“Nocifensor” System Re-Revisited. Focus on “Two Types of C Nociceptor in Human Skin and Their Behavior in Areas of Capsaicin-Induced Secondary Hyperalgesia”

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The report “Two Types of C Nociceptor in Human Skin and Their Behavior in Areas of Capsaicin-Induced Secondary Hyperalgesia” by Serra et al. (this issue, p. 2770–2781) documents, for the first time, the activation and sensitization of a special class of unmyelinated sensory primary afferent fiber (C-mechanically insensitive or CMi) by capsaicin injected a considerable distance (1–5 cm) from the site tested for sensitization.

The important implications of this finding are that this special class of C primary afferent fiber that has only recently been recognized could contribute to the hyperalgesia that occurs at a substantial distance from an injury site (so called “secondary” hyperalgesia as opposed to the hyperalgesia that develops in the injured tissue which is called “primary” hyperalgesia). Further investigations along these lines could improve our understanding of the mechanisms causing secondary hyperalgesia.

The problem of how skin surrounding an injury site becomes painful has interested neurobiologists since Lewis (1936) hypothesized the existence of “nocifensor” nerve fibers that could detect information about a localized injury and distribute this information both to surrounding sensory afferents that encoded pain thereby causing hyperalgesia and to blood vessels to cause local dilation leading to the reddening of the skin (flare) as well as swelling of the tissue (edema). Whether hyperalgesia and flare are functionally linked is still controversial, though Serra et al. (1998) and Sumikura et al. (2003) have documented that they do overlap in territory.

Lewis postulated that one portion of a widely branching sensory fiber responded to the injury, and that action potentials were carried, antidromically to other branches of the fiber where they liberated a chemical substance that caused the flare and enhanced sensitivity of other sensory axons responsible for pain (see Fig. 1). This antidromic activation was termed an “axon reflex.” That nerve fibers were spreading the flare and hyperalgesia from the injury site was suggested because anesthetizing a narrow band of skin blocked the spread of flare and hyperalgesia beyond the band. LaMotte et al. (1991) confirmed and extended these findings using capsaicin, instead of injury to initiate the hyperalgesia. Lewis’ and LaMotte et al.’s findings place constraints on the types of sensory fibers that could function as local “nocifensors” and on the types of sensory fibers that could convey the sensory information interpreted as hyperalgesia to the CNS.

The local nocifensors would 1) be unmyelinated axons (C fibers); 2) be largely chemoreceptive, and less responsive to heat and mechanical stimuli, but could become more responsive to heat and mechanical stimuli after injury; 3) branch widely, over $\geq 5$ cm in the skin of the forearm; and 4) excite or sensitize the axons conveying the hyperalgesia to the CNS, and they must similarly cause vasodilation in the same territory as the hyperalgesia. Lewis and others have presumed that a chemical mediator that performs both of these functions is released by these fibers.

The sensory afferents that convey the hyperalgesia to the CNS would 1) access the pain system; 2) have very low mechanical thresholds for activation because lightly stroking the skin can cause pain in at least part of the zone of secondary hyperalgesia; 3) probably have myelinated axons [LaMotte et al. (1991a) suggested A delta axons, while others suggest more rapidly conducting axons, e.g., Torebjörk et al. (1992)]; and 4) be responsive to heat because hyperalgesia to heat is noted as well as hyperalgesia to punctuate mechanical stimuli.

Numerous experiments in years up until recently had failed to find classes of afferent fibers that fit these criteria that could parsimoniously explain Lewis’ and others’ observations on the nature of flare, edema, and enhanced pain after localized injury.

The previous literature suggested that at least some C fibers contain substances that could dilate blood vessels and directly and indirectly sensitize other nociceptors (substance P, etc., e.g., Brain 1997 for review). However, C-nociceptors had small discrete receptive fields not large receptive fields created by widely branching afferents, and were not activated or sensitized by remote injury or chemicals (see review in Perl 1996). Recently, a class of primary afferent C fibers with unique properties has been identified that does fulfill some of the criteria for Lewis’ nocifensor system (e.g., Schmidt et al. 1995, 2002). These afferents have widely branching, unmyelinated axons with large potential receptive fields. They normally respond poorly if at all to moderately noxious mechanical stimuli but are chemosensitive to noxious agents and can be sensitized by damaging stimuli and by noxious heat and chemicals. These have been called mechanically insensitive C fibers (CMi). These C fibers have unique electrophysiological characteristics suggesting specialized contributions of excitatory channels to their conducting properties (described in Bostock et al. 2003; Serra et al. 2004). Other classes of C fibers have also been recently documented in humans, including low-threshold mechanoreceptive C fibers and C-fibers that are unique for itch, but these classes are not candidates for the nocifensor system.

However, until the study of Serra et al. (2004) remote injection of capsaicin or remote injuries had not been reported to activate or sensitize any type of A or C nociceptor (e.g.,
An alternative mechanism to Lewis’ nocifensor system for the production of flare and hyperalgesia involves dorsal root reflexes. This hypothesis has received experimental support from Willis’ group (Lin et al. 2000, 2004) and from Cervero et al. (2003). Essentially, this hypothesis is that inputs from C nociceptors lead to strong presynaptic depolarization of other primary afferent fibers in the spinal cord. This presynaptic depolarization is strong enough to initiate action potentials that antidromically propagate to the peripheral receptive fields of these fibers. This antidromic activity then causes the liberation of chemokines leading to flare and sensitization of nearby primary afferents causing hyperalgesia. Willis’ group has documented that blocking the central nerve trunks or dorsal roots blocks flare and secondary hyperalgesia in rats. This is at odds with LaMotte’s (LaMotte et al. 1991) experiments in human subjects showing that blocking central nerve trunks did not block flare and with Lewis’ experiments showing that cutting nerves did not block flare until the peripheral nerve fibers had degenerated.

Given the complex seemingly often redundant processing of pain in the CNS, it is quite likely that hyperalgesia is mediated by several, parallel pathways. Thus it is possible that both C- and A-fiber pathways participate in the transmission of hyperalgesia and that peripheral mechanisms, dorsal root reflexes, and CNS plasticity may all play a role in the initiation and maintenance of hyperalgesia. It is not unlikely, that given the urgency of pain information for the protection of an organism, that if one of these pathways is blocked, another may compensate for the loss given the time and proper conditions for compensation.

In summary, the target article in this issue of Journal of Neurophysiology adds to other recent Journal of Neurophysiology articles (Andrew and Greenspan 1999; Schmidt et al. 2002) in demonstrating that CMI afferents have most of the properties required to be the sensors and effectors required to be Lewis’ nocifensor system and may be a major contributor to the all too familiar pain observed in secondary hyperalgesia.

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