Models and Mechanisms of Hyperalgesia and Allodynia

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Sandkühler J. Models and Mechanisms of Hyperalgesia and Allodynia. *Physiol Rev* 89: 707–758, 2009; doi:10.1152/physrev.00025.2008.—Hyperalgesia and allodynia are frequent symptoms of disease and may be useful adaptations to protect vulnerable tissues. Both may, however, also emerge as diseases in their own right. Considerable progress has been made in developing clinically relevant animal models for identifying the most significant underlying mechanisms. This review deals with experimental models that are currently used to measure (sect. II) or to induce (sect. III) hyperalgesia and allodynia in animals. Induction and expression of hyperalgesia and allodynia are context sensitive. This is discussed in section IV. Neuronal and nonneuronal cell populations have been identified that are indispensable for the induction and/or the expression of hyperalgesia and allodynia as summarized in section V. This review focuses on highly topical spinal mechanisms of hyperalgesia and allodynia including intrinsic and synaptic plasticity, the modulation of inhibitory control (sect. VI), and neuroimmune interactions (sect. VII). The scientific use of language improves also in the field of pain research. Refined definitions of some technical terms including the new definitions of hyperalgesia and allodynia by the International Association for the Study of Pain are illustrated and annotated in section I.

I. ABOUT THIS REVIEW

Hyperalgesia and to some degree allodynia are frequent symptoms of disease and may be useful adaptations for better protection of vulnerable tissues. Enhanced sensitivity for pain may, however, persist long after the initial cause for pain has disappeared, then pain is no longer a symptom but rather a disease in its own right. Changes of

signal processing in the nervous system may contribute to or may become the sole cause for hyperalgesia and allodynia. It appears that sensitization of nociceptive Aδ- and C-fiber nerve endings rarely outlast the primary cause for pain and is restricted to the area of injury and thus may be considered adaptive. In contrast, central changes in the processing of nociceptive information may potentially outlast their trigger events for days, months, and perhaps years and may spread to sites somatotopically remote from the primary cause of pain. Thus central mechanisms constitute one of the causes for pain chronicity and pain amplification in pain patients. In this review I address animal models that are currently used to measure (sect. II) or to induce (sect. III) hyperalgesia and allodynia in animals. Context-sensitive expression of hyperalgesia is discussed in section IV. Cellular elements that are indispensable for the induction and/or the expression of hyperalgesia and allodynia are summarized in section V. Peripheral mechanisms contributing to hyperalgesia and allodynia have been reviewed extensively (194, 587). Reorganization of sensory processing in cortical areas may also be long-lasting (138, 518, 519, 532). The peripheral, spinal, and supraspinal elements that are essential for hyperalgesia and allodynia are listed in section V. This review focuses on spinal mechanisms of hyperalgesia and allodynia (sect. VI) and relevant mutual neuron-immune interactions (sect. VII). The new International Association for the Study of Pain (IASP) definitions of technical terms from 2008 are explained and used.

A. Definitions

In an early definition hyperalgesia was considered "a state of increased intensity of pain sensation induced by either noxious or ordinarily non-noxious stimulation of peripheral tissue" (169). Thus no distinction was made between hyperalgesia and allodynia. Later, the IASP took over the task to improve the use of language in the pain field by implementing a task force on taxonomy (recommendations from 1994, revised 2008). For pain elicited by normally nonpainfully stimuli, the made-up word *allodynia* was coined by Professor Paul Potter of the Department of the History of Medicine and Science at The University of Western Ontario (see definitions on the IASP homepage: www.iasp-pain.org). In the year 2008, the IASP modified many of the definitions from 1994 substantially. With respect to the definition of "hyperalgesia," the original definition experienced a revival, and the term *allodynia* is now reserved to those forms of pain only that are clearly caused by excitation of low-threshold sensory nerve fibers. Some of the current definitions of the IASP task force are reproduced here in quotes and modified only if useful for the purpose of the present review.

1) Allodynia: "Pain in response to a nonnociceptive stimulus." The IASP task force comments on this term:

"This term should only be used, when it is known that the test stimulus is not capable of activating nociceptors. At present, dynamic tactile allodynia to tangential stroking stimuli, e.g., brushing the skin is the only established example. Future research may present evidence for other types of allodynia. Whenever it is unclear, whether the test stimulus may or may not activate nociceptors, hyperalgesia is the preferred term." Thus allodynia refers largely to pain evoked by Aβ-fibers (see sect. VI*F* and Fig. 1) or low-threshold Aδ- and C-fibers.

2) Analgesia: "Absence of pain in response to stimulation which would normally be painful."

3) Central sensitization: "Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input." Central sensitization is a popular phrase in pain literature, but unfortunately, it is used in many different and sometimes inconsistent ways. At present, a generally accepted definition does not exist. The IASP task force for taxonomy suggests the above quoted definition. This proposal clearly defines a phenomenon but not its functional meaning. Nociceptive neurons comprise a heterogeneous cell group with putatively many different and sometimes opposing functions, including a large group of inhibitory interneurons. Thus enhanced responsiveness of some of these neurons could contribute to hyperalgesia. On the other hand, enhanced responsiveness of inhibitory nociceptive neurons may well lead to stronger feedback inhibition and analgesia, while still other neurons may not contribute to the experiences of pain but rather to altered motor or vegetative responses to a noxious stimulus. Another often used definition implies that "central sensitization" would be an enhanced responsiveness of neurons in the central nervous system leading to hyperalgesia (76). In this definition "central sensitization" necessarily leads to pain amplification due to enhanced neuronal responsiveness. A causal relationship between firing rates of any type of neurons in the central nervous system and the perceived intensity of pain can, however, presently not be ensured. At best, a tight correlation may be shown. Thus none of the presently proposed central mechanisms of hyperalgesia would strictly fulfill the latter definition of "central sensitization." In the literature "central sensitization" is often not clearly defined, and sometimes two mutually exclusive definitions are used within the same publication.

4) Hyperalgesia: "Increased pain sensitivity." IASP task force comment (2008): "Hyperalgesia may include both a decrease in threshold and an increase in suprathreshold response. In many cases it may be difficult to know whether or not the test stimulus is capable of activating nociceptors. Therefore, it is useful to have an umbrella term (hyperalgesia) for all types of increased pain sensitivity." See also Figure 1 for this new distinction between hyperalgesia and allodynia.
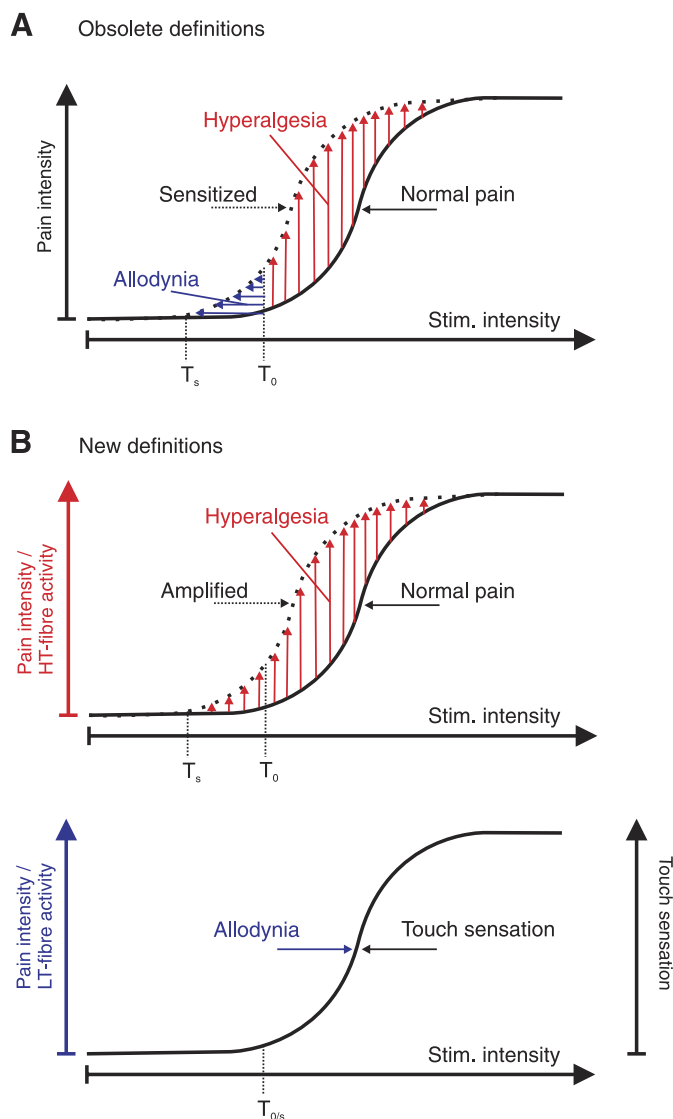
FIG. 1. The changes made in the year 2008 by the IASP task force in defining "hyperalgesia" and "allodynia." In *A*, the obsolete definitions are illustrated: pain in response to previously nonpainful stimuli was defined as "allodynia" (blue area in the stimulus-response function). T_0 refers to the normal pain threshold, and T_S refers to the pain threshold after sensitization. Enhanced responses to normally painful stimuli were called "hyperalgesia" (red area). A single mechanism, for example, the sensitization of nociceptive nerve endings (e.g., during a sunburn) leading to a shift in the stimulus-response function to lower stimulus intensities would always cause allodynia and hyperalgesia in combination but never in isolation, making this distinction meaningless. In *B*, the new definitions are illustrated. All forms of pain amplification including lowering in thresholds are now summarized under the umbrella term *hyperalgesia* (red ordinate and red area in top graph). Only if pain is cleary induced by low-threshold fibers should the term *allodynia* be used (blue ordinate in bottom graph). $T_{0/S}$ refers to the normal threshold for touch sensation which is identical to (or near) the stimulation threshold for allodynia. In all cases where it is not known whether low- or high-threshold sensory nerve fibers are involved, the umbrella term *hyperalgesia* should be used.

5) Hyperalgesia, primary: Hyperalgesia at the site of injury. It is often believed that primary hyperalgesia is mainly due to sensitization of nociceptive nerve endings.

Recent evidence suggests, however, that altered processing in the central nervous system is equally important.

6) Hyperalgesia, secondary: Hyperalgesia in an area adjacent to or remote of the site of injury. This form of hyperalgesia is not caused by sensitization of nociceptive nerve endings but solely due to changes in the processing of sensory information in the central nervous system. While the induction of secondary hyperalgesia requires activity in nociceptive nerve fibers, its maintenance is independent of an afferent barrage as local aesthetic block of the injured site preempts but does not reverse secondary hyperalgesia.

7) Hyperalgesia, referred: Hyperalgesia may not only exist within an area of tissue damage but also in the skin (head zone) remote from the inner organ or muscle which is affected.

8) Long-term potentiation: Long-term potentiation of synaptic strength (LTP) is an intensively studied model of neuronal plasticity. It is defined as an increase in synaptic efficacy that outlasts the duration of the conditioning stimulus for at least 30 min (early LTP), a few hours, or days to months (late LTP). Synaptic strength can be quantitatively assessed by measuring changes of the postsynaptic membrane potential or postsynaptic currents in response to a presynaptic stimulus. Normally synaptic strength is measured as the amplitude or area under the curve of postsynaptic excitatory or inhibitory potentials or currents. Alternatively, extracellular recordings of field potentials are being used. Action potential firing and polysynaptic responses not only depend on the strength of synaptic transmission but also on intrinsic membrane properties (e.g., action potential thresholds) and network properties and can thus not be used to quantify synaptic strength and changes thereof.

9) Nociceptive stimulus: "An actually or potentially tissue damaging event transduced and encoded by nociceptors."

10) Nociceptor: "A sensory receptor that is capable of transducing and encoding noxious stimuli."

11) Noxious stimulus: "An actually or potentially tissue-damaging event."

12) Pain: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".

13) Pain versus nociception: The above definitions of pain and its derivates require a conscious subject that is able to experience pain. The molecular, cellular, and systemic mechanisms which deal with the processing of pain-related information, its amplification, or depression are called nociceptive, pro-nociceptive, and anti-nociceptive, respectively. Pain is just one of many possible end points of nociception. Others include but are not limited to withdrawal reflexes, vegetative and hormonal responses, and vocalization, all of which normally accompany pain experience but may under experimental and

some pathological conditions be observed in the absence of pain experience, e.g., in the intact but deeply anesthetized subject or in lesioned animals.

The experience of pain is not a phenomenological entity but rather a multidimensional process that may include to varying degrees sensory-discriminative aspects and emotional-aversive components, all of which involve activation of different brain areas and neuronal ensembles. Thus, when reporting "hyperalgesia," this always implies a contextual definition which is, in a strict sense, only valid for the experimental context in which it was assessed. In the literature, it often does not reflect a measure of pain but one of its surrogates, i.e., signs of amplified nociception, e.g., exaggerated withdrawal reflexes.

Hyperalgesia and allodynia are classified according to the type of stimulus which elicits the sensation of pain. Thermal (heat or cold) stimuli or mechanical brush, pinch, or pressure stimuli are most often used. In addition, moving (dynamic) or static mechanical touch stimuli are being used. Thereby, mechanical and thermal (heat or cold) hyperalgesia and mechanical dynamic allodynia can be differentiated (see also Fig. 1).

The mechanisms underlying the various forms of hyperalgesia and allodynia are not alike (see Fig. 3) but may differ with respect to molecular genetic, physiological, and pharmacological profiles (271, 359).

It is now generally accepted that excitation of thin high-threshold (i.e., nociceptive) primary afferent nerve fibers which are weakly myelinated (Aδ-fibers) or unmyelinated (C-fibers) triggers nociceptive pain. But not all Aδ- and C-fibers are nociceptive as some respond to low-level natural stimuli. On the other hand, almost all thick and heavily myelinated Aβ-fibers are low threshold, and only few Aβ-fibers may be nociceptive. Thus selective excitation of Aβ-fibers, e.g., by electrical nerve stimulation, normally does not evoke pain. The roles of the many different types of spinal dorsal neurons for a pain sensation are much less clear. Spinal dorsal horn neurons have been classified by some of their properties. A popular scheme is based on the type of excitatory mono- and/or polysynaptic afferent input.

14) High-threshold spinal neurons (nociceptive specific neuron, nociceptor specific neuron, class 3 neuron): These neurons selectively respond to stimulation of primary afferent nerve fibers with high thresholds, i.e., to nociceptive nerve fibers. Thus nociceptor specific neurons are exclusively driven by nociceptors.

15) Wide-dynamic range spinal neurons (multireceptive neuron; class 2 neuron): These neurons nonselectively respond to both primary afferents with high and with low thresholds, i.e., to nociceptive nerve fibers and to touch fibers for example.

16) Low-threshold neuron spinal neurons (class 1 neurons): These neurons respond to primary afferent nerve fibers with low thresholds. They have no excitatory input from nociceptors, thus increasing stimulation intensity into the noxious range does not lead to substantial increases in excitation.

This popular classification scheme rests on the response properties of spinal dorsal horn neurons to natural stimulation within the neurons' receptive field or electrical stimulation of afferent nerve fibers. These response profiles are, however, not static but context sensitive and may change with the level of the membrane potential so that, e.g., lowering membrane potential of "nociceptor specific" neurons may result in their transformation into "multireceptive" neurons (572). Furthermore, when comparing the incidence of recordings made from either low-threshold or wide-dynamic range neurons in awake, drug-free cat, wide-dynamic range neurons are much less often encountered as expected from acute preparations in anesthetized animals (82). When barbiturates are applied, the likelihood of recording from wide-dynamic range neurons increases (82, 83). Another technique to group neurons by their electrophysiological properties including sensory input is the cluster analysis (280).

17) Spinal neuron: Projection neuron: Another way of grouping neurons is by their supraspinal projection. In vivo this can be achieved by electrical deep brain stimulation of the ascending axon and recording the antidromic action potential discharge. Depending on the location of the stimulation electrodes, neurons are then classified according to the ascending tract they project to, e.g., the spinothalamic tract or dorsal column pathway or by their presumed projection territory, e.g., the ventrolateral thalamus (581). One should, however, keep several caveats in mind: *1*) The area from which antidromic spikes can be elicited is not necessarily the area of termination. It is equally well possible that fibers of passage are excited. *2*) An identified projection area must not necessarily be the only or even the main projection area of the neuron under study, as some spinal dorsal horn neurons project to more than one supraspinal site. *3*) Neurons for which no supraspinal projection area could be identified still could be neurons with a projection that just was missed.

For in vitro recordings spinal projection neurons can be identified by retrograde transport of a fluorescent marker such as DiI. This marker can then easily be detected in spinal cord slices prepared 3–4 days after dye injection using a fluorescence microscope (202, 204).

18) Peripheral sensitization: "Increased responsiveness and reduced threshold of nociceptors to stimulation of their receptive fields."

19) Wind-up: Wind-up is an electrophysiological phenomenon seen in some nociceptive neurons in response to repetitive stimulation of primary afferent C-fibers. When C-fibers are stimulated at frequencies between 0.5 and 5 Hz, some postsynaptic neurons respond with an

increasing discharge rate to the first 10–30 stimuli (i.e., in the first few seconds of an ongoing noxious stimulation). Thereafter, the response reaches a plateau or may decline. Wind-up is seen under normal experimental conditions, i.e., in the absence of any intentional inflammation, trauma, or nerve injury and thus constitutes a normal coding property of some nociceptive spinal dorsal horn neurons. Consequently, wind-up per se is not a mechanism of hyperalgesia. However, lowering the wind-up threshold frequency or enhancing the wind-up response may indicate that some form of signal amplification has been induced, for example, LTP of synaptic strength between primary afferent C-fibers and spinal dorsal horn neurons. Thus enhanced wind-up may be a useful marker of increased responsiveness of some spinal dorsal horn neurons to C-fiber stimulation.

B. Hyperalgesia and Allodynia as Symptoms

The proper function of the nociceptive system enables and enforces protective behavioral responses such as withdrawal or avoidance to acutely painful stimuli. In case of an injury, the vulnerability of the affected tissue increases. The nociceptive system adapts to this enhanced vulnerability by locally lowering the nociceptive thresholds and by facilitation of nocifensive responses, thereby adequate tissue protection is ensured. The behavioral correlates of these adaptations are allodynia and hyperalgesia. Thus neither hyperalgesia nor allodynia is per se pathological or a sign of an inadequate response but may rather be an appropriate shift in pain threshold to prevent further tissue damage. Painful syndromes are typical for a large number of diseases and pain intensity if often used by the patients and their health professionals to evaluate the progression of the disease or the success of the therapy.

C. Hyperalgesia and Allodynia as Diseases

The intensity, the duration, and/or the location of pain may not always adequately reflect any known underlying cause. For example, hyperalgesia and allodynia may persist long after the initial cause for pain, e.g., an injury or an inflammation has healed completely. Furthermore, hyperalgesia and allodynia may occur due to dysfunction of parts of the peripheral or central nervous system. Thus, when the location, the duration, or the magnitude of pain, hyperalgesia, and/or allodynia has become maladaptive rather than protective, then pain is no longer a meaningful homeostatic factor or symptom of a disease but rather a disease on its own right.

II. METHODS TO ASSESS HYPERALGESIA OR ALLODYNIA

Because pain cannot be measured directly in animals, it is essential to use quantifiable, sensitive, and specific surrogates of pain sensation. A number of different surrogates have been suggested to fulfill these criteria. One should, however, keep in mind that any reaction to a painful stimulus is not necessarily evidence for a concomitant sensation of pain. Thus none of these tests measures hyperalgesia or allodynia directly, but rather enhanced nociception. This distinction is, however, rarely made in the literature or in this review.

Signs of evoked pain in animals include withdrawal of a paw or the tail from the stimulus source, vocalization upon sensory stimulation, reduced locomotion, or agitation. Motor reflexes may not only be elicited by noxious stimulation but also by innocuous stimuli (470), i.e., may not be specific for nociception. Furthermore, any form of behavior may be modulated by the motor system which constitutes a potential confounding effect (430).

Suggested signs of spontaneous pain include audible and ultrasonic vocalization, conditional place avoidance, analgesic self-administration, excessive grooming, and self-mutilation of a limb, to name a few. These parameters are rarely used in animal studies (360). Autotomy of an affected limb has also been considered a sign of spontaneous pain after nerve injury (75). A systematic methodological review of animal models of pain is provided by Le Bars et al. (275). The impact of strain differences in mice for nociceptive tests is discussed by Mogil et al. (361). Table 1 summarizes presently used methods to assess hyperalgesia and allodynia.

III. METHODS TO INDUCE HYPERALGESIA OR ALLODYNIA IN ANIMALS

A. Animal Welfare Issues: Replace, Reduce, Refine

Most countries have issued animal welfare acts (see, for example, those of Sweden, The Netherlands, Switzerland, or Germany), and most scientific journals enforce full compliance with local and institutional regulations for animal welfare before considering any manuscript for publication. The IASP has issued ethical guidelines for the investigation of experimental pain in conscious animals (see http://www.iasp-pain.org/). These guidelines are, however, from 1982 and outdated by now. A revision incorporating contemporary research is desirable. Furthermore, several publications have also addressed this important topic (see, e.g., Refs. 31, 137, 182, 489, 495). General information on animal welfare issues can be obtained from a number of sources including http://awic.

TABLE 1. *Methods to assess hyperalgesia or allodynia*

Modality	Test Name (Most Common)	Test Method	Testing Site	Outcome Parameter	Reference Nos.
Mechanical	von Frey	Application of nonnoxious calibrated static hairs on skin	Hindpaw, face	Force threshold to elicit paw withdrawal (static mechanical hyperalgesia*)	66, 109
	Randal Sellito	Application of linearly increasing mechanical force in noxious range on skin	Hindpaw	Force threshold to elicit paw withdrawal from noxious stimulus (mechanical hyperalgesia*)	18, 424
	Unnamed	Innocuous brushing, stroking of skin	Hindpaw	Time latency to elicit paw withdrawal or nociceptive behaviors (dynamic mechanical allodynia)	131, 599
	Unnamed	Noxious mechanical stimulation to viscera	Visceral organs (colon, bladder)	Thresholds or number or strength of muscle contractions, autonomic responses (hyperalgesia)	381
Heat	Tail flick	Application of radiant heat on tail or immersion of tail in hot water	Tail	Time latency to elicit tail withdrawal (heat hyperalgesia)	122, 183
	Plantar Hargreave's	Application of radiant heat on skin	Hindpaw	Time latency to elicit paw withdrawal (heat hyperalgesia)	171, 608
	Hot plate	Animal placed on heated metal plate	Hindpaw (forepaws)	Time latency to elicit nociceptive or escape behavior (heat hyperalgesia)	275, 341
Cold	Acetone	Application of acetone on skin	Hindpaw	Duration/intensity of nociceptive behaviors (cold hyperalgesia)	71, 548
	Cold plate	Animal placed on cooled metal plate	Hindpaw	Time latency to elicit nociceptive or escape behaviors (cold hyperalgesia)	11, 209
	Cold water	Animal placed in shallow cold water bath	Hindpaw	Time latency to elicit nociceptive or escape behaviors, duration and intensity of nociceptive behaviors (cold hyperalgesia)	20, 340
Electrical	Unnamed	Electrical current application	Various: tail, paw, viscera, dental pulp	Withdrawal thresholds, vocalization, escape latency (allodynia)	43, 45, 275, 507

* According to the new definition by the IASP: in the previous literature, this was labeled "mechanical allodynia" (see also section I and Fig 1).

nal.usda.gov/. See Table 2 for a summary of contemporary models to study hyperalgesia and allodynia in animals.

B. Drug-Induced Hyperalgesia and Allodynia

Drug-induced pain amplification or pain generation is relevant both in preclinical studies where they serve as tools for animal models of pain and in the clinical situation where they may be unwanted effects of therapeutics including chemotherapeutics and opioids. It is an intriguing yet unproven hypothesis that many of the substances that are sufficient to induce hyperalgesia and/or allodynia may do so by increasing the free cytosolic Ca^{2+} concentration in neuronal and nonneuronal cells, e.g., in spinal dorsal horn. For example, intrathecal injection of a calcium ionophore (A23187) or of a calcium channel agonist (BAY K 8644) may facilitate the second, but not the first phase of the Formalin test (77). Furthermore, nociceptive behavior that can be induced by intrathecal injection of a neurokinin 1 receptor agonist is blocked by intrathecal injection of dantrolene, which reduces the release of calcium from intracellular stores, or by intrathecal injection of thapsigargin, which inhibits the reticular Ca^{2+}-ATPase thereby blocking intracellular calcium storage (16). Likewise, in diabetic mice, intrathecal application of ryanodine, which blocks Ca^{2+} release from Ca^{2+}/caffeine-sensitive microsomal pools, increases tail-flick latencies (391). See Table 3 for a summary of substances that induce hyperalgesia and/or dynamic mechanical allodynia when injected into the intrathecal space.

C. Diet-Induced Hyperalgesia or Allodynia

An early report showed that rats fed a tryptophan-poor corn diet have reduced levels of brain serotonin and display enhanced responsiveness to electric shock. This diet-induced hyperalgesia can be reversed by feeding the animals diets with adequate amounts of tryptophan, or by systemic injections of this amino acid (306).

In rats fed an Mg^{2+}-deficient diet for 10 days, Mg^{2+} levels in plasma and cerebrospinal fluid fall after a few

TABLE 2. *Animal models of pain*

Human Relevance/Disease	Model Primary Mechanism	Induction Method	Model Name (Most Commonly Used)	Nociception Produced					Reference Nos.
				Mechanical allodynia	Mechanical hyperalgesia	Heat hyperalgesia	Cold hyperalgesia	Other behaviors	
Peripheral inflammation and peripheral neurogenic inflammation	Chemical stimulation of primary afferents	Injection of inflammatory agent in hindpaw	Complete Freund's adjuvant (CFA)		●	●			279
			Carageenan		●	●			244, 332
			Mustard oil		●	●			74, 426
			Bee venom	●	●	●		Hindpaw flinching, licking, lifting	67, 68, 270
			Formalin					Hindpaw flinching, licking in two phases	2, 439
Arthritis	Inflammation	Inflammatory mediator injection into joint or into tail	Capsaicin	○	●	●		Hindpaw flinching	152, 591
			Adjuvant-induced mono-arthritis		●	●		Altered gait, stance, spontaneous pain	78, 87, 175
			Adjuvant-induced poly-arthritis		●			Other systemic changes	84, 487
Postoperative pain	Surgical mechanical trauma	Surgery	Incision model	●	●				47, 132
			Ovariohysterectomy	●	●	○		Abdominal postures	156, 273
Sunburn, burn injury	Cell damage by irradiation or thermal injury	UV-B (290–320 nm) dermal irradiation or prolonged noxious heat application on skin	UV model		●	●	●		98, 405
			Burn or thermal injury model		●	●			302, 386
Ischemia-reperfusion injury, complex regional pain syndrome (CRPS), compartment syndrome, peripheral ischemic disease	Ischemia	Temporary hindpaw ischemia and reperfusion or vascular occlusion	Chronic postischemia pain		●	○	●		79, 474
Neuropathic pain, CRPS, nerve entrapment	Traumatic nerve injury	Various methods (constriction, ligation, transection) to injure various peripheral nerves (spinal, sciatic, saphenous) or facial nerves (trigeminal, mental)	Chronic constriction injury (CCI; Bennett)	●	●	●	●	Hindpaw guarding, altered weight bearing	35, 509, 599
			Spinal nerve ligation (SNL; Chung)	●	●	●	●	Hindpaw licking, lifting	71, 131, 240
			Partial sciatic nerve ligation (PSNL; Seltzer)		●	●	●	Hindpaw guarding and licking	315, 473
			Spared nerve injury (SNI)		●	●	●	Hindpaw guarding and altered weight bearing	101, 477
			Sciatic nerve crush		●			Autotomy, hyperesthesia	100, 106
			Cryoneurolysis		●				103
			Phototoxicity		●	●	●		257
			Distal nerve injury		●				486
			Complete nerve transection					Autotomy	554

TABLE 2—*Continued*

Human Relevance/Disease	Model Primary Mechanism	Induction Method	Model Name (Most Commonly Used)	Mechanical allodynia	Mechanical hyperalgesia	Heat hyperalgesia	Cold hyperalgesia	Other behaviors	Reference Nos.
Trigeminal neuralgia	Traumatic nerve injury	Various methods to injure infraorbital nerve (CCI, ischemic injury) or trigeminal ganglia	Infraorbital nerve injury	●	●	●			15, 205, 550
			Trigeminal ganglion compression	●					6
Temporomandibular joint inflammation or orofacial pain	Orofacial inflammation	Acute injection of inflammatory agent (complete Freund's adjuvant, carageenan) in temporomandibular joint or face	Rat or mouse temporomandibular joint pain or orofacial pain		●			Face grooming, scratching	206, 607
Diabetic neuropathy, Postherpetic neuralgia, acute inflammatory demyelinating polyradiculo-neuropathy	Secondary (disease) neuropathy	Administration of streptozotocin to induce diabetes,	Streptozotocin-induced diabetes	●	●	●			90, 133, 314
		inoculation with herpes simplex virus type I,	Herpes simplex virus inoculation	●	●	●	●		97, 460, 508
		immunization with peripheral myelin P2 peptide	Experimental autoimmune neuritis	●	●	●			358
Cancer pain	Compression and inflammation of tissue by cancer cells	Intramedullary, intraplantar, or intragingival injection of cancer cells	Experimental osteolytic sarcoma	●	●			Muscle hyperalgesia	142, 551
			Experimental squamous cell carcinoma		●	●			373, 479
			Experimental melanoma		●	●			617, 461
Inflammatory bowel syndrome	Visceral pain	Injection of irritants into hollow organs or visceral mechanical distention	Injection of acetic acid, capsaicin, mustard oil, turpentine, zymosan into hollow organs		●			Abdominal contraction (writhing) or other visceral nociceptive behaviors, referred hyperalgesia	264, 613
Muscle pain	Peripheral acidosis	Injection of acid in gastrocnemius muscle	Muscle pain		●	○			146, 490
Fever, central nervous system inflammatory diseases	Generalized immune system activation	Systemic, intrathecal, or central lipopolysaccharide/inflammatory mediator administration	Sickness syndrome		●	●		Nonspecific manifestations of inflammation and infection (fever, drowsiness), see sect. VIIA	326, 561

Nociception Produced

TABLE 2—*Continued*

Human Relevance/Disease	Model Primary Mechanism	Induction Method	Model Name (Most Commonly Used)	Nociception Produced					Reference Nos.
				Mechanical allodynia	Mechanical hyperalgesia	Heat hyperalgesia	Cold hyperalgesia	Other behaviors	
Spinal cord injury neuropathic pain	Spinal cord lesions	Ischemic or traumatic contusion, compression, or transection of spinal cord	Spinal cord injury	●	●	●	●		124, 167, 609
Neuritis, neuropathic pain	Neuritis	Acute injection or perineuronal administration of inflammatory agents directly on nerves	Sciatic inflammatory neuritis		●	○	○		65, 556
Migraine	Various	Various manipulations: neurovascular, electrical, genetic	Various	●	●	●		Various measures of spontaneous pain	38, 123
Drug-induced neuropathic pain		Systemic administration of clinically used therapeutic agent	Chemotherapeutic agents (vincristine, paclitaxel)	●	●	●	●	See sect. IIIB	415, 515
			Antiretroviral agents		●		○		222, 555

Solid circles indicate nociception produced, open circles indicate nociception tested but not produced, and empty spaces indicate nociception not tested or controversial effects.

days and recover within 1 day after feeding a normal diet. Mechanical hyperalgesia (Randall-Sellito pressure test) is significant at *day 10*, the first day tested, and outlasts the period of Mg^{2+}-deficient diet for at least 10 days (13). Hyperalgesia induced by Mg^{2+} deficiency is partially reversed by NMDA receptor blockade (119).

Chronic administration of a diet in which all choline is replaced by *N*-aminodeanol, an unnatural choline analog, results in mechanical hyperalgesia in rats along with other classical hypocholinergic symptoms, i.e., progressive loss of learning and memory capacities, hyperkinesis, and hyperactivity (210).

D. Anxiety Level Modulates Pain Sensitivity

In contrast to acute fear, which may lead to stress-induced analgesia (see, e.g., Ref. 285), anxiety may enhance pain sensitivity (410, 433). In some groups of human pain patients, pain sensitivity may positively correlate with basal anxiety levels. Similarly, different strains of rats may also display different levels of baseline anxiety when assessed by the acoustic startle response and open-arm exploration in the elevated plus-maze assay. In these tests, Wistar-Kyoto rats reveal higher anxiety levels than Sprague-Dawley or Fisher-344 rats. When innocuous pressure stimuli are applied to the normal or to the sensitized colon, these strains of rats differ in their responsiveness. Both under normal conditions and after sensitization, high-anxiety Wistar-Kyoto rats respond with significantly more abdominal contraction to colon distension, suggesting that genetically determined anxiety levels are associated with higher visceral sensitivity (160).

E. Chronic Stress Induces Hyperalgesia and Allodynia

Repeated exposure to a cold environment, i.e., to a nonnoxious stressful situation, causes mechanical hyperalgesia (pressure test) that outlasts the stressful period for 3 days (462). Similarly, chronic, but not acute, restraint stress leads to thermal hyperalgesia in the tail-flick assay (145).

IV. GENERAL CONDITIONS THAT INFLUENCE INDUCTION OF HYPERALGESIA OR ALLODYNIA

Both normal nociceptive behavior and susceptibility for the development of hyperalgesia and allodynia may vary between species, strains, sex, and the diet fed, indicating substantial genetic and dietetic impacts (483).

TABLE 3. *Intrathecal chemical induction of hyperalgesia or allodynia*

Class of Substance	Mode of Action	Compound	Behavioral Tests Shown to Produce Nociception					Reference Nos.
			Mechanical allodynia	Mechanical hyperalgesia	Heat hyperalgesia	Cold hyperalgesia	Other behaviors	
Opioids	μ-Opioid receptor activation	Morphine		●	●			111, 321, 537, 585
		DAMGO					Normal motor	538
Plant alkaloid-based chemotherapeutics	Mitotic inhibitors	Paclitaxel		●	●	●		22, 415
		Vincristine		●	○			10, 60
Platinum-based chemotherapeutics	Inhibition of DNA synthesis	Cisplatin		●	●			21
		Oxaliplatin		●		●		294
Glutamate receptor agonists	Activation of NMDA receptors	NMDA		●	●		Scratching and biting	112, 503, 598
		AMPA						598
		Quisqualate		●	●		Scratching and biting	503, 610
		Kainate			○		Scratching and biting	73, 154
	Activation of class I metabotropic glutamate receptor	DHPG		●	●		Scratching and biting	113, 134, 135
Substances acting on nitric oxide metabolism	Nitric oxide donors	Sodium nitroprusside			●			245
		Hydroxylamine			●			245
	Substrate of nitric oxide synthase	L-Arginine	●					333, 353
	Target of nitric oxide	Cell-permeable analogs of cGMP: 8-bromo-cGMP, Db-cGMP			●			148
ATP	Agonist at P2X receptor	ATP, α,β-methylene-ATP		●	●			375
Cytokines	Agonist at specific cell-surface receptors, CX3C receptor 1	Spinal fractalkine (CXC3CL1)		●	●			348
	Binding to TNF-R1, TNF-R2, IL1R1 (CD121a), IL1R2 (CD121b), IL6R (CD126), glycoprotein 130 (gp130, IL6ST, IL6β or CD130)	TNF-α		●	●			428
		IL-1β		●	●			428, 504
		IL-6		●	●	○		549, 557
	Agonist at interferon (IFN)-γ receptor	IFN-γ	●					
Lipopolysaccharides	Binds the CD14/TLR4/MD2 receptor complex, which promotes secretion of pro-inflammatory cytokines	LPS		●	●			52, 334
Lipids		Platelet activating factor (PAF)	●	●	●			366, 367
Prostanoids	Binding to PGE$_2$, EP1, EP3, EP4 receptors	PGE$_1$		●	●			451
		PGE$_2$, PGD$_2$		●	●		Writhing	357, 527
		PGF$_{2\alpha}$		○	○		Agitation	356, 527
Neurotrophic factors	Binding to TrkA, TrkB, p75 receptors, GPRα1	NGF		○	●			53, 313
		BDNF			●			158, 408
		NT-3			○	○		313
		GDNF		○	○			46

TABLE 3—*Continued*

Class of Substance	Mode of Action	Compound	Behavioral Tests Shown to Produce Nociception					Reference Nos.
			Mechanical allodynia	Mechanical hyperalgesia	Heat hyperalgesia	Cold hyperalgesia	Other behaviors	
Endogenous peptides	Agonist at NK-1, NK-2, NK-3 receptors	Substance P		●	●		Vocalization	108, 328, 604–606
		Neurokinin A, B						605
	Binding to CGRP1 and CGRP2 receptors	Calcitonin gene-related peptide (CGRP)		●	●			393, 501
	Unknown	Galanin (porcine)		●	○			258
	Unknown	Cocaine- and amphetamine-regulated transcript (CART) peptide			●			390
	Agonist action at κ-opioid subtype and bradykinin receptors	Dynorphin A	●	●	●	●		263, 274, 539
	Binding to ORL-1 receptor	Nociceptin (Orphanin FQ)	●	●	●			168, 394, 429
	Binding at the kinin B1 and B2 receptors	Bradykinin		●	●			130
Other proteins	Complexing to D1D2 CD4	Glycoprotein: HIV type I: Gp120		●	●			350
	Activation of protease-activated receptors (PARs)	Coagulation protein: thrombin		○	●			251
	ADP-ribosylation and thereby inactivation of G_i proteins	Soluble protein exotoxin: pertussis toxin (PTX)		●	●			584
		Fibronectin		●				523
	Agonists of two G protein-coupled receptors: prokineticin receptor 1 (PKR1) and PKR2	Secretory protein Bv8		●	●			380
Inhibitory neurotransmitter inhibitors	Blocking glycine or $GABA_A$ receptors	Strychnine,	●					303
		Bicuculline	●					303
Protein kinase activators	Activation of protein kinase C and direct actions on ion channels	Phorbol ester		●	●			396
Receptor tyrosine kinases	Eph receptor tyrosine kinases	Ephrins (ephrinB1-Fc, ephrinB2-Fc)		○	●			493
Alkyl-phospholipids	Binding at PAF receptor, phospholipids activation	PAF	●	●	●			367

Solid circles indicate nociception produced, open circles indicate nociception tested, and empty spaces indicate nociception not tested or controversial effects.

A. Gender

Carrageenan injections into a hindpaw at the day of birth affects nociception at adulthood, and this may be different in male and female rats. When a persistent inflammation is induced in adult rats with an intraplantar injection of complete Freund's adjuvant, neonatally injured females display stronger inflammatory hyperalgesia compared with neonatally injured males and controls (269). There are also significant gender differences with respect to the susceptibility to develop neuropathic symptoms. Female Sprague-Dawley and Long-Evans rats display increased hypersensitivity following nerve root injury compared with males. No sex differences were observed, however, in Holtzman rats (261). It is generally believed that endogenous sex steroids play a key role in mediating these sex differences in nociception (260).

B. Genotype

In eight different strains or lines of Sprague-Dawley rats, baseline nociceptive responses to heat and mechanical stimulation as well as heat hyperalgesia, mechanical hyperalgesia, and autotomy following partial sciatic nerve ligation vary greatly. Rats tested included "genetically epilepsy-prone rats," "high autotomy selection line," "low autotomy selection line," "flinders sensitive line," "Lewis rats" (an inbred line), "Fisher 344" (an inbred line), and "Sabra rats," an outbred line. Baseline nociceptive thresholds are highest in "genetically epilepsy-prone rats" and lowest in "Fischer 344" rats. Autotomy scores are lowest in "Lewis rats" and highest in "high autotomy rats" (484). Likewise, baseline nociceptive responses and tactile hyperalgesia after an ischemic lesion of the sciatic nerve are different in four strains or lines of rats: "Sprague-Dawley," "Wistar-Kyoto," "spontaneously hypertensive," and "Dark-Agouti rats" and two substrains of "Sprague-Dawley" rats supplied from two different vendors (Sprague-Dawley-BK and Sprague-Dawley-DK). Nerve lesions lead to cold hyperalgesia in "Wistar-Kyoto" and "Sprague-Dawley-BK" rats only. "Sprague-Dawley-DK" rats develop more severe mechanical hyperalgesia than "Sprague-Dawley-BK" rats (597). Complete Freund's adjuvant-induced thermal hyperalgesia is stronger in "Fisher 344" rats than in "Sprague-Dawley" or "Lewis" rats (619).

Similar differences in nociceptive behavior can be demonstrated in different strains of mice. Baseline paw withdrawal thresholds vary from 0.3 to 1.5 g when 15 different strains of mice are tested. These strains of mice also differ with respect to opioid-induced mechanical hyperalgesia. The degree of hyperalgesia ranges from 30 to 85% reduction in mechanical nociceptive thresholds (290). Likewise, from 10 different mouse strains, one strain displayed an especially robust mechanical hyperal-

gesia following paclitaxel treatment, while another strain was fully resistant to this treatment (491). Some of the species and strain differences in response to manipulations of the sciatic nerve may be due to differences in sciatic nerve anatomy (434).

Mutations in single genes may also have profound effects on nociception. For example, the *reeler* gene is an autosomal recessive mutation that may naturally occur in humans. When a similar mutation is induced in mice, the protein product Reelin, which is a large secreted extracellular matrix type protein, is missing. This protein is involved in proper neuronal positioning during development. The phenotype of mutant mice includes thermal hyperalgesia in the Hargreaves test but reduced sensitivity to noxious mechanical stimuli (von Frey hairs) (8, 547).

C. Age

A large body of evidence suggests that in neonatal and young rats nociception is quantitatively and qualitatively different compared with the adults (see reviews by Fitzgerald and colleagues, Refs. 136, 378). For example, secondary hyperalgesia may be induced only at later developmental stages in contrast to primary hyperalgesia. Mustard oil or capsaicin induce primary hyperalgesia at all postnatal days tested as assessed by electromyography flexion reflex recordings in response to mechanical stimuli at a hindpaw. In contrast, secondary hyperalgesia cannot be demonstrated at postnatal *day 3* but is evident at postnatal *days 10* and *21* (552). Likewise, neuropathic pain behavior is not observed in neonatal rats. In the spared nerve injury model, tactile hyperalgesia does not develop if surgery is performed before the fourth postnatal week. This delayed susceptibility to painful neuropathies may be caused by an immature response profile of spinal microglia (369). On the other hand, intraplantar injections of endothelin-1 produce a longer lasting mechanical hyperalgesia in young (postnatal *day 7*) rats than in adults (330).

D. Diet

Composition of the diet may have profound effects on hyperalgesia and allodynia induced by nerve lesions. In one study, "Wistar" rats were fed with a casein-based, fat-free diet for 1 wk preceding partial sciatic nerve ligation and in addition either hemp oil (20% omega-3 polyunsaturated fatty acids) or corn oil (0.7% omega-3 level). An omega-3-rich diet was associated with a stronger heat hyperalgesia, but tactile hyperalgesia was not different between dietary groups (404). When rats are fed since weaning a diet containing 85% soy protein, partial sciatic

nerve ligation evokes less severe mechanical hyperalgesia (von Frey hairs) and thermal hyperalgesia (Hargreaves test) compared with animals with a normal diet. When a soy-rich diet is terminated 15 h before nerve lesion, rats develop full hyperalgesia (480). In rats fed with a synthetic polyamine-deficient diet, unilateral injection of carrageenan into a hindpaw induces a bilateral mechanical hyperalgesia (Randall-Sellito pressure test) that is less pronounced than in control animals (125).

Male mice with a prolonged restriction of caloric intake (60% of ad libitum) show fewer licking or biting responses in the Formalin test. Also, they show longer response latencies in the hot-plate test. In ad libitum control mice but not in caloric-restricted mice, partial tail amputation induces thermal hyperalgesia. Injections of collagen subcutaneously lead to thermal hyperalgesia (Hot plate test) in some strains. This collagen-induced arthritic hyperalgesia can be blocked reversibly during 9–15 wk of caloric restriction (170).

In rats treated with streptozotocin to induce diabetic polyneuropathy, thermal hyperalgesia (Hargreaves test) and mechanical hyperalgesia (von Frey thresholds) are reduced in those animals that received a 2% taurine-supplemented diet for 6–12 wk. Imaging of Ca^{2+} gradients in sensory neurons suggests that impaired Ca^{2+} homeostasis in diabetic rats is partially reversed by taurine supplemented diet (287).

V. CELLULAR SYSTEMS THAT ARE INDISPENSABLE FOR HYPERALGESIA AND ALLODYNIA

A classical proof for the involvement of a particular element for a given function is by selective inactivation or destruction of that element. In pain research, much information has been gained from targeted inactivation or destruction of brain regions or fiber tracts. The selective destruction of a well-defined group of neuronal or nonneuronal cells by the cell toxin saporin is a novel, powerful tool to assess their role for hyperalgesia and allodynia in the behaving animals (12, 249, 318, 379, 383).

Figure 2 summarizes cellular elements that are required for the full expression of hyperalgesia and/or allodynia in some animal models of inflammatory or neuropathic pain. Obviously not all these elements have been tested in all models and most likely are also not required for all forms of enhanced pain sensitivity.

Sensory nerve fibers consist of the following: 1) capsaicin-sensitive C-fibers (61, 99, 234, 237, 336, 354, 355, 395, 476, 481), 2) IB4-sensitive C-fibers (513, 513), and 3) vagal afferents (310, 567).

Spinal cord cells consist of the following: 4) spinal dorsal horn neurons that express the neurokinin I re-
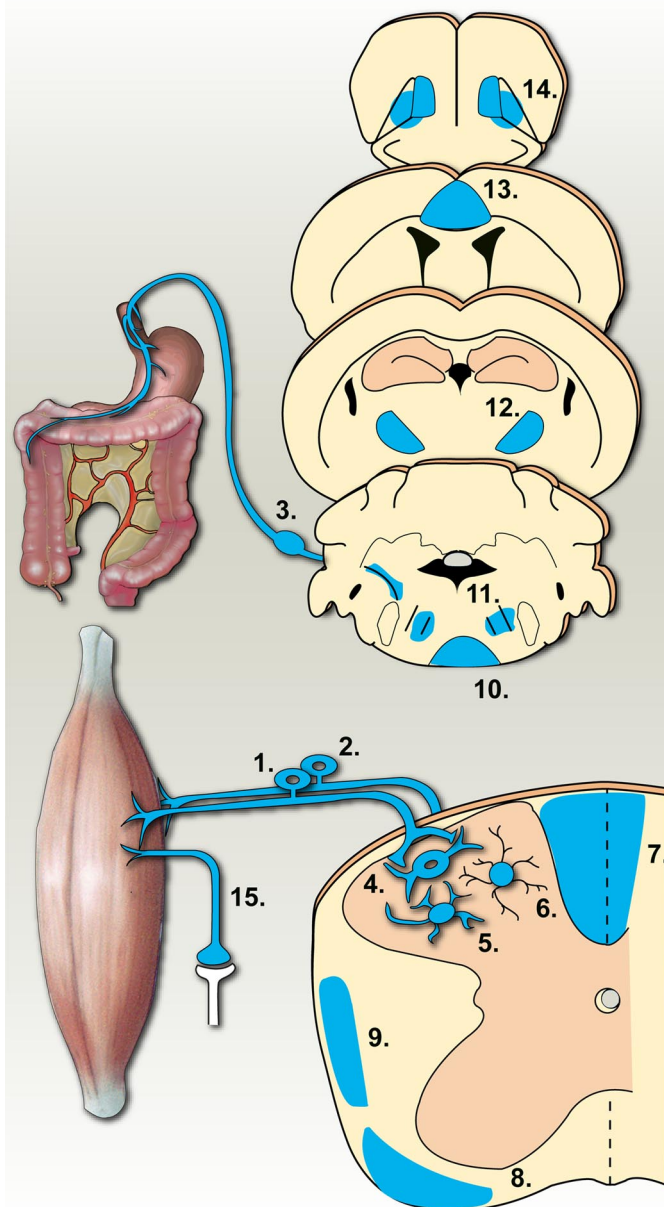

FIG. 2. Neuronal elements that are indispensable for some forms of hyperalgesia and/or allodynia. Afferent fiber systems: 1) C-fibers that express the TRPV1 ion channel, 2) C-fibers that express the marker IB4, 3) vagal afferent fibers. Spinal dorsal horn cells: 4) lamina I neurons that express the neurokinin 1 receptor, 5) microglia, 6) astrocytes. Spinal fiber tracts: 7) dorsal column fibers, 8) fibers traveling in the anterolateral funiculus, 9) fibers traveling in the lateral funiculus. Brain nuclei: 10) rostral ventromedial medulla, 11) nuclei reticularis gigantocellularis, 12) thalamic nuclei, 13) anterior cingulate cortex, 14) lateral and ventral orbital cortex. Efferent fiber systems: 15) sympathetic postganglionic neurons.

ceptor (318, 383, 542, 545, 575, 611), 5) microglia (192, 276, 375, 423, 502, 564, 618), and 6) astrocytes (213, 387, 624).

Spinal cord fiber tracts consist of the following: 7) dorsal columns (185, 239, 397, 399, 447), 8) anterior

lateral quadrant (139, 153, 544), and *9*) lateral funiculus [397; see monograph by Willis for a review (580)].

Brain nuclei consist of the following: *10*) rostral ventromedial medulla (411, 458, 533, 534, 540); *11*) nuclei reticularis gigantocellularis (151, 347, 541, 569); *12*) thalamic nuclei, ventrobasal complex (446, 622); *13*) anterior cingulate cortex (29, 114, 262, 431); and *14*) ventrolateral orbital area (29).

Efferent nerve fibers consist of the following: *15*) sympathetic postganglionic neurons (4, 17, 236, 241, 284, 342, 432, 435, 472, 482).

VI. SPINAL MECHANISMS OF HYPERALGESIA AND ALLODYNIA

The work summarized in the previous sections demonstrates that the pathogenesis of hyperalgesia and allodynia may have important spinal components. Section VI*A* summarizes some of the global changes that have been observed in association with the development of hyperalgesia or allodynia. The subsequent sections (sect. VI, *B–G*) describe spinal mechanisms that are likely involved in the generation or maintenance of hyperalgesia or allodynia.

A. General Changes in Spinal Cord After Induction of Hyperalgesia and Allodynia

A large number of conditions may cause hyperalgesia and some also dynamic mechanical allodynia as outlined above. It is possible that each condition may trigger a characteristic set of changes within the central nervous system. The functional consequences of these changes may vary from being necessary or sufficient for induction of hyperalgesia or allodynia; others may facilitate, inhibit, or prevent changes in pain sensitivity; and still others may be unrelated epiphenomena. An early review on some of these activity-dependent neuroplastic changes in spinal dorsal horn is provided by Dubner and Ruda (118). Here, I focus on three conditions that trigger hyperalgesia and/or allodynia: *1*) supramaximal electrical stimulation of sensory nerve fibers. This conditioning stimulus can be used in humans and in behaving experimental animals, in acute preparations and in vitro. *2*) Activation of transient receptor potential vanilloid 1 channels on a subset of C-fibers by capsaicin is a commonly used model for afferent-induced secondary hyperalgesia in humans, behaving animals, and acute preparations. *3*) The chronic constriction injury of the sciatic nerve is a widely used model for peripheral neuropathic pain.

1. Changes induced in spinal dorsal horn by electrical nerve stimulation

Electrical stimulation of sensory nerves at C-fiber intensity causes spinal release of amino acids including aspartate, glutamate, asparagine, serine, glycine, threonine, alanine, and taurine (400). Furthermore, a number of neuropeptides are released including substance P (266, 282, 465), galanin (85), calcitonin gene-related peptide (464), endomorphins (102), nociceptin (576), and dynorphin A (199). Neurotrophic factors such as brain-derived neurotrophic factor may be released in the spinal cord upon electrical stimulation of sensory nerves in a frequency-dependent manner. Release of brain-derived neurotrophic factor requires high-frequency stimulation at C-fiber strength (100 Hz) (282), whereas low-frequency stimulation is ineffective (1 or 2 Hz) (282, 553).

Electrical nerve stimulation at C-fiber but not at Aβ-fiber intensity also leads to posttranslational modification of proteins in spinal neurons including phosphorylation of extracellular signal-regulated kinase (212). Stimulation of dorsal roots at C-fiber intensity with low frequencies (0.05–10 Hz) (143) or higher frequencies [50 Hz (212) or 100 Hz (283, 595)] induces phosphorylation of extracellular receptor-activated kinase in superficial but not in deep spinal dorsal horn [See also Ji and Suter (214) for a review]. Activation of C-fibers by electrical stimulation (or by capsaicin) leads to an 8- to 10-fold increase in extracellular signal-regulated kinase phosphorylation in superficial spinal dorsal horn in vitro (231).

After the initial study by Hunt et al. (198), a large number of reports confirmed the transsynaptic induction of protein products of immediate-early genes such as c-*fos* in spinal neurons following sensory stimulation (582; for review, see Coggeshall, Ref. 80). Electrical nerve stimulation at C-fiber strength (1 Hz for 6–8 h) causes spinal upregulation of c-Fos protein (291) but no observable changes in gene expression for calcium/calmodulin-dependent protein kinase IIα, or glutamate decarboxylase (291). The pattern and the intensity of c-Fos labeling in spinal dorsal horn depends on the duration of electrical nerve stimulation; brief stimuli (seconds) cause transient labeling in superficial laminae only while longer lasting stimulation (hours) also leads to labeling in deeper layers (50). Electrical stimulation of sciatic nerve at Aδ/C but not at A-fiber intensity leads to expression of transcription factors c-Jun, Jun B, Fos B, and Krox-24 mainly in superficial layers of spinal dorsal horn and of c-Fos and Jun D throughout spinal dorsal horn (179). Expression of c-Fos in dorsal horn neurons is used as an activity marker but provides probably not sufficient evidence for neuronal plasticity and long-term changes in nociception (456). The functional role of enhanced expression of immediate-early genes in neurons of the spinal cord is still largely unknown.

2. Changes induced by capsaicin

Activation of transient receptor potential vanilloid 1 receptor channels on fine primary afferent nerve fibers by

subcutaneous injections of capsaicin causes a large number of global changes within spinal dorsal horn. This includes the release of neurotransmitters and modulators such as glutamate (529), substance P (49, 296, 600), calcitonin gene-related peptide (107, 377), somatostatin (258), and nitric oxide (593).

Capsaicin injections trigger posttranslational changes in spinal dorsal horn cells such as phosphorylation of AMPA receptor subunit GluR1 (374), as well as phosphorylation of NMDA receptor 1 through protein kinase C and protein kinase A (630) in spinal dorsal horn neurons, including those with a projection to the thalamus (631).

Furthermore, capsaicin injections significantly increase the phosphorylation levels of enzymes and transcription factors such as cAMP response element-binding protein (594) and calcium/calmodulin-dependent protein kinase II (126) in the ipsilateral side of the spinal cord. Phosphorylation of extracellular signal-regulated kinase in the superficial spinal dorsal horn in vitro increases 8- to 10-fold following capsaicin injections. The extracellular signal-regulated kinase induction is reduced by blockade of NMDA, AMPA/kainate, group I metabotropic glutamate receptor, neurokinin-1, and tyrosine receptor kinase receptors and by inhibitors of protein kinase A or protein kinase C (231).

c-Fos protein is detected in neurons of ipsilateral spinal dorsal horn after subcutaneous injections of capsaicin (590), including spinothalamic tract neurons and postsynaptic dorsal column neurons (398).

Perineuronal injections of capsaicin near the tibial nerve reduce the number of cells in spinal dorsal horn with GABA immunoreactivity (571).

Intracolonic installation of capsaicin causes referred hyperalgesia in mice and recruitment of GluR1 (but not GluR2/3) AMPA receptor subunits to the plasma membrane fraction of spinal cells within 10 min. At 180 min, the increase is 3.7-fold (144).

3. Changes induced by chronic constriction injury of sciatic nerve

In the chronic constriction injury model of rats, glutamate and aspartate contents are increased on the ipsilateral side of the dorsal horn to nerve ligation on *days 4, 7,* and *14* after nerve injury (229). Likewise, in spinal dorsal horn of hyperalgesic rats with a sciatic nerve ligation (473), extracellular levels of glutamate and aspartate are more than doubled as revealed by microdialysis (94). Furthermore, chronic constriction injury leads to enhanced levels of 5-hydroxytryptamine (serotonin) and norepinephrine bilaterally in spinal cord (463), as well as enhanced content of neuropeptides such as neuropeptide Y (86) and galanin (85). In contrast, substance P immunoreactivity is decreased in ipsilateral spinal dorsal horn 60 days after chronic constriction injury. In the contralat-

eral dorsal horn, calcitonin gene-related peptide and substance P immunoreactivities also decrease 60 days after chronic constriction injury (225). Neuropeptide changes may persist in spinal cord despite resolving mechanical hyperalgesia 100–120 days after chronic constriction injury. Substance P and galanin immunoreactivities are still decreased by ~30% ipsilaterally in laminae I and II of the dorsal horn compared with sham-operated animals, while calcitonin gene-related peptide and neuropeptide Y contents in laminae I and II are no longer different from controls by this time (371). A number of proteins are either up- or downregulated after chronic constriction injury or other models of neuropathic pain. A systematic review on the proteomics in neuropathic pain research is provided by Niederberger and Geisslinger (384).

As soon as 3 days after a chronic constriction injury of the sciatic nerve, the number of GABA- and glutamate decarboxylase-immunoreactive cells decrease bilaterally to the nerve injury. At 1 wk after chronic constriction injury, the number of GABA-immunoreactive cells continues to decline bilaterally, returning to near normal numbers on the side contralateral to the nerve injury by 8 wk after the nerve injury. The number of glutamate decarboxylase immunoreactive cells begins to increase bilaterally to the nerve injury at 1 wk after chronic constriction injury and continues to increase significantly in numbers over normal values by 8 wk after the nerve injury (121). A quantitative stereological analysis of the proportions of neurons in laminae I, II, and III of the rat dorsal horn that show GABA and/or glycine immunoreactivity 2 wk after chronic constriction injury does, however, not reveal any loss of inhibitory interneurons (413), suggesting that GABA synthesis is downregulated under these conditions and that not a loss of GABAergic neurons accounts for reduced GABA immunoreactivity (see also sect. VI*D1A1*).

Nerve injury may also alter expression or binding properties of cell surface receptors. μ-Opioid receptor binding is increased 2–5 days postinjury, bilaterally to the injury in laminae V and X but only ipsilaterally in laminae I-II. Binding returns to control levels within 10 days. δ-Opioid receptor binding declines gradually over 2–10 days postinjury. κ-Opioid receptor binding displays an increase in ipsilateral laminae I–II and in contralateral lamina X but no change on either side in lamina V, followed by a rapid decrease in κ-opioid receptor binding in all three areas on both sides of the spinal cord by day 5 postinjury (499).

Substance P binding significantly increases ipsilateral to the chronic constriction injury in laminae I/II at 5–20 days after injury and in lamina V 5 days after injury (1), while calcitonin gene-related peptide binding remains unchanged (149).

Fractalkine receptor CX3CR1, which is expressed by microglia in the basal state, is upregulated in a regionally specific manner 10 days after chronic constriction injury,

while immunoreactivity and mRNA levels of its ligand remain unchanged in dorsal horn (543).

Synaptic proteins may also be altered in spinal dorsal horn of rats with a chronic constriction injury of sciatic nerve. The period of mechanical and thermal hyperalgesia parallels the duration of enhanced expression of scaffolding proteins Homer and Shank in the postsynaptic density in ipsilateral spinal dorsal horn (346). The distribution and content of synaptophysin are altered following chronic constriction injury as evaluated by immunohistochemistry, Western blotting, and densitometry. Synaptophysin is increased in the ipsilateral dorsal horn with a peak level on *day 14* and then returns to baseline on *day 21* post-chronic constriction injury. Interestingly, synaptophysin levels correlate temporally with thermal but not with mechanical hyperalgesia (72).

Levels and activation of enzymes in spinal cells are also altered in the course of a chronic constriction injury of sciatic nerve. Three to 14 days after chronic constriction injury of sciatic nerve, total calcium/calmodulin-dependent protein kinase II immunoreactivity is enhanced in spinal cord, and this is preceded by an increase in phosphorylated calcium/calmodulin-dependent protein kinase II immunoreactivity beginning on *day 1* (96). Three and 10 days after chronic constriction injury, membrane-bound protein kinase C is increased bilaterally in the lumbar spinal cord (L1–L5) laminae I–IV and V–VI (319). Eight days after chronic constriction injury, protein kinase C-γ immunoreactivity is increased bilaterally in the spinal cord dorsal horn (322).

The number of phosphorylated p38-immunoreactive microglia increases in the laminae I–IV and IX of the spinal cord ipsilateral to a chronic constriction injury (242). Tactile hyperalgesia and activation of microglia may, however, not be closely time locked after chronic constriction injury. When scoring glial responses subjectively by changes in cell morphology, cell density, and intensity of immunoreactivity with specific activation markers (OX-42 and anti-glial fibrillary acidic protein for microglia and astrocytes, respectively), microglial responses are not pronounced in the chronic constriction injury lesioned rats. Spinal astrocytic rather than microglial responses appear to correlate more closely with pain behaviors in rats with a chronic constriction injury (81).

Synaptosomal contents of glutamate and aspartate are enhanced by 45% bilaterally in spinal cord 12 days after unilateral chronic constriction injury to sciatic nerve (492).

The number of apoptotic cells marked by the TUNEL technique plus Hoechst double labeling increases in the ipsilateral dorsal horn of the spinal cord 8 and 14 days following chronic constriction injury compared with the contralateral side and to naive and sham-treated animals (573). Following chronic constriction injury, morphological changes in the ipsilateral L4–L5 lamina II include cell loss and increased TUNEL-positive profiles and reactive gliosis. However, the total number of neurons is apparently unchanged 2 wk after chronic constriction injury when using the quantitative stereological optical dissector method and NeuN immunostaining (412).

Markers for cell activity also change. The amplitude and frequency of spontaneous and miniature excitatory postsynaptic currents increase in superficial dorsal horn neurons of rats with a chronic constriction injury of sciatic nerve for 13–25 days (28). Sciatic nerve ligation produces a bilateral increase in spinal cord 2-[^{14}C]deoxyglucose metabolic activity in four sampling regions (laminae I–IV, V–VI, VII, and VIII–IX) of lumbar segments compared with sham-operated rats (320). The expression of c-Fos protein in spinal cord is also upregulated after chronic constriction injury (224) and may have a biphasic time course (see, however, Ref. 62). The highest number of c-Fos-positive neurons occurs during the first week after chronic constriction injury, followed by a decline at 7 and 14 days and reappearance at day 28 following injury. This biphasic time course does, however, not resemble the monophasic time course of tactile hyperalgesia in the chronic constriction injury model (211). In another study, Fos-positive cells were found bilaterally throughout laminae III–X at all time points examined up to 55 days after surgery in both chronic constriction injury and sham-operated animals (372). The number of c-Fos-positive cells in the ipsilateral spinal cord was positively correlated with the degree of hyperalgesia in one study (195).

Potential spinal mechanisms causing enhanced neuronal responsiveness are shown in Figure 3 and include direct facilitation along the chain of excitation (Fig. 3, *A–C*) or alteration in physiological modulation of spinal nociception, i.e., less than normal inhibition (Fig. 3, *D*, *F*, and *J*), conversion from inhibition to excitation (Fig. 3, *E* and *G*), or stronger than normal excitation (Fig. 3, *H–J*). Generation of epileptiform activity, burstlike discharges, and synchronous discharges could also amplify nociception (Fig. 3*K*). If pain should be caused by a unique pattern of discharges of individual neurons (pattern theory) and/or by a characteristic pattern of active versus silent neurons (population coding), any of the above cellular mechanisms could contribute to altered pain perception.

B. Synaptic LTP

1. Definitions

LTP is a much studied cellular model of synaptic plasticity. It is generally defined as the long-lasting but not necessarily irreversible increase in synaptic strength (42). At least two different stages of LTP can be distinguished depending upon its duration and the signal transduction pathways involved. Early-phase LTP is independent of de novo protein synthesis and lasts for up to 3 h. Late-phase

Site of action

Effect

Normal   Modified

Mechanisms

[Chapters]

A

Nociceptive
nerve fiber

Spinal dorsal horn
projection neuron

Excitatory postsynaptic potentials

LTP of synaptic strength [VI.B]

1. Presynaptic
   Enhanced transmitter release

2. Postsynaptic
   Enhanced transmitter effect

B

Changes in membrane excitability [VI.C]

1. Lower resting membrane potential (solid line)

2. Lowered threshold for action potential discharge (dotted line)

C

Changes in the pattern of action potential discharges

1. Enhanced sodium currents [VI.C.1]

2. Reduced potassium currents [VI.C.2]

3. Plateau potentials [VI.C.3]

D

Inhibitory
interneuron

Inhibitory postsynaptic potentials

Reduced strength of synaptic inhibition
[VI.D.1.A; VI.D.2.A]

1. Presynaptic
   Reduced transmitter synthesis
   Reduced vesicular transport
   Reduced release probability

2. Postsynaptic
   Reduced transmitter effect (e.g. reduced number or sensitivity of receptors)

E

Inhibitory / excitatory postsynaptic
potentials

Conversion from postsynaptic
inhibition to excitation [VI.D.1.B]

1. Shift in anion gradient and Cl⁻ reversal potential

F

Excitatory
interneuron

Inhibitory postsynaptic potentials

Fewer number of inhibitory events
[VI.D.1.A.I]

1. Reduced excitatory drive of inhibitory interneurons
2. Lower number of inhibitory synapses
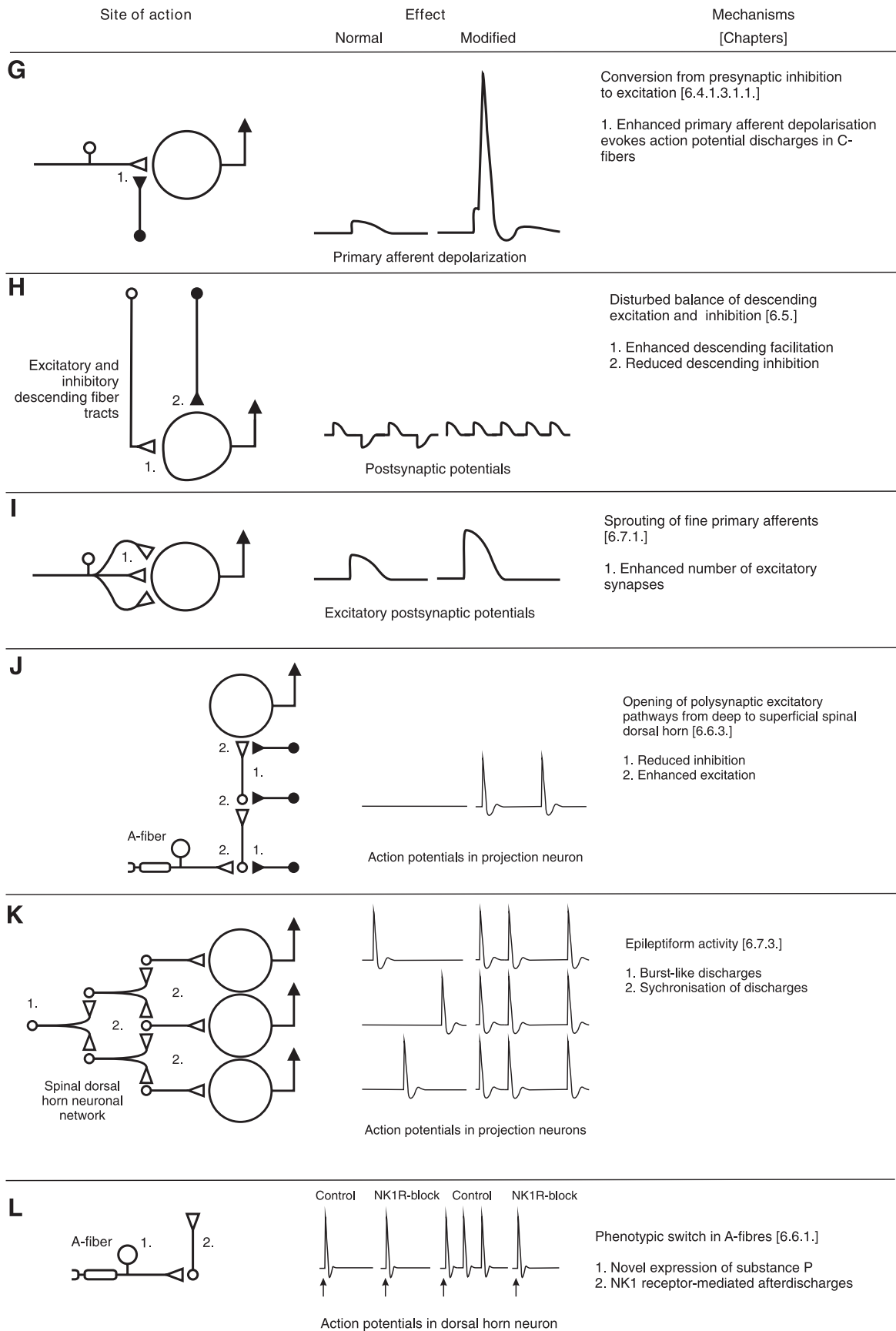3. Reduced release probability of inhibitory neurotransmitter

Site of action	Effect		Mechanisms
	Normal	Modified	[Chapters]

G

Primary afferent depolarization

Conversion from presynaptic inhibition to excitation [6.4.1.3.1.1.]

1. Enhanced primary afferent depolarisation evokes action potential discharges in C-fibers

H

Excitatory and inhibitory descending fiber tracts

Postsynaptic potentials

Disturbed balance of descending excitation and inhibition [6.5.]

1. Enhanced descending facilitation
2. Reduced descending inhibition

I

Excitatory postsynaptic potentials

Sprouting of fine primary afferents [6.7.1.]

1. Enhanced number of excitatory synapses

J

A-fiber

Action potentials in projection neuron

Opening of polysynaptic excitatory pathways from deep to superficial spinal dorsal horn [6.6.3.]

1. Reduced inhibition
2. Enhanced excitation

K

Spinal dorsal horn neuronal network

Action potentials in projection neurons

Epileptiform activity [6.7.3.]

1. Burst-like discharges
2. Sychronisation of discharges

L

A-fiber

Control NK1R-block Control NK1R-block

Action potentials in dorsal horn neuron

Phenotypic switch in A-fibres [6.6.1.]

1. Novel expression of substance P
2. NK1 receptor-mediated afterdischarges

FIG. 3.–Continued

LTP involves protein synthesis and lasts longer than 3 h, up to the life span of an animal. Short-term potentiation of synaptic strength lasts less than half an hour. Synaptic strength is the magnitude of the postsynaptic response (i.e., the postsynaptic potential or the postsynaptic current, but not action potential firing, see below) in response to a presynaptic action potential. LTP can be expressed pre- and/or postsynaptically, i.e., synaptic strength can increase if the release of neurotransmitter(s) is enhanced and/or if the postsynaptic effects of the neurotransmitter(s) become stronger (295). LTP at synapses in hippocampus is the prime model for learning and memory formation (42). Recent studies have shown that LTP can also be induced in pain pathways and may contribute to hyperalgesia caused by inflammation, trauma, or neuropathy (453). This section deals with the latter form of LTP.

2. How to measure LTP properly

LTP is measured as an increase in monosynaptically evoked postsynaptic currents or potentials in response to a single presynaptic action potential. LTP is often studied in in vitro preparations which allow reliable recordings of synaptic strength. Whole cell patch-clamp recording is now the most often used technique. It enables some control over the composition of the intracellular fluid of the postsynaptic neurons, which may be advantageous to study postsynaptic mechanisms of LTP. If, however, a diffusible mediator is involved and dialysis of the postsynaptic neuron has to be avoided, perforated patch-clamp recordings or intracellular recordings with sharp electrodes can be used. To evaluate LTP at the first synapses in nociceptive pathways, transverse slices with long dorsal roots attached can be prepared from lumbar spinal cord of rats or mice to study monosynaptic, Aδ-fiber or C-fiber evoked excitatory postsynaptic potentials or currents in identified dorsal horn neurons (202, 425).

Some aspects of LTP can only be studied in the entire animal with primary afferent nerve fibers and descending pathways from the brain intact. In vivo C-fiber-evoked field potentials can be measured in superficial spinal dorsal horn, e.g., in response to high-intensity electrical stimulation of the sciatic nerve for up to 24 h (300). These extracellularly recorded field potentials reflect summa-

tion of postsynaptic, mainly monosynaptically evoked currents but not action potential firing (300, 469).

Monitoring presynaptic activity at synapses of primary afferent nerve fibers is technically quite demanding. In an attempt to monitor presynaptic activity in primary afferents, optical recording techniques have been utilized. Some voltage-sensitive dyes can be anterogradely transported in primary afferents to the central terminals mainly in lamina I (203) and may serve as an indicator for presynaptic electrical activity but not for transmitter release.

LTP cannot be directly investigated by recording action potential discharges of postsynaptic neurons, as action potential firing not only depends on synaptic strength but also on membrane excitability and the balance between excitatory and inhibitory input to the neuron. For the same reasons, polysynaptically evoked responses can generally not be used to study synaptic strength and changes thereof.

3. Stimuli that induce LTP in pain pathways

A) HIGH-FREQUENCY ELECTRICAL NERVE STIMULATION. The most frequently used form of conditioning stimulation to induce LTP at synapses in the brain consists of high-frequency electrical stimulation (~100 Hz) of an input pathway. Likewise, LTP can be induced at spinal synapses of small-diameter primary afferents by conditioning high-intensity, high-frequency burstlike stimulation (typically 100 Hz bursts given several times for 1 s at C-fiber strength) both in vitro and in vivo. In spinal cord slice preparations, both Aδ-fiber (425) and C-fiber (202, 204) evoked responses are potentiated by high-frequency stimulation when postsynaptic neurons are mildly depolarized to −70 to −50 mV. The same high-frequency stimulation induces, however, long-term depression (LTD) of Aδ-fiber-evoked responses if cells are hyperpolarized to −85 mV, suggesting that the polarity of synaptic plasticity is voltage dependent (425).

Neurons in spinal cord lamina I which express the neurokinin 1 receptor play a pivotal role for hyperalgesia in behaving animals (318, 383). Most of these neurons send a projection to supraspinal areas. Interestingly, high-frequency stimulation induces LTP selectively at C-fiber synapses with lamina I neurons that express the neurokinin 1 receptor and send a projection to the parabrachial

FIG. 3. Schematically illustrated are spinal mechanisms leading to hyperalgesia or allodynia. On the *left* ("site of action"), a nociceptive spinal dorsal horn projection neuron (upward arrow) is shown that receives input from a primary afferent nociceptive nerve fiber (as shown in *A*, *G*, and *I*). This afferent input is omitted for reasons of simplicity only in the remaing parts of the figure. The nociceptive projection neuron also receives inhibitory (GABAergic and/or glycinergic) input (small, black neuron in *D*, *E*, and *F*). The inhibitory neuron has excitatory drive from a spinal interneuron (*F*) and/or from primary afferent nerve fibers (not shown). Spinal inhibitory interneurons may mediate presynaptic inhibition at the terminals of primary afferent nerve fibers (*G*) as well as pre- and postsynaptic inhibition of spinal excitatory interneurons (*J*). Nocicpetive spinal dorsal horn projection neurons are modulated further by long, descending facilitatory and inhibitory pathways (*H*) and by complex network activity of spinal interneurons (*K*). The potential changes in electrophysiological properties and responses under pathological conditions ("Modified") compared with controls ("Normal") are shown in the *middle*. On the *right* ("Mechanisms"), a brief description of the effects and the relevant sections in this review are given for each of the mechanisms described.

area (202), and vice versa, high-frequency stimulation fails to induce LTP at synapses with neurons which express the neurokinin 1 receptor and send a projection to the periaqueductal gray or at synapses with neurons that do not express the neurokinin 1 receptor and which have no identified supraspinal projection (202, 204).

High-frequency stimulation at C-fiber intensity of sciatic nerve fiber afferents induces LTP of C-fiber, but not Aβ-fiber evoked field potentials in superficial spinal dorsal horn of adult, deeply anesthetized rats (299, 300, 307). In contrast, conditioning high-frequency stimulation at A-fiber intensity fails to induce LTP of either A- or C-fiber evoked field potentials in intact animals. In spinalized animals, conditioning high-frequency stimulation at Aδ-fiber intensity induces, however, LTP of C-fiber evoked field potentials (298). Likewise, in rats with a spinal nerve ligation but not in control animals, high-frequency stimulation at a low intensity (10 V, 0.5-ms pulses) induces LTP of C-fiber evoked field potentials, whereas high-intensity high-frequency stimulation (30 V, 0.5-ms pulses) is effective in both control and in neuropathic animals (596). This suggests that the threshold for inducing LTP is lowered under various neuropathic conditions.

B) LOW-FREQUENCY ELECTRICAL NERVE STIMULATION. For most of the C-fiber afferents it is not typical to discharge at rates as high as 100 imp/s. Some C-fibers may, however, discharge at these high rates but only for short periods of time, e.g., at the beginning of a noxious mechanical stimulus (165). Many C-fibers discharge at considerably lower rates, $\sim$1–10 imp/s, e.g., in response to an inflammation or an injury (422). Conditioning stimulation within this lower frequency band is successfully used to induce LTP at C-fiber synapses. In a spinal cord-dorsal root slice preparation, conditioning electrical low-frequency stimulation (2 Hz for 2–3 min, C-fiber strength) of dorsal root afferents induces LTP selectively at C-fiber synapses with lamina I neurons that express the neurokinin 1 receptor and project to the periaqueductal gray (204). C-fiber synapses with lamina I neurons which express the neurokinin 1 receptor and project to the parabrachial area or with no identified supraspinal projection are, in contrast, not potentiated by low-frequency stimulation (204). Thus the pattern and the frequency of discharges in C-fibers determine which synapses at the origin of different ascending pain pathways are potentiated.

In spinal cord slices from neonatal rats, field potentials evoked by electrical stimulation in the tract of Lissauer are potentiated by repetitive burstlike stimulation at 10 Hz (514). Some authors could induce LTP at synapses in deep spinal dorsal horn in slices from young (3–6 day old) but not older (9–16 day old) rats (147) in contrast to a recent study where a robust LTP was induced in superficial dorsal horn by low-frequency stimulation at C-fiber synapses in more mature animals (21- to 28-day-old rats) (204).

In deeply anesthetized adult rats with their spinal cords left intact, low-frequency stimulation (at 2 Hz for 2–3 min) of sciatic nerve fibers at C-fiber intensity but not at Aδ-fiber intensity also triggers LTP of C-fiber evoked potentials (204).

Thus high-frequency stimulation and low-frequency stimulation may have fundamentally different effects on LTP induction at different C-fiber synapses. This finding is in line with previous reports also illustrating that the frequency of afferent barrage in C-fibers may have qualitatively different effects in spinal cord. For example, brain-derived neurotrophic factor is released from primary afferents in spinal cord slices in an activity-dependent manner by high-frequency stimulation at 100 Hz but not by 1-Hz low-frequency stimulation of primary afferent nerve fibers, while substance P is also released by low-frequency stimulation (282).

C) NATURAL NOXIOUS STIMULATION INDUCES LTP. At synapses in the brain, LTP induction requires synchronous, high-frequency presynaptic activity or pairing of low-level presynaptic activity with strong postsynaptic depolarization. At least some of the C-fiber synapses are apparently unique in that LTP can be induced by low-frequency stimulation and by natural, low- or high-frequency, asynchronous and irregular discharge patterns in sensory nerve fibers. In animals with spinal cord and descending pathways intact, intraplantar, subcutaneous injections of capsaicin (100 μl, 1%) or Formalin (100 μl, 5%) induce slowly rising LTP (204).

Some forms of low-level afferent input can induce LTP only if descending, presumably inhibitory pathways are interrupted or weakened. Noxious radiant heating of the skin at a hindpaw induces LTP in spinalized animals but not in animals with spinal cord intact (455). Likewise, repetitive, noxious squeezing of the skin or the sciatic nerve induces LTP of C-fiber evoked field potentials only in spinalized rats (455). These findings indicate that endogenous antinociceptive systems not only raise thresholds for nociception but also those for the induction of LTP.

D) PHARMACOLOGICAL INDUCTION OF LTP. At C-fiber synapses LTP can also be induced in the absence of any presynaptic activity. Spinal application of a dopamine 1/dopamine 5 receptor agonist (SKF 38393) in vivo induces a slowly developing LTP of C-fiber-evoked field potentials which lasts for at least 10 h and which is blocked by a dopamine 1/dopamine 5 antagonist (SCH 23390) (602). In spinalized, deeply anesthetized, adult rats, superfusions of spinal cord segments with NMDA, substance P, or neurokinin A are all sufficient to induce LTP of C-fiber evoked field potentials (297). With spinal cord and descending (inhibitory) pathways intact, spinal applications of NMDA, substance P, or neurokinin A fail, however, to induce LTP of C-fiber evoked field potentials (297). When applied spinally to rats, tumor necrosis fac-

tor-α may also potentiate synaptic strength in C-fibers (301). In vitro, bath application of serotonin (10–50 μM) may initially depress and after wash-out potentiate responses for more than 30 min of some neurons in laminae I-III of spinal dorsal horn slices evoked by stimulating near the dorsolateral margin of the spinal cord (184).

E) LTP OF A-FIBER EVOKED RESPONSES. A-fiber evoked spinal field potentials are depressed by conditioning 50-Hz stimulation of sciatic nerve fibers. After systemic application of the GABA$_A$ receptor antagonist bicuculline, the same conditioning stimulus now produces LTP rather than LTD (345). Similarly, 50-Hz conditioning stimulation produces short-lasting potentiation followed by LTD in control animals but LTP in animals with a chronic constriction injury of sciatic nerve (344). Topical application of muscimol, a GABA$_A$ receptor agonist, to spinal cord prevents tetanus-induced LTP of A-fiber evoked field potentials in animals with a chronic constriction injury (343). This again suggests that the polarity of synaptic plasticity is context sensitive and not solely dominated by the type of afferent input.

4. Signal transduction pathways of LTP at C-fiber synapses

In principle, LTP could be induced and/or expressed by presynaptic or by postsynaptic mechanisms or by any combination thereof (Fig. 3A). At present, there is clear evidence for a postsynaptic, Ca^{2+}-dependent form of LTP induction in spinal cord lamina I neurons (202, 204). Indirect evidence suggests that in addition excitability of presynaptic terminal of primary afferents may be enhanced after LTP-inducing stimuli (203) and that synaptosomal level of aspartate and glutamate, but not that of glycine or GABA, is elevated in rats with a chronic constriction injury of the sciatic nerve (492). These findings are compatible with a presynaptic contribution to synaptic plasticity in spinal dorsal horn.

Induction of LTP at C-fiber synapses requires coactivation of neurokinin 1 and neurokinin 2 receptors (300), opening of ionotropic glutamate receptors of the NMDA type (202, 204, 299), opening of T-type voltage-gated calcium channels (202, 204), and activation of group I but not group II or III metabotropic glutamate receptors (23). Activation of neurokinin 1 receptors by substance P may directly enhance single NMDA channel opening (292) and NMDA receptor-mediated currents in lamina I neurons (202), and all this may lead to a substantial rise in postsynaptic [Ca^{2+}]$_i$. It is presently unknown if Ca^{2+} influx through Ca^{2+}-permeable AMPA receptors is required for LTP induction in pain pathways. Some indirect evidence suggests, however, that this might be the case (172, 612).

In any case, a rise in postsynaptic [Ca^{2+}]$_i$ is essential for LTP induction, and the magnitude in [Ca^{2+}]$_i$ rise is linearly correlated with the magnitude of LTP in vitro (202). Recent data demonstrate that LTP-inducing stimuli cause substantial rise in [Ca^{2+}]$_i$ in lamina I neurons not only in slice preparations, but also in intact animals (204). Not surprisingly therefore, signal transduction involves Ca^{2+}-dependent pathways including activation of protein kinase C, calcium/calmodulin-dependent protein kinase II, protein kinase A, phospholipase C, inositol trisphosphate receptors, mitogen-activated protein kinase, nitric oxide synthase, and ephrin-EphB2 receptor tyrosine kinase signaling (202, 204, 493, 595, 601, 621).

When assessed with voltage-sensitive dyes, the presynaptic facilitation of electrical activity in primary afferents after LTP-inducing stimuli is partially sensitive to inducible nitric oxide synthase inhibitor (AMT), a blocker of glial cell metabolisms (monofluoroacetic acid, MFA), and a metabotropic glutamate receptor group I antagonist (LY367385) (203).

Inhibition of protein synthesis in spinal cord by either cycloheximide or anisomycin selectively inhibits the maintenance of the late phase of spinal LTP but does not affect either LTP induction or baseline responses of C-fiber evoked field potentials (190).

Potential targets of these signaling pathways are synaptic proteins, including glutamate receptors of the AMPA subtype. And, indeed, already 5 min after capsaicin injections that induce LTP (204), the AMPA receptor subunit GluR1 (at Ser-831 and Ser-845) in spinal dorsal horn becomes phosphorylated for at least 60 min (128) via activation of protein kinases A and C (127) and via calcium/calmodulin-dependent protein kinase II (126). Capsaicin injections also trigger the translocation of GluR1-containing AMPA receptors to the postsynaptic membrane of nonpeptidergic nociceptive primary afferent synapses (272). Phosphorylation of the GluR1 subunit is an essential step of LTP at glutamatergic synapses (44, 277).

Importantly, the very same signal transduction pathways are required for full expression of hyperalgesia in animal models of inflammatory and neuropathic pain (335, 407, 452, 578).

5. Prevention of LTP in pain pathways

LTP induction can be prevented by blockade of any of the above-mentioned essential elements of signal transduction for LTP. In mature rats, deep (surgical) level of anesthesia with either urethane, isoflurane, or sevoflurane is, however, insufficient to preempt LTP induction of C-fiber evoked field potentials (36). In contrast, the noble gas xenon, which has NMDA receptor blocking and anesthetic properties, also prevents induction of LTP at C-fiber synapses in intact rats (37). LTP can also be prevented by low-dose intravenous infusion of μ-opioid receptor agonist fentanyl (36). Similarly, LTP of spinal field potentials elicited by stimulation in the tract of Lissauer in spinal cord slices is blocked by

[D-Ala^2,*N*-MePhe^4,Gly-ol]-enkephalin (DAMGO), a more specific agonist at these receptors (514). Activation of spinal α_2-adrenoreceptors by clonidine (150) or spinal application of the benzodiazepine diazepam (191) also prevents LTP induction in vivo.

Functional blockade of glial cells by intrathecal administration of fluorocitrate changes the polarity of high-frequency stimulation induced synaptic plasticity. When high-frequency stimulation is given 1 h but not 3 h after fluorocitrate, LTD but no LTP of C-fiber evoked field potentials is induced (307).

6. Reversal of LTP in pain pathways

LTP of C-fiber evoked field potentials can be reversed by brief, high-frequency conditioning electrical stimulation of sciatic nerve fibers at Aδ-fiber intensity (298). Reversal of LTP by Aδ-fiber stimulation is time dependent and effective only when applied 15 or 60 min but not 3 h after LTP induction (616).

Spinal application of either neurokinin 1 or neurokinin 2 receptor antagonists 1–3 h after high-frequency stimulation, i.e., after LTP is established, does not affect maintenance of LTP (300), suggesting that activation of these receptors, which are required for the induction of LTP, are not essential for its maintenance.

7. Functional role of LTP in pain pathways

Modulation of synaptic strength is a powerful mechanism to control signal flow in selected pathways. A typical consequence of LTP at excitatory synapses would be an increase in action potential firing of the same and perhaps also of downstream neurons in response to a given stimulus. And indeed, LTP-inducing conditioning stimuli have been found to facilitate action potential firing of multireceptive neurons in deep dorsal horn (3, 174, 403, 445, 546). This is likely due to LTP at the first synapse in the nociceptive pathway, but other mechanisms of facilitation should not be excluded. Action potential firing would also be enhanced if membrane excitability is increased, i.e., the thresholds for action potential firing are lowered, and this has been shown for nociceptive neurons in deep spinal dorsal horn. Furthermore, discharges increase also if inhibition is less effective or if inhibition is even reversed and becomes excitatory, e.g., due to a reversal of the anion gradient in the postsynaptic neuron (88, 89).

High-frequency stimulation of sciatic nerve fibers which induces LTP at synapses of C-fibers in spinal cord has behavioral consequences in rats and causes thermal hyperalgesia at the ipsilateral hindpaw for 6 days (621). This suggests that LTP at C-fiber synapses has an impact on nociceptive behavior of laboratory animals and humans (see next paragraph).

8. Perceptual correlates of LTP in pain pathways in human subjects

An indispensable proof for any proposed mechanism of hyperalgesia is an appropriate correlate in humans. And, indeed, conditioning high-frequency stimulation of cutaneous peptidergic afferents in humans causes increased pain perception in response to electrical test stimuli applied through the same stimulation electrode (246). Noxious stimulation with punctate mechanical probes in skin adjacent to the high-frequency stimulation conditioning skin site uncovers a marked (2- to 3-fold) increase in pain sensitivity, i.e., secondary hyperalgesia (246). Touching the skin around the conditioning stimulation electrode with a soft cotton wisp evokes pain only after high-frequency stimulation. Thus high-frequency stimulation also induces secondary mechanical dynamic allodynia, possibly involving heterosynaptic mechanisms in humans (248). Hyperalgesia at the conditioned site but not secondary hyperalgesia at adjacent skin areas is prevented by pretreatment with ketamine (247), a clinically used substance which, among other effects, also blocks NMDA receptors.

Interestingly, all thermal modalities comprising cold and warm detection thresholds, cold and heat pain thresholds, as well as pain summation (perceptual wind-up) remain unaltered after conditioning high-frequency stimulation of peptidergic skin nerve fibers (268).

When verbal pain descriptors are used to evaluate pain in addition to its perceived intensity after high-frequency stimulation, a significant long-term increase in scores for sensory but not for affective descriptors of pain is detected (166). Within the sensory descriptors, those describing superficial pain, those for heat pain, and those for sharp mechanical pain are all potentiated. The authors conclude that brief painful stimuli rarely have a strong affective component and that perceived pain after high-frequency stimulation exhibits predominantly a potentiation of the C-fiber-mediated percept hot and burning (166).

In human subjects, conditioning low-frequency stimulation causes also an increased pain sensitivity in the area around the low-frequency stimulation conditioned skin site but a depression of pain evoked by stimulation through the same electrode (246).

LTP at synapses between primary afferent C-fibers and a group of nociceptive neurons in spinal cord lamina I which express the neurokinin 1 receptor for substance P is a potential mechanism underlying some forms of pain amplification in behaving animals and perhaps human subjects. Both LTP and hyperalgesia involve the same essential elements, i.e., primary afferent peptidergic C-fibers and lamina I neurons which express the neurokinin 1 receptor. Indirect evidence suggests that ongoing activity in primary afferent C-fibers is essential not only for evoked, but also for spontaneous neuropathic and inflam-

matory pain (110). Furthermore, induction protocols, pharmacological profile, and signal transduction pathways are virtually identical (453).

C. Intrinsic Plasticity

Active and passive membrane properties determine the input-output relationship of all neurons. Thus changes of electrical membrane properties constitute another powerful means to modulate signal transmission in neuronal networks. A single neuron may integrate the information from 10^4 synapses, and the resultant output is conveyed by action potentials that are typically generated at the axon hillock and nearby somatic membrane. Changes in membrane excitability of neurons will globally or locally modulate the throughput from synapses impinging on the dendrites and the soma of the postsynaptic neuron. In analogy of synaptic plasticity, long-lasting changes in membrane excitability are called "intrinsic plasticity," which adds to the computational power of neurons. Intrinsic plasticity may include but is not limited to postsynaptic changes in thresholds for action potential firing (Fig. 3B), changes in discharge patterns and accommodation of firing (Fig. 3C), and presynaptic changes in action potential shape (width and height). Intrinsic plasticity may be global or local, e.g., restricted to some dendrites, axonal branches, or presynaptic terminals. In striking contrast to the comprehensive literature on the modulation of membrane properties of primary afferent nerve fibers, little is known about intrinsic plasticity of nociceptive neurons in the central nervous system and their role for hyperalgesia and allodynia.

Spinal dorsal horn neurons may have quite distinct membrane and discharge properties when grouped by morphology (159, 289, 418), supraspinal projection (193, 441), lamina location of their cell bodies (442, 506), type of afferent input in vivo (572) and in vitro (304), transmitter content (116, 176, 217, 466), or developmental stage (181, 450). The ionic basis for some of the discharge and membrane properties of spinal dorsal horn neurons has been explored (337, 338, 441, 448, 449, 583).

1. Voltage-dependent sodium channels

Dissociated lumbar spinal dorsal horn neurons show the characteristic fast-activating and fast-inactivating sodium currents. Spinal cord contusion injury leads to a shift of the steady-state activation and inactivation of the sodium current towards more depolarized potentials. The increased persistent sodium current and ramp current is consistent with an upregulation of voltage-gated sodium channels of the $Na_v1.3$ subtype within dorsal horn neurons that has been observed after spinal cord contusion injury (Fig. 3C) (163, 265). Likewise, several days after a chronic constriction injury of the sciatic nerve, i.e., at a

time point when hyperalgesia is fully expressed, $Na_v1.3$ channels are upregulated in dorsal horn nociceptive neurons. Extracellular recordings reveal enhanced responsiveness of spinal dorsal horn neurons to natural sensory stimuli (164). In another study, chronic constriction injury did not affect resting membrane potential, rheobase, or input resistance of neurons recorded in superficial spinal dorsal horn in slices (28). Neurons in spinal cord laminae III–VI, i.e., in deep dorsal horn, express, however, intrinsic plasticity. In these neurons, associative spike pairing stimulation induces a long-lasting increase in membrane excitability as assessed by lowering the threshold for action potential firing and an increase in the number of action potential firing in response to current injection or synaptic stimulation. Enhanced excitability depends on activation of NMDA receptors and a rise in postsynaptic $[Ca^{2+}]_i$ (238).

2. Voltage-dependent potassium currents

Activation of either protein kinase A or protein kinase C reduces transient outward (A-type) potassium currents (188) and strongly enhances membrane excitability of dorsal horn neurons in cultured neurons from superficial spinal dorsal horn of mice (Fig. 3C), possibly via activation of extracellular signal-regulated kinase (187). Membrane excitability of spinal dorsal horn neurons is dampened by activation of $K_v4.2$ channels. The activation of the extracellular signal-regulated kinase pathways leads to hyperexcitability of spinal dorsal horn neurons in normal mice but not in $K_v4.2$ knock-out mice. These knock-out mice also show reduced hyperalgesia in the second phase of the Formalin test and after carrageenan injections into a paw (186).

3. Plateau potentials

Plateau potentials are intrinsic mechanisms for input-output amplification. The resulting intense firing and prolonged afterdischarges in response to nociceptive stimulation of neurons in layer V in a spinal cord slice preparation depend on nonlinear intrinsic membrane properties (365). Plateau potentials are rarely found under control conditions in spinal dorsal horn neurons in vitro (<10% of lamina V neurons) (105) or in vivo [4/33 neurons (215)]. Pharmacological activation of group I metabotropic glutamate receptors (by 1S,3R-ACPD) converts tonic firing neurons into plateau firing neurons (46% of lamina V neurons) (Fig. 3C). In contrast, activation of $GABA_B$ receptors inhibits plateau responses (444) and converts plateau firing back to tonic firing (105). The antagonistic actions of group I metabotropic glutamate receptors versus $GABA_B$ receptors is mediated by inwardly rectifying potassium channels (Kir3) (105). Simultaneous activation of metabotropic glutamate receptors and blockade of $GABA_B$ receptors induces rhythmic fir-

Role of inhibition	Mechanism of action	Desired effect	Pain type upon failure
Attenuation	Pre- and postsynaptic inhibition of nociceptive spinal dorsal horn neurons	Proper response level to noxious stimulation	Hyperalgesia
Muting	Inhibition of nociceptive dorsal horn neurons and interneurons driving those	Silencing nociceptive neurons in the absence of noxious stimuli	Spontaneous pain
Separating	Inhibition of excitatory interneurons linking Aß-fibre input to nociceptive specific neurons	Inhibition of excitatory crosstalk between sensory modalities	Allodynia
Limiting	Inhibition of excitatory interneurons which cross somatotopic borders	Limiting spread of excitation to somatotopically appropriate areas	Radiating pain, referred pain, mirror-image pain

FIG. 4. The four principal functions of inhibition in the nociceptive system: attenuation of the responses of nociceptive neurons to maintain the proper response levels during nociception; muting nociceptive neurons in the absence of noxious stimuli, thereby preventing spontaneous pain; separating labeled lines for nociceptive and nonnociceptive information to prevent cross-talk between sensory modalities; and limiting the spread of excitation to somatotopically adequate areas of the central nervous system. The proposed underlying mechanism to achieve the desired effect and the type of pain to be expected if the inhibition becomes insufficient are shown.

ing. Switching the discharge mode from tonic to plateau potentials amplifies and improves faithful transmission, whereas rhythmic bursting results in poor transmission capabilities (105). In addition to a role of $GABA_B$ receptors, $GABA_A$ receptors also inhibit plateau potentials, as bicuculline (50 μM) may facilitate plateau responses (444). Inhibition of plateau properties is also observed in the presence of tetrodotoxin, suggesting a direct action on the neuron under study.

Induction of a unilateral peripheral inflammation with complete Freund's adjuvant leads to hyperalgesia, but the principal passive and active membrane properties and the firing patterns of ipsilateral spinal lamina I neurons are not different in transverse spinal cord slices taken from control rats or rats with an inflammation at a hindpaw (370).

Chronic constriction injury of one sciatic nerve leads to tactile and thermal hyperalgesia in transgenic mice which express the enhanced green fluorescent protein (EGFP) under the promoter of glutamate decarboxylase 67 to label GABAergic neurons. In transverse slices from lumbar spinal cord, membrane excitability of lamina II GABAergic neurons from neuropathic or sham-treated animals is indistinguishable, suggesting that intrinsic plasticity of these neurons is not an essential mechanism of neuropathic pain (467).

D. Changes of Inhibitory Control

Spinal nociceptive neurons are under permanent and powerful inhibitory control, which is indispensable for orderly processing of sensory information in spinal dorsal horn and for a normal perception of pain. Inhibitory systems in spinal dorsal horn serve four principle functions to maintain proper nociception [see Fig. 4 and a recent review for details (454)]: 1) attenuation of the responses of nociceptive neurons to maintain the proper response levels during nociception; 2) muting nociceptive neurons in the absence of noxious stimuli, thereby preventing spontaneous pain; 3) separating labeled lines for nociceptive and nonnociceptive information to prevent cross-talk between sensory modalities; and 4) limiting the spread of excitation to somatotopically adequate areas of the central nervous system.

The major fast inhibitory neurotransmitters in spinal dorsal horn are GABA and glycine acting on ionotropic, Cl^--permeable $GABA_A$ or glycine receptors or metabotropic (G protein-coupled) $GABA_B$ receptors. GABA and glycine are coreleased at some inhibitory synapses in spinal cord (221) including laminae I–II, at least in immature rats (235). Junctional codetection by glycine and $GABA_A$ receptors ceases, however, by adulthood, leaving pure glycinergic postsynaptic responses in lamina I and either glycinergic or GABAergic responses at equal proportions in lamina II (235). Another cotransmitter at GABAergic synapses is ATP. ATP is coreleased in a subset of GABAergic but not glutamatergic neurons and evokes excitatory synaptic currents in cultured spinal cord lamina I–III neurons (218). Ongoing release of ATP and hydrolysis to adenosine depresses GABA-mediated inhibitory postsynaptic currents through action on adenosine receptors (218).

1. GABAergic systems

A) MODULATION OF THE SPINAL GABAERGIC SYSTEMS. The spinal GABAergic systems can be modulated by neuropathies, inflammation, pharmacological means, and hormones. GABA-mediated neurotransmission may be altered by changes in release probability, number of release sites, and diffusion. The speed by which GABA is removed from the synaptic cleft may also change. Furthermore, the number, the location, and the subunit composition of synaptic GABA receptors may be modulated, e.g., by phosphorylation as reviewed (Fig. 3D) (69). Changes in the anion gradient of postsynaptic neurons may convert GABA-induced hyperpolarization into depolarization (see sect. VID1CIB).

I) Modulation by neuropathies. A) Peripheral and spinal nerve injuries. Chronic constriction injury of the sciatic nerve induces complex changes in the GABAergic system, but apparently neither the number of GABAergic neurons in spinal dorsal horn nor their electrophysiological properties change. In fact, in rats which develop thermal hyperalgesia following chronic constriction injury of sciatic nerve, the number of neurons in laminae I–III with GABA or glycine immunoreactivity is not different from controls, as evaluated with unbiased stereological methods 14 days after nerve injury (413). Likewise, in rats with a spared nerve injury, the levels of GABA, the vesicular GABA transporter, or the $\beta3$-subunit of the $GABA_A$ receptor at synapses in the medial part of the superficial dorsal horn are not different from controls (414). In mice that express EGFP under the glutamate decarboxylase 67 promoter, the active and passive membrane properties of identified spinal GABAergic neurons can be assessed quantitatively. In mice with a chronic constriction injury of the sciatic nerve and severe mechanical and thermal hyperalgesia action potential thresholds and widths, membrane resting potential and membrane input resistance as well as firing patterns are all unchanged compared with sham-treated animals. This suggests that changes in membrane excitability or discharge patterns of GABAergic neurons in spinal cord lamina II are unlikely causes for pain in the chronic constriction injury model (467).

Other important features of the GABAergic system do, however, change under the conditions of neuropathy. GABA-like immunoreactivity of neuronal profiles is severely reduced mainly in ipsilateral laminae I–II but also on the contralateral side already 3 days after chronic constriction injury of the sciatic nerve (201). At 3 wk following chronic constriction injury, GABA immunoreactivity is almost absent bilaterally. Some recovery begins at 5 wk and is almost complete on the contralateral but not ipsilateral side at 7 wk (201). The number of GABA immunoreactive neurons is reduced 7 days after a partial injury of the tibial nerve, not only in the termination area of the tibial but also of the peroneal nerve ipsi- and contralateral to the lesion site (278). The reduced immunoreactivity is likely due to diminished GABA synthesis, as the number of GABAergic neurons remains stable and GABAergic neurons do not express caspase-3, an indicator of apoptotic cell death (278). Indeed, glutamate decarboxylase 65 but not glutamate decarboxylase 67 protein levels decrease 6 days up to 4 wk after chronic constriction injury and for even longer in the spared nerve injury model (362). After unilateral transection of a sciatic nerve, the number of neurons in spinal dorsal horn with a detectable immunoreactivity for GABA and the GABA content in spinal homogenates decreases 2–4 wk after neurectomy (59). In contrast, spinal content of GABA is enhanced bilaterally 1–30 days after a unilateral chronic constriction injury of sciatic nerve in the rat (463). The reasons for these discrepant results are presently unknown. Daily pretreatment with intrathecal MK-801 to block spinal NMDA receptors abolishes increases in GABA and glycine levels in spinal cord ipsilateral to the chronic constriction injury of sciatic nerve and prevents development of hyperalgesia (463).

In animals with a unilateral chronic constriction injury of the sciatic nerve, spinal levels of GABA transporter GAT-1 are reduced bilaterally to ~40% 7 days after the ligature compared with controls (343, 478). This should lead to a reduction of GABA in the terminals in the spinal dorsal horn. This is in line with the observation that in spinal cord slices taken from rats with spinal nerve ligation potassium-induced release of GABA is reduced compared with sham-operated controls (281). In contrast, GAT-1 downregulation does not lead to detectable changes in synaptosomal contents of GABA which are unchanged in spinal cord 12 days after unilateral chronic constriction injury of the sciatic nerve (492). A recent study found on the other hand an upregulation of GAT-1 in spinal dorsal horn of rats with a chronic constriction injury of the sciatic nerve (95). In this study, pharmacological blockage of GAT-1 reduced tactile and thermal hyperalgesia.

In any way, postsynaptic GABAergic inhibition seems to be impaired in spinal dorsal horn of neuropathic rats. But the animal model used may be of importance. The proportion of neurons in superficial spinal dorsal horn in vitro that express primary afferent-evoked inhibitory postsynaptic currents is diminished in animals with chronic constriction injury and spared nerve injury but not in animals with a sciatic nerve transection (362). Likewise, amplitudes and durations of inhibitory postsynaptic currents are reduced after chronic constriction injury and spared nerve injury but not after sciatic nerve transection (362). After spared nerve injury but not after sciatic nerve transection inhibitory postsynaptic current kinetics are changed, then resembling mostly glycinergic but not GABAergic currents, suggesting a preferential loss

of GABAergic inhibition (362). Similarly frequency but not amplitude of GABAergic but not glycinergic miniature inhibitory postsynaptic currents is reduced after chronic constriction injury or spared nerve injury, which is also consistent with diminished GABAergic release (Fig. 3F) (362).

Unilateral chronic constriction injury of the sciatic nerve also has effects at the receptor level on primary afferent nerve fibers. The number of GABA$_A$-receptor γ2 subunit mRNA-positive medium to large size neurons in ipsilateral L4/L5 dorsal root ganglion neurons is reduced after chronic constriction injury (389). This 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 normal dorsal roots is significantly reduced following sciatic axotomy, dorsal root axotomy, or crush injury. In contrast, chronic sciatic crush injury has no effect on the GABA sensitivity of dorsal root terminals (243).

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. In contrast, GABA$_A$ binding is enhanced following nerve transection (58).

There is, however, also evidence suggesting that spinal GABAergic inhibition may be enhanced under some conditions of neuropathy. Potency of GABA$_A$ receptor blocker bicuculline to enhance Aδ- and C-fiber evoked responses of spinal dorsal horn neurons is higher in rats with a spinal nerve ligation (254). Furthermore, in rats with a chronic constriction injury of the sciatic nerve, activation of GABA$_A$ receptors may lead to a depolarization of postsynaptic neurons rather than to an inhibition as discussed in section vi$D1$cIB.

B) Spinal cord trauma and ischemia. The number of GABA immunoreactive cells in lumbar spinal dorsal horn of rats with a transient spinal cord ischemia and mechanical hyperalgesia is reduced bilaterally at 2–3 days but not at 14 days after injury (615). This suggests a reversible reduction of GABA content rather than a loss of GABAergic neurons. And, indeed, after a spinal cord hemisection at the lower thoracic level, the GABA-synthesizing enzyme GAD67 is reduced bilaterally in laminae I and II of the lumbar spinal dorsal horn (162). This possibly translates into reduced GABAergic function as responses of multireceptive neurons 1–2 segments caudal to the lesion are less strongly inhibited by GABA (117).

Seven days following contusion injury of the thoracic spinal cord and development of mechanical hyperalgesia (von Frey thresholds), impaired GABAergic inhibition may affect various sensory modalities differentially. Iontophoretic application of bicuculline in normal animals results in reversible increases in mechanoreceptive field sizes, spontaneous firing rates, and responses to brushing and pinching the skin. In allodynic rats, bicuculline application also enlarges receptive field sizes but has little or no effect on responses to brushing or pinching the skin (117). This suggests that tonic GABAergic inhibition of dynamic mechanical and noxious mechanical input may be reduced in these neurons.

Finally, after spinal cord injury, the network effects of GABA$_A$ receptor activation may switch from inhibition to facilitation. In rats with a thoracic spinal cord injury but not in normal rats, blockade of GABA$_A$ receptors by iontophoretic application of bicuculline reduces rather than enhances afterdischarges of deep dorsal horn multireceptive neurons to noxious skin pinching (but not to brushing) (117). This suggests that tonic activation of GABA$_A$ receptors directly or indirectly facilitates afterdischarges in hyperalgesic rats. In section vi$D1$c synaptic mechanisms are described by which GABAergic inhibition may turn into excitation.

II) Modulation by inflammation. The spinal GABAergic system may also be modulated by peripheral inflammation. For example, GABA$_B$ receptor subtypes 1 and 2 (GABA$_{B1/2}$) mRNA levels are increased bilaterally in the dorsal horn of the spinal cord 24 h after Formalin injection into a hindpaw (329). This upregulation does, however, not translate into an increased GABA$_B$ receptor function, at least when determined by its activation of G proteins (457). GABA$_{B1}$ but not GABA$_{B2}$ receptors also increase in dorsal root ganglion ipsilaterally but not contralaterally to the injection site (329).

Inflammation may further result in rapid regulation of GABA transporters, as GABA uptake is increased in synaptosomes from mouse spinal cord as soon as 20 and 120 min after subcutaneous injection of Formalin into a hindpaw (189).

Interestingly, the overall modulatory effect of spinal GABA$_A$ receptors on behavioral nociceptive thresholds may be reversed during an inflammation induced by complete Freund's adjuvant in rats. In normal rats, intrathecal application of GABA$_A$ receptor agonist muscimol increases and GABA$_A$ receptor antagonist gabazine lowers nociceptive thresholds. In rats with an inflammation, the effects are inverted (19).

III) Pharmacological modulation of the spinal GABAergic system. The activity of spinal GABAergic neurons, the synthesis, and the release of GABA and the properties and functions of GABA receptors can all be modulated pharmacologically.

Single dose but not repeated systemic administration of morphine at analgesic doses enhances GABA content and glutamate decarboxylase activity in rat spinal dorsal horn (259). However, an acute application of selective μ-opioid receptor agonist DAMGO selectively depresses GABAergic and glycinergic inhibitory postsynaptic currents in lamina II neurons in vitro, probably via a presynaptic mechanism (363). Sustained opioid exposure may lead to apoptotic death of neurons in spinal cord, many of

which express glutamic acid decarboxylase for the synthesis of GABA (323).

Indirect evidence suggests that norepinephrine and phenylephrine may excite GABAergic neurons as they enhance the frequency of action potential-dependent spontaneous GABAergic inhibitory postsynaptic currents in dorsal horn neurons (25). There is also direct evidence of an excitatory action of norepinephrine acting on α_1-adrenoreceptors on GABAergic neurons. In perforated whole cell patch-clamp recordings from lamina II neurons, bath application of norepinephrine directly depolarizes GABAergic neurons identified by the expression of EGFP in transgenic mice. This action of norepinephrine is partially selective for GABAergic neurons as 42% of those but only 5% of the unidentified neurons are depolarized (M. Gassner and J. Sandkühler, unpublished observations).

Release of GABA is enhanced by activation of spinal muscarinic receptors, as determined by enhanced frequencies of spontaneous GABAergic inhibitory postsynaptic currents recorded from lamina II neurons in spinal cord slices (26). Similarly, frequency of $GABA_A$ receptor-mediated miniature inhibitory postsynaptic currents in lamina II neurons increases after acetylcholine application. This effect is blocked by atropine (286). Norepinephrine (and α_1-adrenoreceptor agonist phenylephrine) enhances frequency of GABAergic miniature inhibitory postsynaptic currents with a twofold greater efficacy than glycinergic miniature inhibitory postsynaptic currents. Postsynaptic responses to GABA or glycine are not affected, nor are frequencies of miniature excitatory postsynaptic currents changed by norepinephrine (27). α_2-Adrenoreceptor agonist clonidine and β-adrenoreceptor agonist isoproterenol are without effect (27). Potassium-stimulated release of GABA is facilitated by brain-derived neurotrophic factor in an adult rat isolated dorsal horn preparation (408) by a yet unknown mechanism. In adult pentobarbital anesthetized rats, spinal release of GABA as detected by microdialysis is enhanced by up to 80% by intrathecal application of selective 5-HT$_3$ receptor agonist 1-phenylbiguanide (230).

The release of GABA can be blocked by various substances. Nocistatin selectively blocks neurotransmitter release equally from inhibitory GABAergic or glycinergic spinal dorsal horn interneurons by 50% via a pertussis toxin-sensitive mechanism (614). Glutamatergic transmission is, in contrast, not affected. Bath application of adenosine reduces amplitudes of evoked GABAergic and glycinergic inhibitory postsynaptic currents of rat spinal lamina II neurons and diminishes frequency but not amplitudes of spontaneous inhibitory postsynaptic currents in vitro (603), suggesting presynaptic suppression of inhibitory transmission. The A1 receptor antagonist 8-cyclopentyl-1,3-dimethylxanthine (CPT) reverses this inhibition.

Once GABA is released, its effects can still be modulated at the receptor level. For example, protein kinase C phosphorylation of the β1-, γ_2S-, and γ_2L-subunits of the $GABA_A$ receptor attenuates GABA-induced currents (256). This protein kinase C-dependent modulation may play a role for afferent-induced facilitation of spinal nociception. In the monkey, iontophoretic application of GABA or muscimol near the recording site of multireceptive lumbar spinal dorsal horn neurons reduces responses to pinching the skin. Pharmacological activation of protein kinase C reduces this inhibition by GABA or muscimol. The inhibition by GABA is almost absent when these agonists are applied 15 min after intradermal injection of capsaicin (which activates protein kinase C in spinal neurons). Inhibition returns to normal ~1.5 h after capsaicin injection (293). The inhibition by muscimol is not consistently affected (293). Proinflammatory cytokines may be involved as bath application of either interleukin-1 or interleukin-2 inhibits the frequency of spontaneous inhibitory postsynaptic currents in lamina II neurons (232). The subunit composition of the $GABA_A$ receptor can be modulated within days, e.g., in oxytocin neurons during pregnancy and lactation. Predominance of the α_1-subunit reveals fast channel gating kinetics while predominance of α_2-subunits slows kinetics (48).

In rats with a L5 spinal nerve ligation, mechanical and thermal hyperalgesia is reduced by intrathecal brain-derived neurotrophic factor (281). Bath application of brain-derived neurotrophic factor restores impaired GABA release in spinal cord slices of these rats (281).

B) MODULATION OF HYPERALGESIA AND ALLODYNIA BY THE SPINAL GABAERGIC SYSTEM. *I) Facilitation of hyperalgesia and allodynia by GABA receptor blocker*. Blockade of spinal $GABA_A$ receptors by intrathecal application of bicuculline at doses that do not produce hyperalgesia also do not affect phase 1 of Formalin response. In contrast, the number of flinches and scored pain behavior is enhanced in the interphase period and in phase 2 when bicuculline is given either before or 7 min after Formalin injections (226). Thus expression of the second phase of the Formalin test may be tonically attenuated by spinal GABAergic inhibition. Pretreatment with intrathecal $GABA_A$ receptor agonists isoguvacine or muscimol decreases flinches in both phases of the Formalin test (226).

II) Reversal of hyperalgesia and allodynia by GABA receptor agonists. A number of independent studies show that spinal GABAergic inhibition is impaired in neuropathic animals and that spinal application of $GABA_A$ or $GABA_B$ receptor agonists may reverse neuropathic symptoms. Hyperalgesia induced by spared nerve injury is reversed by subcutaneous injections of $GABA_A$ receptor agonists gaboxadol or muscimol but not isoguvacine (436). In rats, subcutaneous or intrathecal applications of $GABA_B$ receptor agonists (L-baclofen or CGP35024) reverse mechanical hyperalgesia induced by partial sciatic

nerve ligation but not by intraplantar injection of complete Freund's adjuvant (402), suggesting that neuropathic but not inflammatory mechanical hyperalgesia is sensitive to GABA$_B$ receptor blockade.

In rats, ligation of spinal nerves L5 and L6 results in tactile hyperalgesia and reduced withdrawal latencies to noxious skin heating. Intrathecal GABA$_A$ receptor agonist isoguvacine reverses tactile hyperalgesia up to 75% of the maximal possible effect. This action of isoguvacine is completely blocked by intrathecal bicuculline or phaclofen (312). Thermal hyperalgesia is also reversed by intrathecal isoguvacine, while intrathecal GABA$_B$ receptor agonist baclofen disturbs motor behavior (312).

Intrathecal application of a single dose of either GABA$_A$ receptor agonist muscimol or GABA$_B$ receptor agonist baclofen reverses tactile hyperalgesia in rats with spinal nerve ligation for 2–5 h. Intrathecal injections of antagonists at GABA$_A$ receptors (bicuculline) or GABA$_B$ receptors (CGP 35348) at doses that fully block the actions of the respective agonists do not change tactile hyperalgesia (200). This indicates absence of tonic GABAergic inhibition in hyperalgesic rats. When neuronal cells bioengineered to synthesize GABA are transplanted in the lumbar subarachnoid space of rats with a chronic constriction injury of the sciatic nerve, both tactile and thermal hyperalgesia are reversed when transplants are placed either 1 or 2 wk after partial nerve injury. Later graft placements are ineffective (500). One study suggests that even a single dose of GABA may have profound and lasting effects on neuropathic pain. In the rat, chronic constriction injury model tactile and thermal hyperalgesia are permanently reversed by a single dose of GABA given intrathecally 1 or 2 wk but not 3–4 wk after nerve ligation. (120). Specifically targeting spinal GABA$_A$ receptors containing the α_2- and/or α_3-subunits reveals antinociception with minor motor effects (250). Likely, the beneficial effects of GABA receptor agonists in animal models of neuropathic pain translate into the clinic. In five human patients with neuropathic, including phantom limb pain, continuous intrathecal baclofen improved pain scores throughout the observation periods of 6 to 20 mo (632).

III) Paradoxical excitation of nociceptive neurons by GABA. Activation of GABA$_A$ receptors opens a Cl$^-$ ion channel. The direction of Cl$^-$ flux is generally determined by 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 the V_{rest}. In neurons, potassium-chloride cotransporters and sodium-potassium-chloride cotransporters are the two classes of cation-chloride transporters that regulate Cl$^-$ transport. Normally the potassium-chloride cotransporter reduces the concentration of K$^+$ and Cl$^-$ while the sodium-potassium-chloride cotransporters increase intracellular Na$^+$, K$^+$, and Cl$^-$ within neurons (see Ref. 421 for a review). The continuous removal of Cl$^-$ from the cells via a potassium-chloride cotransporter keeps E_{Cl} more negative than the V_{rest}. Thus increasing the Cl$^-$ conductance by activation of GABA$_A$ receptors will lead to a Cl$^-$ influx and hyperpolarization. GABAergic depolarization and eventually excitation can be seen under conditions where E_{Cl} is less negative than the resting membrane potential. This may occur when the potassium-chloride cotransporter becomes insufficient. This results in a Cl$^-$ efflux and membrane depolarization rather than an influx into the cell upon activation of GABA$_A$ receptors. During development and minutes to weeks after trauma of cultured hypothalamic or cortical neurons, GABA may have a depolarizing effect (536). Thus the level of the chloride concentration gradient across the GABA$_A$ receptor expressing postsynaptic cell membrane determines if GABA is hyper- or depolarizing (89).

These general biophysical principles, of course, also apply to the membrane of primary afferent nerve terminals. Here, E_{Cl} is, however, normally less negative than the resting membrane potential, also in mature animals. This is due to the activity of sodium-potassium-chloride cotransporters and regularly results in a Cl$^-$ efflux and membrane depolarization. Thus, under normal conditions, activation of GABA$_A$ receptors leads to a depolarization of the terminals of primary afferent nerve fibers. This primary afferent depolarization is not strong enough to cause action potential firing (i.e., an excitation) under normal conditions. Primary afferent depolarization rather inactivates voltage-gated ion channels that are required for the release of neurotransmitter(s) from the terminals. Therefore, moderate depolarization of terminals by GABA may cause presynaptic inhibition.

A) GABAergic excitation of primary afferent nerve terminals. Cervero and co-workers (63, 64) propose a mechanism of dynamic mechanical allodynia that is triggered by low-threshold mechanosensitive Aβ-fiber afferents. If the GABAergic presynaptic depolarization is much enhanced under the conditions of an inflammation or a neuropathy, then the threshold for activation of voltage-gated sodium channels might be passed and action potential discharges will be elicited in these terminals (Fig. 3*G*). These action potentials may trigger the release of excitatory neurotransmitter. Some of the GABAergic interneurons that impinge on nociceptive nerve terminals can be excited by Aβ-fibers. Therefore, nociceptive specific dorsal horn neurons could be indirectly excited by activity in Aβ-fibers (63, 64, 577). Following an inflammation, the upregulation of the sodium-potassium-chloride (Na$^+$, K$^+$, 2Cl$^-$ type I) cotransporter in primary afferents leads to an excessive depolarization of primary afferent terminals by GABA and cross-excitation between low- and high-threshold primary afferents (421). This finding is in line with the above hypothesis (see, however, Ref. 559).

B) GABAergic excitation of spinal lamina I dorsal horn neurons. In rats with a chronic constriction injury of

the sciatic nerve and dynamic mechanical allodynia, expression of a potassium-chloride exporter (K^+-Cl^- cotransporter-2) in spinal dorsal horn is reduced to about half of the control levels (89). In streptozotocin-induced diabetic rats, neuropathy is also accompanied by a reduced immunoreactivity for K^+-Cl^- cotransporter-2 in laminae I and II (364). This may cause a shift of E_{Cl} from normally −75 to −50 mV. Under these conditions, $GABA_A$-receptor activation results in a Cl^- efflux and membrane depolarization rather than a Cl^- influx into the cell (Fig. 3E). In some neurons, the resulting depolarization may be sufficient to evoke action potential firing. Furthermore, spinal cord lesions may lead to downregulation of Na^+-K^+-Cl^- cotransporter-1 and K^+-Cl^- cotransporter-2 in the lesion epicenter (93), and in rats, thoracic spinal cord injuries lead to downregulation of the K^+-Cl^- cotransporter-2 in the lumbar spinal dorsal horn and to reduced GABAergic inhibition (305). Downregulation of K^+-Cl^- cotransporter-2 in spinal cord and attenuation of GABAergic inhibition or its conversion into excitation may contribute to dynamic mechanical allodynia and to mechanical and thermal hyperalgesia in rats with a diabetic neuropathy (220). Pharmacological blockade of the potassium-chloride exporter in spinal cord slices of naive rats also converts inhibitory action of GABA into an excitation in ~30% of the lamina I neurons, suggesting that a shift in anion reversal potential can be caused by reduced activity of the potassium-chloride exporter. In intact rats, this leads to mechanical and thermal hyperalgesia (89). Taken together, these results suggest a novel mechanism of GABA receptor-mediated hyperalgesia in neuropathic animals through inversion in polarity of $GABA_A$ receptor-mediated action on nociceptive spinal dorsal horn lamina I neurons from inhibition to excitation (89, 421).

Spinal microglia appear to be involved in this process. Stimulation of microglia with ATP causes release of brain-derived neurotrophic factor from activated microglia. Brain-derived neurotrophic factor binding to its TrkB receptor on lamina I neurons is essential for changing the anion gradient and conversion of GABAergic inhibition into excitation (88). A similar brain-derived neurotrophic factor-dependent downregulation of the K^+-Cl^- cotransporter-2 was observed in spinal dorsal horn of rats with a peripheral inflammation (complete Freund's adjuvant) (620).

2. Glycinergic systems

In addition to spinal GABAergic inhibition, spinal glycinergic interneurons also modulate neuronal activity in spinal dorsal horn. Some changes in the glycinergic system have been observed under conditions of experimental hyperalgesia (see Fig. 3, D and F). Glycine may bind to the Cl^--permeable glycine receptor, a member of the nicotinic acetylcholine receptor family of ligand-gated ion channels. Taurine is another agonist at this receptor with perhaps even higher efficacy than glycine in neurons of spinal cord lamina II (592). At glycinergic synapses in superficial spinal dorsal horn, release of glycine may be inhibited by presynaptic $GABA_B$ receptors (70).

A) MODULATION OF SPINAL GLYCINERGIC SYSTEMS. The spinal content of glycine, like that of GABA, is enhanced bilaterally 1–30 days after a unilateral chronic constriction injury of sciatic nerve in rats (463). The number of neurons in lamina I, lamina II, or lamina III with glycine immunoreactivity is, however, not different from controls, as evaluated with unbiased stereological methods 14 days after chronic constriction injury of sciatic nerve (413). It is not known at present if the electrophysiological properties of glycinergic neurons change under conditions of neuropathy or inflammation. The number and function of glycine receptors do, however, change. For example, a unilateral sciatic nerve constriction leads to a bilateral reduction in the number of glycine receptors in rat spinal dorsal horn (488). Furthermore, protein kinase C phosphorylation of the α- and β-subunits of the glycine receptor attenuates glycine-induced currents (535). Iontophoretic application of glycine near the recording site of multireceptive lumbar spinal dorsal horn neurons in monkeys reduces responses to pinching the skin. Activation of protein kinase C (by phorbol 12-myristate 13-acetate) reduces this inhibition by glycine. The inhibition by glycine (or GABA) is almost absent when the agonist is applied 15 min after intradermal injection of capsaicin (which activates protein kinase C in spinal neurons). Inhibition returns to normal ~1.5 h after capsaicin injection (293).

The Cl^- conductance of glycine receptor channels strongly increases via activation of G_s but not G_o or G_i proteins when cAMP or protein kinase A is included into the pipette solution (494). cAMP enhances channel open probability but not mean channel open times or channel conductance, nor binding affinity of glycine to its receptor (494). The authors suggest that the monoamines 5-HT acting on 5-HT_1 receptors and norepinephrine acting on α_2-adrenergic receptors could change cAMP levels in target cells and thereby the cellular responses to glycine through protein phosphorylation. In a spinal cord slice preparation from young rats, glycine receptor-mediated currents are enhanced by 5-HT in superficial spinal dorsal horn neurons (288) via activation of 5-HT_2 receptors. Inhibition of protein kinase C but not inhibition of cAMP-dependent protein kinase A blocks this 5-HT-mediated potentiation of glycinergic currents. A membrane-permeable diacylglycerol analog, like 5-HT, enhances glycine receptor-mediated currents. Thus 5-HT likely activates protein kinase C and potentiates glycinergic currents via a diacylglycerol-dependent pathway (288).

Prostaglandin E_2 is released in spinal dorsal horn during peripheral inflammation and may depress spinal

glycinergic inhibition via the α_2 subtype (173). The inhibitory (strychnine-sensitive) glycine receptor is a specific target of prostaglandin E_2. In fact, prostaglandin E_2, but not prostaglandin $F_{2\alpha}$, prostaglandin D_2, or prostaglandin I_2, reduces inhibitory glycinergic synaptic transmission in spinal dorsal horn in low nanomolar concentrations, whereas $GABA_A$, AMPA, and NMDA receptor-mediated transmissions remain unaffected (5).

ATP acting on P2X receptors enhances the frequency of glycinergic miniature inhibitory postsynaptic currents in dissociated trigeminal neurons. Substance P alone is without effect. The combination of ATP and substance P does, however, reduce ATP-induced facilitation by a presynaptic interaction (558), suggesting that substance P may indirectly diminish glycinergic inhibition. Consistently, in lamina I neurons recorded in rats with an inflamed hindpaw (complete Freund's adjuvant, which releases substance P in superficial spinal dorsal horn), the number of glycinergic miniature inhibitory postsynaptic currents is strongly reduced (370).

B) MODULATION OF HYPERALGESIA AND ALLODYNIA BY THE SPINAL GLYCINERGIC SYSTEM. After a unilateral chronic constriction injury of the sciatic nerve, the potency of glycine receptor antagonist strychnine increases. Intrathecal doses of strychnine that are subthreshold in control animals do, however, lower thermal threshold for withdrawal reflexes ipsi- but not contralateral to the nerve injury (463). Daily pretreatment with intrathecal MK-801 to block spinal NMDA receptors abolishes increases in glycine potency and prevents development of hyperalgesia (463). Furthermore, tactile hyperalgesia in the partial sciatic nerve ligation model is attenuated when the reuptake of glycine either by neuronal glycine transporter 2 or glial glycine transporter 1 is impaired. This was shown by intrathecal injections of inhibitors or knockdown of spinal glycine transporters by siRNA that reduce mechanical hyperalgesia in mice (368).

E. Changes in Descending Modulation

In recent years, considerable evidence has accumulated showing that spinal nociception may be facilitated by descending pathways (347, 417, 505, 532, 561). Inflammation not only causes hyperalgesia in the area immediately surrounding the primary injury (i.e., secondary hyperalgesia) but may also cause more generalized hyperalgesia at areas well apart from the lesion site. For example, inflammation at a hindpaw facilitates nociceptive withdrawal reflexes at the tail (54). Similarly, Formalin injected into the tail enhances responses of lumbar spinal dorsal horn neurons to noxious heating of a hindpaw (41). Both secondary hyperalgesia and the remote sensitization require a spino-bulbo-spinal loop with a descending facilitatory arm (Fig. 3H).

A number of behavioral studies show that neurons in the rostroventral medulla are required for full expression of hyperalgesia in different animal models of inflammation and neuropathy. Secondary hyperalgesia caused in rats by mustard oil involves activation of glutamate receptors of the NMDA type and subsequent activation of nitric oxide synthase in the rostroventral medulla (530). Secondary thermal hyperalgesia induced either by intra-articular carrageenan/kaolin injection into the knee or by topical mustard oil application to the hindleg is completely blocked by bilateral rostral medial medulla lesions produced by the soma-selective neurotoxin ibotenic acid (534). Bilateral destructions of cells in the nucleus reticularis gigantocellularis with ibotenic acid lead to an attenuation of hyperalgesia and a reduction of inflammation-induced spinal c-Fos expression (569). Likewise, mechanical hyperalgesia induced by spinal nerve ligation in rats is reversed by local anesthetic block in the rostroventral medulla (406). Spinal nerve ligation induces tactile and thermal hyperalgesia; both are blocked by bilateral injections of lidocaine (51) or a cholecystokinin type B receptor antagonist (L 365,260) into the rostroventral medulla (255).

Descending facilitation and inhibition of behavioral and dorsal horn neuronal responses to noxious stimulation can be triggered from the same sites in rostroventral medulla. Electrical stimulation at low intensities (5–25 μA) is faciliatory while higher intensities (≥ 50 μA) are inhibitory (626, 628). Likewise, injections of small doses (0.03 pmol) of neurotensin in the rostroventral medulla trigger descending facilitation of multireceptive and nociceptor specific neurons in rat lumbar spinal dorsal horn (531). High doses (≥ 300 pmol) induce descending inhibition. Microinjection of cholecystokinin into the rostroventral medulla of naive rats also produces a robust mechanical and a more modest thermal hyperalgesia (255). The same studies also identified sites in the rostroventral medulla from which only facilitation or inhibition could be elicited.

A neuronal group exists in the rostroventral medulla which increases its firing rates just before the onset of the nociceptive tail-flick reflex. These neurons were termed "ON-cells" and probably mediate descending facilitation. In contrast, "OFF-cells" cease firing shortly before the tail-flick reflex occurs and may be involved in descending inhibition. The roles of ON- and OFF-cells have been reviewed (177, 327, 417). When μ-opioid receptor expressing cells in the rostroventral medulla are selectively destroyed, then spinal nerve ligation no longer induces mechanical and thermal hyperalgesia (416). This is compatible with an involvement of ON-cell in the rostroventral medulla as firing of these neurons is depressed by a μ-opioid receptor agonist (DAMGO) (178). Sensory responses of ON- and OFF-cells are altered in rats with a spinal nerve ligation. Both neuron types exhibit novel

responses to innocuous mechanical stimulation and enhanced responses to noxious mechanical stimulation. This neuronal hypersensitivity correlates with mechanical and thermal hyperalgesia in these rats (57).

Interactions between glial cells and neurons are involved by the activation of descending facilitation from the rostral ventromedial medulla following peripheral nerve injury. Chronic constriction injury of the rat infraorbital nerve leads to an early and transient reaction of microglia and a prolonged reaction of astrocytes in that brain region. Microinjections of microglial and astrocytic inhibitors that prevent glial cell activation also attenuate mechanical hyperalgesia at 3 and 14 days after nerve injury (570).

An early study reported that electrical stimulation in dorsolateral funiculus of decerebrated rats produces largely excitatory effects on projection neurons in contralateral spinal lamina I (331). Bilateral lesions of the dorsolateral funiculus abolish descending inhibition by electrical stimulation or neurotensin microinjection without, however, affecting descending facilitation (531, 628). This suggests that descending facilitation and inhibition can be induced from the same brain stem sites but employ separate descending pathways. Others have found that lesions in ventrolateral funiculus (629) attenuate descending facilitation.

Descending facilitation of behavioral and spinal neuronal responses to noxious stimuli cannot only be induced from the rostroventral medulla (227, 532, 626, 628) but also from more rostral sites in the brain including the anterior cingulate cortex (55), pretectal (427) or dorsal reticular nuclei (14), and periaqueductal gray (406). It has been suggested that the final common descending facilitatory pathway originates from the rostroventral medulla (417) and contributes to enhanced pain sensitivity (532).

ON-cells may be at the origin of the descending facilitatory arm of a spino-bulbo-spinal positive-feedback loop. The ascending arm may arise from a small but well-defined group of spinal lamina I projection neurons. These neurons express the neurokinin 1 receptor for substance P (505) and activity-dependent long-term potentiation at synapses with primary afferent C-fibers (see sect. vi*B* and Refs. 202, 204). Selective ablation of these lamina I neurons reduces mechanical and thermal hyperalgesia by inflammation or nerve injury (318, 383) and the descending facilitation of spinal wide-dynamic range neurons (505).

Descending facilitation involves activation of spinal receptors for serotonin (627). The 5-HT$_3$ receptor subtype appears to mediate descending facilitation originating from spinal neurokinin 1 receptor expressing cells (505). Spinal microglia and astrocytes also play a role. Microglia may be activated by neurotransmitter(s) such as excitatory amino acids or substance P either released from

primary afferents and/or from fibers descending from the rostroventral medulla to spinal dorsal horn (561).

Both descending inhibition and facilitation may serve to temporarily adapt the general pain responsiveness to the individual needs. Descending facilitation contributes to generalized hyperalgesia and allodynia as components of the "sickness response" to infection and inflammation (see sect. vii*A*) (561). This may promote healing. If descending facilitation is inadequate with respect to strength or duration, it may become a cause for chronic pain. The mechanisms of generalized facilitation of nociception may have relevance for some human pain patients as it has been suggested that in fibromyalgia patients endogenous pain modulatory systems are impaired (223).

In addition to enhanced descending facilitation as a promoter of hyperalgesia and allodynia, peripheral inflammation may also enhance descending inhibition that counteracts the development of hyperalgesia. For example, 4 h after a unilateral carrageenan injection into a hindpaw of rats, thermal hyperalgesia is enhanced when the locus coeruleus/subcoeruleus from which descending noradrenergic fibers originate is lesioned bilaterally but not unilaterally (309).

F. Aβ-Fiber-Induced Pain (Mechanical Allodynia)

Touch-evoked pain is a hallmark of neuropathic pain. There is now clear evidence that impulses in large myelinated Aβ-fibers may contribute to mechanical allodynia in animal models and in pain patients (56, 157).

1. Phenotypic switch in Aβ-fibers

Under normal conditions, stimulation of primary afferent Aβ-fibers fails to facilitate spinal nociception and does not induce hyperalgesia or allodynia. In the course of an inflammation, some large myelinated Aβ-fibers may switch their phenotype and begin to synthesize substance P. Upon activation, Aβ-fibers may then release substance P into the spinal dorsal horn, and this may, e.g., via extrasynaptic spread of substance P, contribute to facilitation of spinal nociception and enhanced responsiveness of spinal nociceptive neurons (382). Before considering a "phenotypic switch," it is important to ensure that the markers used for identifying an afferent fiber type do not change also under the experimental conditions. For example, neurofilament (NF) 200 kDa remains a good marker for A-fiber neurons, and isolectin B4 and substance P remain good markers for C-fiber neurons after chronic constriction injury (440).

After sciatic nerve transection, substance P immunoreactivity is induced in medium- and large-sized dorsal root ganglia cells and reduced in small-sized cells (385). The expression of preprotachykinin mRNA encoding substance P and related peptides is strongly upregulated in

large A-type neurons of the rat dorsal root ganglion following unilateral chronic constriction injury of the sciatic nerve (325). After intraplantar injection of complete Freund's adjuvant, mechanical stimulation of the inflamed skin or electrical stimulation at Aβ-fiber intensity of sensory nerve fibers innervating the inflamed tissue leads to a slowly progressing facilitation of flexor motor responses (308). Stimulation of a peripheral nerve at A-fiber intensity normally does not cause afterdischarges in spinal multireceptive neurons in spinalized rats. After a chronic constriction injury of sciatic nerve, however, afterdischarges do occur and can be blocked by a neurokinin 1 receptor antagonist (CP-99,994) (409). This newly acquired capacity of Aβ-fibers to enhance spinal nociception may be due to a novel expression of substance P in these primary afferents, thereby switching their phenotype to one resembling nociceptive C-fibers (382; see also Fig. 3L). In three nerve injury models (sciatic nerve transection, spinal nerve ligation, and chronic constriction injury), substance P is, however, not upregulated to any detectable degree, and stimulation of Aβ-fibers does not cause neurokinin 1 receptor internalization in spinal dorsal horn, challenging the view that substance P would be released from Aβ-fibers under these conditions (196).

In addition to substance P, a large number of other molecules are also either up- or downregulated in dorsal root ganglion neurons in various animal models of pain, as reviewed by Ueda (528), Hucho and Levine (194), and Woolf and Ma (587).

2. Sprouting of Aβ-fibers

After nerve injury but not under normal conditions, impulses in Aβ-fibers may elicit pain sensation. Thus information in large myelinated primary afferent must gain access to the nociceptive system. And, indeed, in neuropathic animals, c-Fos expression, an indication for neuronal activity, is increased in lamina II dorsal horn neurons following repeated touch stimuli. This suggests that low-threshold mechanosensitive fibers may now directly or indirectly activate nociceptor specific lamina II neurons (40). Likewise, in animal models of neuropathic pain (sciatic nerve transection or chronic constriction injury), Aβ-fiber-mediated input to the nociceptive superficial dorsal horn increases substantially (252, 253, 392). An attractive hypothesis was suggested by Woolf et al. (588) who reported that application of the neural tracer horseradish peroxidase to a peripheral nerve results in transganglionic transport to the central terminals of the labeled axons. When the B unit of cholera toxin is conjugated to horseradish peroxidase, normally only myelinated afferents are labeled. When this conjugate is applied to an intact nerve of rats, the marker is consequently found selectively in laminae I, III, and deeper dorsal horn, which

matches the known termination of myelinated primary afferents (588). In animals with a transection of a peripheral nerve, labeling was also found in lamina II, which is normally devoid of A-fiber terminals. This was interpreted as sprouting of A-fibers into an area normally occupied by C-fibers only. This interpretation was substantiated by intracellular labeling of low-threshold primary afferents (588). This labeling method was used in a number of subsequent studies from the same (115, 316, 317) and other laboratories (34, 376, 401, 485) and revealed similar results. Later studies found, however, that cholera toxin B subunit may not be a reliable marker for myelinated fibers following peripheral nerve injury but rather taken up indistinctively by small and large size dorsal root ganglion neurons (475). Thus, after nerve transection, the marker is taken up also by fine primary afferents (516), including unmyelinated C-fibers (459) and cholera toxin B subunit, then no longer selectively labels A-fibers. These authors conclude that after peripheral nerve injury, the label found in lamina II is largely due to the uptake of the marker by injured C-fibers but not due to sprouting of A-fibers (459). This conclusion is in line with recent studies which found only very limited sprouting of single, identified Aβ-fiber afferents after nerve injury (30, 197). Taken together, these studies challenge the hypothesis that sprouting of Aβ-fibers into the superficial laminae after nerve section is substantial (30, 197, 459, 516).

3. Opening of polysynaptic excitatory synaptic pathways

An alternative explanation for novel Aβ-fiber input to superficial spinal dorsal horn neurons is the opening of preexisting polysynaptic pathways between Aβ-fiber afferents that terminate in deeper dorsal horn and nociceptive neurons in superficial spinal dorsal horn (Fig. 3J). Recent studies suggest that indeed some forms of neuropathy or inflammation may facilitate polysynaptic low-threshold input to neurons in laminae I and II of spinal dorsal horn (24, 468). In transversal lumbar spinal dorsal horn slices, electrical stimulation or microinjection of glutamate [which does not excite (sprouted) fibers of passage] into the deep dorsal horn or stimulation dorsal roots at Aβ-fiber intensity excites only very few neurons in the superficial dorsal horn of control animals. In contrast, numerous neurons in the superficial dorsal horn are excited in slices taken from animals with a spared nerve injury (468). Taken together, these results suggest that Aβ-fiber afferents excite interneurons in lamina III, which via polysynaptic pathways trigger excitation of superficial dorsal horn neurons in neuropathic but not in control animals leading to touch-evoked pain (468).

G. Other Potential Mechanisms of Hyperalgesia and Allodynia

1. Sprouting of fine primary afferents

During development, spinal termination patterns of primary afferents including nociceptive C-fibers are finely tuned. Transgene overexpression of nerve growth factor in spinal dorsal horn results in sprouting of a subpopulation of nociceptive primary afferents that express substance P and calcitonin gene-related peptide in spinal dorsal horn (Fig. 3I). This C-fiber sprouting is accompanied by mechanical and thermal hyperalgesia (438). Sprouting of C-fiber afferents has been investigated in some detail by using calcitonin gene-related peptide immunoreactivity for peptidergic and isolectin B4 immunoreactivity as marker for small nonpeptidergic fibers. Following rhizotomy of L4–S1 dorsal roots and injury of the saphenous nerve in rats, L2, L3 dorsal root afferents may regenerate differentially. Isolectin B4 labeling is not much different in lamina II of denervated spinal cord segments. In contrast, labeling for calcitonin gene-related peptide is much enhanced in segments denervated by rhizotomy in a nonsomatotopic manner (33). The authors conclude that peptidergic (calcitonin gene-related peptide-positive) C-fibers sprout vigorously while nonpeptidergic (isolectin B4 positive) C-fibers remain stable after peripheral nerve injury (33). Collateral sprouting, i.e., sprouting of uninjured axons into the denervated territory, not only requires nerve growth factor. In addition, an intact intermediate filament network within nerve fibers is also essential for collateral sprouting of small-diameter primary afferent nerve fibers. Disruption of intermediate filament network in transgenic mice significantly impairs the ability of uninjured small-sized dorsal root ganglion neurons to sprout collateral axons into adjacent denervated skin (32).

Possibly repulsive guidance cues such as semaphoring 3A play a role in limiting sprouting of a subgroup of C-fiber afferents. This repellent is thought to restrict termination of nerve growth factor-responsive nociceptive afferents to superficial laminae. Reduced sprouting of calcitonin gene-related peptide and substance P-containing axons leads to decreased mechanical hyperalgesia tested with von Frey filaments (510). Thermal hyperalgesia is, in contrast, not significantly affected by semaphorin3A (510).

2. "Wind-up" of action potential firing

Some of the neurons in spinal dorsal horn with excitatory input from primary afferent C-fibers display the phenomenon of "wind-up," i.e., the increase in the number of action potential discharges in response to repetitive C-fiber stimulation. When C-fiber afferents are stimulated at low frequencies (0.3–5 Hz), postsynaptic responses increase with almost each stimulus until a saturation level is reached (339). This is the case after ~10–30 C-fiber stimuli, i.e., after 5–60 s. Thus wind-up is a short-lasting phenomenon that enhances action potential firing of some spinal dorsal horn neurons during the first few seconds of an ongoing noxious stimulus. Thereafter, responses no longer increase but may rather decrease. Wind-up is a form of temporal summation of action potential discharges, due to the summation of excitatory postsynaptic potentials. Temporal summation occurs when the duration of excitatory postsynaptic potentials is longer than the interspike intervals of the presynaptic C-fiber discharges. Since NMDA receptor-mediated postsynaptic currents typically prolong excitatory postsynaptic potentials, it is not surprising that wind-up is sensitive to NMDA receptor blockage (589). Wind-up can be observed in normal animals, i.e., in the absence of any pathological changes of spinal nociception. Thus wind-up is a feature of the normal coding properties of some spinal dorsal horn neurons and per se not a sign of "sensitization" in spinal dorsal horn. In other words, the absence or presence of wind-up cannot be used as an indicator for any form of abnormal pain amplification, and consequently, wind-up is not a cellular mechanism of hyperalgesia or chronic pain. A physiological function of wind-up could be to enforce a nocifensive response during a sustained noxious stimulus that triggers discharges in C-fibers at low rates. If the nocifensive response is not triggered within the first few seconds, wind-up will increase the discharge frequencies of some spinal dorsal horn neurons possibly beyond threshold for a response, e.g., a withdrawal reflex. This interpretation is in line with the observation that wind-up can be seen in motoneurons (589) and in motor reflexes (141).

Importantly, a number of changes that may lead to pain amplification may also lead to changes in the properties of wind-up. For example, LTP at synapses between C-fibers afferents and second-order neurons will lead to larger and longer-lasting excitatory postsynaptic potentials and thus may result in stronger wind-up and in lowering of the wind-up threshold frequency of a given neuron. Likewise, increased membrane excitability, i.e., lowering the threshold for action potential firing and/or less negative membrane potentials or changes in discharge patterns from single spiking to burst discharges, all would result in stronger wind-up in response to repetitive C-fiber stimulation. Thus, while wind-up by itself cannot be used as a proof of alterations in spinal nociception changes in the incidence of neurons that display wind-up, increase in wind-up strength or decrease in wind-up threshold frequencies may all indicate that some forms of facilitation occurred in spinal nociceptive pathways.

Wind-up of action potential discharges likely increases activity-dependent Ca^{2+} influx into the respective neurons and thereby Ca^{2+}-dependent signal transduction

pathways. One of the many consequences of which could be activity-dependent changes in synaptic strength, membrane excitability, and discharge patterns. However, wind-up is not necessary for the induction of long-term changes in excitability in most spinal dorsal horn neurons (for review, see also Refs. 180, 586).

Perceptual correlates of action potential wind-up can be studied in normal human subjects (437, 496), in human subjects with an experimental hyperalgesia (471, 560), and in pain patients (267, 497) when repetitive noxious stimuli are given at a frequency that is compatible with the window of wind-up frequencies, i.e., if the interval between C-fiber stimuli is no longer than 3 s. A number of studies suggest that NMDA-receptor-dependent wind-up of C-fiber-evoked second pain is stronger in patients with fibromyalgia compared with normal controls (419, 498).

3. Epileptiform activity in nociceptive pathways

Paroxysmal forms of neuropathic pain share some key features with epileptic seizures. Both can be triggered by harmless sensory stimuli and once started they have a rather stereotyped progression. Another common feature is the refractory period, i.e., during the immediate time after an attack no new attack can be evoked. If not adequately treated, both may end up in a status, i.e., a series of attacks without complete recovery between the attacks. Last but not least, both can be treated successfully by anticonvulsant drugs (443). Epileptiform activity, i.e., highly synchronized, rhythmic discharges of populations of neurons, has been observed in the nociceptive system of the spinal dorsal horn (Fig. 3K). Patch-clamp recordings from individual neurons and Ca^{2+} imaging of multiple single neurons in a slice preparation of the rat lumbar spinal cord revealed epileptic activity in response to bath application of the potassium channel blocker 4-aminopyridine (4-AP) (443). 4-AP is often used to induce epileptic activity in the cerebral cortex. In the spinal cord, epileptiform activity was also observed in lamina I neurons with a direct projection to the parabrachial area, i.e., in neurons that are directly involved in neuropathic pain behavior in animals (318). Bath application of μ-opiate receptor agonist DAMGO or α_2-adrenoreceptor agonist clonidine does not or only weakly attenuates epileptiform activity. In contrast, antiepileptic drugs such as phenytoin, carbamazepine, and valproate are strongly effective (443).

4. Enriched responsiveness of spinal nociceptive neurons

A large number of studies have shown that nociceptive spinal dorsal horn neurons become more excitable by peripheral inflammation or nerve injuries. This includes enhanced responsiveness to normally innocuous natural or electrical nerve stimuli, expansion of low-threshold cutaneous receptive fields, enhanced responses to noxious stimuli, and development of spontaneous action potential discharges. There is still no agreement on the differential roles of the various classes of spinal dorsal horn neurons for acute, inflammatory, and/or neuropathic pain. For example, in intact rats, surgical incision of the hairy skin and subsequent suturing causes mechanical and thermal hyperalgesia from 30 min post incision to 3–5 days (228). In decerebrated, spinalized rats, the same injury triggers enhanced responses of wide-dynamic range, low-threshold and high-threshold spinal dorsal horn neurons during the injury, elevated background activity in wide-dynamic range but not in low-threshold or high-threshold neurons for 30 min and expansion of cutaneous low- and high-threshold mechanoreceptive fields in wide-dynamic range but not low-threshold or high-threshold neurons (228). High-threshold neurons develop responsiveness to low-threshold input only after spinal bicuculline but not after incision (228). The authors conclude that enhanced excitability of wide-dynamic range but not high-threshold or low-threshold neurons mediate mechanical and thermal hyperalgesia after injury of hairy skin (228). Neither of these neuronal cell types investigated is, however, a functionally homogeneous group but comprise excitatory and inhibitory neurons, interneurons, and projection neurons.

Some studies were performed on dorsal horn neurons with a verified projection to brain areas such as spino-thalamic tract neurons. Results from these studies suggest that enhanced neuronal activity in dorsal horn may likely affect nociceptive processing in the brain. These studies have been reviewed extensively before (39, 92, 140, 420, 579, 580, 625).

VII. IMMUNE-CENTRAL NERVOUS SYSTEM INTERACTIONS

A. The Sickness Syndrome

Nonspecific manifestations of inflammation and infection may include fever, drowsiness, and often an increased sensitivity to painful stimuli. A peripheral immune challenge leads to the production of proinflammatory cytokines such as tumor necrosis factor, interleukin-1, and interleukin-6. These peripheral mediators trigger the de novo synthesis of proinflammatory cytokines by cells within the central nervous system including the spinal cord, mainly microglia, and astrocytes (324, 562, 565). These processes subsequently cause the sickness syndrome. The immune-to-brain communication involves blood-borne signaling and neural pathways via sensory vagus nerve fibers (562) and relays in nucleus tractus solitarius and in the ventromedial medulla and descending pathways in the dorsolateral funiculus of the spinal

cord (567). The sickness syndrome can be induced experimentally in animals by intravenous injections of pyrogens such as lipopolysaccharides. Systemic (intraperitoneal) injection of lipopolysaccharides produces thermal hyperalgesia, as revealed by decreased tail-flick latencies (326). Hyperalgesia is accompanied by enhanced spinal cord levels of interleukin-1, a product of glial cell activation (see also review by Watkins and Maier, Ref. 561). However, intrathecal administration of interleukin-1 fails to induce hyperalgesia, while intraperitoneal or intracerebroventricular injections are effective (311, 568). A systemically injected single dose of lipopolysaccharides further induces within 6 h muscle hyperalgesia as measured by the grip force assay in mice (233).

A potential mechanism for immune-to-brain communication (563) arising from the abdomen is discussed by Goehler and colleagues (155). An ascending-descending loop may involve the nucleus tractus solitarius-nucleus raphe magnus-spinal cord dorsolateral funiculus circuit (567). Spinal microglia may be activated by neurotransmitter(s) released from nucleus raphe magnus-spinal cord pathways such as excitatory amino acids or substance P. The respective receptors are all expressed by spinal microglia and astrocytes, and ligand binding activates these glial cells in vitro (561).

Subcutaneous injection of Formalin into the dorsum of one hindpaw induces thermal hyperalgesia also at distant sites, e.g., at the tail as measured by the tail-flick reflex (564, 574). This remote hyperalgesia is not mediated solely by circuitry intrinsic to the spinal cord, but rather involves activation of centrifugal pathways originating within the brain and descending to the spinal cord via pathway(s) outside of the dorsolateral funiculus. At the level of the spinal cord, this hyperalgesic state is mediated by an NMDA-nitric oxide cascade, since hyperalgesia can be abolished by administration of either an NMDA antagonist (D-2-amino-5-phosphonovalerate) or a nitric oxide synthesis inhibitor (L-NAME) (574). The decrease in tail-flick latency is further prevented by intrathecal fluorocitrate, which is a glial metabolic inhibitor. A human recombinant interleukin-1 receptor antagonist or an antibody directed against nerve growth factor, i.e., inhibition of products of glial cell activation, are also effective (564). Thus sickness and inflammation-induced hyperalgesia involve overlapping central nervous system circuits and signal transduction pathways (561).

B. Role of Spinal Glia for Allodynia and Hyperalgesia

Work of the recent years has shown that abnormal pain sensitivity involves altered function of neuronal network in spinal dorsal horn and that activated spinal glial cells act as an intermediary between the initial insult and long-term neuronal plasticity leading to pain amplification. Glial cells, i.e., microglia, astrocytes, and oligodendrocytes, constitute ~70% of the cell population in brain and spinal cord. The physiology of microglial cells has been reviewed recently (129). Spinal microglia and astrocytes are both immunoeffector cells of the central nervous system that are activated following nerve injury or inflammation (104, 520, 566). Furthermore, the number of microglial cells (9) and the number of astrocytes (278) rise in spinal dorsal horn ipsilateral to a peripheral nerve injury. Selective pharmacological blockade of glial cell functions prevents and reverses abnormal pain sensitivity.

1. Activation of spinal glial cells

Microglia can be activated rapidly by neuronal activity (129). One candidate for neuron-glia interaction is the glial excitatory chemokine fractalkine, which is expressed on the extracellular surface of spinal neurons and spinal sensory afferents. After it is released upon strong neuronal excitation, e.g., in response to an insult, it binds to CX3C receptors mainly expressed by microglia. Intrathecal fractalkine causes mechanical and thermal hyperalgesia, while intrathecal fractalkine receptor antagonist delays onset of mechanical and thermal hyperalgesia following chronic constriction injury or inflammatory neuropathy of sciatic nerve (352).

Microglia may also be activated by neurotransmitters such as excitatory amino acids or substance P either released from primary afferents, spinal dorsal horn cells or supraspinal descending fibers, and by ATP, nitric oxide, prostaglandins, and heat shock protein. The respective receptors are expressed not only by spinal microglia but also on astrocytes [520, 561; see also review by Watkins and Maier (562)].

Microglia activation is not a stereotype process but involves various combinations of proliferation and morphological changes, upregulation of surface antigens such as major histocompatibility complex classes I and II antigens, cellular adhesion molecules, cluster determinants 4 and 45 and integrin alpha M, P2X$_4$ receptors (512), and elevated expression of complement receptor 3. From central nervous system injury models it has been suggested that microglia activation releases substances that then activate astrocytes (512). Activation of astrocytes involves hypertrophy and upregulation of the expression of glial fibrillary acidic protein. Astrocytes (but not microglia) closely appose synapses from which they receive signals and which function they modify. For example, activated astroglia may take up less than normal glutamate near excitatory synapses, thereby enhancing its effects on excitatory neurotransmission and neurotoxicity, which in spinal dorsal horn might contribute to hyperalgesia (566).

Already 4 h after L5 spinal nerve transection, the earliest time point investigated, microglial activation markers toll-like receptor 4 and cluster determinant 14 are all upregulated at the mRNA level as assessed by real-time reverse transcription polymerase chain reaction (512). Microglia thus constitute the first noticeable immune responses in spinal cord to several types of peripheral stimuli. Markers remain elevated for 14 days and decline by 28 days. Immunohistochemistry reveals an increase in the number of activated microglial cells as determined by OX42 and glial fibrillary acidic protein in astrocytes of ipsilateral dorsal and ventral horns as early as 2 days after partial sciatic nerve transection lasting for 84 days which parallels the time course of mechanical hyperalgesia (91).

Activation of $P2X_4$ receptor, an ATP-gated ion channel, selectively expressed in microglia of the spinal cord is upregulated after L5 spinal nerve ligation. Likewise, subcutaneous injections of diluted Formalin cause an increase in $P2X_4$ receptor expression on activated microglia in ipsilateral dorsal horn which peaks at *day 7* after the injection (161). This suggests that not only nerve injury but also inflammation may trigger expression of this ATP-gated ion channel. In addition, G protein-coupled purinoreceptors also play a role. Intrathecal application of a glial $P2Y_{12}$ receptor blocker (AR-C69931MX) prevents development of and reverses established tactile hyperalgesia in rats with a tight ligation of a L5 spinal nerve (517). In mice lacking the $P2Y_{12}$ receptor, tactile hyperalgesia but not normal responses to mechanical stimuli is impaired (517). Toll-like receptors are also expressed on microglia and appear to be essential for their activation by peripheral nerve injury. Antisense knockdown of toll-like receptor 3 in spinal cord attenuates activation of spinal microglia and development of tactile hyperalgesia in rats with a L5 spinal nerve lesion (388).

The functional and phenotypic pattern of activation strongly depends on the type of peripheral stimulus. For example, major histocompatibility complex class II and CC chemokine receptor 2 are all upregulated in spinal cord microglia following spinal nerve ligation but not following peripheral inflammation [see review by Tsuda et al. (520)]. In streptozotocin-induced diabetic rats, tactile hyperalgesia develops that is accompanied by several characteristic changes of activated microglia in the dorsal horn, including increases in Iba1 and OX-42 labeling, hypertrophic morphology. Extracellular signal-regulated protein kinase and Src-family kinase are both activated exclusively in microglia (524). The astrocyte marker glial fibrillary acidic protein is upregulated starting on postoperative *day 4* through *day 28* (512). Taken together, it has been suggested that microglia is the initial immunoeffector cell sensor that, if inhibited prior to the onset of astrocytic activation, may prevent mechanical hyperalgesia in various models of neuropathy (512).

2. Substances release by activated microglia

Upon activation microglia produce and release cytokines, prostaglandins, leukotrienes, nitric oxide, reactive oxygen intermediates, proteolytic enzymes, and excitatory amino acids such as glutamate (104). Many of the substances produced and released by microglia and astrocytes may mediate hyperalgesia, including nitric oxide, prostaglandins, interleukin-1, brain-derived neurotrophic factor, nerve growth factor, arachidonic acid, and excitatory amino acids such as glutamate (561). Other molecules that are expressed in spinal microglia such as chemotactic cytokine receptor 2, cannabinoid receptor subtype 2, and major histocompatibility complex class II protein may also modulate neuropathic pain.

Platelet activating factor is another substance released from stimulated microglia cells (208) and by neurons in culture upon stimulation with glutamic acid. It is a potent chemotactic factor for microglia which express receptors for platelet activating factor (7).

3. Pain-related behavior modulated by activated microglia

An early report has shown that peripheral inflammation of a hindpaw by intraplantar zymosan injections leads to mechanical and thermal hyperalgesia which involves spinal glia: selective inhibition of glial metabolism by intrathecal administration of fluorocitrate results in a marked, but reversible, attenuation of the persistent thermal and mechanical hyperalgesia (334, 351). Furthermore, intrathecal injection of fractalkine, which selectively activates spinal microglia, is sufficient to induce tactile and thermal hyperalgesia. Blockade of CX3C receptors to which fractalkine binds reverses hyperalgesia when applied 5–7 days after a chronic constriction injury of the sciatic nerve (352).

Proinflammatory cytokines can stimulate the production of multiple components of the complement cascade. Interruption of complement cascade by intrathecal injection of soluble human complement receptor type 1 reverses mechanical hyperalgesia by sciatic inflammatory neuritis and by chronic constriction injury of sciatic nerve and by intrathecal injection of the human immunodeficiency virus-gp120 (526) without affecting normal responses to touch.

Tight ligation of L4/5 spinal nerves leads to activation of spinal p38 mitogen-activated protein kinase (216, 521), which in spinal cord is selectively expressed in activated microglia. Depression of spinal p38 mitogen-activated protein kinase by intrathecal injection of a blocker (SB203580) has no effect on basal nociceptive responses but reverses established mechanical hyperalgesia after spinal nerve ligation (216, 521). Likewise, mechanical hyperalgesia is attenuated by intrathecal inhibition of a p38 mitogen-activated protein kinase or $P2X_4$ receptor

blocker or antisense oligonucleotide pretreatment (207). p38 activation may regulate the expression of inducible nitric oxide synthase, cyclooxygenase-2, and cytokines in microglia through transcriptional and translational effects. Two weeks after an injury of L5, spinal nerve activated microglia are detected and dually phosphorylated active form of p38 mitogen-activated protein kinase and $P2X_4$ ATP receptors are upregulated in microglia in the ipsilateral spinal dorsal horn (207).

Intrathecal injection of minocycline, an inhibitor of microglial cell activation, inhibits mRNA expression of interleukin-1β, tumor necrosis factor-α, interleukin-1β-converting enzyme, tumor necrosis factor-α-converting enzyme, interleukin-1 receptor antagonist, and interleukin-10 as well as mechanical hyperalgesia induced by either sciatic inflammatory neuritis of by intrathecal injection of human immunodeficiency virus-1 gp120 (276).

Pathogens are detected by specific receptors such as the toll-like receptor 4, which is selectively expressed by microglia. Intrathecal antisense oligonucleotides directed against the expression of toll-like receptor 4 or knock out of toll-like receptor 4 gene reduces mechanical and thermal hyperalgesia following L5 nerve transection in mice (511).

Following L5 spinal nerve ligation, extracellular signal-regulated kinase, a mitogen activated protein kinase, is transiently (for <6 h) activated in neurons of spinal dorsal horn and at *days 1–10* in spinal microglia and later in astrocytes as well (623). Mechanical hyperalgesia is reduced when a high dose of an extracellular signal-regulated kinase inhibitor (PD98059) is injected intrathecally on *days 2*, *10*, or *21* (623), suggesting its involvement in maintenance of neuropathic pain.

When microglia grown in culture and activated by ATP are injected intrathecally in rats, mechanical hyperalgesia similar to that after spinal nerve ligation is induced, while inactive microglia have no effect (522). Antisense oligonucleotide targeting the ATP receptor $P2X_4$ diminishes tactile hyperalgesia after spinal nerve ligation. Blockade of spinal $P2X_{1-4}$ receptors by intrathecal injections of 2′,3′-O-(2,4,6-trinitrophenyl)adenosine 5-triphosphate (TNP-ATP) temporarily reverses tactile hyperalgesia 7 days after spinal nerve ligation (522). Interestingly, blockade of spinal $P2X_{1,2,3,5,7}$ receptors (with PPADS) inhibits pain-related behavior in the first and second phase of the Formalin test and the responses to capsaicin (525) but fails to affect tactile hyperalgesia after spinal nerve ligation (522).

Glia but not neurons express a receptor for interleukin-10. Its activation suppresses release of proinflammatory cytokines. After intrathecal injection, interleukin-10 has a short half-life of ~2 h. Gene therapy with an adenoviral vector encoded human interleukin-10 prevents and reverses mechanical and thermal hyperalgesia by chronic constriction injury of sciatic nerve and mechanical hyper-algesia by either sciatic inflammatory neuropathy or by intrathecal injection of gp120, an envelope glycoprotein of human immunodeficiency virus-1, all of which activates spinal glia (349). These effects last for more than a week but are absent at 3 wk. Normal responses to heat or touch are not affected by this form of gene therapy (349).

Intrathecal morphine application for 5 days but not single intrathecal morphine injection leads to elevated levels of interleukin-1 mRNA and protein in spinal dorsal horn 2 h but not 24 h after discontinuation of morphine (219). Coadministration of morphine and an interleukin-1 receptor antagonist enhances morphine analgesia and reduces development of tolerance to morphine and morphine-induced mechanical and thermal hyperalgesia (219). The intrathecal injection of neutralizing antibody against the fractalkine receptor has similar effects (219). Thus activation of spinal glial cells is an important intermediate step in the pathogenesis of chronic pain of various origins.

4. Concluding remarks

Considerable progress has been made in developing clinically relevant animal models of hyperalgesia and allodynia. Available models cover inflammatory, traumatic, and neuropathic forms of acute or chronic pain. Standardization of animal models across laboratories has much improved the reproducibility of published work. Many efforts are presently being made to unfold the diverse pain mechanisms at the network, cellular, synaptic, and molecular levels. It is highly unlikely that a unifying model will be developed that may explain all forms of hyperalgesia and allodynia. It is more likely that a number of mechanisms are active in parallel and/or in sequence and that a characteristic pattern of mechanisms will be identified for a given pain syndrome. Thus a single "magic pain killer" will hardly be the future treatment of choice; rather, mechanism-based multimodal treatments that match the particular phase of pain development will be successful. Much of the future progress in the field of experimental pain research will rest on the work that is summarized in this review.

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Erratum Fig.3 (Chapters renumbered)

| Site of action | Effect | | Mechanisms |
| | Normal | Modified | [Chapters] |

A

Nociceptive nerve fiber   Spinal dorsal horn projection neuron

Excitatory postsynaptic potentials

LTP of synaptic strength [VI.B]

1. Presynaptic
Enhanced transmitter release

2. Postsynaptic
Enhanced transmitter effect

B

Changes in membrane excitability [VI.C]

1. Lower resting membrane potential (solid line)

2. Lowered threshold for action potential discharge (dotted line)

C

Changes in the pattern of action potential discharges

1. Enhanced sodium currents [VI.C.1.]

2. Reduced potassium currents [VI.C.2.]

3. Plateau potentials [VI.C.3.]

D

Inhibitory interneuron

Inhibitory postsynaptic potentials

Reduced strength of synaptic inhibition [VI.D.1.A; VI.D.2.A]

1. Presynaptic
Reduced transmitter synthesis
Reduced vesicular transport
Reduced release probability

2. Postsynaptic
Reduced transmitter effect (e.g. reduced number or sensitivity of receptors)

E

Inhibitory / excitatory postsynaptic potentials

Conversion from postsynaptic inhibition to excitation [VI.D.1.B]

1. Shift in anion gradient and Cl⁻ reversal potential

F

Excitatory interneuron

Inhibitory postsynaptic potentials

Fewer number of inhibitory events [VI.D.1.A.I]

1. Reduced excitatory drive of inhibitory interneurons
2. Lower number of inhibitory synapses
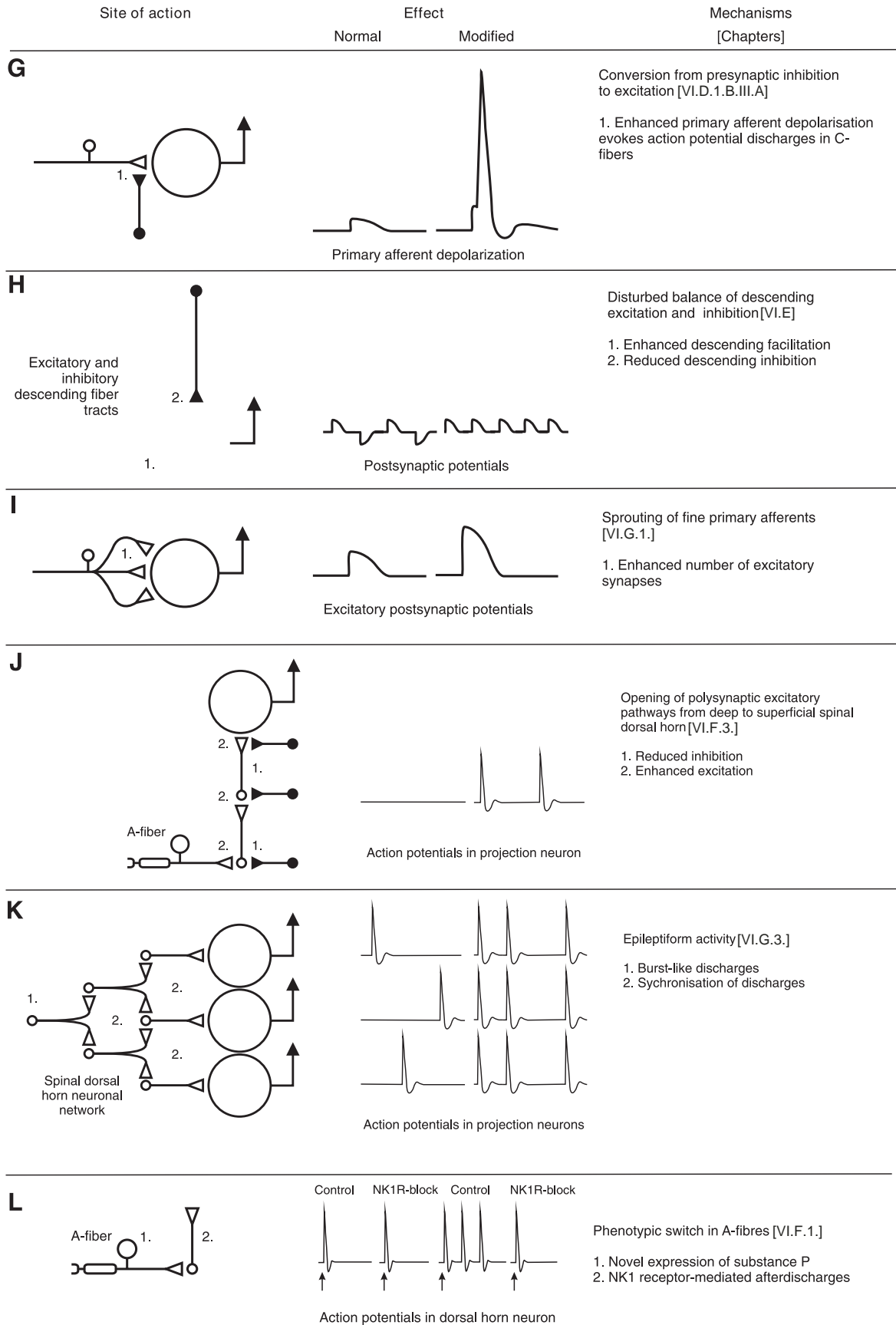3. Reduced release probability of inhibitory neurotransmitter

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| Site of action | Effect | | Mechanisms |
| | Normal | Modified | [Chapters] |

G

Conversion from presynaptic inhibition to excitation [VI.D.1.B.III.A]

1. Enhanced primary afferent depolarisation evokes action potential discharges in C-fibers

Primary afferent depolarization

H

Excitatory and inhibitory descending fiber tracts

Disturbed balance of descending excitation and inhibition [VI.E]

1. Enhanced descending facilitation
2. Reduced descending inhibition

Postsynaptic potentials

I

Sprouting of fine primary afferents [VI.G.1.]

1. Enhanced number of excitatory synapses

Excitatory postsynaptic potentials

J

Opening of polysynaptic excitatory pathways from deep to superficial spinal dorsal horn [VI.F.3.]

1. Reduced inhibition
2. Enhanced excitation

A-fiber

Action potentials in projection neuron

K

Epileptiform activity [VI.G.3.]

1. Burst-like discharges
2. Sychronisation of discharges

Spinal dorsal horn neuronal network

Action potentials in projection neurons

L

Control   NK1R-block   Control   NK1R-block

A-fiber

Phenotypic switch in A-fibres [VI.F.1.]

1. Novel expression of substance P
2. NK1 receptor-mediated afterdischarges

Action potentials in dorsal horn neuron

FIG. 3.–Continued