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Nociception: CNS

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Introduction

Nociception provides a means of neural feedback that allows the central nervous system (CNS) to detect and avoid noxious and potentially damaging stimuli in both active and passive settings. The sensation of pain divides into four large types: acute pain, nociceptive pain, chronic pain, and neuropathic pain. This article will consider the categories of acute and nociceptive pain together. Acute noxious stimuli (e.g., heat, cold, mechanical force, or chemical stimulation) trigger nociceptors. Acute pain becomes inflammatory pain when the noxious stimulus persists long enough to allow nociceptive neurons to release their pro-inflammatory markers and sensitize or activate responsive cells in their local environment [1]. Nociceptive pain arises from tissues damaged by physical or chemical agents such as trauma, surgery, or chemical burns, while neuropathic pain arises from diseases or damage mediated directly to sensory nerves, such as diabetic neuropathy, shingles, or post herpetic neuralgia [2]. Differentiating acute and nociceptive pain from neuropathic pain aids in understanding the broader study of pain; however, neuropathic pain will not be evaluated further in this article.

Regarding active settings, stimulated nociceptive neurons convey high-threshold noxious stimuli to the CNS. The nociceptive signal may either get redirected immediately in a spinal reflex loop, producing a rapid and reflexive withdrawal or transported to the areas of the brain responsible for integrating the information with higher-ordered sensations such as pain [3]. In addition to spinal afferent transmission to the CNS, nociceptive neurons are also capable of responding to noxious stimuli by secreting chemical signals from their peripheral nerve endings. Local actions on nearby neuronal and non-neural cells undergo mediation through the release of vesicles containing preformed pro-inflammatory cytokines and growth factors.

Description

Depending on the specific monomial sensitivity of a previously inactive nociception, specific noxious stimuli are detected by expressed receptors that open their action channels in response to activation. The open action channels on the nociceptive neurons depolarize the nociception, inducing vesicle fusion and cytokine release. The cytokines are pro-inflammatory, and once released, they elicit and propagate a matched release of pro-inflammatory cytokines from local epithelial, endothelial, and lymphoid cells. The responding cells may then migrate or otherwise disseminate their pro-inflammatory signals that go on to sensitize or activate surrounding nociceptors originally outside of the primary nociceptive field [4] .

The spread of nociception-induced inflammation occurring over an area greater than that of the original nociception(s) involved is referred to as neuroinflammation. The propagation from nociceptive neurons to the surrounding cells, which may in-turn sensitize nearby nociceptive neurons, is why neuroinflammation is considered to be a self-reinforcing phenomenon. Not only do the released pro-inflammatory molecules activate local inflammatory cells, but they are also capable of directly activating other nociceptive nerve endings because almost all nociceptive nerve endings possess receptors for all of the pro-inflammatory markers they are capable of releasing. The pro-inflammatory molecules released from a directly stimulated nociceptive neuron are capable of binding to and activating a local nociceptive neuron entirely unaffected by the original stimulus. As with direct activation, the pro-inflammatory molecules bind the receptors on nociceptive nerve endings and depolarize the cell. Depolarization induces mitogen and protein activated kinases that phosphorylate other transducer proteins, such as TRPV1. This will activate and reinforce the depolarization, which, if of sufficient amplitude, will recruit voltage-gated sodium channels and truly depolarize the nerve fibre.

Nociceptive signals cease with the termination of the stimulus, dephosphorylating, and suppression of the receptor, or once the influx of calcium through the open membrane proteins induces the nociceptive nerve ending to collapse and become refractory to reticulation in either neuronal or secretory mechanisms. The collapse of the nociception following stimulation supports the finding that noxious stimuli quickly adjust, and their conscious perception abates quickly once their peripheral activity ceases.

There is also a mostly unexplored role of passive nociception. Passive nociception refers to the involvement of inactive nociceptors, by their presence and previous activations, in guiding conscious actions so that the individual performs them in a manner least likely to produce pain or injury. Inactive nociceptors may provide less-than conscious "nudges" that strongly encourage the avoidance of potentially injurious and hazardous exposures. Maliki and Apiarian presented this explanation and differentiated the subconscious, unconscious, or preconscious processes through which nociception may guide behaviours from those more active processes that steer actions through the conscious and subjective experience of pain. Their results demonstrate the effects that an absence of nociceptive input may have in three poignant studies; the general disregard for injury seen in patients with painless channelopathies, the self-destructive gait seen in patients rendered insensitive to pain due to leprosy, and the bone destruction of weight-bearing joints seen in patients with painless Charcot joints of tabs dorsal is. They postulate that the act of walking with proper gait, sitting with proper posture, or standing and stretching at regular intervals during long sedentary periods spent studying, are unconsciously motivated by nociceptive signals. These studies illustrate the various injuries that are possible in the absence of the protective nociceptive signals that protect the body from avoidable joint injuries, muscle spasms, or pressure ulcers that would otherwise be difficult to imagine in an unaffiliated individual capable of perceiving and avoiding these injuries.

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Cellular

RT-PCR has provided the means to discover and classify nociceptive neurons based on the specific receptors they possess, which are sensitive to noxious stimuli. Nociceptors in the skin and other peripheral organs form highly complex and interconnected networks with each other. Schwann cells are peripheral glial cells that envelop these networks everywhere except where the terminal axons project through the basement membrane of the epidermis and the nerve endings become 'free' or 'naked' (i.e., unmyelinated). Unfortunately, the complex and sequestered nature of nociceptors in vivo has made them difficult to study, and much of what researchers know about the activity, gene expression, and important factors present in nociceptors has been discovered by studying nociceptive neurons grown in culture [5]. While nociceptors grown in culture have been found to possess many of the same molecules found in vivo, it is not currently possible to discern the absence of any in vivo molecules that only receive the necessary signals produced when the nociceptive neuron is fully imbedded in cutaneous tissue.

Polygonal Nociceptors: Thermal, Mechanical, Chemical

Thermal nociceptive receptors are a subdivision of the transient receptor potential action channel (TRP) family of receptors. Of the TRP channel family, which is composed of several ligand-specific subfamilies, the vanillin variant (TRPV) is found in thermal nociceptors and is responsible for the transduction of thermal stimuli. TRPV monomers form tetrameric structures that contain a central pore through the cell membrane, and these tetramers may be homo-tetrameric or hetero-tetrameric regarding their composition of the four TRPV subunits. TRPV1 expresses on heat-sensitive C-fibres and TRPV2 is expressed on heat-sensitive A-delta-fibres; these receptors are the primary noxious thermo receptors, they are stimulated at 40 to 43 degrees Celsius and 52 degrees Celsius respectively [6]. It is important to note that these temperature-regulated receptors get dynamically set; while such high base-thresholds indicate inactivity under physiologic conditions, the temperatures necessary to stimulate TRPV channels may be significantly lowered during states of inflammation. The two remaining members of the family, TRPV3 and TRPV4, function at 33 to 39 degrees Celsius and 27 to 34 degrees Celsius, respectively. Taken together, the TRPV family is capable of detecting a wide ride range of thermal energy levels that represents a range spanning normal, physiologic conditions through to those that are noxious and potentially harmful.

When TRPV1 and TRPV2 detect sufficiently high temperatures, they open and allow an influx of calcium, which depolarizes the neuron. Although TRPV1 and TRPV2 channels prefer calcium, by definition, they are non-selective action channels. Calcium-induced depolarization stimulates nearby voltage-gated sodium channels that generate an afferent action potential. In addition to detecting noxious thermal energy, TRPV receptors are also capable of detecting many chemical molecules, as well. TRPV chemical ligands include prostaglandins (proinflammatory), bradykinin (proinflammatory), capsaicin (natural product), anandamide (neurotransmitter), olvanil (anti-inflammatory), resiniferatoxin (natural product), and acidic pH (protons). TRPV sensitivity to capsaicin and acidic pH illustrates the polygonal sensitivity of nociceptors seen in vivo and may explain why such stimuli share the sensation of burning. TRPV1 and TRPV2 are found throughout the central and peripheral nervous systems, as well as within the spleen and lung. TRPV3 and TRPV4 are expressed as TRPV1 and TRPV2 but are also present in the skin, sperm, and many visceral organs.

In comparison to the amount of information known about thermal nociceptors, very little is known regarding mechanical nociceptors and the transduction of noxious mechanical force. Provided mechanical nociceptors, also called mechanoreceptors, function similarly to other force-sensitive ion channels, it can be presumed that these channels are present and expressed on the free nerve endings that have penetrated the basement membrane of the epidermis – the unmyelinated nerve endings. As explained previously regarding thermo receptors, the sequestered nature of mechanoreceptors in vivo has prevented their careful study. Much of what is known has been gathered by studying nociceptive neurons grown in culture. While such studies have identified several mechanic-sensitive ion channels, the currents produced by these channels are both nociceptive as well as anti-nociceptive. Inhibitory mechanoreceptors, named TREK and Kv1.1, may play a role in keeping the threshold for noxious mechanical force sufficiently high to prevent over activity of other mechanoreceptors, which is an idea somewhat analogous to TRPV3 and TRPV4 being responsible for lower thermal energy levels than TRPV1 and TRPV2. One final hypothesis, yet to be studied in mammalian tissue, is that noxious mechanical forces break the delicate nociceptive nerve endings, and the release of intracellular contents such as ATP and neuropeptides lead to inflammation, neural depolarization, and sensation of pain.

Conclusion

Nociceptive neurons arise from neural crest stem cells that have migrated out of the neural tube before the tube closed. More specifically, nociceptors develop from the dorsal population of neural crest stem cells within the neural crest tissue. Although transcription factors necessary for nociceptive differentiation remain unknown, all nociceptive neurons express the TrkA receptor to nerve-growth factor.

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Conflict of Interest:

None

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