It is a general rule that in the nervous system, all forms of activation are balanced by some kind of inactivation or inhibition. This principle also applies, of course, to all levels of the nociceptive system, from the activation of nociceptive Aδ or C fibers to the excitation of nociceptive neurons in the spinal dorsal horn and the brain. This chapter focuses on spinal mechanisms of inhibition, but it is likely that similar findings also apply to the processing of nociceptive information in the trigeminal system and to supraspinal nociception. In the dorsal horn of the spinal cord, about 30–40% of all neurons are inhibitory [51], using γ-aminobutyric acid (GABA) as their fast inhibitory neurotransmitter, which acts on ionotropic GABA$_\text{A}$ or G-protein-coupled metabotropic GABA$_\text{B}$ receptors. A significant proportion of these neurons use glycine as a cotransmitter, which acts on ionotropic glycine receptors (see also Chapter 3 by Todd, this volume). Inhibitory spinal interneurons may also use endogenous opioids, and supraspinal descending fiber systems may further use monoamines as neurotransmitters to modulate spinal nociception [30,42]. The peptidergic and monoaminergic systems are not considered here. Spinal
inhibition may be impaired under conditions of neuropathy and inflammation, and the available evidence suggests that disinhibition in the spinal dorsal horn may lead to characteristic symptoms of neuropathic pain such as hyperalgesia, dynamic mechanical allodynia, and spontaneous paroxysmal pain (see the new definitions of technical terms by the International Association for the Study of Pain from 2008 and comments and illustrations in Sandkühler [42a]).

**Mechanisms of Impaired Inhibition in the Spinal Dorsal Horn**

The properties and functions of inhibition in the spinal dorsal horn have attracted much attention, and considerable progress has been made in understanding the role of inhibitory systems in nociception. These systems could be impaired at all sites, from the input to inhibitory neurons to their transfer functions and their output. Potential changes of spinal inhibition include (1) a reduced afferent drive to inhibitory neurons, (2) apoptotic or necrotic cell death of inhibitory spinal neurons, (3) reduced excitability or changes in discharge properties of inhibitory neurons, (4) reduced levels of inhibitory neurotransmitters due to lower rates of synthesis or reuptake, (5) reduced efficacy of receptors for inhibitory neurotransmitters, and (6) a reduced or inverted driving force for chloride ions (see Fig. 1).

**Reduced Drive of Spinal GABAergic Neurons**

Transgenic mice are now available that selectively express green fluorescent protein (GFP) in GABAergic neurons under the promoter of GAD67, one of the GABA-synthesizing enzymes [19,44]. Another mouse line expressing GFP in glycinergic neurons has also been developed [57]. This advance facilitates research on the electrophysiological properties of identified neurons in slice preparations of the spinal dorsal horn. In mice with a chronic constriction injury (CCI) of the sciatic nerve and mechanical hyperalgesia, the global excitatory drive to GABAergic neurons in the superficial lumbar spinal dorsal horn is greatly reduced. This conclusion is evident from the lower rate and reduced amplitude of miniature excitatory postsynaptic currents in these neurons [26]. Our recent data
suggest that the primary afferent drive from Aδ and C fibers is reduced in these animals (J. Leitner et al., unpublished observations).

**Fig. 1.** Inhibition of a nociceptive spinal dorsal horn projection neuron (in red) by an inhibitory interneuron (in black), which in turn receives excitatory inputs (in blue and red). Six sites are shown where inhibition may be altered. (1) Reduced afferent drive to the inhibitory neuron, either from primary afferents (in blue), from excitatory spinal interneurons (in red), or from supraspinal descending pathways (not shown). (2) Apoptotic or necrotic cell death of inhibitory spinal neurons. (3) Reduced excitability or changes in discharge properties of inhibitory neurons. (4) Reduced levels of inhibitory neurotransmitters due to lower rates of synthesis or reuptake. (5) Reduced efficacy of receptors for inhibitory neurotransmitters. (6) Reduced or inverted driving force for chloride ions.

**Cell Death of Inhibitory Interneurons?**

Some studies have provided evidence for a programmed cell death of GABAergic neurons in animals with a spared nerve injury [31]. Others, however, have challenged this conclusion by determining the number of neurons—including identified GABAergic neurons—in the spinal dorsal
horn of control rats and rats with a spared nerve injury [33,34]. In neuropathic animals with mechanical hyperalgesia, neither the number of neurons nor that of GABAergic profiles was any different from controls.

**Stable Membrane and Discharge Properties of GABAergic Neurons**

Inhibition would be impaired if membrane excitability were to decrease in inhibitory neurons or if their discharge patterns were to switch to low activity patterns. We assessed the membrane properties of GABAergic neurons. Recordings were made from GFP-labeled GABAergic neurons in lamina II [44] or lamina III [16] in transverse slices from the lumbar spinal cord. Resting membrane potentials, input resistance, and thresholds for action potential firing were unchanged in neurons recorded from animals with a CCI of the sciatic nerve. The distribution of typical discharge patterns also did not differ in neuropathic animals [16,44]. This finding suggests that (1) these GABAergic neurons do not change membrane excitability in the course of an injury of the sciatic nerve, and (2) the reduced excitatory input to these neurons faithfully translates into a reduced inhibitory output, because the transfer function of these GABAergic neurons remains stable.

**GABA Synthesis, Reuptake, and Release**

There is evidence that after a peripheral nerve lesion, levels of GABA may be reduced in the spinal dorsal horn. GABA immunoreactivity decreases 2–4 weeks after a transection or a CCI of the sciatic nerve [5,14]. This decrease could be caused by a loss of GABAergic neurons. However, GABA immunoreactivity recovers 8 weeks after nerve lesion [14], which suggests that it is not the number of neurons but rather the content of GABA within the neurons that might be changed. And indeed, levels of GAD65 (one of the two GABA-synthesizing enzymes) are reduced in the spinal dorsal horn ipsilateral to a CCI, and to a lesser extent, levels of GAD67 decrease as well [14,31]. Furthermore, reuptake of GABA after its release may also be impaired in neuropathic animals, given that the GABA transporter GAT-1 is downregulated bilaterally to about 40% 7 days after a CCI of the sciatic nerve as compared to controls [29,46]. In line with this finding, potassium-induced GABA release in spinal cord slices taken from rats
with spinal nerve ligation is reduced as compared to slices from sham-operated controls [27]. However, a recent study found no changes in the level of GABA or of the vesicular GABA transporter in animals with a spared nerve injury [34]. Other studies have reported that the synaptosomal level of GABA is unchanged in animals with a CCI of the sciatic nerve [49]. Some authors found that the spinal content of GABA is even enhanced bilaterally 1–30 days after a unilateral CCI of sciatic nerve in the rat, as measured by high-performance liquid chromatography (HPLC) with electrochemical detection [43]. The reasons for these discrepant results are presently unknown.

Altered Functions of Inhibitory Neurotransmitter Receptors

The inhibitory effects of GABA or glycine depend on a variety of factors, all of which could change during neuropathy or inflammation. These include the number, subunit composition, and sensitivity of postsynaptic receptors and the driving force for Cl−. Ipsilateral to a CCI of the sciatic nerve, the number of dorsal root ganglion (DRG) cells that express the γ 2 subunit of the GABA A receptor is reduced [32]. This finding suggests that GABA A receptors may be downregulated at the central terminals of primary afferent nerve fibers. If so, the sensitivity of these terminals to GABA should be diminished. And indeed, the mean depolarization elicited by GABA on dorsal roots is significantly reduced after chronic sciatic axotomy, dorsal root axotomy, or crush injury. In contrast, chronic sciatic crush injury has no effect on dorsal root GABA sensitivity [24]. Two to four weeks after a unilateral neurectomy of the sciatic nerve, GABA B-receptor binding in lamina II of the spinal cord is downregulated [4]. In contrast, expression of GABA A receptors may remain unchanged in laminae I and II after a spared nerve injury [34], and GABA A-receptor binding is enhanced following nerve transection [4].

Furthermore, receptor functions may be modulated by neuroactive substances released in the spinal dorsal horn during inflammation. For example, prostaglandin E2 is released in the spinal cord during peripheral inflammation. Subsequent activation of EP 2 receptors (a subtype of prostaglandin E2 receptor), cholera-toxin-sensitive G proteins, and cyclic adenosine monophosphate (cAMP)-dependent protein kinase depresses glycinergic receptor subtype α 2 function [18] and reduces glycinergic currents [1]. This
pathway seems to be relevant for peripheral inflammation, but not for neuropathic pain, in mice with a CCI of the sciatic nerve [20].

**Altered Driving Force for Chloride Ions**

Even if all of the elements of the inhibitory chain mentioned above were to remain the same, inhibition through ionotropic GABA_A or glycine receptors could still be reduced, eliminated, or converted into paradoxical excitation by changes in the driving force for chloride ions.

**Diminished Postsynaptic Inhibition**

Activation of GABA_A or glycine receptors opens Cl^- permeable ion channels. The direction of Cl^- flux is generally determined by the level of the Cl^- equilibrium potential (E_Cl^-) with respect to the resting membrane potential (V_{Rest}) of the cell. In most neurons of mature animals, E_Cl^- is more negative than V_{Rest}, partly because of the continuous removal of Cl^- from the cells, e.g., via the potassium-chloride cotransporter KCC2. Thus, given the relatively low Cl^- concentration in neurons, Cl^- will move into the cell when the Cl^- conductance increases upon activation of GABA_A or glycine receptors, thus causing membrane hyperpolarization. This situation could, however, be quite different under conditions of a neuropathy. CCI of the sciatic nerve leads to the activation of spinal microglia and to the release of brain-derived neurotrophic factor in the spinal cord. These events depress the function of the KCC2 potassium-chloride cotransporter and thereby enhance the Cl^- concentration inside the neurons. This, in turn, leads to a reduced (or even inverted) driving force for Cl^- and thus causes reduced postsynaptic inhibition [10] (see also Chapter 8 by De Koninck, this volume).

**Paradoxical Postsynaptic Excitation**

In its most extreme case, the activation of postsynaptic GABA_A or glycine receptors may lead to depolarization and eventually excitation. This situation may occur, for example, when the function of the potassium chloride cotransporter is severely impaired and E_Cl^- becomes less negative than the resting membrane potential. This event reverses the direction of Cl^- flux across the membrane, leading to a Cl^- efflux and membrane depolarization rather than to an influx into the cell. During development, and also minutes to weeks after trauma of cultured hypothalamic or cortical neurons, GABA may have
such a depolarizing effect [53]. Thus, it is neither the kind of neurotransmitter nor the type of neurotransmitter receptor alone that determines if neurotransmission is inhibitory or excitatory. The level of the Cl\(^-\) concentration gradient across the cell membrane determines whether GABA and glycine are hyper- or depolarizing [11]. In animals with a CCI of the sciatic nerve, KCC2 may be downregulated so severely that the driving force of Cl\(^-\) is reversed and in extreme cases may even cause action potential firing of the postsynaptic neuron (paradoxical postsynaptic excitation) [10,11].

**Paradoxical Presynaptic Excitation**

The anion gradient across the membrane of primary afferent nerve terminal is different as compared to most other neurons in mature animals. Here, the activity of the sodium-potassium-chloride cotransporter NKCC1 enhances the Cl\(^-\) concentration in the nerve terminals, so that \(E_{Cl^-}\) is normally less negative than the resting membrane potential. This activity regularly results in a Cl\(^-\) efflux and membrane depolarization upon binding of GABA to the GABA\(_A\) receptor. Thus, under normal conditions, activation of GABA\(_A\) receptors will depolarize the terminals of primary afferent nerve fibers. This primary afferent depolarization is not strong enough to cause action potential firing (i.e., excitation) under normal conditions. Primary afferent depolarization inactivates voltage-gated ion channels, which are required for the release of neurotransmitter(s) from the terminals and may shunt currents of the incoming action potentials [37,54]. Thereby, moderate depolarization of the terminals may inhibit neurotransmitter release. It has been proposed that under conditions of inflammation or neuropathy, depolarization at primary afferent C fibers may become steeper and stronger, eventually reaching the thresholds for activating voltage-gated sodium channels and for triggering action potential firing. This event would cause paradoxical presynaptic excitation by GABA [7,36].

**Role of Normal and Impaired Spinal Inhibition in Pain**

Virtually all neurons in the spinal dorsal horn are subject to a powerful tonic and phasic inhibitory control via GABAergic, glycinergic, or other inhibitory spinal interneurons or descending inhibitory systems arising
from supraspinal sites. The functional consequences of impaired or altered inhibition critically depend on the site within the neuronal network where inhibition is altered. Inhibitory spinal dorsal horn neurons serve at least four crucial functions for proper nociception (see Table I): (1) attenuating nociceptive responses, (2) muting nociceptive neurons in the absence of a noxious stimulus, (3) separating information from different sensory modalities, and (4) limiting the spread of excitation in the spinal cord to appropriate somatotopic borders.

### Table I

<table>
<thead>
<tr>
<th>Role of Inhibition</th>
<th>Mechanism of Action</th>
<th>Desired Effect</th>
<th>Pain Type upon Failure</th>
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<td>Inhibition of nociceptive dorsal horn neurons and the interneurons that drive them</td>
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<td>Limiting</td>
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<td>Limiting spread of excitation to somatotopically appropriate areas</td>
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### Attenuation of Nociception

Glycinergic inhibition is postsynaptic, whereas inhibition by GABA may be pre- or postsynaptic. This includes presynaptic inhibition at terminals of nociceptive nerve fibers, inhibition of spinal nociceptive projection neurons, and inhibition of any neuron that is part of the ascending nociceptive pathways. Blocking either spinal GABA<sub>∆</sub> or glycine receptors greatly increases spinal dorsal horn neuronal responses to noxious stimuli in vivo [41,58] as well as responses to stimulation of dorsal root afferents at Aδ- or C-fiber intensity in slice preparations [2,23]. Thus, the magnitude of nociceptive responses and the intensity of perceived pain are not a simple monotonic or even linear function of stimulus intensity but rather result
from the balance between the strength of excitatory input and attenuation by inhibitory systems. Fluctuations in the activity of endogenous antinociceptive systems contribute to variations in pain sensitivity among human subjects and account for stress-induced analgesia and diurnal variations in pain thresholds [30,42].

**Muting Nociceptive Circuits**

In the absence of any noxious stimulus, nociceptive-specific spinal dorsal horn neurons are largely silent and do not display any significant spontaneous activity [6,22], whereas the background activity of wide-dynamic-range neurons may be more variable under the given recording conditions [6,17]. The quiescence of these neurons requires a permanent inhibitory control. If GABA or glycine receptors are blocked in the spinal cord, virtually all neurons—including nociceptive-specific neurons—become spontaneously active, and many may also discharge rhythmically and in synchrony [38,45]; see Fig. 2. This form of spinal network activity resembles epileptiform activity in cortical neurons during epileptic seizures and also engages nociceptive-specific neurons in the superficial spinal dorsal horn with a direct projection to the brain [38]. In behaving animals, blockade of spinal GABAA receptors leads to scratching and biting behavior, which is often interpreted as an indication for spontaneous pain and/or dysesthesia [28]. If similar epileptiform activity also occurs in nociceptive spinal or trigeminal neurons of pain patients, it could underlie spontaneous paroxysmal pain attacks.

**Separating Sensory Modalities**

Labeled lines that exclusively subserve either nociception or touch exist at the level of the spinal cord. Nociceptive Aδ and C fibers may excite nociceptive-specific neurons in the superficial spinal dorsal horn, some of which have a direct projection to the brain. On the other hand, low-threshold Aβ fibers may excite low-threshold neurons in the deep dorsal horn that have different projection areas in the brain. In addition to these labeled lines, some neurons in spinal dorsal horn receive afferent input from Aδ and C fibers and from Aβ fibers (“wide-dynamic-range neurons”). Their function in nociception has been discussed extensively [9,12,13,35,47], but it is unlikely that these neurons discriminate between
the sensory modalities of touch and pain [8,56]. In any case, to prevent touch from becoming painful, these sensory modalities must be kept separate. By definition, nociceptive-specific neurons are not excited by Aβ fibers; however, activity in Aβ fibers may activate inhibitory interneurons, which in turn depress the activity in nociceptive spinal dorsal horn neurons. Presently, three mechanisms are proposed by which impaired or altered inhibition in the spinal cord may initiate an excitatory crosstalk between low-threshold Aβ fibers and nociceptive-specific neurons in the superficial spinal dorsal horn.

1) The postsynaptic GABAergic inhibition of nociceptive-specific neurons in the superficial spinal dorsal horn may turn into excitation. Some of these GABAergic neurons may receive excitatory input from low-threshold Aβ fibers. Thus, touch stimuli may lead to activation of GABAergic neurons, which then would no longer depress, but rather excite, nociceptive-specific neurons in the spinal dorsal horn lamina I [10,11], possibly leading to touch-evoked pain. This mechanism is discussed in greater detail in Chapter 8 by De Koninck. However, spinal application of a GABA_A-receptor agonist attenuates, rather than evokes, pain or allodynia [15,21,25]. This finding suggests that the overall pharmacological effect of GABA is still antinociceptive. Possibly, the paradoxical excitation by GABA at specific sites along the nociceptive pathways is overruled by global depressant effects.

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**Fig. 2.** Blockade of GABA_A and glycine receptors induces synchronous network activity in laminae I/II of SNI rats. Examples are shown of the network activity in slices from the lumbar spinal cord of (A) control or (B) neuropathic animals arising after preincubation with bicuculline (10 μM) and strychnine (4 μM). (A) Panel Aa shows a 380-nm image of the region selected for recording. In slices from control animals, spinal disinhibition did not evoke simultaneous Ca^{2+}-transients. (Ab) Original traces show the time course (10–15 minutes after bicuculline/strychnine application) of the Ca^{2+} concentration of the neurons that are marked by arrows in panel Aa. Pseudocolor F340/F380 ratio images taken at the time points marked in panel Ab (arrows, A1–A6) are displayed in panel Ac. Red indicates a high intracellular Ca^{2+} concentration. While some spontaneous activity was seen, it was not synchronized between neurons. (B) In the slice from a neuropathic animal, blockade of GABA_A and glycine receptors induced repetitive spontaneous Ca^{2+} transients that were synchronized in many of the recorded neurons, as illustrated in the original traces (Bb). (Bc) Pseudocolor F340/F380 ratio images of the time points marked in panel Bb (arrows, B1–B6) show that intracellular Ca^{2+} concentration was high at the time of simultaneous Ca^{2+} transients and intracellular Ca^{2+} concentration was low between two transients in spinal dorsal horn neurons. Modified from [45], with permission.
2) It has further been proposed that presynaptic GABAergic inhibition at C-fiber terminals may also turn into excitation. The evidence for this proposal has been reviewed [7,36]. GABAergic neurons that contact C-fiber terminals may be activated by low-threshold Aβ fibers, normally mediating Aβ-fiber-induced inhibition of C-fiber-evoked responses in the spinal dorsal horn. If a paradoxical presynaptic excitation were to be triggered by activity in Aβ fibers, pain evoked by touch may be the consequence. In an attempt to test this hypothesis, we made intracellular recordings from DRG cells in a transverse spinal cord slice preparation with dorsal roots, DRG, and spinal nerves left intact. Preparations were from animals with a CCI of the sciatic nerve and from sham-treated animals. In slices taken from control animals, electrical thresholds for action potential discharges were low in A-type neurons attached to A fibers and high in C-type neurons attached to C fibers. If a paradoxical excitation of C-fiber terminals were to occur in neuropathic animals, action potentials would be antidromically transmitted to the site of recording in the DRG, and some C fibers should be activated at low, A-fiber intensities. Under the given experimental conditions, however, there were no differences in the stimulus-response functions of C-type neurons.

**Fig. 3.** Electrical stimulation and glutamate microinjection in the deep dorsal horn excite superficial dorsal horn neurons in neuropathic animals. (A) Outline of the dorsal quadrant of a transverse spinal cord slice. The dashed line indicates the approximate border between laminae II and III. The superficial dorsal horn regions in the somatotopic area of the transected tibial and the intact sural nerve selected for imaging are shown by the boxes. The sites of electrical stimulation or glutamate microinjection are indicated by the tip of the stimulation pipettes. (B) Slices were incubated with fura-2 AM. The ratio of the images captured at 340 and 380 nm illuminations was then used to detect changes in intracellular Ca\(^{2+}\) concentration. Examples of ratio images of control animals (B1, B3) and neuropathic animals (B2, B4) 500 ms after stimulation are shown in pseudocolor. Pseudocolor images show values of the difference between the F340/F380 ratio images before stimulation and at the time of the usual peak reaction to stimulation (0.5 seconds after stimulation). Red indicates areas that were excited by the stimulation, whereas blue indicates unexcited areas. Superficial dorsal horn neurons of control animals did not show Ca\(^{2+}\) transients in the frame after electrical stimulation (B1) or glutamate microinjection (B3) in the deep dorsal horn. However, in neuropathic animals, numerous superficial dorsal horn neurons were excited following electrical (stimulation B2) and glutamate microinjection (B4). (C and D) Summary of the results showing that electrical stimulation and glutamate microinjection in the deep dorsal horn in the area of the tibial (C) or the sural nerve (D) excited superficial dorsal horn neurons significantly more often in neuropathic than in control animals (**P < 0.01 in the Mann-Whitney rank sum test). Modified from [45], with permission.
neurons between control and neuropathic animals. Thus, we were unable to find evidence for a paradoxical excitation of C fibers [40]. Of course, this absence of evidence should not be mistaken as evidence of absence of such a mechanism.

3) There is direct evidence for an excitatory pathway from the deep to the superficial spinal dorsal horn [45]. Given that Aβ fibers terminate in the deep dorsal horn and nociceptive-specific neurons are in the superficial dorsal horn, these findings could explain the novel polysynaptic input from low-threshold Aβ fibers to nociceptive-specific neurons [52] in animals with a neuropathy [45] or a peripheral inflammation [3].

To demonstrate the existence of this excitatory pathway, we used a transverse slice preparation from the rat lumbar spinal cord with long dorsal roots attached. Calcium-imaging techniques were employed to simultaneously monitor neuronal activity in the deep dorsal horn (laminae III–IV) and in the superficial dorsal horn (laminae I and II; see Fig. 3). We microinjected glutamate through fine glass micropipettes into the deep dorsal horn in order to excite a few neurons, while leaving fibers that pass through the site of injection unaffected. In slices taken from control animals and with spinal inhibition intact, these microinjections excited no or very few neurons in the superficial dorsal horn (see Fig. 3). When GABA_A and glycine receptors were blocked, however, the same microinjections of glutamate in the deep dorsal horn now excited numerous superficial dorsal horn neurons [45]. These data provide direct evidence for the existence of an excitatory pathway from the deep to the superficial dorsal horn that is tonically depressed by GABAergic and/or glycinergic interneurons.

We next used slices taken from animals with a CCI of the sciatic nerve and mechanical hyperalgesia. In these slices, glutamate microinjections into the deep dorsal horn caused excitation of numerous neurons in the superficial dorsal horn, even in the absence of GABA_A or glycine receptor blockers (Fig. 3) [45]. These data suggest that the excitatory pathway from the deep to superficial dorsal horn is closed in sham-treated animals but open in neuropathic animals with mechanical hyperalgesia and allodynia.

Finally, we provided evidence that this pathway can apparently be activated not only by microinjections of glutamate at or near the
termination sites of primary afferent Aβ fibers in the deep dorsal horn, but also by activation of Aβ fibers. In slices from animals with a CCI but not in sham-treated animals, a substantial proportion of lamina I/II neurons were excited by stimulation of Aβ fibers [45]. Similar results were found

Fig. 4. Initiation and propagation of Ca²⁺ waves in the superficial dorsal horn. (A) A spinal slice section is shown at 380-nm illumination with a superimposed outline of the dorsal horn. Fura-2-loaded cells are visible as small bright spots. (B) A sequence of images taken of the region indicated by the box in (A) during a population Ca²⁺ transient is shown. To highlight the wave front moving over the spinal dorsal horn, the difference between the 380 nm image at the indicated point in time and the image obtained 180 ms previously is displayed in pseudocolor. On the color scale, red indicates large changes of fluorescence, and blue indicates little or no change. The points in time indicated above the images correspond to the time scale in (C) that illustrates the same Ca²⁺ wave as (B). (C and D) The time courses of two different Ca²⁺ waves recorded from the slice shown in (A) are illustrated. Fifteen neurons lying near the dashed line in (A) were selected, and the onset of their individual Ca²⁺ transients during a population transient were analyzed. The latency relative to the neuron with the earliest onset was then plotted against the distance from the most medial neuron, and the plots were fitted by linear regression. The mediolateral location of the neurons marked with “a” and “b” is shown in (A). (E) A lateromedially propagating wave from another slice. Examples (C–E) illustrate that Ca²⁺ waves can be initiated at various sites in the superficial dorsal horn and that these waves propagate laterally as well as medially. Modified from [39], with permission.
by recording from single cells in superficial dorsal horn neurons of animals with a peripheral inflammation [3].

In behaving animals, blocking GABA or glycine receptors leads to agitation in response to light tactile stimuli [56] and to a drastic reduction of mechanical withdrawal thresholds [48]. This finding suggests that an excitatory crosstalk between Aβ-fiber afferents and nociceptive pathways has been initiated, causing Aβ-fiber-mediated mechanical allodynia. If similar mechanisms apply to human pain patients, impaired separation of sensory modalities in the spinal dorsal horn would cause touch-evoked pain.

Limiting the Spread of Excitation

The known termination patterns of primary afferents suggest that sensory information from different modalities and different regions of the body is processed in a highly organized and spatially segregated fashion [50,55]. However, when spinal GABA_A and glycine receptors are blocked, excitation may spread to virtually all sites in the spinal dorsal horn, both ipsilateral and contralateral to the site of afferent stimulation [39]; see Fig. 4. Thus, somatotopic borders are not secured anatomically but need to be actively maintained by the function of inhibitory systems in the spinal dorsal horn. If similar violations of somatotopic borders were to occur in humans, then lancinating, projecting, and mirror-image pain would be the result.

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