Peripheral Mechanisms of Pain Transmission and Modulation

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Thomas S. McDowell

Introduction

The human peripheral nervous system consists of 12 cranial nerves, 31 pairs of spinal nerves and their ganglia, and a variety of supporting glial cells. It includes efferent axons of motor neurons, afferent axons of sensory neurons, and the cell bodies of sensory neurons which reside in the dorsal root ganglia and trigeminal ganglia. The afferent transmission of noxious or painful stimuli from the periphery to the central nervous system is accomplished by a specialized group of sensory neurons, the primary nociceptive neurons [1].

Anatomy

The cell bodies of primary nociceptive neurons, or primary nociceptors, reside in the dorsal root ganglia and trigeminal ganglia. Each neuron has a single (pseudo-unipolar) axon that divides into an afferent, or peripheral, branch and an efferent, or central, branch. Afferent branches of the axon lead to peripheral terminals that detect noxious stimuli. Efferent branches of the axon enter the central nervous system, where they form excitatory synapses with second order nociceptive neurons [1, 2].

T. S. McDowell (✉)
Department of Anesthesiology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
e-mail: thomas.mcdowell@wisc.edu

Function

Activation of primary nociceptive neurons by noxious stimuli leads to the generation in the peripheral terminals of an "all-or-none" regenerative depolarizing electrical signal known as the action potential. The initial depolarizing upstroke of the action potential is due to the opening of voltage-gated sodium channels in the neuronal membrane. Repolarization occurs within milliseconds and is accomplished by spontaneous inactivation of sodium channels along with the somewhat slower activation of delayed rectifier voltage-gated potassium channels. Once an action potential is generated, it travels like a wave along the entire nerve axon until it reaches the central terminals of the nociceptor, where the depolarization stimulates the release of excitatory neurotransmitters in the dorsal horn of the spinal cord and medulla.

Voltage-gated sodium channels are composed of two subunits. The α-subunit is the main, pore forming subunit of the channel. There are 9 different α-subunits of the sodium channel, Na_v 1.1–1.9. Many of these are expressed in primary nociceptors, including the tetrodotoxin (TTX)-sensitive channels Na_v 1.1, 1.6, and 1.7, and the TTX-resistant channels Na_v 1.8 and 1.9. Na_v 1.7 appears to be particularly important in pain transmission. Expression of Na_v 1.7 is upregulated in inflammation, and there are many known gain-of-function mutations in this channel that cause congenital chronic pain syndromes like Paroxysmal

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Extreme Pain Disorder (PEPD) and Inherited Erythromelalgia (IEM). In contrast, mutations that produce non-functioning Na_v 1.7 channels (loss-of-function) are associated with a complete loss of pain sensation, a condition known as Congenital Insensitivity to Pain (CIP) [2].

Axons of Primary Nociceptors

The axons of all primary nociceptors are small in diameter. They may be either thinly myelinated (Aδ-fibers) or unmyelinated (C-fibers). Both of these properties give nociceptors some of the slowest conduction velocities of all types of sensory nerves. Aδ-fiber nociceptors transmit action potentials faster than C fiber nociceptors, with conduction velocities ranging from about 3 m/s up to around 25 m/s or higher. Because of this, Aδ-fiber nociceptors are thought to be responsible for "first" or fast pain that is sharp, stabbing or pricking. Unmyelinated C-fiber nociceptors are slower, with conduction velocities of less than 2 m/s, and are thought to transmit "second" or slow pain that is often poorly localized and described as dull, burning, or aching [1–3].

Aδ-fiber nociceptors innervating skin can be classified as either Type I or Type II nociceptors. Type I Aδ-fiber nociceptors are most sensitive to noxious mechanical stimuli, though they can respond to extreme noxious heat (>53 °C). They are most likely responsible for fast pain responses to mechanical stimulation. In contrast, Type II Aδ-fiber nociceptors are more sensitive to noxious heat stimuli (>43 °C) (though they can respond to very high threshold mechanical stimuli) and thus likely mediate fast pain responses to noxious heat [1–3].

Efferent Functions of Nociceptors

Nociceptors also serve an efferent function. Peripheral terminals of cutaneous nociceptors contain peptides such as Substance P and CGRP that can be released when the terminals are depolarized. This can occur as an axon reflex, when action potentials from an activated terminal travel antidromically into an adjacent axon branch. These peptides cause neurogenic inflammation by increasing plasma extravasation (wheal) and vasodilation (flare) in cutaneous blood vessels [1, 3].

Peripheral Sensitization

Many primary nociceptors can become sensitized by persistent stimulation or by inflammatory chemical mediators. This is characterized by increased responsiveness to noxious stimuli, leading to primary hyperalgesia and increased pain [1–3]. Some "silent" C-fiber nociceptors, which do not appear to be activated by typical noxious stimuli in the resting state, can become responsive to these stimuli after being sensitized [3].

Many mediators that cause nociceptor sensitization are released by inflamed tissues after injury. They act through specific receptors on the nociceptor peripheral terminals to either directly activate or further sensitize the nociceptors. They include metabolites of arachidonic acid ("eicosanoids") such as PGE_2 and PGI_2, which decrease the activation threshold of the nociceptor-specific voltage-gated sodium channel $Na_v1.8$. Bradykinin can also both activate and sensitize nociceptors, by modulating the sensitivity of the heat- and capsaicin-sensitive ion channel TRPV1. Protons (H^+), serotonin, cytokines, purines, and nerve growth factor (NGF) are other inflammatory mediators known to activate and/or sensitize primary nociceptors [1, 2].

Peripheral Analgesia

The responsiveness of primary nociceptors can also be decreased by a variety of analgesic modulators that act through G protein-coupled receptors (GPCRs) such as opioids, muscarinic agents, and endocannabinoids. For example, opioid receptors on peripheral terminals are activated by endogenous opioid peptides released from several types of inflammatory cells such as macrophages and lymphocytes, as well as keratinocytes.

Once activated, these receptors modulate the function of sodium channels, potassium channels, calcium channels, and TRPV1 channels through several G protein-mediated pathways to reduce nociceptor excitability [1, 4].

High Yield Points

- When primary nociceptors are activated by noxious stimuli, action potentials travel like a wave along the axon from the peripheral to the central terminals. The initial rapid depolarization phase of the action potential is due to opening of voltage-gated sodium channels, while repolarization occurs when sodium channels inactivate and potassium channels open.
- Upregulation of one type of sodium channel, $Na_v1.7$, during inflammation can cause increased neuronal excitability and increases in pain. Some mutations in the gene for $Na_v1.7$ are associated with several congenital pain syndromes (gain-of-function mutations), while mutations that lead to nonfunctioning channels (loss-of function mutations) cause congenital insensitivity to pain.
- Aδ-fiber axons are thinly myelinated and have moderately fast conduction velocities, making them responsible to fast pain. C-fiber axons are unmyelinated, have slow conduction velocities, and transmit slow pain responses.
- Substance P and CGRP released from nociceptor peripheral terminals in skin cause neurogenic inflammation with plasma extravasation leading to skin wheal and vasodilation causing the skin flare response.
- Primary nociceptors can become sensitized by inflammatory mediators like bradykinin and eicosanoids which modulate the function of sodium channels and TRPV1 channels. Sensitization of primary nociceptors leads to primary hyperalgesia.
- Peripheral terminals of primary nociceptors express several types of G protein-coupled receptors that can produce analgesia. Opioid receptors, for example, when activated by endogenous opioid peptides released by inflammatory cells in the tissue, can modulate the activity of several ion channels to decrease nociceptor excitability.

Questions

1. $Na_v1.7$ voltage-gated sodium channels
   A. Help produce action potentials in primary nociceptors
   B. Are upregulated during inflammation
   C. Are subject to mutations that cause congenital pain syndromes
   D. All of the above
   Answer: D
2. Which of the following statements about primary nociceptors is true?
   A. Aδ-fiber nociceptors have large, heavily myelinated axons
   B. C-fiber nociceptors have small, thinly myelinated axons
   C. Aδ-fiber nociceptors are classified as Type I or Type II based on their conduction velocities
   D. Aδ-fiber nociceptors transmit fast pain, while C fiber nociceptors transmit slow pain
   Answer: D
3. Which of the following are known to modulate nociceptor function?
   A. Inflammatory mediators like eicosanoids and bradykinin
   B. Endogenous opioid peptides
   C. Upregulation of $Na_v1.7$
   D. All of the above
   Answer: D

References

1. Ringkamp M, Raja SN, Campbell JN, Meyer RA. Peripheral mechanisms of cutaneous nociception. In: McMahon SB, Koltzenburg M, Tracey I, Turk DC, editors. Wall and Melzack's textbook of pain. 6th ed. Philadelphia: Saunders; 2013. p. 1–30.
2. Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. Cell. 2009;139:267–84.
3. Dubin AE, Patapoutian A. Nociceptors: the sensors of the pain pathway. J Clin Invest. 2010;120:3760–72.
4. Hua S. Neuroimmune interaction in the regulation of peripheral opioid-mediated analgesia in inflammation. Front Immunol. 2016;7:293.