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Development of Analgesics: A Little Help from Mitogen and Stress-Activated Kinases 1 and 2

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Pain is a physiological response that is vital for survival. Hence, when potentially tissue-damaging impacts act on naive tissues, a warning signal that consists of a pain experience and an escape reaction such as a withdrawal reflex is generated [1-3]. If the impact does not produce tissue damage, the warning signal's pain component, called "acute nociceptive pain", ceases shortly after the termination of the insult [1-3]. However, if the insult does induce tissue damage, a different pain experience develops [1-3]. This tissue injury-associated pain usually lasts during the entire course of the underlying disease. Therefore, this type of pain is termed "prolonged pain" [1-4].

Prolonged pain, if it lasts until the underlying condition is resolved, is considered adaptive because it provides the biological benefits of tissue protection and the promotion of healing. However, conditions that underlay prolonged pain might not resolve. Further, prolonged pain may persist after the healing process is completed. In these circumstances, pain does not provide any biological benefit and is considered maladaptive [4].

In spite of significant efforts to develop novel and effective analgesics, controlling prolonged pain is still a major unmet medical need. Uncontrolled prolonged pain however, is a disease on its own, which is associated with unnecessary suffering, interferes with physical and emotional recovery, dramatically ruins the quality of life, induces co-morbidities, imposes an undue demand on health and social systems and generates loss for the economy [4]. Therefore, further putative targets for new analgesics should be found.

Acute and prolonged pain, in addition to their duration, also differ in quality because tissue injury-associated pain is characterised by the development of pathological pain experiences, which manifest themselves as hypersensitivities of the injured tissues and surrounding areas to thermal and/or mechanical stimuli. Depending on the intensity of stimulus which hypersensitivity develops to, the hypersensitivity can be either hyperalgesia, which is an increased pain response evoked by a normally painful stimulus, or allodynia, which is pain evoked by a normally innocuous stimulus [1-3].

Previous studies have identified that use-dependent increase in the activity and excitability, known as sensitisation, in neurons involved in pain signal (nociceptive) processing, constitutes the key mechanism that underlies both the temporal and qualitative differences between acute nociceptive and tissue injury-associated pain [1-3,5]. The sensitisation process results in changes in the cellular and molecular pathways through which nociceptive information is processed. Sensitisation occurs in all nociceptive processing areas in the nervous system. However, peripheral sensitisation, which describes the development of increased activity and excitability of nociceptive primary sensory neurons, and spinal sensitisation, which refers to the development of increased activity and excitability in spinal cord neurons are considered the most important for the development of pain [1,2].

The importance of nociceptive primary sensory neurons and spinal cord neurons is based on their function. Nociceptive primary sensory neurons are responsible for the detection of painful stimuli and "reporting" tissue damage to the central nervous system. Further, the activity and excitability of nociceptive primary sensory neurons drives nociceptive processing, including sensitisation in the spinal cord [6].

Spinal cord neurons on the other hand perform "first stage" processing of nociceptive information that determines the quality and quantity of nociceptive signals forwarded to various supraspinal centres. Based on the characteristics of the nociceptive information provided by the spinal cord, supraspinal centres including the cortex, where the pain experience is generated, develop responses [7].

Both peripheral and central sensitisations depend on two major components [1,2]. A few seconds-minutes after the injury, an early component develops which includes post-translational modification and translocation, from the cytoplasm to the cytoplasmic membrane, of various receptors and ion channels expressed by the sensitised neurons [1,2]. A second component then ensues within a few tens of minutes after the injury and it involves transcriptional changes. The second component is particularly important for the maintenance of the sensitised state hence for the maintenance of prolonged pain [1,2].

Tissue injury and the subsequent inflammatory reaction activate the mitogen-activated protein kinases p38 and extracellular signal-regulated kinases 1 and 2 (ERK1/2) in nociceptive primary sensory neurons and spinal cord neurons [1,2,8,9]. Blocking ERK1/2 activation reduces mechanical and/or thermal hypersensitivity following tissue injury/inflammation [8,10,11]. Phosphorylated ERK1/2 have a series of downstream targets including the mitogen- and stress-activated kinases 1 and 2 (MKS1/2) [12]. However, the ERK1/2 activation-induced transcriptional changes appear to be mediated predominantly by MSK1/2 [13,14].

In this context, we have recently made a highly significant discovery. We found that deleting MSK1/2 results in the failure of thermal hypersensitivity associated with tissue injury/inflammation to develop [15]. A series of evidence indicates that this inhibitory effect of MSK1/2 deletion must be due to the lack of inflammation-induced transcriptional changes hence the lack of the second phase of sensitisation to develop. MSK1/2 are located in the nucleus and known to induce transcriptional changes in a series of cell types including neurons following environmental challenges [13,14]. Hence, MSK1/2 have been shown to induce chromatin-remodelling and transcriptional alterations in neurons, which then produce changes in neuronal signalling and subsequently in behaviour [14,16,17]. Our recent findings [15] as well as a recent report from Tochiki and co-workers [18] have demonstrated a MSK1/2-dependent up-regulation in the expression of the immediate early gene product c-Fos, a well-established spinal marker for nociceptive processing [19], as well as phosphorylated (p) serine (S) 10 in histone H3 (H3; [15]) that is known to promote the expression of a series of genes including *cfos* [17]. We have also found most recently [20,21] that the induction of various types of animal models of inflammatory pain results in the up-regulation of p-S10H3 in a group of primary sensory neurons.

Although MSK1/2-/- mice lack these enzymes globally, the importance of peripheral and spinal sensitisation in the development of prolonged pain suggests that the lack of MSK1/2 in primary sensory neurons and/or spinal dorsal horn neurons could be the major reason for the failure of inflammatory heat hypersensitivity to develop.

Based on this assumption we propose that MSK1/2, or some of their downstream effectors, might serve as putative targets for novel analgesics.

MSK1/2's downstream effects include, in addition to the phosphorylation of S10H3, phosphorylation of S18H3, activation of the cAMP response element-binding protein and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB; [13,14]). All those effectors promote gene expression in neurons [22-24]. Therefore, further studies are needed to elucidate first the cell type (i.e. primary sensory neurons or spinal cord neurons) that contributes the most, through MSK1/2 activity, for the development of inflammatory heat hypersensitivity. Second, elucidating MSK1/2-dependent changes in gene expression may identify crucial regulatory molecules involved in the development of inflammatory heat hyperalgesia. Together these studies may reveal useful targets for further drug development.

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