# Peripheral and central sensitization

*Sensibilização periférica e central*

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## ABSTRACT

**BACKGROUND AND OBJECTIVES**: Central sensitization is an important phenomenon for pain chronicity and is present in neuropathic pain. This study aimed at addressing some pathophysiological aspects of this phenomenon.
**CONTENTS**: Some extra and intracellular aspects responsible for central sensitization genesis, especially phenotypic changes in plasticity of neurons involved in the process are described.
**CONCLUSION**: Pain chronicity may result from changes in central nervous system neurons properties by the central sensitization phenomenon with constant changes in membrane excitability, inhibitory transmission reduction and increase in synaptic efficacy mediated by several convergent and divergent molecular mechanisms over a background of phenotypic and structural changes. Neuroplasticity deeply alters painful sensation, contributing for many clinical painful syndromes and may represent a major target for therapeutic intervention.

**Keywords**: Central sensitization, Ionophores, Neural plasticity, Neuropathic pain.


## RESUMO

**JUSTIFICATIVA E OBJETIVOS**: A sensibilização central é um fenômeno importante na cronificação da dor e presente na dor neuropática. O objetivo deste estudo foi abordar alguns aspectos fisiopatológicos deste fenômeno.
**CONTEÚDO**: São descritos alguns aspectos extra e intracelular responsável pela gênese da sensibilização central, principalmente aspectos de alterações fenotípicas que ocorrem na plasticidade dos neurônios envolvidos no processo.
**CONCLUSÃO**: A cronificação da dor pode surgir como resultado de alterações nas propriedades dos neurônios no sistema nervoso central pelo fenômeno da sensibilização central com constantes mudanças e alterações na excitabilidade da membrana, reduções na transmissão inibitória e aumento da eficácia sináptica, mediada por muitos convergentes e divergentes mecanismos moleculares sobre um fundo de modificações fenotípicas e alterações estruturais. A neuroplasticidade altera profundamente a sensação dolorosa, contribuindo para muitas síndromes clínicas da dor e pode representar um importante alvo para intervenção terapêutica.

**Descritores**: Dor neuropática, Ionóforos, Plasticidade neuronal, Sensibilização central.

## INTRODUCTION

Before the definition of central sensitization, prevalent view of central pain processing was that it was a passive process, where action potentials bringing information on site, intensity, onset and quality of peripheral stimuli were brought to central nervous system (CNS) up to brain cortex where they were brought to consciousness. As from Melzack and Wall's Gate Theory, it was proposed that painful stimuli could be inhibited in spinal cord[1]. The Gate Theory, together with the discovery of enkephalins and endorphins[2,3] and diffuse inhibitory pain control have enhanced the knowledge of inhibitory nociception systems[4]. However, no model considered that pain could result from transformations in CNS neuronal properties, characterizing central sensitization. This article addresses some central sensitization aspects.

Central sensitization is a major phenomenon, together with peripheral sensitization, which helps understanding chronic or amplified pain. There is central sensitization after intense or repetitive stimulus of the nociceptor present in the periphery, leading to reversible increase of excitability and of synaptic efficacy of central nociceptive pathway neurons. It is manifested as hypersensitivity to pain called tactile allodynia and hyperalgesia secondary to puncture or pressure. These CNS changes may be detected by electrophysiological or imaging techniques.

Central sensitization may be temporary or permanent, depending on neuronal phenotypic changes. Sensitivity induced in the somatosensory system nociceptor is adaptive, making the system hyper-alert in conditions where there is higher risk of causing further injuries, such as immediately after exposure to intense or noxious stimuli.

Painful sensation (allodynia or not) is exaggerated and prolonged in response to generating stimuli and may be distributed to beyond injury site as from receptive field enhancement. Central sensitization explains changes observed in sensitivity threshold, time and region of pain in clinical situations of acute and chronic pain, where painful sensations exist even in the absence of peripheral diseases or nociceptive stimuli.

## DEFINITION

Central sensitization is a change in functional state of neurons and nociceptive pathways throughout the neuraxis, caused by increased membrane excitability and synaptic efficiency or by decreased inhibition on this system[5]. There are several phenomena involved in central sensitization: activation of wide dynamic range neurons (WDR), which start to respond to nociceptive and also previously non-nociceptive stimuli; progressive increase of responses provoked by a standard series of repeated stimuli (temporal windup); expansion of stimulus spatial extension; and triggering of changes lasting longer than the initial stimulus[6].

There is central sensitivity in neuropathic pain[7], inflammatory pain[8], migraine[9] and irritable bowel syndrome[10], among other painful syndromes. In these patients, central sensitization is involved with the production of abnormal responses to nociceptive and painless stimuli and there is a dispersion of sensitivity beyond peripheral pain-generating sites. Central sensitization may also play a critical role in widespread and abnormal pain in fibromyalgia patients[11].

Due to its important role in the generation of clinical pain hypersensitivity, it is essential to understand triggers and mechanisms responsible for somatosensory system induction and maintenance in physiologic state, where sensory experiences evoked by low intensity stimuli (harmless sensations) and painful stimuli are largely different and separate, for a dysfunctional hypersensitivity system where this discrimination is lost.

## HISTORY

The first evidence of a central acute hypersensitivity component was supplied in 1983[5]. Electrophysiological responses of motoneurons $\alpha$ of femoral biceps of rats were used to measure response to the nociceptive system, in this case the flexor reflex response of flinching provoked by nociceptive stimuli. This experiment has shown, as expected, that in normal conditions there was no spontaneous activity of the motor neuron and that its activation was needed for a mechanical or thermal stimulus noxious to skin.

These neurons have high nociceptive threshold and specific receptive fields to hind paw toes. Peripheral thermal stimuli generate mild paw inflammation. However, increased excitability of motor neurons was detected and

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has lasted several hours including decreased threshold and increased skin receptive fields. Motor neurons were not more specific to nociceptive stimuli, but could be activated by non-nociceptive low intensity stimuli such as light or mild touch[5]. Other experiments have shown that these changes in receptive field properties were due to changes in CNS rather that in peripheral nervous system (PNS).

After the first demonstration of central sensitization in flexor motor neurons, virtually identical changes were soon described in different studies in laminae I and V of spinal dorsal horn neurons[12], as well as in spinal nucleus, *pars caudalis*[13], thalamus[14], amygdala[15] and anterior cortex cingulated area[16]. More recently, nuclear magnetic resonance (MRI), positron emission tomography and magnoencephalography images have shown in healthy volunteers that other brain structures were also implied in central pain processing (parabrachial core of the periaqueductal gray matter, superior colliculus, prefrontal cortex) which also show changes compatible with increased sensitivity corresponding to central sensitization[17].

Central sensitization refers to changes in neuronal activity, also known as neuronal plasticity, which may be temporary or permanent.

These neuronal changes, in case of central sensitization, are triggered by dorsal horn neurons activity in response to nociceptor stimuli present in C fibers, such as thermal stimuli above 49ºC and repeated stimuli[5], electric C fibers stimulation (1 Hz for 10 to 20 seconds)[8] and chemical stimulation by the activation of nociceptors by irritating compounds such as allyl-isothiocyanate (mustard oil) and formalin, which act by activating TRPA1 channels, and by capsaicin, which activates TRPV1 channels[19,20].

Central sensitization is induced after intense, repeated and sustained nociceptive stimuli. The entrance of many fibers is required along tens of seconds; a single stimulus, such as a prick is insufficient. Peripheral tissue injury is not necessary; however the level of nociceptive stimulus producing tissue injury almost always induces central sensitization.

The phenomenon is very prominent after traumatic or surgical injury. And interestingly, afferent nociceptors responsible for innervations of muscles and joints generate more long- lasting central sensitization as compared to those innervating the skin[18].

Phenomena generating central sensitization are molecular. Most common scientific way to obtain new knowledge is by using the mechanicist approach to look for mechanisms responsible for phenomena. When using this approach care is needed so that the understanding of mechanisms does not impair a more general view of the painful phenomenon.

## NEUROTRANSMITTERS AND RECEPTORS

Glutamate, neurotransmitter of primary afferent neurons, binds to several post-synaptic receptors on spinal dorsal horn, including ionophores such as amino-3-hydroxy-5-methyl-4-isoxazole proprionate (AMPAR), N-methyl-D-aspartate (NMDAR), kainate (KA), metabotropic receptors (coupled to G protein) and other subtypes of glutamate receptors (mGluR).

In dorsal horn superficial laminae, AMPAR and NMDAR are present in virtually all synapses, and are disposed in mosaic shape, while mGluRs are located in the extremities of the post-synaptic density zone (SDZ). NMDAR is a tetramer with two NR1 subunits of low affinity glycine binding and two subunits of the 6 different types of NR2A-D or NR3A/B[21]. Most common NMDAR complexes formed in dorsal horn are composed of NR1-NR2A/B subunits[22].

AMPA receptor is also a tetramer and its more abundant subunits are calcium-permeable ($Ca^{2+}$) GluR1 and GluR3, and subunit GluR2 not $CA^{2+}$-permeable in physiologic conditions[23]. Inhibitory interneurons preferably express GluAR1 since excitatory neurons seem to preferably express GluR2[24]. AMPAR complex may also be a GluR1/GluR2 heteromer, in this case the receptor primarily shows GluR2 properties[25]. The mGluR family is made up of 8 receptors which form 3 groups based on their sequence similarities and on their coupling with specific G proteins.

Group I, made up of mGluR1/mGluR5, is coupled to G-αq proteins, the activation of which increases $CA^{2+}$ inflow, while group II (mGluR32 and 3) and group III (mGluR4, 6, 7 and 8) are coupled to G-αi/o proteins. All mGluRs, except mGluR6 and 8, are expressed in the spinal cord, being GluR6 the only not expressed in primary afferent neurons[26]. In addition, a specific expression lamina pattern has been characterized by mGluR1a (lamina V), mGluR5 (lamina II) and mGluR2/3 (lamina II), suggesting precise and distinct physiologic functions for different subtypes.

## ROLE OF MAGNESIUM, SUBSTANCE P, PEPTIDE OF CALCITONIN-RELATED GENE, AND BRADYKININE IN CENTRAL SENSITIZATION

In normal conditions, NMDAR ionophore is voltage-dependent blocked by a magnesium ion ($Mg^{2+}$) located in the receptor´s pore. Sustained release by glutamate nociceptors, neuropeptides, substance P (SP) and gene related peptide calcitonin (CGPR) leads to enough depolarization of plasma membrane, forcing $MG^{2+}$ ion to leave NMDA receptor pore when then glutamate binding to the receptor generates an internal current and $CA^{2+}$ inflow. This large amount of calcium ions inflow activates numerous intracellular pathways which contribute for the maintenance of central sensitization[27]. In addition to NMDAR critical role in increasing nociceptive neurons excitability, the activation of group I mGluRs by glutamate also seems to be important for the development of central sensitization[6].

SP which is co-released with glutamate by unmyelinated peptidergic nociceptors (C fibers), is also involved in central sensitization generation[28,29]. SP is bound to neurokinin-1 (NK1), receptor coupled to G protein, causing long lasting membrane depolarization. The ablation of neurons expressing NK1 receptor in spinal cord leads to decreased central sensitization induced by capsaicin, confirming the importance of SP in this phenomenon.

The CGRP, also synthesized by small sensory neurons, potentiates SP effects and participates on central sensitization by means of CGRP1 post-synaptic receptors which activate protein kinase A and C (PKA and PKC)[30]. CGRP also increases brain-derived neurotrophic factor (BDNF) release of trigeminal nociceptors which may contribute for its participation on migraine and other primary headaches[31].

Bradykinin, pro-inflammatory substance activating and sensitizing the primary afferent, is also produced in the spinal cord in response to intense peripheral painful stimuli and acts by means of its B2 receptor, which is expressed by dorsal horn neurons, increases synaptic efficiency by activating protein kinase A (PKA), protein kinase C (PKC) and kinases regulated by extracellular stimuli (ERK). ERK may also be activated by serotoninergic descending pathway (5-HT) involving receptor 5-HT3 and possibly receptor 5-HT7.

## ROLE OF CALCIUM ION AND NEURONAL PLASTICITY

Increased intracellular $Ca^{2+}$ as from a certain concentration seems to be the primary trigger of central sensitization. Calcium inflow by means of MNDAR seems to be particularly important in the induction phase. Inflow may also occur by means of calcium-permeable AMPARs and as from intracellular release by microsomes stored in response to the activation of metabotropic receptors[32]. Increased intracellular calcium makes AMPAR and NMDAR receptors to be phosphorilated by PKA/PKC which change its activities and the traffic of receptors to plasma membrane[33].

AMPAR and NMDAR receptors phosphorilation during central sensitization increases density and activity of such receptors leading to post-synaptic hyperexcitability. The first central sensitization phase is a fast increase in dorsal horn excitatory and glutamatergic synapses, strengthening nociceptive transmission and recruiting non-nociceptive stimuli to this pathway. This is obtained by phosphorilation of numerous receptors and ion channels which leads to changes in channels threshold and kinetics, in addition to changes in receptors transmission in the synapse[34,35].

AMPAR and NMDAR stimulation participates in the activation of intracellular pathways which support central sensitization and include phospholipase C pathway (PLC) and PKC, phosphatidilinositol-3-kinase pathway (PI3K) and proteinokinase system pathway activated by mytogen/kinase and regulated by extracellular signal (MAPK/ERK)[36-38]. ERK activation by its phosphorilation occurs after intense nociceptive stimulation coming from the periphery, similar to that present in central sensitization. ERK phosphorilation is considered a marker of neuronal plasticity occurring in central sensitization[39,40].

PKC activation also contributes and is an important phenomenon for the hyperexcitability of second order neurons by different ways. First, PKC decreases NMDAR $Mg^{2+}$ block increasing the possibility of channel opening, making easier NMDAR activated state[41]. Activated PKC decreases inhibitory transmission, decreasing gamma amino butyric acid (GABA) levels of tonic glycin inhibition[42], of descending inhibition conducted by periaqueductal gray matter PAG. Disinhibition is another mechanism making fibers

more susceptible to excitatory stimuli, being central sensitization triggering and maintenance mechanism[43].

In summary, one may say that central sensitization is a general phenomenon producing different changes in somatosensory processes, generated and mediated by different mechanisms which, in response to nociceptor stimuli may: (1) increase membrane excitability, (2) help synaptic transmission or (3) decrease inhibitory influences in dorsal horn neurons.

Central sensitization may become pathologic in situations when it becomes autonomous and is maintained even in the absence of active peripheral event. Central sensitization is not only a state where pain may be triggered by less intense stimuli, but also where it can be maintained by a different type of stimulus.

There may be central sensitization with different types of pain. Following we shall address its onset in neuropathic pain (NP), object of this edition of the journal.

After peripheral nerve injury, injured C and A fibers start to generate spontaneous action potentials and may start and maintain central sensitization[44,45]. Uninjured sensory fibers may also participate in the afferences inducing central sensitization in dorsal horn neurons[46]. After peripheral nervous system injury there might be C fiber terminations degeneration in the dorsal horn with consequent loss of this pre-synaptic stimulus and beginning of sprouting of other axons such as those of Aβ fibers which start to have synapses in different laminae[47,48].

Changes in neuronal plasticity after peripheral nerve injury are more severe than those induced by inflammatory pain. There are changes in ion channels, receptors, neurotransmitters and intracellular action proteins transcription[49,50-52]. There is important disinhibition of most superficial spinal dorsal horn laminae in NP, with decreased gabaergic and glycinergic currents, in part due to apoptosis[53]. Neuronal death seems to be result of cytotoxicity induced by increased expression of NMDA receptors and their activation[54].

After peripheral neuronal injury there is also increased activity of descending excitatory controls coming from brainstem and decreased action of inhibitory controls[55,56].

Glial activation is very intense after peripheral nerve injury, as well as the infiltration of immune cells. The activation of microglia and astrocytes, both in quantity and temporally, is higher after neuronal injury than in response to inflammation[57,58]. Activated microglia and astrocytes produce and release trophic factors, neurotransmitters, cytokines, chemokines, release substances such as nitric oxide and BNDF and may also lead to neuronal apoptosis[59,60]. In general, microglial activation is earlier and participates in the onset of central sensitization process and astrocytes activation is slower, but remains for a longer time, with more important role in the maintenance of neuronal hypersensitivity as compared to microglia[61].

## CONCLUSION

Pain chronicity may be result of changes in CNS neuron properties by central sensitization phenomenon. Nociceptive pathways are subject to excitatory and inhibitory modulations.

Changes in the balance of such modulations may change neuronal functional properties and decrease pain threshold, increase magnitude and duration of responses to nociceptive afferences allowing that normally painless afferences start to generate painful sensations. Pain is not simply a reflex of peripheral afferences, but a dynamic reflex of central neuronal plasticity. Neuroplasticity deeply changes painful sensation, contributing to many clinical pain syndromes and may be an important target for therapeutic intervention.

The complexity is daunting because the essence of central sensitization is a mosaic of constant changes and alterations in membrane excitability, reductions on inhibitory transmission and increased synaptic efficacy, mediated by several convergent and divergent molecular mechanisms on a background of phenotypic and structural changes.

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