Kainate Receptors and Pain: From Dorsal Root Ganglion to the Anterior Cingulate Cortex

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Abstract: Ionotropic glutamate receptors contain three subtypes: NMDA, AMPA and kainate receptors. The former two receptor subtypes have well defined roles in nociception, while the role of kainate receptors in pain is not as well characterized. Kainate receptors are expressed in nociceptive pathways, including the dorsal root ganglion, spinal cord, thalamus and cortex. Electrophysiological studies show that functional kainate receptors are located postsynaptically, where they mediate a portion of excitatory synaptic transmission, or are located presynaptically, where they modulate excitatory or inhibitory neurotransmission. Recent genetic and pharmacological studies suggest that kainate receptors can regulate nociceptive responses. These results highlight kainate receptors as a target for the development of new treatments for chronic pain.

Key Words: Kainate receptor, nociceptive pathways, spinal cord, anterior cingulate cortex, chronic pain.

INTRODUCTION

Chronic pain is characterized by a heightened responsiveness to both noxious and non-noxious stimuli, that is, hyperalgesia and allodynia, respectively. Despite recent progress in dissecting the pathophysiological mechanisms of chronic pain, the cellular and molecular mechanisms by which these inappropriate and pathological sensations develop remain unclear [1]. It is now generally believed that chronic pain involves both peripheral and central components of the nervous system, including the pain-related cortex [2-5]. Glutamate is a major excitatory neurotransmitter in the pain pathway that exerts its effect on ionotropic glutamate receptors (N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy- 5-methyl-4-isoxazolepropionic acid (AMPA) and kainate (KA) receptors). Fast excitatory transmission is largely mediated by AMPA and NMDA receptors and both NMDA and AMPA receptor antagonists are reported to be useful in the treatment of chronic pain. Unfortunately, the use of these drugs is hindered by the presence of serious side effects, such as memory impairment, psychotomimetic effects, ataxia, loss of motor coordination etc. [6-8].

KA receptors function as mediators and modulators of synaptic transmission and plasticity. Moreover, KA receptors may also be involved in pathological processes such as epilepsy, Down's syndrome, amyotrophic lateral sclerosis, schizophrenia, and chronic pain [9-12]. In this review, we will focus on the role of KA receptors in nociceptive transmission. First, we will discuss what is currently known about the functional expression of KA receptors in the pain pathway, from dorsal root ganglion (DRG) to the anterior cingulate cortex (ACC). We will then discuss recent studies that utilize genetic and pharmacological tools to dissect the role of KA receptors in pain transmission. Finally, based on current results from animal and human studies, we will discuss how KA receptors may serve as a potential target for the development of new therapies designed for the treatment of chronic pain.

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KAINATE RECEPTORS: DIVERSITY, STRUCTURE AND SYNAPTIC FUNCTION

KA receptors are one of three subtypes of ionotropic receptors for glutamate and are composed of five different subunits: GluR5, GluR6, GluR7, KA1 and KA2 [13]. Similar to AMPA and NMDA receptors, KA receptors are thought to exist as tetramers. Each subunit of KA receptors contains four hydrophobic domains M1-4, with the NH2-terminal domain lying extracellularly and the COOH-terminal intracellularly. Among these hydrophobic domains, M1, 3 and 4 cross the membrane while the M2 domain forms a hairpin-like loop in the membrane comprising the pore-forming domain [14-16]. While GluR5-7 homomers are functional, KA1 and KA2 can not produce functional homomeric channels, although they are functional in combination with GluR5-7 [17]. Interestingly, GluR5-7 can also coassemble to form heteromers [18-20]. The diversity of KA receptors is increased by the existence of splice variants for GluR5 (GluR5a, 5b and 5c), GluR6 (GluR6a and 6b) and GluR7 receptor subunits (GluR7a and 7b) [21, 22].

With the development of KA receptor specific drugs and knockout mice, studies have defined the functional roles of KA receptors in both mediating and modulating synaptic transmission and synaptic plasticity [9, 10, 23]. Postsynaptic KA receptors that mediate excitatory synaptic transmission were initially found at hippocampal mossy fiber synapses by repetitive stimulation [24, 25] and in spinal cord slices using a single stimulation [26]. A number of studies have reported KA receptor-mediated synaptic responses in other central

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synapses [27-33]. In addition to a postsynaptic location, KA receptors also target to presynaptic terminals, where they regulate either excitatory or inhibitory neurotransmitter release [34, 35]. Moreover, KA receptors are also reported to be involved in both long-term synaptic plasticity in the hippocampus [36-38], amygdala [12, 39] and cortex [12, 29].

FUNCTIONAL EXPRESSION OF KAINATE RECEPTORS IN THE PAIN PATHWAY

Kainate Receptors in the DRG

Most KA receptor subunits, but predominantly GluR5, are expressed mainly on small-diameter neurons in DRG. In situ hybridization shows that GluR5 is expressed in small, but not large, rat DRG neurons [40]. Consistently, northern blot analysis of DRG mRNA revealed that, while all KA receptor subtypes were present, GluR5 was predominantly expressed [41]. Due to the lack of subunit specific KA receptor antibodies, details of the location and compartmentalization of KA receptors in DRG neurons remain largely unknown. An anti-GluR5/6/7 antibody revealed expression of these subtypes in a large number of primary afferent and central synaptic terminals of DRG [42]. This study further reported that 40% of myelinated primary afferent fibers and 20% of the unmyelinated fibers in superficial dorsal horn showed immunoreactivity to GluR5/6/7 [42]. The presynaptic location of KA receptors favors an earlier hypothesis which postulates that KA receptors may function as presynaptic autoreceptors at primary afferent synapses in the dorsal horn [43]. Moreover, KA receptors are also expressed in peripheral fibers of rat skin [44, 45], suggesting that they might serve as sensory receptors to detect glutamate release following tissue damage.

In DRG neurons, KA receptors play functional roles in modulating sensory transmission (Fig. **1A**). Pioneering studies by Evans and colleagues showed that KA treatment produced selective blockade of action potential conduction along C-fibers [43]. Using whole-cell patch clamp recordings from isolated DRG neurons, Huettner was the first to report the presence of functional KA receptors on small diameter sensory neurons [46]. Subsequent studies tried to discern the subunit composition underlying these currents and uncovered strong similarities in the physiological properties between native KA receptors expressed by DRG cells and those of recombinant receptors formed by homomeric expression of the GluR5 subunit [47-49]. Using GluR5 and GluR6 knockout mice, Kerchner *et al.* found that functional KA receptors on cultured DRG neurons exhibit an absolute requirement for the GluR5 subunit [50]. KA receptor-mediated currents were not detected in GluR5 knockout DRG cells, indicating that the GluR5 subunit is critical for the formation of functional KA receptors. The essential role of GluR5 in the formation of functional KA receptors in the DRG is supported by the high expression of GluR5 in this area [40, 51]. Taken together, these results suggest that homomeric GluR5 receptors predominate in DRG neurons, although a minor population of heteromeric receptors cannot be ruled out.

Presynaptic KA receptors in primary afferents can regulate glutamate release from sensory afferent inputs to dorsal horn neurons. Activation of KA receptors by 10 μM KA initiated action potential firing in cultured DRG neurons and increased spontaneous TTX-insensitive postsynaptic currents in spinal dorsal horn neurons [52]. However, recent studies using DRG-spinal neuron co-cultures and spinal cord slices showed that activation of presynaptic KA receptors in primary afferents reduced either evoked excitatory postsynaptic currents (EPSCs) or miniature EPSCs [53-55], indicating a reduction, not increase, of glutamate release by presynaptic KA receptors. Using knockout mice, both groups found that presynaptic GluR5 and GluR6 are involved in this regulation [53-55]. Further studies showed different subunit compositions for KA receptors in different afferent fibers: GluR6 is involved in both A_δ and C fiber terminals, while GluR5 is only in the C fiber, inhibiting the release of glutamate [55]. However, in the absence of synaptic inhibition mediated by $GABA_A$ and glycine receptors, a facilitatory effect of glutamate released by weak activation of KA receptors in afferent fibers was reported in the spinal dorsal horn [55]. Although the molecular mechanism for the bi-directional regulation of glutamate release remains unknown, these results provide compelling evidence for presynaptic KA receptors in the regulation of spinal sensory transmission between DRG cells and spinal dorsal horn neurons.

Kainate Receptors in the Spinal Cord Dorsal Horn

Early studies using in situ hybridization [56, 57] or immunocytochemistry [58] reported that KA receptors are not prominently expressed in the spinal cord dorsal horn. Moreover, in situ hybridization studies showed that this expression undergoes strong developmental regulation [57]. For example, all KA receptor subunits are widely expressed in the spinal cord at postnatal day 2; however, at postnatal day 10, only GluR5 and KA2 are expressed and are mainly restricted to laminar II; at postnatal day 22, only KA2 is detected in the adult spinal cord. More recent studies, however, show that KA receptors are expressed in the adult spinal cord dorsal horn. RT-PCR showed that the transcripts of all five KA receptor subunits were detected in the adult rat spinal cord [59]. Using single-cell RT-PCR, Dai *et al.* found mRNA for all the subunits in cultured spinal cord neurons, with GluR5, GluR7 and KA2 being more highly expressed then GluR6 and KA2 [60]. Immunostaining of rabbit spinal cord slices with GluR5/6/7 antibodies revealed that only the superficial laminar I-III exhibited punctuate staining, while the deeper dorsal horn (laminar IV-VI) and ventral horn clearly showed cell body staining [61]. A recent study using GluR5, GluR6/7, KA1 and KA2 antibodies showed that all these subunits were expressed in the adult rat superficial dorsal horn. Interestingly, 20-35% of GAD65 positive terminals, a marker for GABAergic interneurons, contained KA receptor subunits [62].

Electrophysiological studies have revealed the functional role of KA receptors in spinal cord neurons (Fig. **1A**). Using selective AMPA receptor antagonists, postsynaptic KA receptors that mediate synaptic responses were initially found at hippocampal mossy fiber synapses [24, 25]. In spinal cord dorsal horn slices, Li *et al.* first characterized KA receptor-mediated EPSCs [26]. Whole-cell recordings in dorsal horn laminar II neurons, including some projection neurons marked by a retrograde tracer, revealed a slow component of primary afferent transmission that is mediated by KA recep-

tors [26]. These KA receptor-mediated currents can only be elicited after stimulation of the afferent axon at an intensity strong enough to activate high threshold A_δ and C fibers [26], suggesting the critical role of spinal dorsal horn KA receptors in nociception. In contrast, a recent study showed that KA receptors make little or no contribution to C-fiber evoked excitatory responses in laminar I projection neurons [63]. In cultured spinal dorsal horn neurons, functional KA receptors were activated by application of KA [49, 53, 54, 64]. Using GluR5 or GluR6 knockout mice combined with pharmacological tools, Kerchner *et al.* confirmed that KA receptors in cultured spinal dorsal horn neurons are comprised of heteromeric receptors containing both GluR5 and GluR6 [54]. GluR6 may play a more important role in the assembly of functional KA receptors in spinal dorsal horn neurons compared to GluR5 [49, 54, 64].

Functional presynaptic KA receptors are also shown in spinal dorsal horn neurons, which modulate the release of neurotransmitters like GABA or glutamate [53-55, 64, 65] (Fig. **1B**). In spinal dorsal horn cultures, inhibitory interneurons express presynaptic KA receptors [54, 64, 65]. Activation of these receptors could facilitate GABA release from presynaptic terminals. The mechanism for this modulation involves the depolarization of presynaptic terminals, leading to calcium entry through voltage-gated calcium channels, thereby triggering presynaptic GABA release. Interestingly, this increased GABA release activates presynaptic $GABA_B$ receptors and suppresses evoked transmission, which forms a negative feedback modulation of GABA release regulated by presynaptic KA receptors [64]. Similar results were found using acute spinal slices [64]. Moreover, GluR5 and GluR6 were shown to be equally important in the presynaptic KA receptor regulation of inhibitory interneurons [54]. In contrast to their role in inhibitory interneurons, activation of presynaptic KA receptors in cultured excitatory neurons decreased glutamate release [53]. Both GluR5 and GluR6 are

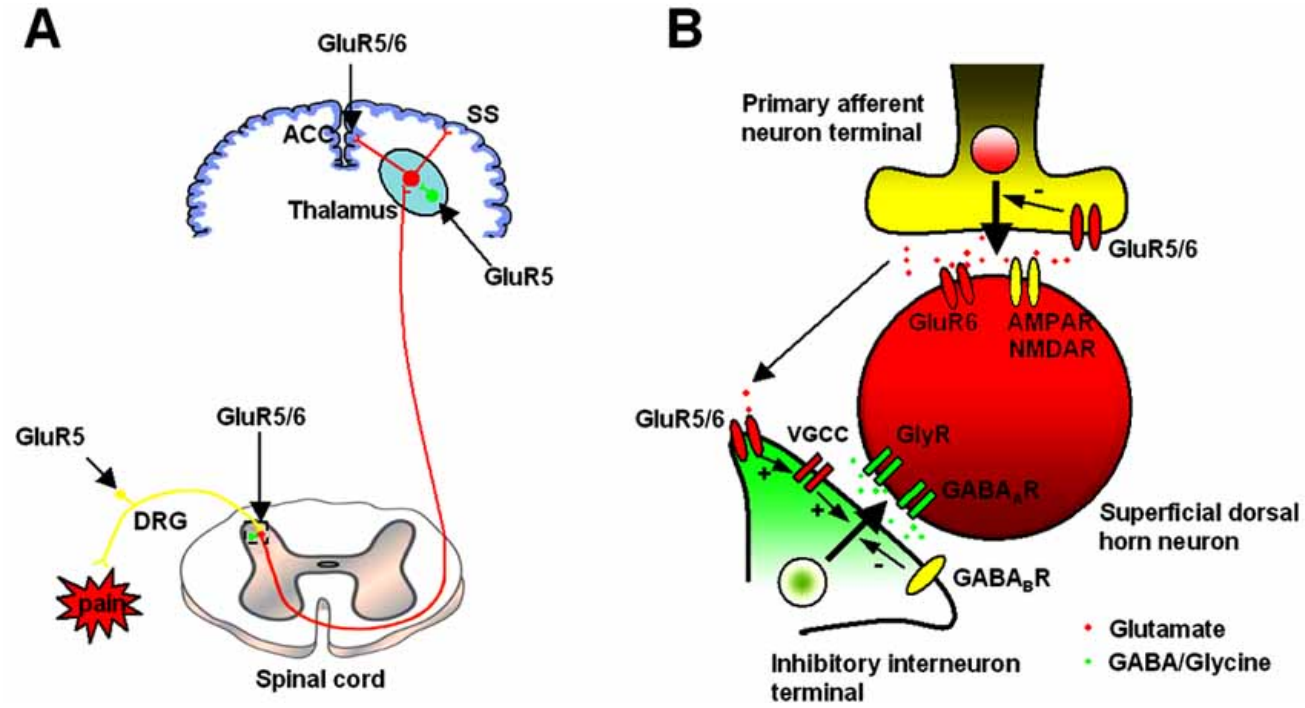

Fig. (1). Functional KA receptors in the nociceptive pathway. **(A)** Peripheral nociceptive information starts from DRG, where GluR5 is predominantly expressed. GluR5 is required for functional KA receptors in the DRG. Nociceptive information then transmits to the spinal dorsal horn, where both GluR5 and GluR6 are involved in functional KA receptors in dorsal horn neurons, primary afferent and inhibitory interneuron terminals. Projection neurons in the dorsal horn relay nociceptive information to the thalamus, where the subunit composition of functional KA receptors remains largely unknown. However, GluR5-containing KA receptors in interneurons where shown to be important in sensory processing in the thalamus. The thalamus then relays information to the somatosensory cortex (SS) and anterior cingulate cortex (ACC), where both GluR5 and GluR6 are required for functional KA receptors. Functional GluR5 in the interneuron has been shown to facilitate GABA release and the subsequent tonic GABA current in the ACC. The box is magnified in (**B**). **(B)** KA receptors in the spinal dorsal horn. Functional KA receptors are located both postsynaptically and presynaptically. Postsynaptic KA receptors, which are comprised of both GluR5 and GluR6, solely mediate nociceptive information transmitted by high threshold A_δ and C fibers. Activation of presynaptic KA receptors in primary afferent neuron terminals reduces glutamate release. This glutamate could diffuse to inhibitory interneuron terminals, where it activates presynaptic KA receptors and increases GABA/glycine release by triggering the opening of voltage-gated Ca^{2+} channels (VGCC). GABA release, in turn, may activate presynaptic $GABA_B$ autoreceptors ($GABA_BR$), reducing action potential-dependent transmitter release. Both GluR5 and GluR6 are involved in presynaptic KA receptors in the spinal dorsal horn. AMPAR, AMPA receptor. NMDAR, NMDA receptor. $GABA_AR$, $GABA_A$ receptor. GlyR, glycine receptor.

involved in the presynaptic KA receptor modulation of excitatory synaptic transmission [54]. Similar results were also obtained in neurons from adult spinal cord slices [55]; however, the origin of the synapse (primary afferent or local excitatory neurons) was not identified [55].

Kainate Receptors in Supraspinal Structures

In addition to DRG and spinal cord, KA receptors are also functionally expressed in supraspinal structures such as the thalamus and cortex, where they may also contribute to sensory transmission (Fig. **1A**). However, studies of supraspinal KA receptors are still in their infancy. In the primate thalamus, in situ hybridization showed that only GluR6 transcripts were expressed at detectable levels [66]. Conversely, all five KA receptor subunit mRNAs were expressed in the thalamus of humans [67]. Recently it was shown that GluR5-containing KA receptors in neurons of the ventrobasal thalamus play a critical role in sensory function [68, 69]. Although KA receptors do not appear to mediate postsynaptic responses in these neurons, presynaptic GluR5 activation reduced GABAergic IPSCs. Moreover, *in vivo* studies showed that the blockade of GluR5 decreased excitatory responses of ventrobasal neurons by natural somatosensory stimuli, which is dependent on GABAergic transmission [69]. Therefore, GluR5-mediated disinhibition appears to be important in sensory processing in the ventrobasal thalamus.

In situ hybridization and immunostaining results show that KA receptor subunits are widely expressed in the cortex [70, 71]. For example GluR5, GluR6, GluR7 and KA2 are highly expressed, whereas KA1 is either weakly detectable during postnatal days or not expressed at all [71]. Functional pre- and postsynaptic KA receptors were found in the barrel cortex [29, 72], where both KA receptor-mediated EPSCs and activity dependent plasticity decreases during development [29]. In contrast to the facilitatory effect in mossy fibers, presynaptic KA receptors depressed excitatory synaptic transmission in thalamocortical synapses. Presynaptic KA receptors are developmentally down regulated in postnatal week one [72]. However, the subunit composition underlying either pre- or postsynaptic KA receptors in thalamocortical synapses remains unknown.

The ACC is critically involved in nociception and pain perception [3-5, 73, 74]. Synaptic and somatodendritic KA receptors were reported in ACC pyramidal neurons of adult mice [75]. In this study, single shock stimulation could induce small KA receptor-mediated excitatory postsynaptic currents (EPSCs). KA receptor EPSCs had a significantly slower rise time course and decay time constant compared to AMPA receptor-mediated EPSCs. High frequency repetitive stimulation significantly facilitated KA receptor EPSCs. Genetically modified mice with deletions of GluR5 and/or GluR6 were then used to show that both GluR5 and GluR6 are involved in synaptic transmission in the adult ACC [75]. Functional KA receptors were also reported to be located mainly at extracellular sites in layer V pyramidal neurons of the somatosensory cortex [33]. Very recently, functional GluR5 has been found in the interneuron in the ACC [76]. Activation of interneuronal GluR5 caused action potential-dependent GABA release, showing that GluR5 is mainly somatodendritic but not presynaptic in the interneurons. Endogenous activation of GluR5 also enhanced GABA release to ACC pyramidal neurons and the corresponding postsynaptic tonic GABA current [76]. Taken together, these results showed that KA receptors contribute to synaptic transmission and modulation in cortical neurons and provide a synaptic basis for the pathophysiological function of KA receptors in the pain-related cortex [1].

ACTIVATION AND MODULATION OF KAINATE RECEPTORS BY NOCICEPTIVE STIMULI

Immunohistochemical and electrophysiological studies clearly show that KA receptors are expressed in the pain pathway, including DRG, spinal cord dorsal horn, the thalamus and cortex, where they play functional roles in synaptic transmission and modulation. Therefore, it is conceivable that the activation or modulation of KA receptors may be involved in pain sensation. The high expression of GluR5 on small diameter DRG neurons prompted researchers to study the role of GluR5 in nociceptive pathways [77]. Stanfa and Dickenson reported that intrathecal application of the selective GluR5 antagonist LY382884 suppressed C-fiber evoked responses, post-discharge and wind-up of rat dorsal horn neurons [78]. Moreover, their results showed that the spinal actions of LY382884 were enhanced three hours after carrageenan injection [78]. A recent study in monkeys showed that LY382884 (administered to the spinal dorsal horn *via* a microdialysis fiber) could attenuate responses of spinothalamic tract neurons to mechanical and thermal stimuli under both normal and neuropathic conditions [79]. Activation of GluR5 KA receptors may actually enhance nociceptive responses and contribute to nociception, whereas blockade of GluR5 inhibits nociceptive transmission and therefore has analgesic effects.

In addition to the involvement of KA receptor activation in nociceptive transmission, recent studies found that inflammatory pain could regulate the peripheral and central expression of KA receptors. For example, GluR5-7 immunoreactivity was significantly increased in peripheral sensory axons (both unmyelinated and myelinated axons) two days after CFA inflammation [80]. Another study showed that the expression of GluR5 and GluR6 was selectively upregulated in the spinal cord from two hours to three days after CFA inflammation, correlating well with the development of inflammation and hyperalgesia [59]. Considering the role of KA receptors in nociceptive transmission and modulation, these results suggest that KA receptors may be a contributing factor to peripheral and central sensitization after inflammatory pain.

KAINATE RECEPTORS AS POTENTIAL ANALGESIC TARGETS

We have presented considerable evidence to show that pain associated with peripheral tissue or nerve injury involves KA receptor activation, highlighting the role of KA receptors in physiological and pathological pain. In accordance with this idea, systemic administration of kainic acid produces persistent hyperalgesia in rodents [81]. A myriad of studies report that KA receptor antagonists alleviate pain-related behaviors in animal models and clinical settings, although negative or conflicting results have also been reported (Table **1**).

Table 1. Pharmacological and Genetic Manipulation of Kainate Receptors on Nociception

		Targets	Drug Administration	Pain Model	Phenotype	Species	Ref.
Agonist	**Kainic acid**	AMPA/KA receptors	Intraperitoneal	Hot plate/Tail flick	Hyperalgeisa	Mice	[80]
			Intrathecal		No effect		
			Subcutaneous		Hyperalgeisa		
			Intraperitoneal	Mechanical stimulation	Hyperalgeisa	Rats	
				Acetic acid nociception	No effect	Mice	
	ATPA	GluR5	Intraperitoneal	Hot plate	No effect	Mice	[76]
			Intrathecal	Hot plate	Analgesia	Rats	[82]
				Mechanical stimulation			
Antagonist	**CNQX**	AMPA/KA receptors	Intrathecal	Hot plate/Tail flick	Analgesia	Rats	[24]
				Cold plate	No effect		
	NBQX	AMPA/KA receptors	Intraperitoneal	Formalin inflammation	Analgesia	Rats	[83]
			Intrathecal	CFA inflammation	Analgesia	Rats	[57]
			Intraperitoneal	Hot plate	No effect	Rats	[86]
				Formalin inflammation	No effect		
				Chronic constriction injury	Analgesia		
	NS-102	KA receptors	Intrathecal	CFA inflammation	Analgesia	Rats	[57]
	SYM2081	KA receptors	Intrathecal	Hot plate/Tail flick	Analgesia	Rats	[24]
				Cold plate	No effect		
			Intraperitoneal	Chronic constriction injury	Analgesia	Rats	[81]
			Intraperitoneal	Freeze injury	Analgesia	Rats	[84]
			Intraperitoneal Intrathecal	Capsaicin hyperalgesia	Analgesia	Rats	[85]
			Subcutaneous		No effect		
			Intraperitoneal	Carrageenan inflammation	Analgesia		
	NS1209	AMPA/GluR5 receptors	Intraperitoneal	Hot plate	Analgesia	Rats	[86]
				Formalin inflammation			
				Chronic constriction injury			
	LY293558	AMPA/GluR5 receptors	Intraperitoneal	Formalin inflammation	Analgesia	Rats	[83]
			Intravenous	Capsaicin hyperalgesia	Analgeisa	Humans	[88]
			Intravenous	Migraine	Analgeisa	Humans	[89]
	LY382884	GluR5	Intraperitoneal	Formalin inflammation	Analgesia	Rats	[83]
			Intrathecal	CFA inflammation	Analgesia	Rats	[57]
	LY467711/ LY525327	GluR5	Oral	Capsaicin hyperalgesia	Analgesia	Rats	[87]
				Formalin inflammation			
				Carrageenan inflammation			

(Table 1) contd….

		Targets	Drug Administration	Pain Model	Phenotype	Species	Ref.
Knockout	**GluR5**$^{-/-}$	GluR5	-	Hot plate/Tail flick	No effect	Mice	[10]
				Capsaicin hyperalgesia	Analgesia		
				Formalin inflammation	Analgesia		
				CFA inflammation	No effect		
	GluR6$^{-/-}$	GluR6	-	Hot plate/Tail flick	No effect		
				Capsaicin hyperalgesia	No effect		
				Formalin inflammation	No effect		
				CFA inflammation	No effect		

GluR5 is involved in both *in vitro* and *in vivo* nociceptive responses; however, intraperitoneal injection of either ATPA or LY382884 had no effect on hot-plate responses [77]. Moreover, hot-plate and tail-flick responses were unaltered in GluR5 and GluR6 knockout mice when compared to wild-type controls [12]. It is interesting to point out that other studies report a role for spinal KA receptors in acute nociception. This was first demonstrated by Li and colleagues, who found that intrathecal injection of the AMPA and KA receptor antagonist CNQX produced greater antinociceptive effects than an antagonist selective for AMPA receptors alone in the hot-plate and tail-flick, but not cold-plate, tests [26]. The same study showed that the nonselective KA receptor antagonist, SYM2081 alone could have analgesic effects [26]. SYM2081 had a similar effect on acute pain induced by mechanical or thermal stimulation [82]. In contrast, intrathecal injection of ATPA was reported to have antinociceptive effects in mechanical or thermal stimulation-induced acute pain [83].

A number of recent studies have focused on the role of KA receptors in chronic pain. Behavioral experiments using systemic drug administration showed that GluR5-containing KA receptors may play a role in formalin-induced inflammatory pain [59, 84], while SYM 2081 was shown to attenuate mechanical allodynia and thermal hyperalgesia in a rat model of nerve injury [82]. Similar analgesic effects were found by several groups using different chronic pain models and pharmacological tools; such as intraperitoneal injection of SYM2081 in a freeze injury neuropathic pain model [85], intrathecal injection of NS-102 (KA receptor antagonist) or LY382884 in the CFA inflammation model [59], intrathecal or intraperitoneal injection of SYM2081 in capsaicin-induced hyperalgesia or carrageenan induced inflammation [86], intraperitoneal injection of NS1209 (AMPA/GluR5 antagonist) in the formalin test or chronic constriction nerve injury model [87], and oral administration of LY467711 or LY525327 (GluR5 antagonist) in capsaicin-induced hyperalgesia, formalin or carrageenan inflammation [88]. Results from these studies, employing a wide variety of pain models and pharmacological tools, highlight the potential utility in targeting the GluR5 subunit when developing new drug therapies.

The selective role of GluR5 in mediating nociceptive responses was reported recently using GluR5 knockout mice. Ko *et al*. found that GluR5, but not GluR6, knockout mice showed reduced responses to capsaicin or formalin-induced inflammatory pain while acute nociceptive responses and CFA-induced allodynia were unchanged compared to controls [12]. Furthermore, GluR6 mice showed a deficit in fear memory while remaining intact in GluR5 knockout mice. This study points out the subunit specificity of KA receptors to different behaviors and further suggests that the GluR5 subunit plays a selective role in nociception.

While these animal studies reinforce the role or KA receptors in nociception, clinical studies also provide some preliminary evidence for the role of KA receptors in pain. Sang *et al.* reported that intravenous infusion of LY293558 reduced capsaicin-evoked hyperalgesia in humans, reducing pain intensity, pain unpleasantness, and the receptive field [89]. Moreover, a recent study reported that intravenous administration of LY293558 was efficacious in the treatment of acute migraines [90].

Collectively, these behavioral studies indicate that pharmacological or genetic manipulation of KA receptors has the potential to affect acute or chronic nociceptive transmission. Although the exact contribution of each KA receptor subunit to acute nociception versus chronic pain remains unexplored, selectively targeting different KA receptor subunits may provide a useful strategy for treating persistent pain, considering the potentially different distribution and function of KA receptor subunits in the pain pathway [12].

CONCLUSION AND FUTURE DIRECTIONS

It is well documented that NMDA and AMPA receptors are critically involved in the induction and maintenance of chronic pain. Over the past ten years, with the development of selective AMPA and KA receptor antagonists, functional KA receptors were revealed in the pain pathway, from DRG to the ACC. KA receptors not only directly mediate, but finely modulate, synaptic transmission at all levels along the pain pathway. Accordingly, activation of KA receptors affects pain transmission and processing. Different KA receptor subunits, with distinct functional expression, highlight

the potential for pharmacological selectivity, which is particularly attractive from a clinical perspective. While the use of mixed AMPA/KA receptor antagonists as analgesic drugs is hindered by unwanted side effects, KA receptor antagonists seem to have more specific antinociceptive actions [84]. KA receptors, therefore, have been heralded as a promising new drug target for the treatment of chronic pain.

However, due to the immaturity of selective pharmacological agents for KA receptors, the synaptic function of KA receptors, as well as their molecular identities, is not well understood. Moreover, although behavioral studies demonstrate the important role for KA receptors in pain, the exact site that these drugs target may be anywhere from receptors in the periphery, the spinal cord, or even in supraspinal structures. Clearly, more work must be done before useful therapeutic tools can be developed.

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