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Central Sensitization

Uncovering the Relation between Pain and Plasticity

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Evidence for a Central Component of Post-injury Pain Hypersensitivity. By Clifford J. Woolf. Nature 1983; 306: 686–8. Reprinted with permission.

Noxious skin stimuli which are sufficiently intense to produce tissue injury, characteristically generate prolonged poststimulus sensory disturbances that include continuing pain, an increased sensitivity to noxious stimuli and pain following innocuous stimuli. This could result from either a reduction in the thresholds of skin nociceptors (sensitization) or an increase in the excitability of the central nervous system so that normal inputs now evoke exaggerated responses. Because sensitization of peripheral receptors occurs following injury, a peripheral mechanism is widely held to be responsible for postinjury hypersensitivity. To investigate this I have now developed an animal model where changes occur in the threshold and responsiveness of the flexor reflex following peripheral injury that are analogous to the sensory changes found in man. Electrophysiological analysis of the injury-induced increase in excitability of the flexion reflex shows that it in part arises from changes in the activity of the spinal cord. The long-term consequences of noxious stimuli result, therefore, from central as well as from peripheral changes.

IN contrast to hypothesis-driven science, discovery science is an exploration of the unknown. There are no road maps from the National Institutes for Health, just narrow, twisting paths, many dead ends, and very occasionally, a totally unexpected byway. I am delighted to share here how I discovered the phenomenon of central sensitization in the early 1980s. On completion of my medical training and Ph.D. in South Africa, I was extremely fortunate to meet Patrick Wall, then one of the foremost neuroscientists of his era and the major driving force behind the emerging field of pain neurobiology (Patrick D. Wall, D.M., F.R.S., Professor, Department of Anatomy and Developmental Biology, University College London, England; 1925–2001). Pat invited me to join his laboratory at University College London, where he provided me with two of the greatest gifts any young scientist could ask for: an intellectually challenging environment where all was possible if only one tried hard enough in smart enough a way, and complete freedom to operate. Pat used single unit analysis of dorsal horn neurons to reveal their functional characteristics and, from this, constructed enormously insightful theories about the circuitry of the spinal cord and the mechanisms that drove pain. These essentially were that active inhibition from large fibers in the periphery or descending inputs from the brainstem turned off pain transmission in the spinal cord, whereas any reduction in the level of such inhibition, such as after nerve injury, turned it on—the spinal gate control hypothesis.[1] The work was cutting-edge systems neurobiology, and while I eagerly learned the trade from a true master, I became increasingly concerned. The reason for this was essentially one of sampling. In any given experiment, one could maximally record from perhaps five of the many millions of neurons in the lumbar spinal cord, and each was different. Although there were overall patterns, some responded only to innocuous

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stimulation such as light touch, others only to intense pinch, and most to a combination of low- and high-intensity stimuli; the spatial extent and temporal properties differed considerably from cell to cell. How, I asked myself, would it ever be possible to decode these action potential patterns into meaningful messages related to the sensation of pain? Intracellular dye injection enabled the morphology of individual neurons to be mapped in exquisite detail,[2] but I could detect no organizing principle other than the apparent uniqueness of each cell.

I realized that the overall function of the pain system would not likely emerge from studying one neuron at a time, no matter how many and for how long. What I thought I really needed to understand was the biologic significance of the bursts of action potentials that I was recording. How would I do this? I decided instead of recording from dorsal horn neurons, to record activity in flexor motor neurons. The reasoning was simple. The firing of these neurons in response to a peripheral stimulus leads to a clear unambiguous outcome, contraction of muscles that flex a limb. These motor neurons are the output of the flexion withdrawal reflex, and by recording from them, I could treat the spinal cord essentially as a black box. The withdrawal reflex is an integral part of the nocifensive response defined exactly 100 yr ago by Sherrington (Sir Charles Scott Sherrington, M.B., F.R.S., Professor, Department of Physiology, Oxford University, England; 1857–1952). When exposed to a noxious stimulus, we simultaneously experience an unpleasant sensation and withdraw from the stimulus. The threshold for activating pain and the withdrawal reflex are essentially identical, and in animal behavioral investigations as well as studies in human neonates, withdrawal responses are used as a surrogate for pain.

When I first recorded from rat flexor motor neurons, I was amazed to find that they had crisp high-threshold cutaneous receptive fields and seemed much more like "pain cells" than most in the dorsal horn of the spinal cord. I then set about systematically characterizing the response properties of biceps motor neurons, examining the location, intensity, and types of skin stimuli that activated the cells. I found that most cells responded only to pinch or noxious heat of one or more toes. Some, however, had very large receptive fields encompassing the whole leg and could be driven by innocuous mechanical stimuli. This was strange because the flexion withdrawal reflex is normally activated, like pain, only by noxious stimuli.[3] It took me several months of recording to finally realize that all of the anomalous motor neurons with low-threshold receptive fields were only recorded at the end of the day, after the repeated noxious stimulation of the hind paw required for recording from many neurons. This was my "eureka" moment; cells with large low-threshold receptive fields were not a different class of neuron, but instead cells that had somehow changed as a result of the repeated input I had applied. This was, I appreciated immediately, a possible manifestation of functional plasticity of the central nervous system, and I was then able to show this definitively by recording for prolonged periods from single neurons and documenting that in the absence of injury, the receptive fields were stable, but peripheral injury induced profound alterations in their threshold and responsiveness. Moreover, once the injury had produced these alterations, local anesthesia to the site of the injury did not revert them. The changes outlasted the trigger. The discovery is described in my *Nature* article of 1983, defining for the first time central sensitization.[4] Imagine my excitement as a young, unknown scientist in getting a single-author article into *Nature*!

It is difficult now to reconstruct our view of the nervous system as it was 23 yr ago, but it was then thought of as a hard-wired system whose connections and properties, once set up during development, remained essentially fixed. Synaptic plasticity in the hippocampus had been discovered, but was considered a specific mechanism related only to memory, and there was little sense of the dynamic, modifiable neuronal system we now appreciate. Because, I surmised, the trigger for the change in receptive field properties was repeated noxious input applied only to the toes, recruitment of receptive fields outside of this region, on the leg, for example, meant a change within the central nervous system and not an increased sensitivity of the peripheral terminals of sensory fibers innervating injured tissue—peripheral sensitization. Increased excitability triggered within the spinal cord by peripheral noxious inputs represented "central sensitization," a state where the response to normal inputs was greatly enhanced (fig. 1). A corollary of this was that pain does not simply reflect the presence, intensity, or duration of specific "pain" stimuli in the periphery but also changes in the function of the central nervous system.

I then showed with Pat Wall that a very brief (10- to 20-s) period of low-frequency stimulation of a nerve at C-fiber strength could trigger central sensitization for up to an hour, a central synaptic modification representing a kind of short-term pain memory, and that nerves innervating muscles and joints produced longer lasting changes than cutaneous nerves.[5] I and my colleagues found similar changes in the receptive field properties of high-threshold dorsal horn neurons[6] as those that I had first reported in motor neurons, and we showed that these were the result of the recruitment of normally subthreshold synaptic inputs.[7] Central sensitization was, we found, a manifestation of activity-dependent plasticity due to an increase in synaptic strength, driven to a substantial extent, by *N*-methyl-D-aspartic acid glutamatergic re-

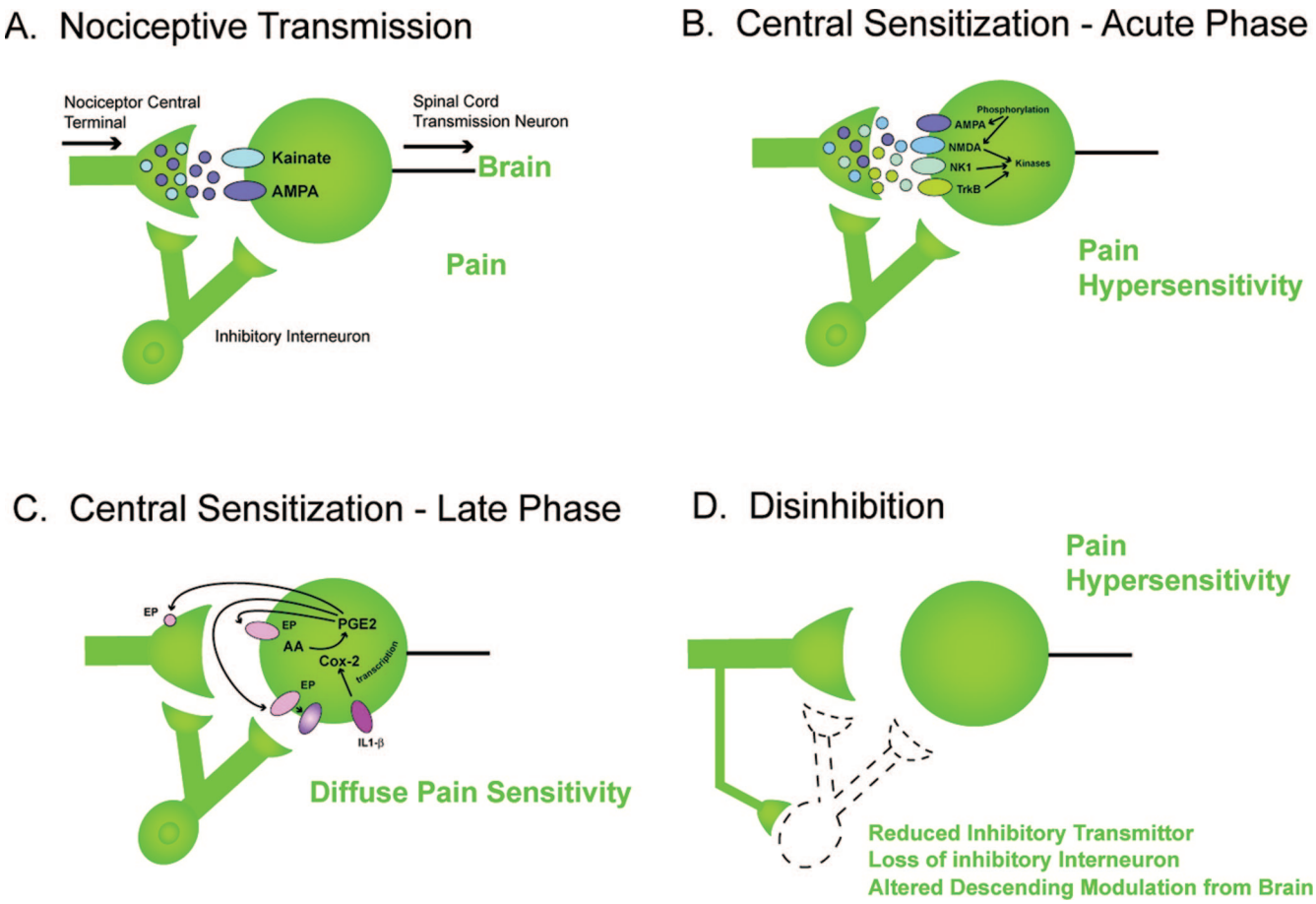

Fig. 1. Normal and enhanced transmission in the spinal cord. (*A*) Nociceptive transmission represents the faithful synaptic transfer from nociceptors to dorsal horn neurons of information about the intensity, duration, and location of peripheral noxious stimuli. (*B*) The early phase of central sensitization is a form of activity-dependent synaptic plasticity driven by high levels of nociceptor input that, *via* transmitter release and action on the multiple receptors expressed on dorsal horn neurons, results in activation of intracellular kinases that phosphorylate ion channels and receptors, altering their distribution and function and increasing excitability and thereby pain sensitivity. (*C*) The delayed or late phase of central sensitization involves changes in transcription in dorsal horn neurons. Some alterations in gene expression are activity driven, and restricted others are widespread, like the induction of cyclooxygenase 2 (Cox-2) in central neurons after peripheral inflammation. (*D*) Inhibitory interneurons play a major role in damping down sensory processing. After peripheral nerve lesions, there is a reduction in the action of inhibitory transmitters and a loss of γ-aminobutyric acid–mediated interneurons, resulting in a loss of inhibition (disinhibition) producing pain hypersensitivity. AA = arachidonic acid; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole propionate; EP = prostaglandin receptor; IL1β = interleukin 1β; NK1 = neurokinin 1; NMDA = *N*-methyl-D-aspartic acid; PGE2 = prostaglandin E2; TrkB = tyrosine kinase B. From Woolf CJ: Pain: Moving from symptom control toward mechanism-specific pharmacologic management. Ann Inter Med 2004; 140:441–51; reproduced with permission.

ceptors.[8] Since then, considerable work from my own and many other laboratories has shown that central sensitization operates after noxious stimuli, peripheral inflammation, and nerve injury in the spinal cord and higher brain centers, and involves multiple presynaptic and postsynaptic changes producing changes in transmitter release and action, as well as synthesis of novel neuromodulators such as prostaglandin E2.[9,10] Many features of central sensitization resemble those that are responsible for memory.[11] Central sensitization is produced not only by increases in excitability as originally discovered but also by a reduction in inhibitory transmission due to reduced synthesis or action of inhibitory transmitters and to a loss of inhibitory interneurons, which may produce a persistent enhancement of pain sensitivity[12] (fig. 1).

We now appreciate that central sensitization is responsible for secondary hyperalgesia, the spread of tenderness or enhanced pain sensitivity outside of an area of injury, and tactile allodynia, pain in response to light touch, and is a common component of both inflammatory and neuropathic pain. Furthermore, we recognize that there are several clinical syndromes characterized by pain hypersensitivity in the absence of tissue injury, inflammation, or a lesion to the nervous system such as fibromyalgia, tension-type headache, or irritable bowel syndrome, where it seems as if an autonomous central sensitization drives the pain by a central amplification of peripheral inputs. The discovery of central sensitization also led to an appreciation that because injury triggered long-lasting changes at many levels in the central nervous system, it made sense to try adapt treatment strat-

egies to prevent these—the concept of preemptive analgesia.[13] Furthermore, central sensitization offered new targets for novel analgesic approaches, ones that do not ablate the painful response to a noxious stimulus (nociceptive pain) but instead normalize a hypersensitive pain system. Anticonvulsants, such as gabapentin or pregabalin, and drugs that block amine uptake, such as duloxetine, reduce central sensitization.

At the time I first discovered central sensitization, I had abandoned the bedside for the bench and was working purely to understand the operation of the nervous system and had no sense of the implications of the experimental observations I was making for patients. It has been very gratifying to contribute in some small way to both an increased understanding of pain and its management. Much remains still to be done; we need to understand what switches central sensitization on and off particularly in dysfunctional syndromes such as fibromyalgia, develop tools to identify those patients where central sensitization is the major driver of their pain, and of course discover more effective treatments that reduce central sensitization and do not produce adverse effects. I have greatly enjoyed exploring the secrets of central sensitization for more than 20 yr and have had the enormous privilege of sharing this voyage with many wonderful colleagues, all of whom I thank with great pleasure.

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