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**Hans-Georg Schaible**
**Frank Richter**

# Pathophysiology of pain

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H.-G. Schaible (✉) · F. Richter
Institut für Physiologie,
Friedrich-Schiller-Universität Jena,
Teichgraben 8, 07740 Jena, Germany
e-mail:
Hans-Georg.Schaible@mti.uni-jena.de
Tel.: +49-3641-938810
Fax: +49-3641-938812

**Abstract** Pain is a major symptom of many different diseases. Modern pain research has uncovered important neuronal mechanisms that are underlying clinically relevant pain states, and research goes on to define different types of pains on the basis of their neuronal and molecular mechanisms. This review will briefly outline neuronal mechanisms of pathophysiological nociceptive pain resulting from inflammation and injury, and neuropathic pain resulting from nerve damage. Pain is the sensation that is specifically evoked by potential or actual noxious (i.e. tissue damaging) stimuli or by tissue injury. Pain research has not only explored the neuronal and molecular basis of the "pain system" of the healthy subject but has also provided insights into the function and plasticity of the "pain system" during clinically relevant pains such as post-injury pain, inflammatory pain, postoperative pain, cancer pain and neuropathic pain. This review will briefly describe the "pain system" and then address neuronal mechanisms that are involved in clinical pain states.

**Keywords** Nociceptive system · Nociceptive pain · Inflammatory pain · Neuropathic pain · Peripheral sensitisation · Central sensitisation

## The "pain" system

Precisely, the "pain system" should be called the "nociceptive system" because pain is a subjective result of nociception. Nociception is the encoding and processing of noxious stimuli in the nervous system that can be measured with electrophysiological techniques. A scheme of the nociceptive system is shown in Fig. 1. A noxious stimulus activates nociceptors (A$\delta$ and C fibres) in the peripheral nerve. Their sensory endings are so-called free nerve endings, i.e. they are not equipped with corpuscular end organs. Most of the nociceptors are polymodal, responding to noxious mechanical stimuli (painful pressure, squeezing or cutting of the tissue), noxious thermal stimuli (heat or cold), and chemical stimuli [1]. Sensor molecules in the sensory endings of nociceptors transduce mechanical, thermal and chemical stimuli into a sensor potential, and when the amplitude of the sensor potential is sufficiently high, action potentials are triggered and conducted by the axon to the dorsal horn of the spinal cord or the brainstem. Nociceptors can also exert efferent functions in the tissue by releasing neuropeptides [substance P, calcitonin gene-related peptide (CGRP)] from their sensory endings. Thereby, they induce vasodilatation, plasma extravasation and other effects, e.g. attraction of macrophages or degranulation of mast cells. The inflammation produced by nociceptors is called neurogenic inflammation [2, 3].

Nociceptors activate synaptically nociceptive dorsal horn neurons (Fig. 1). The latter are either ascending tract neurons or interneurons that are part of segmental motor or vegetative reflex pathways. Ascending axons in the spinothalamic tract activate the thalamocortical system that produces the conscious pain sensation. The pain sensation has a sensory discriminative aspect, i.e. the noxious stimulus is analysed for its location, duration and intensity. This is produced in the *lateral thalamocortical system*, which consists of relay nuclei in the lateral

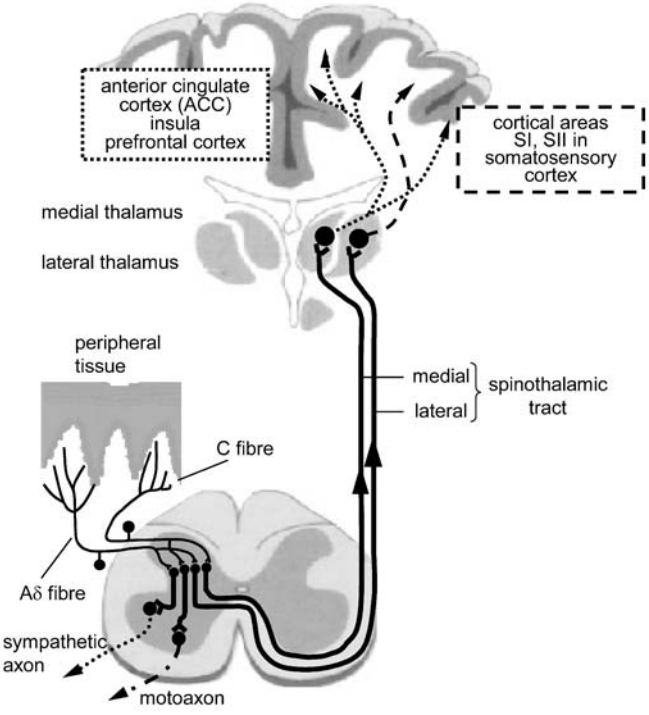


**Fig. 1** Scheme of the nociceptive system with nociceptive free nerve endings in the peripheral tissue, afferent nerve fibres and their synapses in the dorsal horn of the spinal cord. From there the medial and lateral spinothalamic tracts ascend to the medial and lateral thalamus, and interneurons project into motor and sympathetic reflex pathways

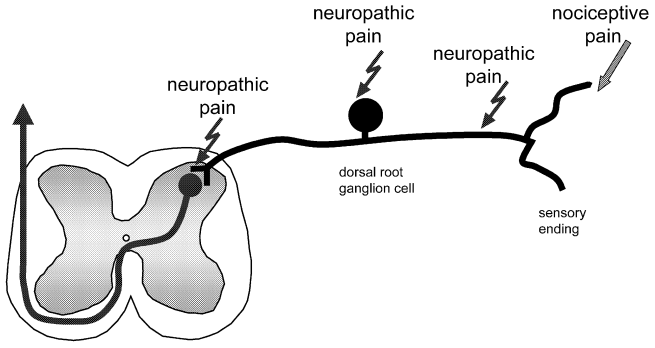


**Fig. 2** Sketch of a nociceptive afferent with its synapse in the dorsal horn of the spinal cord. Noxious stimulation of the nociceptor at its sensory ending causes nociceptive pain. Pathological stimulation of the axon, the dorsal root ganglion or of neurons in the central nervous system causes neuropathic pain

thalamus and the areas SI and SII in the postcentral gyrus. A second component of the pain sensation is the affective aspect, i.e. the noxious stimulus feels unpleasant and causes aversive reactions. This component is produced in the *medial thalamocortical system*, which consists of relay nuclei in the central and medial thalamus and the anterior cingulate cortex (ACC), the insula, and the prefrontal cortex [4, 5].

The spinal cord is under the influence of descending tracts that reduce or facilitate the nociceptive processing. Descending inhibition is formed by pathways that originate from brainstem nuclei (in particular, the periaqueductal grey, nucleus raphe magnus) and descend in the dorsolateral funiculus of the spinal cord. This system is able to suppress nociceptive information processing via interneurons in the dorsal horn of the spinal cord [4].

## Types of pain

When a noxious stimulus is applied to *normal* tissue, *acute physiological nociceptive pain* is elicited (Fig. 2). This pain protects tissue from being further damaged, because usually withdrawal reflexes are elicited. *Pathophysiological nociceptive pain* occurs when the tissue is *inflamed* or *injured*. This pain may appear as spontaneous pain (pain in the absence of any intentional stimulation) and/or as hyperalgesia and/or allodynia. Hyperalgesia is a higher pain intensity that is felt upon noxious stimulation, and allodynia is the occurrence of pain that is elicited by stimuli that are normally below the pain threshold. Some authors include the lowering of the threshold in the term hyperalgesia in non-neuropathic pain.

While nociceptive pain is elicited by noxious stimulation of the sensory endings in the tissue, *neuropathic pain* results from *injury* or *disease* of neurons in the peripheral or central nervous system (Fig. 2). This pain does not primarily signal noxious tissue stimulation and, therefore, feels abnormal. It often has a burning or electrical character and can be persistent or occur in short episodes (e.g. trigeminal neuralgia). It might be combined with hyperalgesia and allodynia. In the allodynic state even the touching of the skin with a soft brush can cause intense pain. Numerous pathological processes can cause neuropathic pain, e.g. axotomy or nerve or plexus damage, metabolic diseases such as diabetes mellitus, or herpes zoster. The complex regional pain syndrome (CRPS) is a neuropathic pain syndrome that involves the sympathetic nervous system (one form was previously called sympathetic reflex dystrophy or Sudeck's disease) [6]. Damage to central pain processing neurons (e.g. in the thalamus) can cause central pain [4, 7].

## Chronic pain

Originally pain was called "chronic" when it lasted longer than 6 months [8]. More recently, chronic pain is often defined by its character. In many chronic pain states the causal relationship between nociception and pain is not tight and the pain does not reflect tissue damage. Rather,

psychological and social factors seem to determine the pain, e.g. in many cases of low back pain [9]. However, chronic pain might also result from a chronic disease and might then actually result from persistent nociceptive processes. It may be accompanied by neuroendocrine dysregulation, fatigue, dysphoria, and impaired physical and even mental performance [10].

## Peripheral mechanisms of pathophysiological nociceptive pain

During inflammation, polymodal nociceptors are sensitised (peripheral sensitisation, Fig. 3). In the normal tissue these fibres have relatively high mechanical and thermal thresholds, and high intensity stimuli are required to excite the neurons. In the course of inflammation the excitation threshold drops, such that even light, normally innocuous stimuli activate the fibres. Thus, when sensitised "pain fibres" are activated by normally non-painful stimuli these stimuli cause pain. Noxious stimuli evoke stronger responses than in the non-sensitised state [7, 11]. In addition, inflammation is also able to recruit so-called silent nociceptors. These are C-fibres that are inexcitable by noxious mechanical or thermal stimuli in normal tissue. However, during inflammation these primarily mechanosensitive fibres are sensitised, and then they are activated by stimuli [12]. Both the enhanced activity of sensitised polymodal nociceptors and the recruitment of silent nociceptors generate the pathophysiological nociceptive input to the spinal cord.

The sensitisation during inflammation is evoked by the action of inflammatory mediators on the nociceptors.

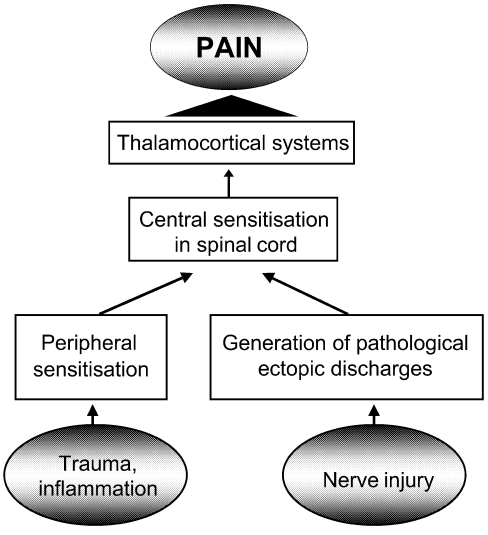


**Fig. 3** Flowchart of the generation of pain in different pain states. Central sensitisation can result both from peripheral sensitisation and from pathological discharges in the afferent nerve fibre

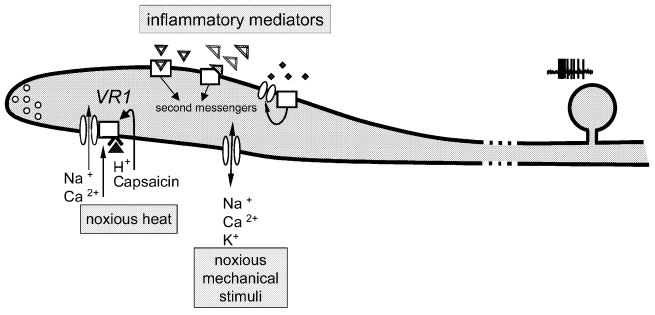


**Fig. 4** Sketch of the enlarged ending of a nociceptor in the tissue and its axon and cell body. *Bottom* the proposed ion channel that is activated by mechanical stimuli, and the TRPV1 receptor complex that is activated by capsaicin, protons and by noxious heat. *Top* receptors for inflammatory mediators. *The circles in the cone* symbolise vesicles filled with neuropeptides (substance P, CGRP) that can be released from the ending

Numerous inflammatory mediators are produced and released in the course of inflammation, and they cause the classical signs of inflammation, i.e. swelling, redness, hyperthermia, and pain. As mentioned, nociceptors express receptors for the transduction of mechanical, thermal or chemical stimuli into electrical potentials. In Fig. 4 a scheme of a sensory ending of a nociceptor is shown, with a variety of ion channels and receptors [13, 14, 15]. Not all receptors and ion channels are expressed in each nociceptor.

Mechanoreception is thought to result from an opening of cation channels leading to a depolarisation of the ending. During inflammation the swelling may more effectively open these channels than under normal conditions [1]. Heat sensitivity and thermal hyperalgesia during inflammation are, at least in part, mediated by the activation of an ion channel that is part of the capsaicin-sensitive vanilloid 1 receptor (TRPV1). This receptor is also activated by capsaicin, the compound in the hot pepper that causes pain [16, 17].

Inflammatory mediators (prostaglandins, bradykinin, histamine, ATP and acetylcholine, and others) interact with specific receptors on the sensory ending. They either activate the neurons directly or sensitise them for other stimuli [13]. The mediators activate second messenger cascades, which then influence ion channels in the membrane. This process leads to enhanced excitability of the neuron, with lowered threshold and increased action potential frequency elicited during suprathreshold stimulation [18]. Up to now, drug treatment interferes only with the synthesis of prostaglandins (see below) but many other important molecules are not directly targeted.

Primary afferent neurons also express receptors for neurotrophins. Neurotrophins are survival factors during the development of the nervous system, but during inflammation of the tissue, the level of nerve growth factor (NGF) is substantially enhanced. By acting on the

tyrosine kinase A (trk A) receptors, NGF increases the synthesis of substance P and CGRP in the primary afferents. The release of these peptides from the endings produces neurogenic inflammation (see above). NGF may also act on mast cells and, thereby, activate and sensitise sensory endings by mast cell degranulation [19].

The sensitisation of nociceptors is rapidly induced, i.e. the changes mentioned can be observed within a few minutes. If noxious stimuli persist, changes in the expression of receptors in the primary afferents are induced. For example, the expression of neurokinin 1 receptors (activated by substance P) and bradykinin receptors is enhanced in rat dorsal root ganglia and in peripheral nerve fibres during persistent inflammation [20].

## Peripheral mechanisms of neuropathic pain

While in healthy sensory nerve fibres action potentials are generated in the sensory endings upon stimulation of the receptive field, impaired nerve fibres often show pathological ectopic discharges (Fig. 3). These action potentials are generated at the site of nerve injury or in the cell body of impaired fibres in dorsal root ganglia. The discharge patterns vary, from rhythmic firing to intermittent bursts [21, 22].

Ectopic discharges do not only occur in A$\delta$-fibres and C-fibres but also in thick myelinated A$\beta$-nerve fibres that encode innocuous mechanosensory information. This has led to the idea that, after nerve injury, low threshold A$\beta$-fibres, as well as A$\delta$-fibres and C-fibres, are involved in the generation of pain. In particular, two mechanisms have been proposed as to how impaired A$\beta$-nerve fibres might cause pain. First, A$\beta$-fibres might evoke exaggerated responses in spinal cord neurons that have undergone the process of central sensitisation (see below). Second, A$\beta$-fibres might sprout into spinal cord layers that are usually only a target of C-fibres, and, thus, these fibres might activate the "wrong" neurons [23]. These hypotheses are currently being further explored. Recently, however, the hypothesis was put forward that pain is not generated by the injured nerve fibres themselves but by intact nerve fibres in the vicinity of injured nerve fibres. After an experimental lesion had been introduced in the L5 dorsal root, spontaneous action potential discharges were observed in C-fibres in the uninjured L4 dorsal root. These fibres might have been affected by the Wallerian degeneration [24].

Different mechanisms are thought to produce ectopic discharges: changes in the expression of ionic channels, pathological activation of axons by inflammatory mediators, and pathological activation of injured nerve fibres by the sympathetic nervous system. At least six different types of sodium channels were found in primary afferents, two of them being tetrodotoxin (TTX)-insensitive [14]. Sodium influx through TTX-sensitive sodium channels into the neuron inactivates very quickly; sodium influx through TTX-insensitive sodium channels is more slowly inactivating [25]. After nerve injury the expression of TTX-sensitive sodium channels is increased, and the expression of TTX-insensitive sodium channels is decreased. These changes are thought to alter the membrane properties of the neuron, such that rapid firing rates (bursting ectopic discharges) are favoured [25]. Changes in the expression of potassium channels of the neurons have also been shown [26].

Injured axons of primary afferent neurons might be excited by inflammatory mediators, e.g. by bradykinin, NO [22, 27, 28, 29, 30], and by cytokines [31]. The source of these inflammatory mediators might be white bloods cells and Schwann cells around the damaged nerve fibres. The sympathetic nervous system does not activate primary afferents in normal tissue. Injured nerve fibres, however, might become sensitive to adrenergic mediators [32, 33, 34]. This cross-talk might occur at different sites. Adrenergic receptors might be expressed at the sensory nerve fibre ending. A direct connection between afferent and efferent fibres (so-called ephapses) is considered. Sympathetic endings are expressed in increased numbers in the spinal ganglion after nerve injury. The cell bodies of injured nerve fibres are surrounded by "baskets", consisting of sympathetic fibres [35]. Currently, the best treatment is the application of drugs that reduce the excitability of neurons (e.g. carbamazepine or gabapentin).

## Central sensitisation

Pathological nociceptive input often causes central sensitisation (Fig. 3). This is an increase of excitability of spinal cord neurons [36]. Hyperexcitable spinal cord neurons are more susceptible to peripheral inputs and respond, therefore, more strongly to stimulation. Central sensitisation amplifies the processing of nociceptive input and is thus an important mechanism that is involved in clinically relevant pain states (Fig. 3). It consists of the following phenomena: (a) increase of the responses to input from the injured or inflamed region; (b) increase of the responses to input from regions adjacent to and even remote from the injured/inflamed region, although these areas are not injured/inflamed; (c) expansion of the receptive fields of the spinal cord, i.e. the total area from which the neuron is activated, is enlarged. Presumably the latter accounts for secondary hyperalgesia, i.e. hyperalgesia in normal tissue surrounding the injured/inflamed area (Fig. 5) [37].

Figure 5 shows a model of how central sensitisation could work. The top graph shows the original receptive field in the leg (hatched area) of a spinal cord neuron. Pressure on this area causes a response of the neuron.

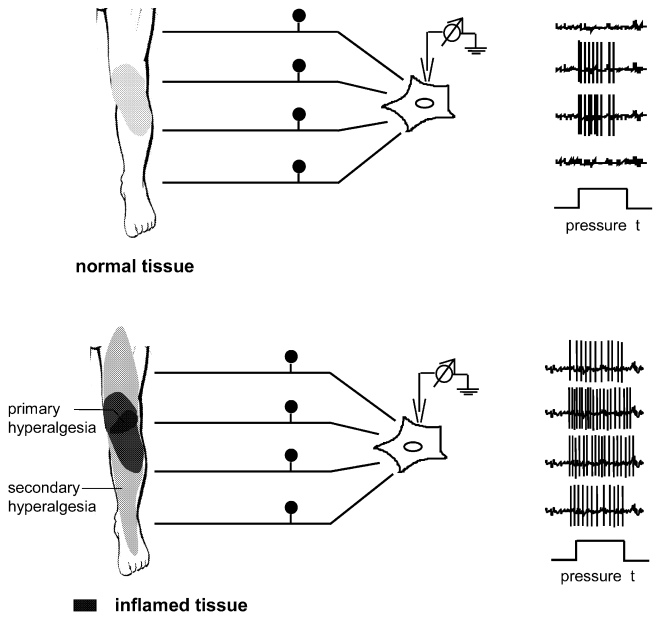


**Fig. 5** Development of central sensitisation in a spinal cord neuron. In normal tissue (*top*) this spinal cord neuron is activated (see action potentials *at the right*) only by pressure on its normal receptive field (*shaded area*) but not by pressure on adjacent or remote tissue (no action potentials elicited). During inflammation in the receptive field (*bottom*), stimulation of the inflamed area within the receptive field elicits a stronger response. A stronger response is also elicited by stimulation of the adjacent area, and the total receptive field expands. This creates a zone of secondary hyperalgesia, i.e. an area which is hyperalgesic although the tissue is normal

Stimulation of the surrounding adjacent area does not cause a response, although some afferent fibres from this fringe area project to the same neuron. Under normal conditions, synaptic activation by these afferents is too weak to evoke a suprathreshold response. During injury, nociceptors in the receptive field are sensitised, and their increased activity causes activation and sensitisation of the spinal cord neuron. When the spinal cord neuron is rendered hyperexcitable, the weak inputs from the adjacent regions outside the original receptive field are sufficient to excite the spinal cord neuron, and, hence, the receptive field shows an expansion. Another consequence of peripheral inflammation and spinal sensitisation is that, in the spinal segments with input from the lesioned/injured regions, a higher proportion of neurons respond to stimulation of peripheral tissue [36, 37, 38, 39].

In many cases, central sensitisation persists for as long as the nociceptive input persists, and it disappears when the peripheral input is reduced. In other cases, however, central sensitisation may outlast the peripheral nociceptive process. Possibly, nociceptive inputs have triggered a so-called long-term potentiation, a persistent increase of synaptic efficacy [40]. Such a process could account for pain states that persist even when the peripheral nociceptive process has disappeared.

Different receptor/transmitter systems are involved in the induction and maintenance of central sensitisation [41]. Glutamate is the main transmitter in nociceptors [42]. It activates ionotropic *N*-methyl-D-aspartate (NMDA) and non-NMDA receptors and metabotropic glutamate receptors in spinal cord neurons. When non-NMDA receptors are opened by glutamate, sodium influx depolarises the neuron. This is the basal response of a neuron. When NMDA receptors are opened by glutamate, large amounts of calcium flow into the neuron. Calcium ions induce second-messenger cascades that increase neuronal excitability. NMDA receptors are only opened when the neuron is strongly depolarised. Under resting conditions, and during weak depolarisation, a magnesium ion closes the channel. During noxious stimulation, both non-NMDA and NMDA receptors are opened. Administration of antagonists to the NMDA receptor can prevent central sensitisation [43], and established hyperexcitability can be reduced by NMDA receptor antagonists. Thus, NMDA receptors play a key role in the induction and maintenance of central sensitisation [43]. A potent blocker of NMDA receptors is ketamine. This drug is antinociceptive, but the use of NMDA antagonists in non-operative pain treatment is hampered by side effects such as psychosis because NMDA receptors are expressed and are important throughout the brain.

Neuropeptides and spinal prostaglandins are also involved in the process of central sensitisation. Many neurons in the spinal cord express receptors for the tachykinins substance P, neurokinin A, and CGRP [41]. During peripheral inflammation, the spinal release of substance P, neurokinin A and CRGP from nociceptors is increased [44, 45, 46], and these neuropeptides support the generation of spinal cord hyperexcitability. Spinal application of antagonists to these receptors attenuates the development of inflammation-mediated hyperexcitability [47, 48, 49], probably by facilitation of glutamatergic synaptic transmission [50, 51].

As mentioned above, prostaglandins (PGs) play an important role as inflammatory mediators in the periphery. Non-steriodal anti-inflammatory drugs (NSAIDs) block cyclo-oxygenases (COXs) and, hence, reduce the production of PGs. Application of NSAIDs reduces the activity and responsiveness of primary afferents [52]. This is the peripheral basis of their analgesic action. New COX inhibitors block only COX-2. However, PGs are also important in synaptic processing in the spinal cord. During inflammation in the periphery $PGE_2$ is released in the spinal cord [53]. Topical application of $PGE_2$ to the spinal cord causes nociceptive reactions in conscious animals [54]. Electrophysiological recordings have shown that topical application of $PGE_2$ to the spinal cord causes central sensitisation similar to peripheral inflammation, and application of the PG synthesis inhibitor indometh-

acin to the spinal cord, prior to induction of inflammation, attenuates the development of spinal hyperexcitability [55]. Thus, PGs are also important in spinal nociceptive processing.

## Conclusions

Pain research has begun to pinpoint neuronal mechanisms that underlie clinically relevant pain states, and currently the molecular basis of these neuronal events is being explored. There is already some understanding of which molecules transduce noxious stimuli in the sensory endings and how nociceptors are sensitised, and considerable knowledge has been achieved on the role of the central nervous system in the generation of pain response and on nociception-induced neuroplasticity (e.g. central sensitisation). Efforts are being made to transfer knowledge from experimental findings to the clinical situation and, vice versa, to explore clinical problems in experimental approaches. This will finally lead to a more rational basis for pain therapy and, hopefully, also to the development of further drugs with new targets.

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