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REVIEW

Spinal cord hyperexcitability and its role in pain and hyperalgesia

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Abstract Sensitization of spinal cord nociceptive neurons is commonly interpreted as the cause for the hypersensitivity that characterizes chronic pain states in humans. However, in spite of much basic research in this area it has not been possible to demonstrate a direct link between the hyperexcitability of spinal cord neurons observed experimentally and the underlying mechanism of a chronic pain state. The word sensitization is also used in the literature with various and different meanings from the qualification of a cellular process of enhanced excitability at synaptic level to the characteristics of a chronic pain syndrome. In this article the various meanings of sensitization are described and the relevance of the hyperexcitability of spinal cord neurons to the generation of clinically relevant pain states is discussed. A proposal is made to restrict the use of the word sensitization to the cellular process of enhanced excitability observed experimentally after repetitive stimulation of nociceptive afferents. Caution is also recommended when associating neuronal sensitization in the spinal cord with the mechanisms of chronic pain conditions.

Keywords Sensitization · Hyperalgesia · Spinal cord · Wind-up · Chronic pain

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Introduction

The question that I would like to address in this article is what role do spinal cord mechanisms play in the generation and maintenance of chronic pain states. Pain is a dynamic sensation and the most prominent feature of this dynamism is the enhanced pain sensitivity, known as hyperalgesia, that develops after injury or inflammation and that in some cases persists in the form of a chronic pain state (Treede et al. 1992; Cervero et al. 2004). The main features of hyperalgesia are pain produced by non-painful stimuli (allodynia), enhanced pain sensitivity to noxious stimuli and spontaneous pain. Hyperalgesia develops normally after an injury and persists until the injury has healed. However, hyperalgesia can also continue as a feature of chronic inflammatory diseases or be the main symptom of conditions characterized by pain in the absence of an apparent injury (functional pain states). Spontaneous pain, allodynia and hyperalgesia are also prominent in neurological diseases caused by peripheral or central neuropathies and are thus critical features of neuropathic pain states.

Hypersensitivity is usually interpreted as due to an increased excitability of the neural mechanisms responsible for the generation of the sensation. At neuronal level, this can be the result of an intrinsic cellular process induced by the originating stimulus or of a disinhibition of the neural networks that transmit injury-related information. I either case the phenomenon is known as sensitization whereby the responses of a given neuron are progressively enhanced following continuous noxious stimulation and the neuron remains in a hyperexcitable state even after the originating stimulus has waned (Sandkuhler 2007). Features of sensitization of the pain system include the generation of spontaneous activity, of increased responses to noxious stimulation and the

acquisition by nociceptor-specific neurons of responses to low intensity stimulation (Woolf and Salter 2000). These cellular properties are though to lead to the perception of spontaneous pain, to hyperalgesia and to allodynia.

Sensitization of nociceptive neurons has been demonstrated at every location along the pain pathway, from peripheral nociceptors to cortical neurons. However, a direct relationship between sensitization as a cellular process and the maintenance of a chronic pain state has not yet been established. We also do not know what are the relative contributions to the final experience of pain of the various components of the pain network. The question addressed in this article focuses on the specific role of the sensitization of nociceptive neurons in the spinal cord in the generation of chronic pain states.

This question is relevant here for two reasons. First, the spinal cord has been regarded for over a century as a potential site of pain modulation and not just a simple transmission line from the periphery to the brain. As far back as 1909, MacKenzie (1909) already proposed that the arrival of impulses to the spinal cord from an injury site produced a "focus of irritation" which rendered spinal cord neurons more excitable and led to enhanced pain perception as well as increased motor and autonomic activity. In the 1960's the gate control theory (Melzack and Wall 1965) also focused on the spinal cord as a prime site for pain modulation and proposed a detailed mechanism of interaction between the spinal projections of large and small afferent neurons that would lead to changes in pain perception. This focus on the spinal cord as a prime site for pain modulation has continued until the present time even though a direct relationship between spinal cord sensitization and pain perception has not been demonstrated.

The second reason has to do with the dedication of the present issue of Experimental Brain Research to the work of Robert Schmidt. Many of his scientific contributions are directly related to spinal cord mechanisms of nociceptive processing and it seems appropriate that we take this opportunity to examine the current state of the question. His detailed studies of the mechanisms of presynaptic inhibition in the spinal cord (Schmidt 1971) and of the contribution of interactions between afferent neurons to the transmission of nociceptive signals through the cord are essential reading in this field. His work on the sensitization of nociceptors led to the discovery of silent nociceptors (Schaible and Schmidt 1988), which are believed to play a prominent role in the generation of chronic pain. To address the role of spinal cord sensitization in pain processing is a fitted tribute to the fundamental contributions of Robert Schmidt to the study of pain mechanisms in the spinal cord.

What is sensitization?

The term sensitization is used in the pain literature with two different and somewhat contradictory meanings (Sandkuhler 2007). On the one hand, sensitization is used to describe a cellular process of enhanced excitability whereby repetitive noxious stimulation leads to an increase in responsiveness of a given nociceptive neuron to its normal afferent input. On the other hand, sensitization is also used to refer to any status of increased sensitivity to pain observed in normal subjects or in pathological conditions or to any form of increased excitability within the central nervous system (CNS) that is assumed to cause a hyperalgesic state. The main problem with this ambiguous use of the word and the reason for much confusion is the implication that a chronic pain state is the direct consequence of the sensitization of nociceptive neurons.

As Sandkuhler (2007) has pointed out the first meaning of the word is the correct one. Sensitization is well defined as a cellular process of increased excitability. The hyperexcitability is caused by repetitive stimulation of the neuron, either directly, as in the case of peripheral nociceptors, or via its afferent inputs when expressed by central neurons. We can study in detail the properties of the sensitizing stimuli, the time course of the process, the molecular mediators of the excitability increase and the changes induced in the whole network. The sensitization process is illustrated by a leftward shift in the stimulus-response curves of a given neuron (Fig. 1a) or in the acquisition of novel afferent inputs as a consequence of the sensitization of the cell (Fig. 2).

The use of the same word to qualify a behavioral process of enhanced pain sensitivity creates much confusion, especially as it implies that sensitization of nociceptive neurons is the cause of pain hypersensitivity. In animal experiments it is not difficult to detect behavioral changes in hyperalgesic states that mimic the leftward shift in stimulus-response function characteristic of a sensitization process (Fig. 1b, c). In normal humans, under laboratory conditions, it is also possible to show similar shifts in pain perception (Meyer and Campbell 1981; Meyer et al. 1985). This is what has generated the opinion that the two processes are directly linked and therefore, that studying the sensitization of nociceptive neurons equals studying the mechanisms of clinically relevant pain. Yet, some of the neurons that express sensitization to nociceptive stimuli may have little to do with pain perception and be related to the organization of motor or autonomic responses or to non-sensory components of the response to injury. Other sensitized neurons may be part of inhibitory networks and therefore be concerned with pain reduction rather than excitation. Since it is impossible, at least at present, to establish the behavioral contribution of a single neuron or groups of neurons when

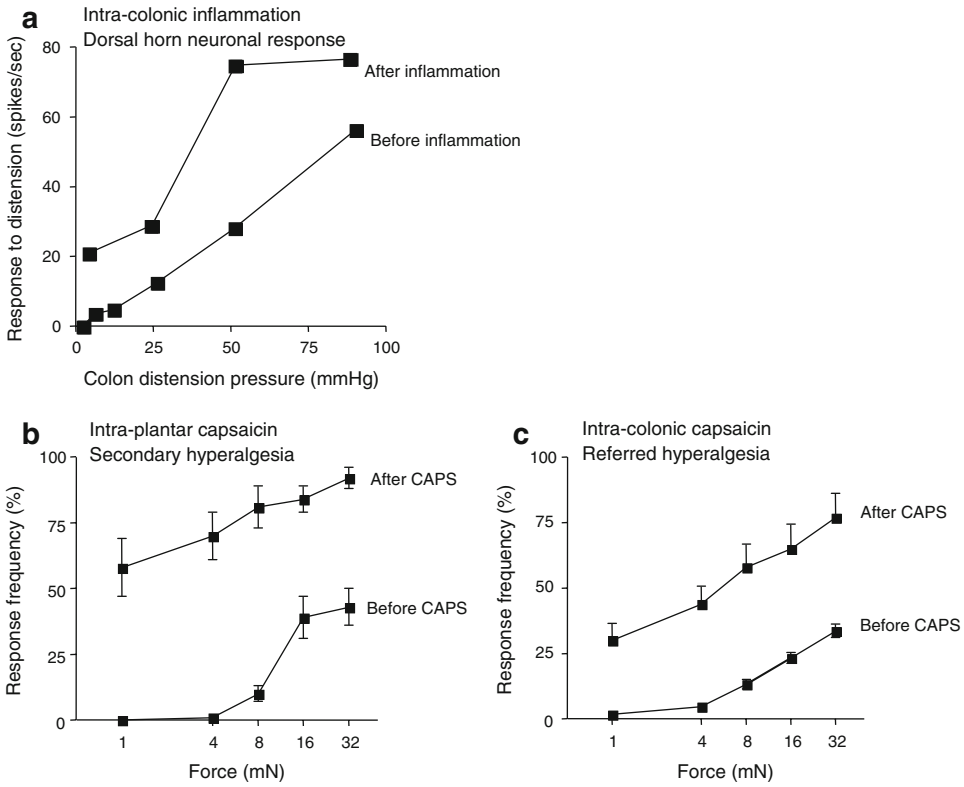

Fig. 1 Different expressions of sensitization and hyperalgesia. The three graphs include experimental data that show the distinctive leftward shift that characterizes sensitization and hyperalgesic states. The graph in **a** shows data from an electrophysiological study in an anaesthetized rat in which the responses of a dorsal horn neurone to colonic distension were recorded before and after inflaming the colon by instillation of acetic acid. **b** and **c** are graphs from behavioral studies in awake mice in which the mechanical sensitivity of areas away from an injury site was tested. In **b**, the tests were conducted at a site in the paw adjacent to the point were an intradermal injection of capsaicin was applied. In **c** the tests were conducted at a site in the abdominal wall remote from a capsaicin instillation into the colon. Data from the author's laboratory

studied in vivo or in vitro, it is better to reserve the term sensitization to the cellular process observed in these cells and to be cautious about the implication that an enhanced pain sensitivity is caused by the sensitization of the neurons in a particular study.

Peripheral sensitization and primary hyperalgesia

The aim of this article is to address the relevance of the sensitization of spinal cord neurons to the generation of chronic pain states. It is appropriate, however, to dedicate a few words to the sensitization of peripheral nociceptors, for it is here where the term was first used and it is also the location where the molecular mechanisms that mediate the process of cellular sensitization are best known.

It has been known for over 40 years that repetitive stimulation of peripheral nociceptors triggers a process of enhanced nociceptor excitability that was called sensitization (Burgess et al. 1973). The increased excitability correlates well with the enhanced sensitivity to pain of the area innervated by the sensitized nociceptors and this has led to the belief that primary hyperalgesia, i.e. enhanced pain sensitivity in an area of injury, is mostly mediated by nociceptor sensitization (Meyer et al. 1985; Treede et al. 1992).

The process of sensitization of nociceptive primary afferents has been studied in detail and numerous molecular mechanisms of sensitization have been identified (Julius and Basbaum 2001). In the end, sensitization always involves, one way or another, changes in the expression and in the functional properties of voltage-gated ion channels. Behavioral studies in mice carrying a null mutation of the tetrodotoxin-resistant (TTX-r) Nav1.8 gene have revealed a complete absence of responses to a tonic noxious mechanical stimulus and attenuated primary hyperalgesia evoked by intraplantar injection of nerve growth factor (Akopian et al. 1996). Inhibiting the expression of Nav1.8 protein using antisense oligonucleotides also reduces primary hyperalgesia produced by intraplantar prostaglandin E2 or Freund's adjuvant in rats (Khasar et al. 1998; Porreca et al. 1999). Nav1.8-null mice also show normal responses to acute noxious visceral stimuli such as intraperitoneal injection of acetylcholine, which excites nociceptors without sensitizing them and also provokes intense smooth-muscle contractions sufficient to excite visceral receptors (Cervero and Sharkey 1988). However, Nav1.8-null mice show blunted responses to sensitizing visceral stimuli such as intracolonic instillation of capsaicin which is also unable to induce the characteristic referred hyperalgesia normally seen after intracolonic capsaicin (Laird et al. 2002). Therefore, Nav1.8 is not essential for normal behavioral responses to acute noxious stimuli or for behavioral response to tonic noxious chemical stimuli but is required for the expression of normal visceral pain and hyperalgesia to intracolonic capsaicin. This would indicate that this sodium channel plays a key role in the generation of spontaneous activity in

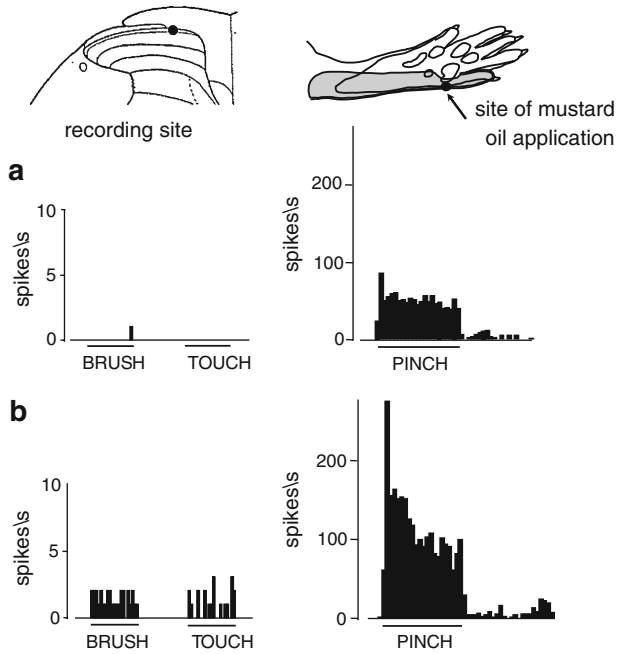

Fig. 2 Sensitization of a nociceptor-specific (NS) neuron in the superficial dorsal horn of the spinal cord of an anesthetized rat. The dorsal horn location of the neuron and its cutaneous receptive field (RF) are also shown at the *top* of the figure. **a** Responses of the neuron to low intensity (*brush, touch*) and high intensity (*pinch*) stimulation of its RF. **b** Responses of the neuron after an application of mustard oil to the RF (at the site indicated in the RF figurine). Note the increased response of the neurone to noxious pinch and the acquisition of novel inputs to tactile stimulation after sensitization. Data from Garcia-Nicas et al. (2006)

sensitized visceral nociceptors and would contribute to the spontaneous pain observed in an area of primary hyperalgesia. Interestingly, we have also demonstrated (Roza et al. 2003) that afferent C-fibers from experimental neuromas generated in mice with a null mutation of the Nav1.8 gene lack the characteristic spontaneous activity that is thought to cause spontaneous pain but still retain the abnormal mechanosensitivity that develops in damaged afferent fibers and that is a feature of neuropathic pain caused by peripheral nerve damage (Woolf and Mannion 1999). This shows that the mechanisms of peripheral sensitization of nociceptors are complex and that not all the expressions of sensitization of afferent nociceptive fibers can be attributed to a single molecular mechanism.

Central sensitization and spinal cord hypersensitivity

Numerous studies have demonstrated that spinal cord neurons do increase their excitability on repetitive stimulation of their afferent drives. Expressions of such sensitization include the phenomenon known as "wind-up" (Herrero et al. 2000) defined as a frequency-dependent facilitation of the excitability of spinal neurons induced by repetitive electrical stimulation of afferent C-fibers. Other expressions of sensitization are illustrated by leftward shifts in stimulus-response curves of spinal neurons (Fig. 1a), enlargement of peripheral receptive fields (RFs) or acquisition of novel low threshold afferent inputs by nociceptor-specific cells (Fig. 2). All these experimental phenomena are induced by repetitive stimulation of nociceptive afferent fibers and the resulting enhanced excitability persists beyond the originating stimulus, which has led to the proposal that many of these forms of sensitization are expressions of the synaptic property known as long term potentiation (LTP) (Sandkuhler 2007).

Some of the early studies of spinal cord sensitization focused on the motor output of the cord as the measured variable (Woolf 1983). The rationale was that the generation of an enhanced excitability state in the spinal cord would also be reflected in an enhanced motor output. Therefore the activity of motorneurons or of the muscles innervated by spinal motorneurons was used as a surrogate to draw conclusions about pain hypersensitivity. Other studies have reported increases in excitability of spinal dorsal horn neurons following a variety of stimulation protocols of nociceptive afferents (Cervero et al. 1984). There is little doubt that the arrival of a nociceptive message to the spinal cord sets up a "focus of irritation" (MacKenzie 1909), which renders spinal cord neurons more excitable to further afferent input. There is also considerable evidence that this phenomenon outlasts, but is not totally independent from, the duration of the conditioning afferent stimulus and that the increases in excitability can be observed in motorneurones as well as in interneurons and neurons of ascending sensory pathways. The study of the molecular mechanisms of spinal cord sensitization has also shown that much of this phenomenon is an expression of synaptic LTP, although the properties of the neuronal network and the involvement of spinal–supraspinal loops and of descending excitation from the brain also play a role (Cervero and Wolstencroft 1984; Tattersall et al. 1986).

As mentioned above, the phenomenon of wind-up has been extensively studied as an expression of the sensitization of spinal cord neurons. It has often been described as one of the earliest forms of sensitization following the arrival into the cord of a barrage of afferent impulses in nociceptive afferents. Wind-up can be observed in motor as well as sensory neurons and it can be studied by a variety of means, from cumulative depolarizations of single neurons to the electromyographic activity of muscles involved in withdrawal reflexes. The basic rationale of studies of wind-up using motor output parameters implies that the activity of a withdrawal reflex correlates with the perception of a pain sensation. The fact that wind-up appears to be mediated by the activation of glutamate NMDA receptors

(Herrero et al. 2000) supports the use of wind-up as a measure of LTP and hence of neuronal sensitization.

There is much debate as to whether wind-up is an expression of central sensitization and even a valid parameter of pain hypersensitivity (Woolf 1996). Even if we accept that wind-up demonstrates a quick enhancement of excitability of spinal neurons after a brief period of nociceptive stimulation there are serious problems with the notion that wind-up is directly related to the development of central hyperexcitability in chronic pain states. For instance, noxious visceral stimulation is a powerful generator of pain hypersensitivity, both under laboratory conditions and in clinical conditions. Yet, spinal cord neurons with visceral drives are notoriously difficult to sensitize by repetitive visceral stimulation (Laird et al. 1995), which suggests that it is possible to develop visceral hypersensitivity without a wind-up correlate.

In a recent series of experiments in my laboratory we have looked at the expression of wind-up in motor and sensory systems during development, using an in vitro spinal cord preparation from young mice. Robust wind-up was observed in very young animals (up to 3 weeks old) in both motorneurones and ascending sensory neurons, induced by repetitive stimulation of dorsal root afferents (Fig. 3). However, the motor wind-up was progressively smaller as the animals grew older and after 4 weeks of age it was undetectable (Fig. 4). Yet a robust wind-up could be recorded in ascending sensory neurons in both young and older animals (Figs. 3, 4). Although it is possible that technical problems with the preparation could account for this dissociation, it is also possible that the expression of wind-up differs between motor and sensory systems and therefore that we should not assume a direct correlation between the spinal cord motor output and the perception of pain.

Wind-up, like many other manifestation of spinal cord excitability is a short-lived phenomenon triggered by a relatively brief stimulus. It demonstrates the plasticity of spinal synapses and the way in which afferent drives can alter the excitability of spinal cord cells. But it cannot be regarded as a form of long term sensitization of neurons or as an expression of a chronic pain state. Wind-up is useful in so far as the molecular mechanisms that mediate synaptic plasticity probably play a role in chronic pain states but it cannot be used as a marker of such chronic states.

A fundamental problem in trying to establish a direct relationship between spinal cord sensitization and the generation of a chronic pain state is that sometimes the basic experimental data fails to generate clinically relevant applications. A case in point is the role of Substance P (SP) and of its postsynaptic receptor, Neurokinin 1 (NK1), in the maintenance of chronic pain.

For a long time, it has been thought that the tachykinin family of peptide neurotransmitters, which include

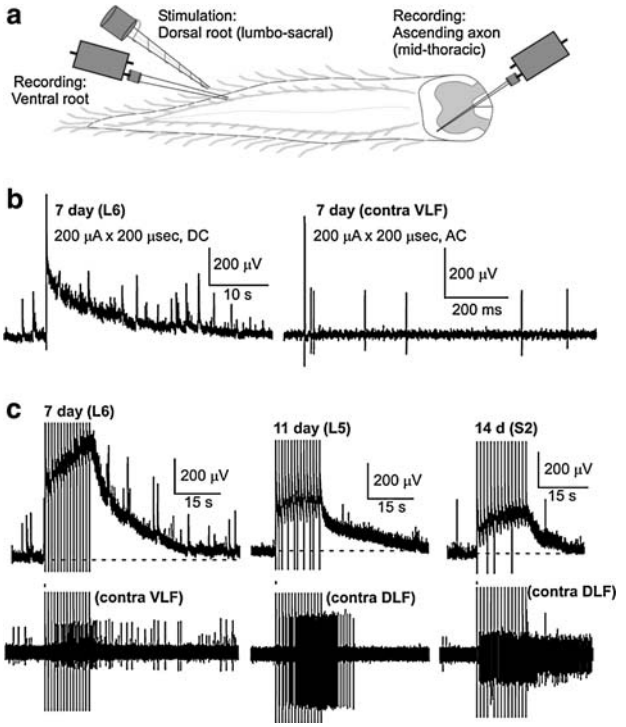

Fig. 3 Simultaneous recording of ventral root potentials (VRP) and ascending axon spikes following electrical stimulation of a dorsal root in an in vitro whole spinal cord preparation. **a** Schematic drawing of the experimental set-up. **b** Recordings of VRP (*left trace*) and single-unit spikes in an ascending axon in the contralateral ventro-lateral funiculs (VLF, *right trace*) from a 7-day-old pup evoked by stimulation of the L6 dorsal root. **c** Simultaneous recording of wind-up of the VRP (observed as a cumulative depolarization, *top traces*) and of the ascending axons responses (observed as a progressive increase in spike count, *bottom traces*) evoked by the application of a train of stimuli to the dorsal root of 7, 11 and 14 day old mice. The ventral roots from which VRPs were recorded and the ascending pathways from which spike activity was recorded are indicated on *top* of each trace (*DLF* dorso-lateral funiculus; *VLF* ventro-lateral funiculus). Note the gradual decrease in amplitude and duration of the cumulative depolarization in the ventral root potentials with increasing age of the mice and the maintenance of the ascending axons wind-up. In all the examples shown the VRPs were recorded in DC mode and the ascending axons responses in AC mode. Unpublished data from the author's laboratory (Rashid, Lopez-Garcia and Cervero)

Substance P, are involved in pain and hyperalgesia (Iversen 1998). A high proportion of afferent neurones contain Substance P (Perry and Lawson 1998) and the highest concentration of NK1 receptors in the spinal cord is found in the regions concerned with nociceptive processing. Studies using mice with disruptions of the gene encoding for the tachykinins substance P and neurokinin A (pptA −/− mice), or for the Substance P/neurokinin A (NK1) receptor have shown that this system contributes to nociception (Cao et al. 1998; De Felipe et al. 1998; Zimmer et al. 1998; Laird et al. 2000). For instance NK1 null mice do not express visceral pain and hyperalgesia normally evoked by sensitizing noxious stimuli like acid and capsaicin (Laird

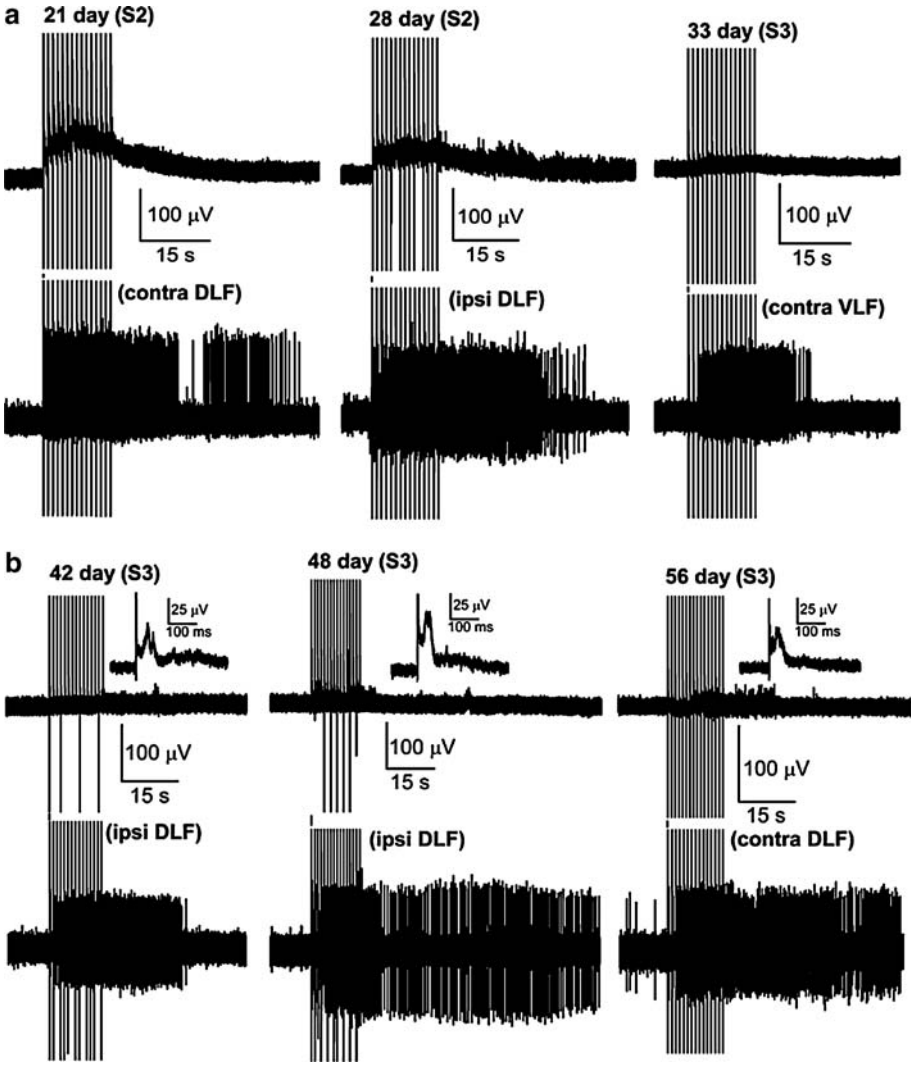

Fig. 4 Simultaneous recording of wind-up of VRP (*top traces*) and ascending axon spikes (*bottom traces*) from mature mice with increasing age. The ventral roots from which VRPs were recorded and the ascending pathways from which spike activity was recorded are indicated on *top* of each trace (*DLF* dorso-lateral funiculus; *VLF* ventro-lateral funiculus). **a** In a 21 day old mouse, the cumulative depolarization in the ventral root potentials was much smaller than in juvenile mice (see Fig. 3) while the wind-up in ascending axon was still prominent. In 28 and 33 day old mice, wind-up of VRP was further reduced but the ascending axonal wind-up was unchanged. **b** Wind-up of VRP and ascending axons in 42, 48 and 56 day old mice. While the wind-up of VRP was no longer present in these animals, wind-up in the ascending axons could still be evoked. Some wind-up responses in ascending axons are truncated to fit the traces into the figure. Insets in **b** (*top traces*) are the single-shock VRP responses in an extended time scale to show that the responses were still present. In all the examples shown the VRPs were recorded in DC mode and the ascending axons responses in AC mode. Unpublished data from the author's laboratory (Rashid, Lopez-Garcia and Cervero)

et al. 2000) (Fig. 5a, b) and these mice also show a reduced or absent wind-up of withdrawal reflexes (De Felipe et al. 1998) (Fig. 5c).

Using a selective tachykinin NK1 receptor antagonist we have also been able to demonstrate a spinal cord action of Substance P in the generation of hypersensitivity of nociceptive neurons. Both electrical stimulation of the pelvic nerve, which bypasses the sensory receptors of colorectal afferents, and colorectal distension, which activates peripheral nociceptors directly, can generate hyperexcitability of spinal cord neurons and in both cases, this phenomenon can be blocked by the administration of a selective NK1receptor antagonist (Laird and Cervero, unpublished observations) (Fig. 5d). Therefore tachykinin NK1 receptors appear to be involved, via a spinal cord mechanism, in the generation of visceral hyperalgesia resulting from acute colon inflammation.

In spite of all this experimental evidence, NK1 antagonists have notoriously failed to show analgesic activity in several clinical trials of various acute and chronic pain conditions (Hill 2000). There are has been intense discussion about the appropriateness of the use of NK1 antagonists

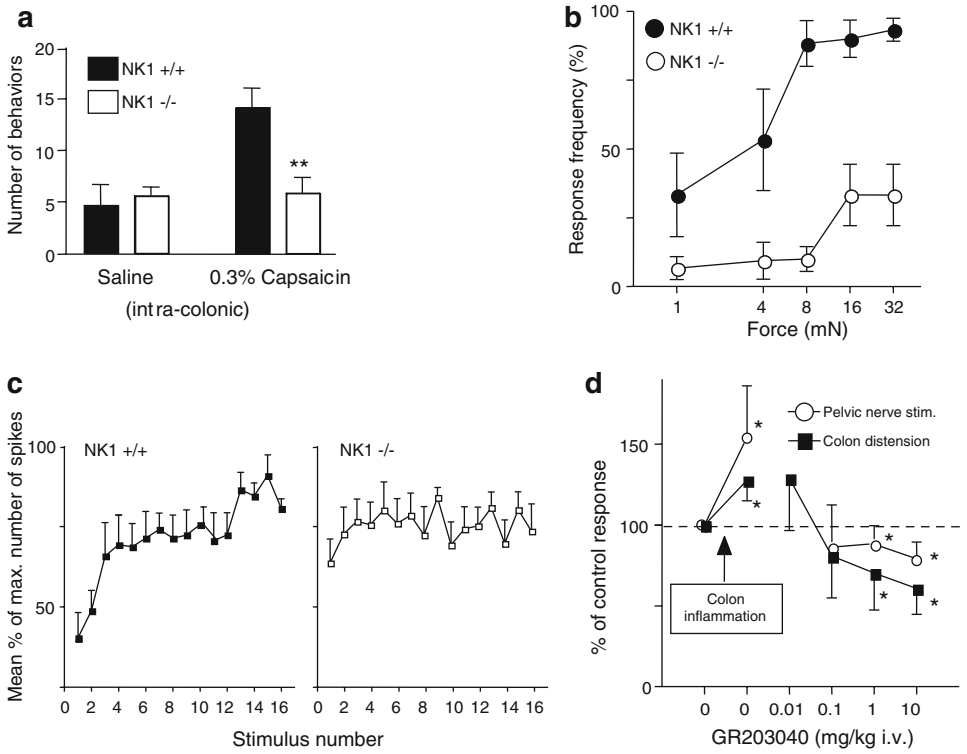

Fig. 5 Experimental evidence showing that NK1 receptors play a role in pain hypersensitivity. **a** Behavioral responses to noxious chemical stimulation of the colon. An intracolonic instillation of saline evokes behavioral responses lasting for a brief amount of time in both wild type (+/+) and NK1 receptor KO (−/−) mice. However, an instillation of capsaicin evokes responses in wild type (+/+) mice, which are significantly greater than those evoked in NK1 receptor KO (−/−) mice. Data from Laird et al. (2000). **b** Referred hyperalgesia evoked by capsaicin instillation into the colon. The graphs show the responses to mechanical stimulation of the abdomen (mean percentage response frequency ± SEM) after stimulation of the colon with 0.3% capsaicin. Note the prominent referred hyperalgesia in wild type mice (+/+) and its absence in NK1 receptor KO (−/−) mice. Data from Laird et al. (2000). **c** Wind-up of spinal reflexes. Withdrawal reflexes (mean ± SEM of spike responses) were recorded in a flexor muscle of the hind limb evoked by electrical stimulation of the skin. Responses are normalized to their maximal value. Note the prominent wind-up of the response in the wild type mice (+/+) and the absence of wind-up in the NK1 KO mice (−/−). Data from De Felipe et al. (1998). **d** Effect of the administration of cumulative doses of the NK1 receptor antagonist GR 203040 on the mean ± SEM spike responses of rat dorsal horn neurons to 80 mmHg distensions of the colon and to electrical stimulation of the pelvic nerve. Responses were obtained before and after inflammation of the colon with acetic acid. The data are presented as percentage of control response before the inflammation of the colon. *Asterisks* indicate responses significantly different from vehicle responses ($P < 0.05$). Unpublished observations from the author's laboratory (Laird and Cervero)

for the conditions tested in the clinical trials (Laird 2001). Although some of the problem may be due to testing the wrong drugs for a given pain condition the fact remains that there is a big gap between the mass of experimental evidence showing a role of Substance P in pain modulation and the negative data from the clinical trials. One persuasive explanation to explain this discrepancy would be that the measurements used in experimental studies as surrogates of chronic pain states are inadequate. In other words, we are assessing clinically relevant pain hypersensitivity using short-term changes in the excitability of motor or sensory systems in experimental animals that have little consequence to the mechanisms that mediate a chronic hyperalgesic state in the clinical world. A corollary would also be to question the extent to which spinal cord sensitization, that is often the prime experimental paradigm in basic science studies, does actually mediate clinically relevant pain syndromes. This is especially important when studying complex pain experiences, such as those of chronic pain, in which the higher functions of the brain play a crucial role.

Questions and answers

The truth knocks on the door and you say, "Go away, I'm looking for the truth," and so it goes away. Puzzling.
Robert M. Pirsig (Zen and the Art of Motorcycle Maintenance, 1974).

I have tried to address two main questions regarding the role of spinal cord sensitization in pain. Have we got any answers?

1. *What is sensitization?* Sensitization is a term that best describes the cellular process of enhanced excitability that can be observed in neurons after a repetitive stimulation is applied to them either directly or via their afferent drives. When dealing with nociception, sensitization refers to the increased excitability of nociceptive neurons (i.e. those that are activated by noxious stimuli) that follows a brief period of repetitive stimulation (either natural or electrical). As such, sensitization is a well-defined cellular process that can be studied with clearly defined hypothesis and tools. The alternative use of the word sensitization to described any state of increased excitability or the behavioral manifestations of a chronic pain state can be misleading as it implies a direct link with the cellular process of sensitization. When sensitization is studied at cellular level it is obviously impossible to ascertain if the hyperexcitability of the neurons under study would be the cause of an enhanced hypersensitivity to pain in the experimental animal or, even less, in a clinically relevant condition. To establish this link it is necessary to manipulate a given process of cellular sensitization, either increase it or decrease it, and show that these changes always lead to a modification of pain sensitivity of the same magnitude and sign. It is also important to separate the mechanisms that underlie non-sensory responses to injury (motor, autonomic etc.) and that may also be subserved by a cellular sensitization process from those that impinge directly on perception.
   Sensitization of peripheral nociceptors is a well-established phenomenon of which we know a fair amount in terms of its cellular and molecular mechanisms. There is good evidence that nociceptor sensitization mediates the increased sensitivity to pain from an area of injury (primary hyperalgesia) although other factors in the CNS can certainly modulate this pain sensitivity.
   There is also considerable experimental evidence that CNS neurons can enhance their excitability following a period of repetitive stimulation of their afferent inputs. This process of central sensitization is expressed by many neural systems, including motor, autonomic and sensory pathways and it is probably mediated by mechanisms of synaptic plasticity akin to LTP. The relationship between the sensitization of a given cell or group of cells and the mechanisms of pain hypersensitivity, especially in a chronic pain condition, is still unclear. It is likely that some forms of sensitization do not have a perceptual correlate and conversely that the sensory experience associated with a chronic pain state requires mechanisms additional to the simple sensitization of a nociceptive pathway.

2. *Is spinal cord sensitization the cause of pain hypersensitivity in chronic pain?* There is considerable experimental data showing that sensitization of spinal cord neurons (of all kinds) occurs after a period of intense and repetitive stimulation. This has been demonstrated for motorneurons, interneurons and ascending sensory neurons. In addition to the cellular process of sensitization there is also evidence that networks involving spinal–supraspinal loops and generating descending excitation can also contribute to the state of enhanced excitability of spinal cord cells.
   However, such enhanced excitability does not necessarily mean an enhanced pain perception. Some of the increases affect motor systems, which seem to be dissociated from the activity that is sent to the brain via ascending pathways. Stimuli capable of generating considerable pain hypersensitivity are unable to enhance the excitability of spinal cord neurons (for example of viscerally driven cells). And antagonism of transmitter systems such as those mediated by neurokinins, which has been shown to reduce or even abolish spinal cord sensitization, are ineffective in clinical trials of acute and chronic pain. Some discrepancies between the experimental data and the clinical observations cannot be easily reconciled. The precise contribution of spinal cord sensitization to the generation of chronic pain remains an open question, although some of the available information seems to indicate that supraspinal mechanisms can play a greater role, especially in prolonged and complex pain states.

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