‘For every complex issue, there is an answer that is simple, neat...and wrong!’ There are no ‘pain fibers’ in nerves and no ‘pain pathways’ in the brain. Pain is not a stimulus. The experience of pain is the final product of a complex information-processing network.

**AFFERENT RECEPTORS**

Peripheral sensory receptors are specialized terminations of afferent nerve fibers exposed to the tissue environment, even when the fiber is myelinated more centrally. Such receptors are plentiful in the epidermis/dermis and display differentiated functions (2):

- Low-threshold mechanoreceptors: A\(\alpha\), A\(\beta\) in humans; A\(\alpha\), A\(\beta\), A\(\delta\), and C in animals.
- Displacement: Ruffini endings–stretch; hair follicle with palisade endings of 10–15 different nerve fibers each.
- Velocity: Meissner corpuscle.
- Vibration: Pacinian corpuscle, fluid environment with onion-like lamellae acting as high-pass filter.
- Thermal receptors:
  - Cold: discriminates 0.5ºC, 100 µm diameter field, A\(\delta\).
  - Warm: mostly C fibers.
- Nociceptors:
  - Myelinated: A\(\delta\) most conduct in 5–25 m/s range, 50–180 µm field, 10–250 receptors/mm\(^2\).
  - C polymodal nociceptors; pain.

As terminations of afferent nerve fibers, peripheral sensory receptors allow the receptor to transduce or translate specific kinds of energy into action potentials. Most peripheral receptors act either by direct coupling of physical energy to cause changes in ion channel permeability or by activation of second messenger cascades. Chemoreceptors detect products of tissue damage or inflammation that initiate receptor excitation. Free nerve endings are also in close proximity to mast cells and small blood vessels. Contents of ruptured cells or plasma contents, together with neurotransmitters released from activated nerve terminals, create a milieu of proteins, allowing the free nerve endings, capillaries, and mast cells to act together as an evil triumvirate to increase pain (3).

Although there are no pain fibers or pain pathways, there are anatomically and physiologically specialized peripheral sensory neurons–nociceptors–which respond to noxious stimuli, but not to weak stimuli (Table 1). These are mostly thinly myelinated A\(\beta\) and unmyelinated C afferents, and they end as free, unencapsulated peripheral nerve endings in most tissues of the body including skin, deep somatic tissues like muscles and joints, and viscera. (The brain itself is not served by these sensory fibers, which is why cutting brain tissue does not hurt.) Thickly myelinated A\(\beta\) afferents typically respond to light tactile stimuli. They also respond to noxious stimuli, but they do not increase their response when the stimulus changes from moderate to strong, i.e. they do not encode stimuli in the noxious range. Although A\(\beta\) afferents do respond to painful stimuli, electrical stimulation, even at high frequency, normally produces a sensation not of pain, but of nonpainful pressure. Convergence of large- and small-diameter afferents of various sorts at the level of the dorsal horn, with further processing in the brain, gives rise to a variety of everyday sensations.

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**Table 1 Nociceptors and fiber types.**

<table>
<thead>
<tr>
<th>Nociceptors</th>
<th>Fiber type and response</th>
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<tbody>
<tr>
<td>A(\delta)</td>
<td>Small myelinated fibers; slowest conducting are nociceptors</td>
</tr>
<tr>
<td>AMH type I (A mechano-heat)</td>
<td>Respond to mechanical stimuli; have heat threshold of 53ºC, but sensitize rapidly to heat; most common</td>
</tr>
<tr>
<td>AMH type II</td>
<td>Respond to mechanical stimuli; threshold 47ºC, also respond to noxious cold</td>
</tr>
<tr>
<td>AM</td>
<td>Respond only to noxious mechanical stimulation</td>
</tr>
<tr>
<td>CMH</td>
<td>Most common C (polymodal nociceptor); responds to mechanical stimuli; thermal threshold 45–49ºC; noxious cold ≤4ºC</td>
</tr>
<tr>
<td>CH</td>
<td>Responds to heat only; thermal threshold 45–49ºC</td>
</tr>
<tr>
<td>CMC</td>
<td>Like CMH, responds to noxious cold instead of heat</td>
</tr>
<tr>
<td>CC</td>
<td>Responds to noxious cold only</td>
</tr>
<tr>
<td>Silent nociceptors</td>
<td>Do not fire in absence of tissue injury</td>
</tr>
</tbody>
</table>
A change in temperature or an agonist binding to a membrane may cause a conformational change in the shape of a receptor protein allowing influx of ions or triggering second messenger pathways (4). When transient receptor potential (TRP) (vanilloid or capsacin) receptors are activated, they directly allow calcium ion cell influx, which can be sufficient to initiate neurotransmitter release.

Primary afferents will fire action potentials at different adaptive rates. For example, touch receptors or vibration detectors and hair follicle afferents fire at the beginning and sometimes at the end of a maintained stimulus—they respond to the change (delta) of a stimulus. In contrast, nociceptors never fully adapt and stop firing in the presence of a stimulus. They are difficult to turn off once they are activated.

The term vanilloid refers to a group of substances related structurally and pharmacologically to capsacin, the pungent ingredient of chili peppers. The principal action of capsacin and other vanilloids on the sensory neuron membrane is to produce a nonselective increase in cation (+) permeability, associated with the opening of a distinct type of cation channel. The inward current responsible for depolarization and excitation of the neurons is carried mainly by sodium ions, but the channel is also permeable to divalent cations, including calcium. The vanilloid receptor VR1 (also called TRPV1) shows a remarkable characteristic of heat sensitivity (and also acidic pH), with robust channel opening in response to increases in ambient temperature. The physiological effects of capsacin are numerous:

- Immediate pain.
- Various autonomic effects caused by peripheral release of substance P (SP) and calcitonin gene-related peptide (CGRP), inducing profound vasodilatation, while release of SP promotes vascular leakage and protein extravasation; components of the neurogenic inflammatory response: rubor (redness), calor (heat), and tumor (swelling).
- An antinociceptive effect of varying duration, associated with desensitizing effect of capsacin on the peripheral terminals of C fibers. The cellular mechanisms underlying the neurodegenerative consequences of capsacin likely involve both necrotic and apoptotic cell death.
- A fall in body temperature: a reflex response generated by thermosensitive neurons in the hypothalamus following capsacin activation of primary afferent fibers. Capsacin acts on nonmyelinated peripheral afferent fibers to deplete SP and other transmitter peptides; the net effect is first to stimulate and then to destroy C fibers.4

A number of receptor systems reportedly play a role in the peripheral modulation of nociceptor responsiveness. The vanillloid receptor, TRPV1, is present on a subpopulation of primary afferent fibers and is activated by capsacin, heat and protons. Following inflammation, axonal transport of TRPV1 mRNA is induced, with the proportion of TRPV1-labeled unmyelinated axons in the periphery being increased by almost 100%.5 The inflammatory mediator bradykinin lowers the threshold of TRPV1-mediated heat-induced currents in dorsal root ganglion (DRG) neurons, and increases the proportion of DRG cells that respond to capsacin.4

In addition, there is a synergism between an acid pH and the capsacin (VR1) receptor, such that transmembrane current is significantly increased from the inflammatory environment.4 To date, strong evidence exists showing that nociceptor firing and human perception of pain are correlated (the animal corollary is not yet validated).

Cell bodies manufacture neurotransmitters and modulators of all kinds, as well as receptors and ion channels. These are transported from the DRG both centrally and peripherally ($). Glutamate is the major excitatory neurotransmitter of nociceptors. SP and CGRP are peptide transmitters of nociceptors. Ion channels exist along the length of the primary afferent fibers and functional receptors, while mechanisms to release at least some neurotransmitters also prevail along the length of the axon. Several neurotransmitters can exist in a single neuron.

Depolarization induces the release of neurotransmitters ($), and excesses of released neurotransmitters (e.g. glutamate) are recycled by the presynaptic terminal. Further, it has been shown that calcium flow through transient receptor potential (TRP) receptors along the course of the axon is sufficient to cause release of neurotransmitters, independent of axon depolarization.6 This implies that inflammatory mediators, heat, or changes in pH can cause release of potentially pain-producing substances along the entire length of a nerve. However, the patient will sense the pain emanating from the peripheral terminations. It is also noted that the release of some neurotransmitters cannot be evoked by individual inflammatory mediators, such as prostaglandin (PG) E2; however, together with bradykinin, PGE2 can enhance neurotransmitter release.

4 Receptor activation may allow ion influx or trigger a second messenger pathway that initiates an action potential.

6 At the synapse, there is a chemical transmission of the nerve impulse.
PHYSIOLOGY OF PAIN

MEDIATORS OF PAIN

Prostaglandins (PGs) are not the only chemical mediators of inflammation and hypersensitivity. The acidity and heat of injured, inflamed tissue enhances pain and hypersensitivity through response of the capsaicin/vanilloid receptor (TRPV1). SP and CGRP can be released from the peripheral terminals of activated C fibers and contribute to neurogenic inflammation by causing vasodilatation. Affected tissues are subsequently in a state of peripheral sensitization. SP is an 11-amino-acid peptide neurotransmitter, often co-occurring with CGRP, which, when released in the spinal dorsal horn, activates second-order transmission neurons that send a nociceptive (‘pain’) signal to the brain.

PLASTICITY ENCODING

René Descartes (1596–1650) proposed that ‘pain’ was transmitted from the periphery to a higher center through tubes of transfer. From the concept of Descartes came the Cartesian model: a fixed relationship between the magnitude of stimulus and subsequent sensation.

The Cartesian model has evolved over the centuries through the contributions of many, including C.S. Sherrington (1852–1952), who coined the term ‘nociception’, stating that a nociceptive stimulus will evoke a constellation of responses which define the pain state. Nociception, per se, separates the detection of the event (noxious stimulus) from the production of a psychological or other type of response (pain). In a simple example, injury in the legs of a paraplegic produces nociception from impulses in nociceptors, exactly as in a normal subject, but there is no pain perceived. A common clinical example is routine surgery, where neurological data confirms nociception (response to the noxious stimulus), but pain is not experienced while the patient is at an appropriate stage of anesthesia, i.e. there is no cognitive processing of the nociception.

Neurotransmitters are noted as such only if they have a receptor for binding. Other criteria include: (1) synthesis in the neuron DRG, (2) seen in presynaptic terminal (central or peripheral) and released in sufficient quantities to exert a defined action on the postsynaptic neuron or tissue, (3) exogenous administration mimics endogenously released neurotransmitter, (4) a mechanism exists for its removal, and (5) it is released by neuronal depolarization in a Ca++-dependent fashion. Many different neurotransmitters exist, most notably glutamate, SP, and CGRP. Glutamate is the most prevalent neurotransmitter in the CNS, and is synthesized not only in the cell body, but also in the terminals.

Several receptors reside on primary afferent terminals, which regulate terminal excitability: serotonin, somatostatin, interleukin, tyrosine kinase, ionotropic glutamate, etc. (7).

In the seventeenth century, René Descartes proposed that pain was transmitted through tubes of transfer.

Cartesian model: psychophysical experience (pain report) = f (stimulus intensity).

Prostate pain is transmitted through the peripheral terminals of activated C fibers and contribute to neurogenic inflammation by causing vasodilatation. Affected tissues are subsequently in a state of peripheral sensitization. SP is an 11-amino-acid peptide neurotransmitter, often co-occurring with CGRP, which, when released in the spinal dorsal horn, activates second-order transmission neurons that send a nociceptive (‘pain’) signal to the brain.

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Cartesian model: psychophysical experience (pain report) = f (stimulus intensity).
It is now appreciated that there exists a plasticity of pain encoding. A diminished response (as with the analgesic morphine) to a given noxious stimulus can give rise to hypoalgesia/analgesia. On the other hand, local injury can shift the stimulus–response curve to give rise to hypoalgesia. A left shift in the stimulus–response curve can result in allodynia, i.e. a normally non-noxious stimulus becomes noxious.

Hyperalgesia to both heat and mechanical stimuli that occurs at the site of an injury is due to sensitization of primary afferent nociceptors. Mechanisms of the phenomenon have been studied in various tissues, including the joint, cornea, testicle, gastrointestinal tract, and bladder. Hyperalgesia at the site of injury is termed primary hyperalgesia, while hyperalgesia in the unjured tissue surrounding the injury is termed secondary hyperalgesia.

**GATE THEORY**

The existence of a specific pain modulatory system was first clearly articulated in 1965 by Melzack and Wall in the gate control theory of pain. This was the first theory to propose that the CNS controls nociception. The basic premises of the gate control theory of pain are that activity in large (non-nociceptive) fibers can inhibit the perception of activity in small (nociceptive) fibers and that descending activity from the brain also can inhibit that perception, i.e. interneurons of the substantia gelatinosa regulate the input of large and small fibers to lamina V cells, serving as a gating mechanism. Most simplistically: fast moving action potentials in myelinated fibers activate inhibitor neurons that shut down second-order neurons before slower arriving signals reach the inhibitor neurons via nonmyelinated fibers (11). These signals from unmyelinated fibers would normally shut down inhibitor neurons, thereby allowing further transmission through second-order neurons. With the gate theory, Melzack and Wall formalized observations that encoding of high-intensity afferent input was subject to modulation. Although their concept was accurate, details of their explanation have since been more accurately modified.

As an example, transcutaneous electrical nerve stimulation (TENS) therapy is a clinical implementaion of the gate theory. TENS is thought to act by preferential stimulation of peripheral somatosensory fibers. This results in a stimulation of inhibitory interneurons in the second lamina of the posterior horn (substantia gelatinosa) that effectively blocks nociception at the spinal cord level. Further, the gate theory may explain why some people feel a decrease in pain intensity when skin near the pain region is rubbed with a hand ('rubbing it better'), and how a local area is ‘desensitized’ by rubbing prior to insertion of a needle. An additional example would be the shaking of a burned hand, an action that predominantly activates large nerve fibers.

**ACTIVITY OF NOCICEPTORS**

Injured nerve fibers develop ectopic sensitivity. A substantial proportion of C fiber afferents are nociceptors, and abnormal spontaneous activity has been observed in A fibers and C fibers originating from neuronal-resultant nerve transections. In patients with hyperalgesic neumas, locally anesthetizing the neuroma often eliminates the pain.9 Nociceptor activity induces increased sympathetic discharge. In certain painful patients, nociceptors acquire sensitivity to norepinephrine (NE; noradrenalin) released by sympathetic efferents. Pain caused by activity in the sympathetic nervous system is referred to as sympathetically maintained pain. In human studies of stump neumas and skin,10 it is concluded that apparently sympathetically maintained pain does not arise from too much epinephrine (adrenalin), but rather from the presence of adrenergic receptors that are coupled to nociceptors. In sympathetically maintained pain, nociceptors develop α-adrenergic sensitivity such that the release of NE by the sympathetic nervous system produces spontaneous activity in the nociceptors. This spontaneous activity maintains the CNS in a sensitized state. Therefore, in sympathetically maintained pain, NE that normally is released from the sympathetic terminals acquires the capacity to evoke pain. In the presence of a sensitized central pain-signaling neuron (second order), pain in response to light touch is induced by activity in low-threshold mecanoreceptors–allodynia. In this circumstance, α1-adrenergic antagonists lessen nociceptor activity and the resultant hyperalgesia or allodynia.

**VOLTAGE-GATED ION CHANNELS**

Following thermal, mechanical or chemical stimulation of primary afferents, the excitatory event must initiate a regenerative action potential involving voltage-gated sodium, calcium or potassium channels culminating in neurotransmitter release, if sensory information is to be conveyed from the periphery to the second-order afferent neuron located in the spinal cord dorsal horn.
Within the dorsal horn, the CNS ‘decides’ if the message lives or dies. The hypersensitization of windup is testimonial that the CNS dorsal horn is dynamic, and the important role of these voltage-gated ion channels makes them attractive targets for novel and selective analgesics. Voltage-gated calcium channels open when the membrane potential depolarizes and their cause intracellular calcium concentration to rise. The calcium then causes depolarization of the cell membrane that causes a tissue. The sodium channel is activated in response to arrival at the nerve terminal, the action potential facilitates an inward movement of calcium, which triggers the discharge of neurotransmitters from storage vesicles into the junctional cleft. The calcium ions play an important role in neurotransmission in sensory neurons, but relatively less important for excitatory transmission in the CNS. Therefore, it is important that the most effective of these voltage-gated potassium channels are not essential for the action potential, but influence the shape of action potentials and tune their firing time. When open, they steer the membrane potential toward the potassium equilibrium potential, thereby decreasing the excitability of a cell. This makes them prime molecular targets for suppressing hyperactive neurons and suppressing hyperalgesia. Excitability of a neuron can be changed by channels as well as receptors:
- Na\(^+\): increased excitability with increased permeability.
- K\(^+\): increased excitability with decreased permeability, and vice versa.
- Ca\(^+\): increased neurotransmitter release; increased second messenger action.
- Cl\(^-\): variable, depending on chloride equilibrium potential.
VGSC are complex, transmembrane proteins that have a role in governing electrical activity in excitable tissue. The sodium channel is activated in response to depolarization of the cell membrane that causes a voltage-dependent conformational change in the channel from a resting, closed conformation to an active conformation, the result of which increases the membrane permeability to sodium ions (12). Based on the sensitivity to a toxin derived from puffer fish, tetrodotoxin (TTX), sodium currents can be subdivided as being either TTX-sensitive (TTXs: Na\(^+\), 1.7 channel, plentiful in the DRG) or TTX-resistant (TTXR: Na\(^+\), 1.8 and Na\(^+\), 1.9, which are exclusively expressed in cells of the DRG, and predominantly in nociceptors). Loss of function mutation of the gene that encodes Na\(^+\), 1.7 is associated with the condition of insensitivity or indifference to pain, e.g. hot-ember barefoot walkers. In contrast, a gain of function mutation is the major cause of erythromelalgia—a condition of heat allodynia in the extremities of humans.

Accumulating evidence shows that upregulation of subtypes of sodium channels takes place in both neuropathic and inflammatory models of pain. Many drugs used clinically to treat human peripheral neuropathies, including some local anesthetics (e.g. lidocaine), antiarrhythmics (e.g. mexiletine), and anticonvulsants (e.g. phenytoin and carbamazepine) are VGSC blockers.

In contrast to VGSCs, voltage-gated potassium channels act as brakes in the system, repolarizing active neurons to restore baseline membrane potentials. The hyperpolarization-activated cyclic nucleotide-gated (HCN) channel is structurally homologous to the potassium channel, prevails in cardiac tissue and DRG neurons, and modulates rhythm and waveform of action potentials—thereby also contributing to resting membrane potentials.

Calcium ions play an important role in neurotransmission, being essential for transmitter release from terminals (13). They also play a key role in neurons, linking receptors and enzymes, acting as intracellular signals, forming a channel-gating mechanism, and contributing to the degree of depolarization of the cell. The means by which calcium enters the neuron and terminal is via calcium channels, making calcium channels targets for a variety of neurotransmitters, neuromodulators, and drugs. Two families of voltage-dependent calcium channels (VDCC) exist:
- Low threshold, rapidly activating, slowly deactivating channels (low-voltage activated (LVA) also referred to as T-type).
- High threshold, slowly activating, fast-deactivating channels (high-voltage activated (HVA)).

Ziconotide (a synthetic version of ω-conotoxin found in the venoms of predatory marine snails) blocks depolarization-induced calcium influx through VDCC binding.