Minireviews

Cellular and Molecular Mechanisms of Calcium/Calmodulin-Dependent Protein Kinase II in Chronic Pain

Ya-Qun Zhou,1 Dai-Qiang Liu,1 Shu-Ping Chen, Jia Sun, Xue-Rong Zhou, Fang Luo, Yu-Ke Tian, and Da-Wei Ye

Anesthesiology Institute, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China (Y.-Q.Z., D.-Q.L., S.-P.C., J.S., F.L., Y.-K.T.) and Cancer Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China (X.-R.Z., D.-W.Y.)

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ABSTRACT

Chronic pain, often defined as any pain lasting more than 3 months, is poorly managed because of its multifaceted and complex mechanisms. Calcium/calmodulin-dependent protein kinase II (CaMKII) is a multifunctional serine/threonine kinase that plays a fundamental role in synaptic plasticity, learning, and memory. Recent emerging evidence demonstrates increased expression and activity of CaMKII in the spinal cord and dorsal root ganglia of various chronic pain models. Moreover, our previous studies also find that inhibiting CaMKII could attenuate inflammatory pain and neuropathic pain. In this review, we provide evidence for the involvement of CaMKII in the initiation and development of chronic pain, including neuropathic pain, bone cancer pain, and inflammatory pain. Novel CaMKII inhibitors with potent inhibitory effect and high specificity may be alternative therapeutic strategies for the management of chronic pain in the future.

Introduction

Chronic pain represents a major public health concern with a high prevalence ranging from 19–50% of the population (van Hecke et al., 2013; Macfarlane, 2016; Zhou et al., 2016b). In addition to significantly affecting patient quality of life, chronic pain has a high economic burden (Crown, 2012; Pizzo and Clark, 2012; Zhou et al., 2016a). Currently, nonsteroidal anti-inflammatory drugs, opioids, and gabapentinoids (pregabalin and gabapentin) remain the first-line therapeutics in the treatment of chronic pain (Moulin et al., 2015; Alles and Smith, 2016; Paice et al., 2016). Unfortunately, these conventional drugs often lead to undesirable side effects that eventually limit their use. Despite marked advances in neuroscience research, few new drugs with potent antinociceptive effects and minimal adverse effects have been developed. Therefore, further understanding of the cellular and molecular mechanisms of chronic pain is warranted to promote discovery of novel targets for the development of effective analgesic drugs.

Calcium/calmodulin-dependent protein kinase II (CaMKII), a multifunctional serine/threonine kinase, comprises 12 subunits, each encoded by one of four genes (α, β, γ, and δ) (Rosenberg et al., 2005). Each of these subunits contains a highly conserved N-terminal catalytic domain responsible for enzymatic activity of the kinase, followed by a core regulatory domain and a C-terminal-associated domain responsible for assembly of the dodecameric holoenzyme (Fig. 1). The regulatory domain of CaMKII contains a calmodulin binding region and various regulatory sites (Lisman et al., 2012; Erickson et al., 2013; Stratton et al., 2013). Under inactive conditions, the activity of the catalytic domain of CaMKII is restrained by the autoinhibitory sequences within the regulatory domain (Griffith, 2004; Coultrap and Bayer, 2012). CaMKII can be activated when it binds to calcium/calmodulin and releases the catalytic domain from the inhibitory effects of the regulatory domain (Hund and Mohler, 2015). The activation

ABBREVIATIONS: AIP, autocamtide 2-related inhibitory peptide; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AS, antisense; BCP, bone cancer pain; CaMKII, calcium/calmodulin-dependent protein kinase II; CCI, chronic constriction injury; CFA, complete Freund’s adjuvant; CNP, central neuropathic pain; CXCR4, C-X-C motif chemokine receptor 4; DRG, dorsal root ganglia; HO-2, heme oxygenase type 2; IL-33, interleukin 33; iNOS, inducible nitric oxide synthase; K2P, potassium channels; LTP, long-term potentiation; NMDA, N-methyl-D-aspartate; pCaMKII, phosphorylated CaMKII; pCREB, phosphorylated CAMP-response element–binding protein; ROS, reactive oxygen species; SCI, spinal cord injury; SNL, spinal nerve ligation; tCaMKII, total calcium/calmodulin-dependent protein kinase II; Y1472F-KI, mice lacking phosphorylation of NR2B subunits at Tyr1472.
leads to autophosphorylation of the kinase at the sites Thr286 or Thr287, depending on the specific isoform (Mattiazzi et al., 2015). CaMKII autophosphorylation markedly enhances the binding affinity of calmodulin and blocks the regulatory domain from inhibiting catalysis, thereby generating autonomous kinase activity (Colbran and Brown, 2004). This autonomous activity persists until dephosphorylated by a regulatory phosphatase (Erickson, 2014) (Fig. 2).

It is well established that CaMKII plays a fundamental role in synaptic plasticity (Shen et al., 2000; Bejar et al., 2002; Sanhueza et al., 2007; Fukushima et al., 2008). Long-term potentiation (LTP) is a synaptic substrate for memory and learning (Lynch, 2004). Emerging evidence suggests that LTP can also be induced in pain-related sensory central synapses (e.g., spinal cord dorsal horn) and cortical areas that are important for pain perception (e.g., cingulate cortex, amygdala) (Luo et al., 2014). Moreover, LTP at spinal C-fiber synapses is considered as a synaptic model of pathologic pain since the spinal LTP can only be induced by noxious stimulus (Liu and Zhou, 2015). Interestingly, although there are differences between the synaptic plasticity contributing to central sensitization and LTP, there are also striking similarities, indicating that pain and memory may share similar mechanisms (Ji et al., 2003).

CaMKII is preferentially localized in the superficial laminae of the spinal cord dorsal horn and in the primary sensory neurons in dorsal root ganglia (DRG), which are vital for transmission and processing of nociceptive signals (Bruggemann et al., 2000; Carlton, 2002). Emerging evidence suggests that CaMKII may be a novel therapeutic target for the management of chronic pain. Our laboratory has been investigating the mechanisms of chronic pain for decades (Tian et al., 2009; Ye et al., 2014; Guan et al., 2015; Song et al., 2016; Sun et al., 2016; Chen et al., 2017). Previously, we have demonstrated that blocking CaMKII attenuated complete Freund's adjuvant (CFA)-induced inflammatory pain (Luo et al., 2008) and spinal nerve ligation (SNL)-induced neuropathic pain (Chen et al., 2009). Our recent study also found a critical role of CaMKII in the laterocapular division of the central amygdala (CeLC) in opioid-induced hyperalgesia (Li et al., 2016). Moreover, there is accumulating evidence demonstrating increased expression and activity of CaMKII in the spinal cord and DRG of various chronic pain models (Liang et al., 2004a; Crown et al., 2012; Ferhatovic et al., 2013a; Hung et al., 2014; Wang et al., 2014). Additionally, CaMKII inhibitors could alleviate pain-related behaviors in a dose-dependent manner in these models. These studies indicated a pivotal role of CaMKII in chronic pain, suggesting that novel analgesic drugs may be developed targeting CaMKII. Therefore, in this review, the evidence for the involvement of CaMKII in chronic pain is discussed.

**CaMKII and Neuropathic Pain**

Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system (www.iasp-pain.org/Taxonomy#Neuropathicpain). Patients with neuropathic pain may suffer from abnormal sensations (paresthesia, e.g., tingling, tickling, pricking, numbness, with no apparent physical cause) and pain from normally nonpainful stimuli (allodynia) (Treede et al., 2008; Jensen et al., 2011). Many animal models successfully mimic the clinical symptoms of neuropathic pain patients, including significant mechanical allodynia. The mechanical allodynia in rodent models are often assessed by measuring the withdrawal threshold of the paw ipsilateral to the site of injury in response to mechanical stimuli delivered by von Frey hairs. A positive response was defined as a brisk withdrawal of the hind paw upon stimulation.

**CaMKII and Peripheral Neuropathic Pain.** Peripheral neuropathic pain is caused by damage to the peripheral nerve fibers (Woolf and Salter, 2000; Xu et al., 2008). Numerous animal models have been developed to examine the cellular and molecular mechanisms of chronic pain that results from peripheral nervous system injury. Among these models, surgical intervention of on sciatic nerve is used most frequently (Bennett and Xie, 1988; Mosconi and Kruger, 1996; Decosterd and Woolf, 2000; Jaggi and Singh, 2011). A growing body of studies have shown the pivotal role of CaMKII in the generation and maintenance of peripheral neuropathic pain. Garry et al. (2003) first reported that an intrathecal injection (i.t.) of a very low dose (120 pmol) of CaMKII inhibitor KN-93 reversed chronic constriction injury (CCI)-induced peripheral neuropathic pain in mice. The analgesic effect of autacamtide 2-related inhibitory peptide (AIP) was also examined. AIP is a nonphosphorylatable analog of autacamtide-2 that was identified to be a highly specific...
and potent inhibitor of CaMKII (Ishida et al., 1995). The results showed that 1 nmol of AIP significantly suppressed the thermal hyperalgesia and mechanical allodynia in CCI mice. Using a rat model of mononeuropathy, the CCI model, Dai et al. (2005) explored the time course of activation of CaMKII and the role of CaMKII in the initiation and development of peripheral neuropathic pain. Their immunohistochemistry data demonstrated that the immunoreactivity of total CaMKII (tCaMKII) was remarkably increased in the superficial laminae of the ipsilateral dorsal horn of CCI rats from 3 to 14 days after surgery, whereas the immunoreactivity of phosphorylated CaMKII (pCaMKII) showed an increase at 1 day after model establishment, which was 2 days before tCaMKII upregulation. Their Western blot data verified that the protein level of tCaMKII was upregulated in CCI rats starting at 3 days after surgery, but not at 1 day after surgery. To further examine the specific cell type that expressed CaMKII, they performed double immunofluorescence staining with anti–neuronal nuclei (NeuN; neuronal nuclei marker) or anti–microtubule-associated protein 2 (MAP2; neuronal dendrites marker). They found that pCaMKII were colocalized with NeuN and MAP2 in the ipsilateral dorsal horn of CCI rats, and it was mainly located in cell bodies in the contralateral dorsal horn. Moreover, they examined the effect of KN-93 on the pain behavior of CCI rats. They found that intrathecal injection of KN-93 before CCI surgery, but not at 7 days after surgery, significantly delayed the development of mechanical allodynia and thermal hyperalgesia in CCI rats. Furthermore, the upregulation of tCaMKII and pCaMKII were significantly attenuated by intrathecal administration of an N-methyl-D-aspartate (NMDA) receptor antagonist MK801 before CCI surgery. Their findings were corroborated by Hasegawa et al. (2009), who found that the immunoreactivity of pCaMKII was markedly increased in the ipsilateral L5 DRG following L5 SNL, but not contralateral L5 DRG. Additionally, treatment with KN-93 (10 nmol, i.t.) before L5 SNL surgery significantly attenuated the development of tactile allodynia in SNL. Interestingly, a single injection of KN-93 near L5 DRG at 7 days after SNL surgery also greatly suppressed the tactile allodynia in SNL rats. Besides, pretreatment with KN-93 blocked the phosphorylation and translocation of cytosolic phospholipase A2 in injured DRG neurons, which contributed to the mechanical allodynia after spinal nerve injury (Tsuda et al., 2007).

The results indicating that KN-93 treatment could reverse peripheral neuropathic pain were controversial and could be explained by the difference in animal model, route of administration, and drug dosage. Considering that these conflicting results might be resolved by observing the degree of CaMKII activity before and after KN-93 treatment, we conducted a study to examine the analgesic effect of KN-93 (15–45 nmol, i.t.) in SNL mice on day 5, at which time the SNL-induced mechanical allodynia and thermal hyperalgesia were well established (Chen et al., 2009). Our behavioral results showed that acute intrathecal treatment with KN-93 at the dose of 30 and 45 nmol, but not 15 nmol, 2 hours before behavioral test was able to reverse the established mechanical allodynia and thermal hyperalgesia. Moreover, KN-93 (30, 45 nmol, i.t.) dose dependently inhibited CaMKII autophosphorylation, which represents CaMKII activity. To further confirm the role of CaMKII in peripheral neuropathic pain, we tested the analgesic effect of trifluoperazine, a clinically used antipsychotic drug that shows potent inhibitory effect on CaMKII activity. As with KN-93, intraperitoneal or oral administration of trifluoperazine dose dependently reversed SNL-induced pain behaviors and the upregulation of pCaMKII. Our results supported a critical role of CaMKII in SNL-induced neuropathic pain and suggested that trifluoperazine may be used for neuropathic pain by targeting CaMKII in clinical settings. In another study, Wang et al. (2011) examined the antihyperalgesic effect of AIP in a peripheral neuropathic pain model established by partial sciatic nerve ligation. Pre-treatment with AIP (0.1 nmol, i.t.) considerably delayed the onset of tactile allodynia for 3 days, whereas postoperative treatment with AIP (0.1 nmol, i.t.) only transiently reversed the developed mechanical allodynia. Moreover, AIP treatment significantly inhibited the protein levels of pCaMKII and phosphorylated CAMP-response element–binding protein (pCREB) in the spinal cord, suggesting that spinal activation of CaMKII participates in CREB phosphorylation during central sensitization processing. The analgesic effect of AIP (3, 6, and 12 μg) was also demonstrated via intra–nucleus accumbens (NAc) injection in a peripheral neuropathic pain model induced by left common sciatic nerve ligation (Bian and Yu, 2015). Recently, spinal interleukin 33 (IL-33) (Liu et al., 2015) and interleukin 17A (Yao et al., 2016) were reported to contribute to peripheral neuropathic pain via activation of neuronal CaMKII/CREB signaling pathway. The critical role of CaMKII was further proven by Matsumura et al. (2010), who found that knockin mice lacking phosphorylation of NMDA receptor containing subunit 2B (NR2B) at Tyr1472 [mice lacking phosphorylation of NR2B subunits of NMDA receptors at Tyr1472 (Y1472F-KI mice)] failed to exhibit neuropathic pain induced by L5 spinal nerve transsection (SNT). Moreover, autophosphorylation of CaMKII at Thr286, but not Thr305, was evidently impaired in Y1472F-KI mice following SNT. This result further demonstrated that autophosphorylation of CaMKII at Thr286 contributed to persistent neuropathic pain state. However, it is worth mentioning that a recent study reported that loss of CaMKII signaling in DRG neurons may contribute to SNL-induced neuropathic pain (Bangaru et al., 2015), which conflicted with other studies. This inconsistency remains to be elucidated. Nevertheless, increased CaMKII activity was also found in a rat model of oxaliplatin-induced peripheral neuropathic pain, in which KN-93 (50 nmol, i.t.) and trifluoperazine (0.1 and 0.3 mg/kg, by mouth) both suppressed tactile allodynia and increased CaMKII phosphorylation (Shirahama et al., 2012). Similarly, diabetic peripheral neuropathy (DPN) models showed upregulated expression of CaMKII both in the spinal cord and in the DRG (Herathovic et al., 2013a,b; Jelicic Kadic et al., 2013, 2014). Interestingly, Jelicic Kadic et al. (2013, 2014) found that only intraganglionic injection of CaMKII inhibitors, but not intrathecal injection, could alleviate pain-related behaviors in DPN rats.

To sum up, CaMKII, which can be activated by NMDA receptor-mediated Ca2+ influx, is obviously upregulated in animal models of peripheral neuropathic pain. Moreover, CaMKII inhibitors considerably alleviated pain-related behaviors in neuropathic pain models. Additionally, IL-33/ST2 signaling and IL-17/IL-17R signaling were demonstrated to contribute to nerve injury-induced neuropathic pain through activation of the neuronal CaMKII/CREB signaling pathway. These studies provided strong evidence for the essential role of CaMKII in peripheral neuropathic pain, suggesting that CaMKII may be a novel therapeutic target for the management of peripheral neuropathic pain.

**CaMKII and Central Neuropathic Pain.** Central neuropathic pain (CNP) refers to pain initiated or caused by a...
primary lesion or dysfunction in the central nervous system (No author, 1986; Hulsebosch et al., 2009; Han et al., 2015). Multiple diseases may lead to CNP, including spinal cord injury (SCI), multiple sclerosis, and stroke (Siddall and Loeser, 2001; Osterberg et al., 2005; Frese et al., 2006). Currently, various established rodent models are used to investigate the initiation and maintenance of CNP after such injuries as spinal contusion (Basso et al., 1996; Hulsebosch et al., 2000), spinal hemisection (Gwak et al., 2009; Martini et al., 2016), and intrathecal injection of quisqualic acid (Yezierski et al., 1993; Yezierski et al., 1998). One of the mechanisms of CNP is neuronal hyperexcitability, which may in part be caused by unbalanced neurotransmitter release (e.g., glutamate) (Gray, 2007). It is well established that enhanced glutamate release contributes to neuropathic pain (Osikowicz et al., 2013). Interruption of the calcium influx may lead to reduced glutamate release, thus alleviating CNP.

Using a rat model of CNP established by a contusion injury at spinal level T10, Crown et al. (2012) provided the first converging evidence that chronic activation of CaMKII contributed to CNP after SCI. They found that the expression of pCaMKII was markedly increased in the T7/8 spinal dorsal horn of SCI rats in neurons but not glial cells. Compared with sham rats, SCI rats showed considerably greater neuronal activity without stimulation and to brush, press, pinch, and mechanical stimuli. Moreover, intrathecal administration of KN-93 dose dependently reversed the mechanical allodynia in SCI rats. Most importantly, KN-93 not only significantly decreased the background rate of neuronal firing in SCI rats but also decreased the neuronal responses to brush, press, pinch, and mechanical stimuli. These data suggested that CaMKII phosphorylation plays a pivotal role in neuronal membrane hyperexcitability under SCI conditions. In another study, Gwak et al. (2013) reported that SCI-induced overproduction of reactive oxygen species (ROS) may contribute to the activation of CaMKII, which leads to CNP following T10 spinal contusion injury. Their results showed that treatment with phenyl-\textit{N-tert}-butyl nitritone (PBN, an ROS scavenger) significantly attenuated mechanical allodynia and dorsal horn hyperexcitability in SCI rats. The upregulated expression of pCaMKII was also suppressed by PBN treatment. Furthermore, naive rats treated with t-BuOOH (an ROS donor) showed significantly decreased paw withdrawal threshold (a sign of mechanical allodynia) and increased expression of pCaMKII, indicating that ROS may contribute to CNP via activation of CaMKII.

Taken together, increased activity of CaMKII in the spinal cord was detected under SCI conditions. The enhanced expression of pCaMKII may be the result of spinal cord injury-induced increased production of ROS, as ROS scavengers suppress the upregulation of pCaMKII in SCI rats and ROS donors lead to increased expression of pCaMKII in naive rats. Therefore, targeting CaMKII may alleviate CNP.

**CaMKII and Bone Cancer Pain**

Among advanced cancer patients 75% suffer from severe pain owing to bone metastasis, which significantly affects their quality of life (Costantini et al., 2009; Zhou et al., 2015; Fu et al., 2016). Currently, the role of CaMKII in bone cancer pain (BCP) remains largely unknown. KIF17 is a member of the kinesin superfamily motor proteins, which play a critical role in the dendritic transport of NR2B (Hirokawa and Take-mura, 2004). Using a mouse model of BCP established by intramedullary injection of osteosarcoma cells, Liu et al. (2014) reported that the protein levels of pCaMKII, NR2B, and KIF17 were significantly upregulated in BCP mice. Moreover, intrathecal injection of KN-93 obviously alleviated BCP in a time- and dose-dependent manner and suppressed the upregulation of pCaMKII, NR2B, and KIF17, indicating an important role of CaMKII-mediated KIF17/NR2B trafficking in the development of BCP. A recent study provided various lines of evidence demonstrated that the C-X-C motif chemokine receptor 4 (CXCR4) contributed to the development of BCP via activation of the neuronal CaMKII/CREB signaling pathway (Hu et al., 2017). Their Western blot and immunohistochemistry results showed upregulated expression of pCaMKII and pCREB in the spinal cord neurons in BCP rats. Moreover, intrathecal injection of the CaMKII-specific inhibitor AIP suppressed mechanical allodynia and thermal hyperalgesia and upregulation of pCREB in BCP rats. Interestingly, intrathecal injection of CXCR4 siRNA inhibited the upregulated expression of both pCaMKII and pCREB in BCP rats, thus exhibiting analgesic effect. To further the understanding of the role of the CaMKII/CREB signaling pathway in CXCR4-mediated BCP, they used intrathecal injection of stromal-derived factor-1 (SDF-1), a principal ligand for CXCR4, into naive rats. They found that both pCaMKII and pCREB expression levels were upregulated after SDF-1 injection, which was prevented by post-treatment with the CXCR4 inhibitor plerixafor. Taken together, these results provided strong evidence that the CaMKII/CREB signaling pathway may be a critical downstream pathway of CXCR4 under BCP situation, indicating that suppressing the activation of CaMKII/CREB signaling pathway may be an alternative therapeutic strategy for the management of BCP. In addition, our recent study also confirmed the role of CREB under BCP condition (Zhou et al., 2017).

**CaMKII and Inflammatory Pain**

Inflammatory pain is associated with tissue injury-induced hyperexcitability of peripheral nociceptive sensory neurons (Ji, 2004). Numerous animal models are established to investigate the mechanisms of inflammatory pain, including intraplantar injection of formalin, capsaicin, carrageenan, and CFA (Jeske, 2015). Fang et al. (2002) provided the first evidence that CaMKII contributes to spinal cord central sensitization of nociceptive dorsal horn neurons after intradermal capsaicin injection. Their Western blot results showed that the protein level of CaMKII significantly increased by 15 minutes and pCaMKII significantly increased by 5 minutes following the intradermal injection of capsaicin. Moreover, the increased expression of CaMKII and pCaMKII were only detected in the ipsilateral side of the spinal cord but not in the contralateral side. The immunohistochemistry data confirmed that the expression of CaMKII and pCaMKII were increased in the superficial laminae of the spinal cord dorsal horn ipsilateral to the capsaicin injection site. Additionally, treatment with KN-93 (100 µM) considerably blocked the capsaicin injection-induced increases in background activity and in the responses of nociceptive dorsal horn neurons, indicating that these electrophysiological responses are CaMKII-dependent. Intrathecal injection of KN-93 also prevented capsaicin...
In this review, we discussed the cellular and molecular mechanisms of CaMKII in the initiation and development of chronic pain, including neuropathic pain, BCP, and inflammatory pain. The role of CaMKII under neuropathic pain situation has been extensively studied (Fig. 3). IL-33/ST2 signaling and IL-17/IL-17R signaling were demonstrated to contribute to nerve injury-induced neuropathic pain through activation of the neuronal CaMKII/CREB signaling pathway. Increased activity of CaMKII in the spinal cord was detected under CNP situation. The enhanced expression of pCaMKII may be the result of spinal cord injury-induced increased production of ROS, as ROS scavengers suppress the upregulation of pCaMKII in CNP rats and ROS donors lead to increased expression of pCaMKII in naive rats. Under BCP situation, the CaMKII/CREB signaling pathway may be a critical downstream pathway of CXCR4, as the CXCR4 inhibitor could attenuate BCP-related pain behaviors by suppressing the phosphorylation of CaMKII and CREB (Fig. 4). Moreover, selective CaMKII inhibitor AIP also attenuated BCP, indicating that suppressing the activation of CaMKII/CREB signaling pathway may be an alternative therapeutic strategy for the management of BCP. Currently, there are only a few studies investigating the role of CaMKII in inflammatory pain (Fig. 5). It was reported that CaMKII phosphorylation was enhanced after intraplantar injection of CFA, which was abolished by α2 noradrenergic receptor agonists and cAMP-dependent protein kinase inhibitor. Moreover, HO-2 null mutant mice showed no significant change in CaMKIIα mRNA expression after formalin injection. However, further studies are warranted to investigate the detailed mechanisms.

It is worth mentioning that CaMKIIα may also play a fundamental role in hyperalgesic priming, a phenomenon implicated in the transition from acute to chronic pain.
(Ferrari et al., 2013). Intradermal injection of PKCε agonist ψRACK could induce hyperalgesic priming, which was prevented by intrathecal administration of αCaMKII oligodeoxynucleotide (ODN) antisense (AS) combined with local inhibition of CaMKII inhibitor CaM2INtide. Additionally, intradermal injection of activated αCaMKII on the dorsum of the hindpaw produced hyperalgesia, which was not prevented by pretreatment with PKCε AS, indicating that PKCε is upstream of αCaMKII in the induction of priming. Moreover, intradermal injection of ryanodine-induced hyperalgesic priming was also prevented by intrathecal administration of αCaMKII ODN AS combined with CaM2INtide, suggesting that the priming induced by ryanodine is dependent on αCaMKII activation. These results demonstrated an indispensable role for αCaMKII in the induction of hyperalgesic priming. Interestingly, a recent study reported that CaMKII may control whether touch is painful (Yu et al., 2015). The sensation of touch is initiated when impulses at the terminals in the skin were generated by specialized sensory neurons termed fast-conducting low-threshold mechanoreceptors (Aβ-LTMRs) (Abraira and Ginty, 2013). It was shown that the flow of sensory information in Aβ-LTMR sensory neurons (e.g., impulse generation, AP propagation, and dorsal horn synaptic transmission) was regulated by CaMKII (Yu et al., 2015). Moreover, loss of CaMKII signaling in sensory neurons may contribute to neuronal dysfunction and pain, indicating a vital role of CaMKII in the transition of touch pathway to pain system (Bangaru et al., 2015; Yu et al., 2015).

In summary, treatment with CaMKII inhibitors could attenuate chronic pain-induced mechanical allodynia and thermal hyperalgesia in rodent models. Currently, the most commonly used CaMKII inhibitors in animal experiments are KN-93, KN-62, and AIP. Our previous study also demonstrated a potent inhibitory effect on CaMKII activity of trifluoperazine, a clinically used antipsychotic drug. However, no CaMKII inhibitors have been tested in clinical trials yet owing to their absence of highly specific inhibition. Therefore, novel CaMKII inhibitors with potent inhibitory effect and high specificity should be developed in the future researches. Additionally, further studies are warranted to investigate the intensive mechanisms of how activation of CaMKII contributes to chronic pain.

**Authorship Contributions**

Wrote or contributed to the writing of the manuscript: Y.-Q. Zhou, Liu, Chen, Sun, X.-R. Zhou, Luo, Tian, Ye.

**References**


Targeting CaMKII for Chronic Pain


Address correspondence to: Dr. Da-Wei Ye, Cancer Center, Tongji Hospital, Tongji Medical college, Huazhong University of Science and Technology, No. 1095 JieFang Ave., Wuhan 430030, China. E-mail: dy0711@gmail.com