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 cronicização da dor e presente na dor neuropática. O objetivo deste estudo foi abordar alguns aspectos fisiopatológicos deste fenômeno.

CONTÊUDO: São descritos alguns aspectos extra e intracelular responsáveis pela gênese da sensibilização central, principalmente aspectos de alterações fenotípicas que ocorrem na plasticidade dos neurônios envolvidos no processo.

CONCLUSÃO: A cronicização 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 inhibitória 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 cord1. The Gate Theory, together with the discovery of enkephalins and endorphins2,3 and diffuse inhibitory pain control have enhanced the knowledge of inhibitory nociception systems4. 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 hypersensitization 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. Sensitization 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 system5. 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 stimulus6.

There is central sensitivity in neuropathic pain7, inflammatory pain8, migraine9 and irritable bowel syndrome10, 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 patients11. 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 198312. Electrophysiological responses of motoneurons 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
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. Other experiments have shown that these changes in receptive field properties were due to changes in CNS rather than 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, as well as in spinal nuclei, pars caudalis, thalamus, amygdala and anterior cortex cingulated area. More recently, nuclear magnetic resonance (MRI), positron emission tomography and magnocnecephalography 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.

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 peripheral 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 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.

Phenomena generating central sensitization are molecular. Most common scientific way to obtain new knowledge is by using the mechanistic 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.

ROLE OF CALCIUM ION AND NEURONAL PLASTICITY

Increased intracellular Ca⁺⁺ as from a certain concentration seems to be the primary trigger of central sensitization. Calcium inflow by means of NMDAR 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. Increased intracellular calcium makes AMPAR and NMDAR receptors to be phosphorylated by PKA/PKC which change its activities and the traffic of receptors to plasma membrane.

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 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.

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more susceptible to excitatory stimuli, being central sensitization triggering and maintenance mechanism. 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 might 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. Uninjured sensory fibers may also participate in the affereces inducing central sensitization in dorsal horn neurons. 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. 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. There is important disinhibition of most superficial spinal dorsal horn laminae in NP with decreased gabaergic and glycinegic currents, in part due to apoptosis. Neuronal death seems to be result of cytotoxicity induced by increased expression of NMDA receptors and their activation. After peripheral neuronal injury there is also increased activity of descending excitatory controls coming from brainstem and decreased action of inhibitory controls. 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. 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. 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.

CONCLUSION

Pain chronicity may be related 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 affereces allowing that normally painless affereces start to generate painful sensations. Pain is not simply a reflex of peripheral affereces, 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 structural and genomic changes.

REFERENCES


