EDITORIAL

Mechanisms of Nociceptor Sensitization

Nociceptor sensitization by proinflammatory mediators is a pivotal mechanism underlying the aetiology of several painful conditions. Sensitized nociceptors display a tremendous increase in their excitability which give rise to an exaggerate response to mild noxious stimuli and even to non-noxious stimuli leading to the phenomena known as hyperalgesia and allodynia. It appears that sensory neuron overexcitability is the main event triggered by proalgesic agents. The discovery of the TRP family of receptors and, in particular, the members involved in thermosensation has thrust a significant advance in our knowledge of the cellular and molecular mechanisms underlying nociceptor sensitization. In recent years, the contribution of TRPV1, TRPM8 and, lately, of TRPA1 has been well confirmed and it is opening new venues for drug intervention. It is obvious that these are not the only channels intervening in nociceptors potentiation, but they are probably at the onset of such process. In addition, these ion channels are also the targets of diverse food spices that act as chemical irritants capable of sensitizing sensory neurons. In this hot topic Mini-Review, all our knowledge on this exciting topic will be addressed, focusing on the role of thermoTRP channels to the response of sensory neurons. Although many questions have been resolved, it is clear that many more are emerging and that we still are at the tip of the iceberg regarding the physiology and pathology of these sensory receptors. Nonetheless, the information accrued is paving the road for the design of new anti-inflammatory and analgesic molecules that may become in the future a realistic clinical option for pain therapy.

Nociceptors are specialized sensory neurons that respond to noxious stimuli alerting the brain of a hazardous situation. These neural receptors are functionally diverse encompassing form pure mechanoreceptors to polymodal neurons that recognize thermal and mechanical stimuli. Nociceptors can be classified attending to their conducting properties as Aδ fibers which are highly myelinated neurons with a conduction velocity of 20 m/s, and unmyelinated, C-fibers that conduct much slower (2 m/s). Under normal physiological conditions, nociceptors are silent neurons that are only activated if a dangerous stimulus is detected. In marked contrast, in pathological conditions, nociceptors are quite active, displaying strong excitability that results from a decrease in the threshold of activation and an amplification of their signalling. The higher excitability may lead to an exaggerated response to mild noxious stimuli (hyperalgesia) or mistakenly recognizing as harmful non-noxious stimuli (allodynia). These two phenomena are hallmark conditions of nociceptor sensitization under inflammatory conditions.

It is well known that nociceptors are highly sensitized by pro-inflammatory mediators that are released upon tissue damage. Pro-algesic agents activate intracellular signalling pathways that lead to the modulation of the levels and activity of several ion channels. Among the sensitized ionotropic receptors is the TRPV1, a polymodal ion channel that is activated by vanilloids, acidic pH, voltage and by noxious temperatures (>42ºC). TRPV1 has been signalled as a key receptor contributing to the onset and maintenance of nociceptor sensitization under inflammation. This tenet is supported by the drastic potentiation of the channel activity by proinflammatory mediators. The function of other ionotropic channels, as well as metabotropic receptors, is also upregulated by algogens contributing to the nociceptor sensitization characteristic of inflammatory conditions.

In this Mini-Hot topic reviews, we have compiled 4 papers that timely and accurately review several aspects of nociceptor sensitization. First, the paper by Jara-Oseguera *et al.* describes in detail our current knowledge underlying the mechanism of activation of TRPV1. As mentioned, this ion channel is capable of recognizing both chemical and physical stimuli and transduces them into channel activity by using the activation energy to gate the channel. The understanding of how channels work in terms of their underlying protein structure is a first and critical step to comprehend how their activity is modulated by intracellular signalling proteins such as PKA, PKC and Src that chemically modify the protein. Unfortunately, we have not yet available the atomic structure of this receptor, although recent progress in structure-function studies is shedding light on the mechanisms of channel gating. Because of the overall structural conservation among thermoTRPs, these data may also outline some general features of channel gating in this family of ion channels.

In a second paper, Fisher *et al.* thoroughly expose the existing information on the role of ion channels in the sensitization of nociceptors. The review walks through our knowledge on the participation of the different ion channels and how they are altered under inflammatory conditions. In addition, it nicely unveils the contribution of these molecular devices to both the onset and maintenance of neuronal sensitization. This review is complemented by Michaela Kress who address the role of proinflammatory cytokines and chemokines in the inflammatory process. These algogens act on both ionotropic and metabotropic receptors increasing drastically the excitability of sensory neurons. In addition, they also act on non-neuronal cells, stimulating the release of more pro-algesic compounds which, in turn, further excite nociceptors. This vicious cycle creates a neuroimmune feedback loop that potentiates the consequences of inflammation.

The molecular mechanisms participating in the inflammatory potentiation of nociceptors encompass a quite active research field. There are several hypotheses that involve the direct (or indirect) action of the pro-algesic compounds on ion channels function as well as the modulation of channel expression at the neuronal surface. For instance, it is well known that algogens activate intracellular signalling cascades involving PKA, PKC, PI3K and Src, that can phosphorylate ion channels altering their

1876-3863/10 2010 Bentham Open

gating properties. In this regard, phosphorylation of TRPV1 appears to decrease the threshold of temperature activation from 42ºC down to 35ºC. In addition, TRPV1 phosphorylation may also affect the rate and extent of desensitization, leading to channel overactivation. In addition, to this modulation of channel activity, it has been also shown that pro-inflammatory agents such as NGF and IGF-I potentiate TRPV1 channels by increasing its expression in the neuronal surface by a mechanism that also involves the contribution of PKC and Src. Recent results in DRG neurons have unveiled that some proinflammatory compounds potentiate TRPV1 and nociceptors primarily by recruiting channels to the neuronal plasma membrane, while other sensitize the thermoTRP by direct action on intracellular signalling cascades. These data may suggest the existence of different sensitizing mechanisms in distinct nociceptor subpopulations or diversity in the molecular components of the activated intracellular signalling cascades. The review by Camprubí-Robles *et al.* dwells in this exciting topic and presents the later results, not only with TRPV1 but also with other ion channels involved in nociceptor inflammation.

In the past years, there has been an important progress in our knowledge of the molecular components and mechanisms underlying the manifestation of nociceptor inflammation. Several channels, and their complexes, have been signalled as key for the onset and maintenance of this phenomenon. Although we have accrued significant information, our understanding of the process is still at its infancy and the future will probably bring us surprising, novel and exciting data that will build up a precise molecular blueprint of nociceptor sensitization for improved therapeutic intervention.

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