PAIN® 155 (2014) 1911–1912

PAIN®

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Commentary

What to call the amplification of nociceptive signals in the central nervous system that contribute to widespread pain?

What's in a name? That which we call a rose by any other name would smell as sweet.

In *Romeo and Juliet*, Shakespeare argues that the names of things are not as important as the thing itself and how we identify it. Hansson's Topical Review [4] asks whether central sensitization is the right name for clinical pain conditions characterized by widely distributed pain hypersensitivity, a timely and pertinent question because it forces us to ask what are these pain conditions, how can we recognize them, how are they generated, and what should we call them? This is an important issue, and I appreciate Dr. Hansson for raising it.

Dr. Hansson uses 3 names in his review, "activity-dependent central sensitization," "central sensitization induced by primary afferent activity," and "central sensitization," interchangeably as if all are identical. In my opinion, they are not. Central sensitization is the genus of all forms of pain sensitization that arise within the central nervous system (CNS), as the name indicates. Central sensitizations induced by primary afferent activity are those subsets of central sensitization demonstrably induced by primary afferent input, which excludes, for example, conditions in which sensitization in the spinal cord results predominantly from changes in descending pathways or in which changes, however generated, are fully autonomous, whereas activity-dependent central sensitization is a subset of those forms of central modification that are specifically triggered by changes in neural input (afferent, local, or descending) and not due to alterations in connectivity, glial activity, or loss of inhibitory neurons. In many cases, multiple mechanistic drivers may be present or change over time.

The International Association for the Study of Pain definition of central sensitization, "increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input," does not include the term activity-dependent, nor is it contingent on peripheral input; instead, it is an operational definition of change in neuronal sensitivity (threshold, gain, spatial input) defined in terms of changes in responsiveness. This is quite precise and I believe satisfactory because it contains enough information to aid clinical diagnosis without having to record from neurons (looking for consequences of changes in responsiveness), while containing mechanistic information.

Why then does Dr. Hansson attempt to restrict the meaning of central sensitization to one of its specific forms? It seems he disagrees with the spatial extent of pain hypersensitivity and suspects that if a patient has chronic widespread pain this may reflect psychological rather than neurological changes, because as he sees it, central sensitization from a focal conditioning input is associated with only limited rostrocaudal spread. This resembles the argument that symptoms in conditions such as fibromyalgia are perhaps not "real," at least as defined in terms of changes in somatosensory pathways, but instead reflect the effects of catastrophizing, somatization, or depression due to dysfunction of nonnociceptive cortical circuits. Whether or not primary psychological factors are sufficient by themselves to change pain thresholds is certainly an interesting question. If activity in the forebrain circuits that drive mood and anxiety can alter nociceptive neuronal responsiveness, then this is, I consider, another cause of central sensitization, this time with a central rather than a peripheral driver. However, as with the chicken and egg question, it is very difficult to tease out which one comes first.

Dr. Hansson narrows the definition of central sensitization to that related to its discovery, which our group spearheaded [2,12,14]. We also were the first to use the phrase, at least in print [15]. The first manifestation of the phenomenon, as evoked by peripheral tissue injury or brief activation of nociceptors electrically or chemically, was certainly both activity-dependent and induced by peripheral input, and its rostrocaudal extent in the spinal cord was somewhat restricted, but this does not mean that this is the only central generator of pain hypersensitivity—it just happens to be the one first discovered, and certainly not all causes of central sensitization are single or focal.

The term central sensitization captures that slew of changes in the CNS that produce pain hypersensitivity, and that is how it is currently largely used. The first sets of experiments that discovered central sensitization were done in model organisms under conditions quite different from that of chronic pain patients, and were not designed to represent disease surrogates of conditions such as fibromyalgia, but were instead mechanistic neurophysiological studies with defined and spatially restricted inputs. Central sensitization continues, in my opinion, to have utility because it helps to distinguish those forms of pain that arise predominantly peripherally (such as nociception, peripheral sensitization, and spontaneous pain associated with ectopic activity after peripheral nerve lesions) from those in which there is a combination of a definable central component and an increase in pain sensitivity. Obviously, mechanistic qualifiers regarding what specific neural or glial change in which particular part of the CNS generates the pain hypersensitivity will have important diagnostic power and potential therapeutic value, and should be used wherever possible.

Central sensitization is categorically different from symptoms such as allodynia or hyperalgesia, even though they may help

☆ DOI of original article: http://dx.doi.org/10.1016/j.pain.2014.07.016

http://dx.doi.org/10.1016/j.pain.2014.07.021

identify its presence; other more sophisticated approaches are possible [5]. Similarly, changing from central sensitization to a term such as cognitive-emotional sensitization, as suggested by Dr. Hansson, does not seem a useful step forward unless supported by data showing that such sensitization exists and is the cause of the pain.

I have reviewed elsewhere the features of central sensitization, amplification in the CNS resulting in recruitment of low-threshold afferents as drivers of pain, spread of pain sensitivity outside an area of injury, and dynamic changes in the relationship between stimulus and response [6,13], and will not say more here. On the issue of spatial spread we do, however, need to appreciate that the spread of altered excitability and synaptic strength in the dorsal horn from even a single brief focus of input (such as evoked by a subcutaneous injection of capsaicin in a human volunteer) answered an issue that had long puzzled neurologists—how pain can spread across boundaries of nerve innervation territories. This tendency for pain to spread had been considered before to constitute evidence of hysteria, but instead turned out to have a firm neurobiological basis. I recall Peter Nathan, a distinguished neurologist from Queen Square London, saying to me something like, and I paraphrase, "Trust your patient, they are telling you the truth, it is up to you to find out why. If your patient tells you they have widespread pain, they do, even if you cannot understand it."

Dr. Hansson is not alone in not understanding the nature and causes of widespread pain, but that does not mean that it does not exist; on the contrary, there is solid and growing evidence that it does, as these three recent studies illustrate [9–11]. Does it represent a disease state or is it at the extreme of the normal variance in pain threshold due to genetic polymorphisms [3] or sleep deprivation [7]; might it be due to widely distributed peripheral sensitization or disseminated ectopic firing in a small-fiber neuropathy [8], or the consequence of anatomical changes at different levels of the neuraxis that might affect multiple somatotopic distributions [1]; all are possible, and we need to do much more work to find out which operate under what circumstances. Nevertheless, there is overwhelming evidence that changes in neural processing in the CNS occur and contribute to pain hypersensitivity [13], and the term central sensitization as defined by the International Association for the Study of Pain therefore remains useful to capture this, and I suspect it will continue to be widely used.

Conflict of interest statement

The author reports no conflict of interest.

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