Li and Schild, 2002; Doan et al., 2004; Li et al., 2008; Wladyka et al., 2008). An intact preparation is particularly useful as the afferent fiber type can be reliably classified as myelinated or unmyelinated according to measures of baroreceptor fiber conduction velocity (CV). The patch clamp studies were most often carried out using voltage or current clamp techniques. In conjunction with selective VGC antagonists, voltage clamp protocols make possible the chemical and electrical isolation of a particular VGC for high resolution study of the voltage and time dependent dynamics of channel activation, deactivation and inactivation. Likewise, current clamp protocols provide an opportunity to investigate the contribution a particular VGC makes to the integrated discharge properties of each afferent subtype.

3. Identification of voltage gated channels in baroreceptor neurons

Table 1 provides a compendium of the VGC presently known to be expressed in nodose neurons. The molecular identity of a particular VGC has been resolved using one or more of the following methodologies; immunohistochemical techniques which make possible identification of