ELSEVIER

Brain Research Reviews 40 (2002) 215–222

BRAIN RESEARCH REVIEWS

www.elsevier.com/locate/brainresrev

Review

Role of kainate receptors in nociception

Ruth Ruscheweyh, Jürgen Sandkühler*

Cellular and Integrative Neurophysiology, Brain Research Institute, Vienna University Medical School, Spitalgasse 4, A-1090 Vienna, Austria

Abstract

Nociceptive nerve fibers use L-glutamate as a fast excitatory neurotransmitter and it is therefore not surprising that both, ionotropic and metabotropic glutamate receptors play pivotal roles for transmission of nociceptive information in spinal cord. A subtype of ionotropic glutamate receptors, the kainate receptor, is present in spinal dorsal horn. However, its role has remained obscure as specific antagonists and agonists have become available only recently. Kainate receptors are present on small, including nociceptive, dorsal root ganglion cells and on intrinsic dorsal horn neurons, and those two locations can be targeted separately by appropriate agonists and antagonists. Postsynaptic kainate receptors on spinal dorsal horn neurons are activated by high intensity electrical stimulation of the dorsal root entry zone that activates nociceptive primary afferent fibers. In contrast, low intensity stimulation that activates only non-nociceptive fibers is ineffective. Selective blockade of kainate receptors may produce analgesia. Here, we review what is known about localization of kainate receptors in dorsal root ganglia and spinal dorsal horn and their physiological and pathophysiological importance with special reference to nociceptive pathways. A short overview on molecular biology and agonist and antagonist pharmacology is included.

Theme: Sensory systems

Topic: Pain modulation: anatomy and physiology

Keywords: Spinal cord; Dorsal horn; Pain; Dorsal root ganglion; Antinociception

Contents

*Corresponding author. Tel.: +43-1-4277-62834; fax: +43-1-4277-62865.
E-mail address: juergen.sandkuehler@univie.ac.at (J. Sandkühler).

0165-0173/02/$ – see front matter
PII: S0165-0173(02)00203-5

1. Structure and functional properties of kainate receptors

1.1. Structure

Kainate receptors, in analogy to AMPA receptors, are thought to be tetramers formed by homo- or heteromeric association of the kainate receptor subunits KA1, KA2, GluR5, GluR6 and GluR7 [43]. Kainate receptor subunits have a molecular mass of ~100 kDa and are divided into high affinity subunits (KA1 and KA2, K_D=5–15 nM) [23,63] and low affinity subunits (GluR5-7, K_D=30–100 nM) [6,53]. While homology within these groups is 70–80% [6,63], it is only 45% between the two groups, and both groups share a 40% homology to AMPA receptor subunits [5,63] and a 20% homology to NMDA receptor subunits [49]. While GluR5-7 homomers are functional kainate gated ion channels [23,48], KA1 and KA2 only form functional channel as heteromers with subunits from the low affinity group [23,63]. Each subunit carries its own ligand binding site [3,60,66].

Kainate receptor subunits, similar to AMPA receptors, consist of four hydrophobic domains M1–M4 where M1, M3 and M4 cross the membrane while the pore-forming domain M2 forms a loop in the membrane.

1.2. Functional properties

When activated, kainate receptors become permeable to monovalent cations (Na^+, K^+). Some types are also permeable to Ca^{2+} and Cl^- (see below). Unitary conductance mostly lies in the low picosiemens range. In DRG neurons, native kainate receptors showed a unitary conductance of 4–18 pS [24]. Current-voltage relations were found to be linear in DRG neurons [24] but inward and outward rectification occur in other systems [23]. Rapid (in the ms–s range) and strong desensitization is characteristic for kainate receptors [23,24,40,44,58]. Moreover, desensitization occurs at agonist concentrations two orders of magnitude lower than receptor activation [40]. This means that prolonged exogenous agonist application may lead to a functionally antagonistic effect due to desensitization. Furthermore, rapid drug application is needed to detect and accurately quantify agonistic effects. The time course of recovery from desensitization is in the range of tens of seconds and depends on the nature of the agonist [40].

The functional properties of kainate receptors are strongly modulated by different mechanisms like alternative splicing, mRNA editing and heteromeric subunit assembly. Alternative splicing in the rat gives rise to the GluR5-1 and GluR5-2a-c isoforms of the GluR5 subunit [39,53] and to the GluR7a and GluR7b isoforms of the GluR7 subunit [48]. No alternative splicing of KA1, KA2 or GluR6 has been reported in the rat, but is present in other species [21]. The functional role of alternative splicing remains unknown. In contrast, another form of structural variability, mRNA editing, has profound functional implications, including regulation of single channel conductance and Ca^{2+} permeability. GluR5 and GluR6 are subject to mRNA editing at the glutamine/arginine (Q/R) site in the pore-forming M2 segment [30]. The introduction of a positively charged arginine in place of a neutral glutamine leads to decreased Ca^{2+} and increased Cl^- permeability and modification of unitary conductance and rectifying properties of the channel [11,12,17,30,56]. mRNA editing is developmentally regulated. For example, most of the GluR5 subunits in the rat DRG are unedited at E16 while 95% are edited at P7 and this leads to decreased Ca^{2+} permeability of postnatal as compared to embryonic DRG kainate receptors [31]. GluR6 can additionally undergo editing at two sites situated in the M1 domain (I/V and Y/C) [30]. Functional diversity is also conferred by heteromeric assembly of subunits. Thus, while KA1 and KA2 cannot form functional homomeric channels, they form functional heteromeric channels with the low affinity subunits GluR5-7 [23]. KA2/GluR6 channels are gated by AMPA while GluR6 homomers are not [23]. GluR5/KA2 heteromers show more rapid desensitization and different rectification than homomeric GluR5 channels [23]. Heteromeric assembly of edited and unedited subunits provides an additional mechanism of functional modulation.

2. Pharmacology of kainate receptors

2.1. Agonist pharmacology

The classical agonists for kainate receptors, kainate itself and domoate, show little selectivity at kainate receptors over AMPA receptors. However, they can be used as specific kainate receptor agonists in the presence of the selective noncompetitive AMPA antagonists SYM 2206 or GYKI 53655 [7,39]. In addition, recent studies have identified ligands which show selectivity for the GluR5 or GluR5 and GluR6 subunits.

ATPA ((*R*,*S*)-2-amino-3(3-hydroxy-5-*tert*.-butylisoxazol-4-yl)propanoic acid) is a GluR5-preferring agonist with strong activity at homomeric GluR5 receptors (EC_{50} 2.1 μM) and native DRG kainate receptors (EC_{50} 0.3–0.6 μM) but only weak activity at AMPA receptors (EC_{50} 300–400 μM in hippocampal neurons, 96 μM in cultured spinal cord neurons) and no activity at GluR6 homomers [15,65]. However, it is not completely selective for homomeric GluR5 receptors and not even the GluR5 subunit as it also activates heteromeric GluR5/KA2 receptors (EC_{50} 6.3 μM), GluR5/GluR6 receptors (EC_{50} 21 μM) and GluR6/KA2 receptors (EC_{50} 84 μM) [32,38].

LY 339434 also prefers GluR5 homomers (EC_{50} 0.8 μM) and native DRG kainate receptors (EC_{50} 2.5 μM) over GluR6 homomers (no activation at 100 μM) or

AMPA receptors (EC_{50}>300 μM) but shows strong activation of NMDA receptors (EC_{50} 2.5 μM) [52].

Some halogenated willardiine derivatives also show selectivity at kainate over AMPA receptors. Highest selectivity was found for (*S*)-5-iodowillardiine (IW) that prefers native DRG kainate receptors (EC_{50} 140 nM) over hippocampal AMPA receptors (EC_{50} 19 μM) [68]. IW potently activates homomeric GluR5 receptors and heteromeric GluR5/KA2 receptors but shows no activity on homomeric GluR6 or GluR7 receptors and only weak activity on heteromers of GluR6 and 7 with KA2 [26,57].

(2*S*,4*R*)-Methylglutamate (SYM 2081) strongly activates homomeric GluR5 and GluR6 receptors [52] but only weakly activates AMPA and NMDA receptors [22]. It elicits a potent and complete desensitization of both recombinant GluR6 and native DRG kainate receptors and can therefore be used as a functional antagonist [27].

2.2. Antagonist pharmacology

The classical AMPA/kainate receptor antagonists CNQX and NBQX display very poor selectivity at AMPA versus kainate receptors [7,34,41,53,64]. Recent development of the decahydroxyisoquinoline carboxylates allows the GluR5 receptor to be selectively targeted, but other types of kainate receptors cannot be selectively inhibited up to now.

LY 382884 is the newest and most specific compound from the decahydroxyisoquinoline carboxylate group. It specifically binds to GluR5 subunits but not to GluR6, GluR7, KA2 or AMPA receptor subunits [10,51]. It inhibits kainate-evoked currents in DRG neurons with an IC_{50} of 1 μM. Synaptically evoked AMPA responses in the hippocampus are inhibited with a much higher IC_{50} (87 μM). It has no effect on homomeric GluR6 receptors and on NMDA-evoked currents in hippocampal neurons at 10 μM [10].

Two older compounds, LY 294486 and LY 293558, show similar selectivity for GluR5 over other kainate receptor subunits (IC_{50} 3.9 μM and 2.5 μM in GluR5 homomers and IC_{50} 0.62 μM and 1 μM in DRG cells, respectively) but less or no selectivity over AMPA receptors (IC_{50}>30 and 0.5 μM, respectively) [8,15].

NS-102 acts at GluR5 and GluR6 and has been shown to have good selectivity for kainate receptors over AMPA receptors in some systems [62,64] but very poor selectivity in others [41] and in addition, active concentrations of NS-102 are close to its solubility limit.

2.3. Inhibitors of desensitization

The rapid desensitization at agonist application characteristic for kainate receptors is strongly reduced by the plant lectin concanavalin A (Con A), and this effect is specific for kainate over AMPA receptors [32,37,67]. Con A binds to *N*-glycosylated residues present on kainate receptors [18,19].

3. Distribution of kainate receptors in dorsal root ganglia and spinal dorsal horn

3.1. Dorsal root ganglia

The first evidence for the existence of kainate receptors on dorsal root ganglion cells came from the fact that kainate but not NMDA depolarized dorsal roots of neonatal rats [1]. The action of kainate on dorsal roots seemed to be selective for slowly conducting C-fibers as kainate abolished only the late phase of the dorsal root volley [1]. This was confirmed later by results showing that kainate selectively depolarized DRG cells with small to intermediate diameters (<30 μm, corresponding to Aδ- and C-fibers) but not large DRG cells (corresponding to Aβ-fibers) [24]. This response was mediated by kainate receptors as the EC_{50} for kainate was 15 μM as compared to 520 μM for AMPA. More accurately, 92% of neonatal dorsal root ganglion cells reacting to kainate were labeled by antibodies to IB4, a marker for C-fibers, and 60% were immunoreactive for vanilloid receptor 1 that is expressed by noxious-heat sensitive receptors [31]. However, very few dorsal root ganglion cells reacting to kainate showed immunoreactivity for substance P, another marker for nociceptors [31]. In situ hybridization showed that the kainate-receptor subunit GluR5 is expressed in small but not large adult rat DRG neurons [47]. In adult rat dorsal roots, 10% of the myelinated and 20% of the unmyelinated fibers showed immunoreactivity to GluR5/6/7 [25]. Northern blot showed that all kinds of kainate receptor subunits are present in DRG neurons but that GluR5 largely predominates [37]. The pharmacology, including sensitivity to AMPA, and desensitization kinetics of homomeric GluR5 in transfected cells closely match those of native DRG kainate receptors [24,53], suggesting that homomeric GluR5 may be the predominant kainate receptor type in DRG neurons. However, in small rat trigeminal ganglion neurons, GluR5/KA2 heteromers seem to be the prevalent kainate receptor type [44]. In embryonic (E17) rat DRGs, KA2 is expressed in significant quantities [23], suggesting that GluR5/KA2 heteromers may be another candidate for native DRG kainate receptors. In any case, the GluR5-subunit-preferring agonist ATPA activates all DRG neurons that are activated by kainate [65].

Although kainate receptors are thought to be centripetally distributed on primary afferent fibers [1], kainate receptors are also present in measurable quantities on unmyelinated fibers in the rat skin [2,14] and on both myelinated and unmyelinated fibers in rat peripheral sensory and sensomotor nerves [16]. The proportion of

unmyelinated and myelinated peripheral nerve fibers immunoreactive for GluR5-7 increased significantly from 27 and 28% to 47 and 43%, respectively, 47 h after inflammation of the innervated area with complete Freund's adjuvant [13].

3.2. Spinal dorsal horn

Autoradiographic analysis in cat spinal cord showed a high density of [^{3}H]kainate binding in laminae I and II and lower density in deeper dorsal horn laminae [35]. In situ hybridization showed a strong developmental regulation of dorsal horn kainate receptors. While all subtypes were present at postnatal day 2, virtually no GluR6 or KA1 was seen on p10. On p22 and in adult rats, only KA2 was expressed in rat spinal dorsal horn in significant amounts [20,54,61]. In contrast, immunohistochemistry showed strong GluR5/6/7 labeling in laminae I–III of adult rat spinal cords that was not limited to central terminals of primary afferents as it was present both in perikarya and neuropil [69]. Much of this immunostaining seems to originate from both myelinated and unmyelinated primary afferents as it extensively colocalizes with orthogradely transported isolectin B4 and cholera toxin subunit B and about two-thirds of the immunostaining for GluR5/6/7 disappear after rhizotomy [25]. In rabbit spinal cord, only neuropilar elements were immunostained with GluR5/6/7 in laminae I–III while cell bodies were stained in deeper dorsal horn laminae [9]. PCR showed the presence of GluR5 mRNA in adult rat spinal cord homogenates [4]. Electrophysiological studies have shown that kainate receptors exist on intrinsic dorsal horn neurons and are selectively activated by stimulation of high-threshold, i.e., nociceptive primary afferents [33]. Kainate receptors on intrinsic dorsal horn neurons seem to be of another type than those on DRG neurons as they are mostly insensitive to the GluR5-preferring agonist ATPA [28,29].

4. Contribution of kainate receptors to nociception

Kainate receptors are specifically localized on small to intermediate diameter DRG neurons that give rise to thinly myelinated or unmyelinated Aδ- and C-fibers, including nociceptive fibers [24]. This prompted investigators to study the role of kainate receptors in the transmission of nociceptive information and pain perception.

4.1. Electrophysiological studies

The effects of kainate receptor agonists and antagonists in spinal cord were studied in various in vivo and in vitro models. It has been reported that activation of kainate receptors on presynaptic nerve terminals of primary afferents by kainate or the GluR5-preferring agonist ATPA

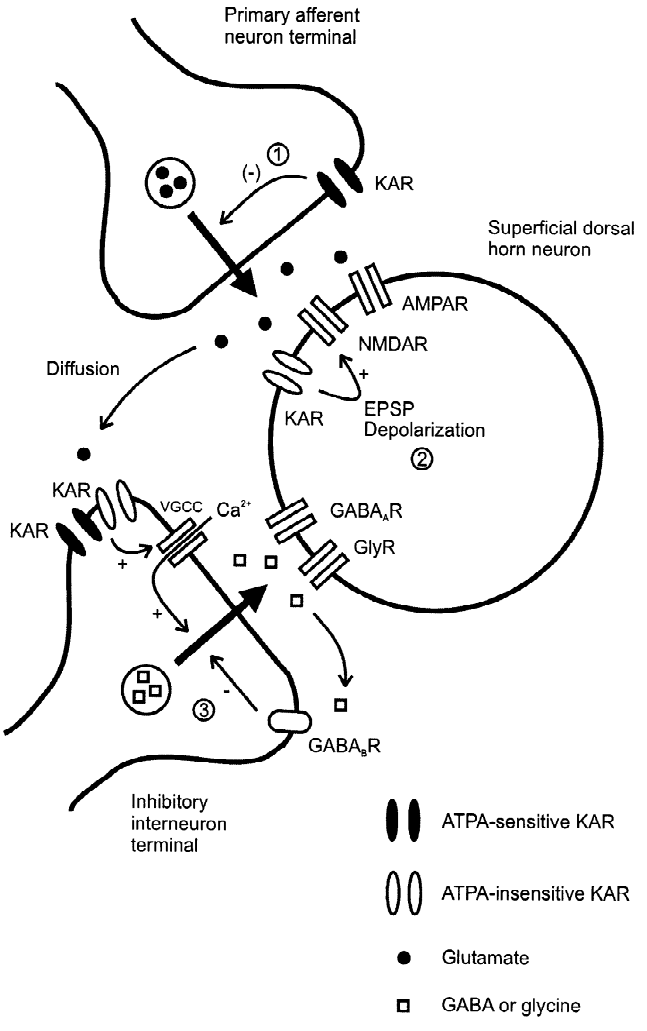

Fig. 1. Superficial spinal dorsal horn kainate receptors are strategically placed to regulate sensory transmission. At different locations, they can be differentially targeted by the GluR5-preferring agonist ATPA and the unselective agonist kainate. (1) Glutamate acting on ATPA-sensitive kainate autoreceptors on primary afferent terminals has been shown to inhibit further glutamate release. However, these findings have to be interpreted with caution because desensitization of kainate receptors may have occurred by prolonged applications of kainate [29]. (2) Glutamate released from primary afferents following high-intensity- but not low-intensity-stimulation acts on ATPA-insensitive kainate receptors on superficial dorsal horn neurons, inducing an excitatory postsynaptic potential, thus promoting the transmission of nociceptive information [33]. In addition, the kainate receptor-mediated depolarization may remove the magnesium block from neighboring NMDA receptors, allowing Ca^{2+} entry that is necessary for the induction of long-term potentiation. (3) Activation of dorsal horn kainate receptors reduces the evoked release of inhibitory transmitter. The proposed mechanism involves the diffusion of glutamate released from primary afferents to neighboring terminals of inhibitory interneurons. There the glutamate has been shown to act on kainate receptors of both the ATPA-sensitive and -insensitive type, inducing a membrane depolarization that allows Ca^{2+} entry through voltage-gated calcium channels (VGCCs). Elevated Ca^{2+} levels in the terminal promote spontaneous release of glycine and GABA that by acting on $GABA_B$ autoreceptors inhibits action potential-evoked release of inhibitory transmitter [28]. Figure adapted from Ref. [28].

reduces glutamate release in the superficial spinal dorsal horn [29]. Glutamatergic transmission between intrinsic dorsal horn neurons was also depressed by kainate but not by ATPA. This suggests that intrinsic dorsal horn neurons express another type of kainate receptors than primary afferents that is insensitive to ATPA [29]. However, part of the inhibitory dorsal horn neurons are sensitive to ATPA [28]. Dorsal root-evoked ventral root potentials in hemisected neonatal rat spinal cord showed reduction of A- and C-fiber-evoked polysynaptic responses following application of the GluR5-preferring agonist ATPA while the GluR5 antagonist LY 382884 reversed the action of ATPA but had no effects on its own [42]. In these studies, kainate and APTA generally showed depressant actions on glutamatergic transmission in spinal cord. However, when kainate receptor agonists were applied exogenously for prolonged periods of time, the rapid desensitization of kainate receptors may have converted the agonistic into an antagonistic effect. Indeed, it has been shown that brief activation of postsynaptic kainate receptors on superficial dorsal horn neurons by stimulation of primary afferents leads to inward currents [33]. These kainate receptor-mediated excitatory currents had a peak amplitude of 30% of the combined AMPA/kainate-receptor-mediated currents and showed slower rise and decay kinetics than mixed currents. Kainate receptors were activated following high-intensity but not low-intensity dorsal root entry zone stimulation, suggesting that kainate receptors are only localized at synapses receiving input from high-threshold primary afferents. Another probably pronociceptive mechanism of the activation of spinal dorsal horn kainate receptors involves a reduction of the evoked release of inhibitory transmitters [28]. The proposed mechanism is rather complex. Glutamate released from primary afferents following strong sensory input would reach presynaptic kainate receptors on terminals of inhibitory dorsal horn neurons by diffusion in the synaptic glomerulus. Activation of those kainate receptors lead to an increased spontaneous release of GABA which by a negative feedback at $GABA_B$ autoreceptors reduced the action-potential-evoked release of GABA and glycine from the same nerve terminal [28]. For a summary of the present knowledge on the significance of kainate receptors in spinal dorsal horn, refer to Fig. 1. According with a tonic amplification of sensory input by activation of kainate receptors, the GluR5 antagonist LY 294486 reduced single spinal motor unit responses to percutaneous low- or high-intensity stimulation but ATPA had no effect. Similarly, LY 294486 reduced responses of dorsal horn wide dynamic range neurons to noxious heat in adult rats and this seemed to be a presynaptic effect as responses to exogenously applied AMPA or NMDA were not affected [42]. Phasic excitation of nociceptive neurons by kainate receptor agonists fits with the results of some behavioral studies showing an antinociceptive effect of kainate receptor antagonists in models of acute pain.

4.2. Behavioral studies

Mixed results were reported for the effects of kainate receptor antagonists in models of phasic pain. The functional kainate receptor antagonist SYM 2081 given i.t. or i.p. to adult or neonatal rats had antinociceptive actions in tail-flick, hot-plate and mechanical pain threshold tests [33,55]. In contrast, the GluR5-preferring antagonist LY 382884 given i.p. to mice did not increase hot-plate thresholds [42]. This could either represent a species difference or an indication that kainate receptors that contain the GluR5 subunit are not involved in the transmission of all forms of acute pain. As most studies used i.p. drug application, it is also not clear if the antinociceptive effects of kainate receptor antagonists are due to actions on kainate receptors in the spinal cord or elsewhere.

4.3. Role of kainate receptors in plasticity of nociceptive pathways

Activity- and calcium-dependent plasticity in nociceptive pathways may contribute to allodynia and hyperalgesia following trauma, inflammation and nerve injury [36,45]. The roles of calcium-permeable glutamate receptors of the NMDA type, and to some extent that of the AMPA type have been described previously. Recent studies suggest that kainate receptors may also be involved. The calcium permeability of kainate receptors strongly depends upon post-transcriptional mRNA editing of the GluR5 and GluR6 subunits which is developmentally regulated [31]. In addition, opening of voltage-dependent calcium channels and removal of the voltage-dependent Mg^{2+} block of the NMDA receptor channel can be achieved by kainate receptor-mediated depolarization. At hippocampal synapses an NMDA receptor-independent form of long-term potentiation was depressed by blockade of kainate receptors [10]. In superficial spinal dorsal horn a long-lasting depression of NMDA receptor-mediated postsynaptic excitatory synaptic currents was induced by application of kainate [50]. These results suggest that kainate receptors are involved in long-term modification of synaptic transmission including nociceptive pathways.

Results from behavioral studies consistently show antinociceptive effects of specific kainate receptor antagonists in models of persistent pain. The functional kainate receptor antagonist SYM 2081 given i.p. significantly reduced mechanical allodynia and thermal hyperalgesia in the chronic constriction injury model [55] and the cold injury model [59] of neuropathic pain. The GluR5-preferring antagonist LY 382884 produced antinociception in the late phase of the rat formalin test [51]. Interestingly, a study in humans using i.v. application of the mixed AMPA/kainate receptor antagonist LY 293558 showed reduction of spontaneous pain and mechanical allodynia following capsaicin injection into the skin but no effect on brief pain sensations evoked in normal skin [46].

5. Conclusions

Kainate receptors are involved in the processing of nociceptive information at several steps, including primary afferent fibers and intrinsic spinal dorsal horn neurons. Small, including nociceptive dorsal root ganglion neurons express kainate receptors containing the GluR5 subunit, probably GluR5 homomers or GluR5/KA2 heteromers that modulate glutamate release from primary afferents. Postsynaptic kainate receptors on superficial dorsal horn neurons seem to be activated selectively by stimulation of high-threshold primary afferents thereby contributing to the transmission of nociceptive information. Furthermore, kainate receptors on intrinsic spinal dorsal horn neurons seem to be of another type than those on primary afferents, the former probably not containing the GluR5 subunit to a large extent. This will allow the differential targeting of both groups of kainate receptors by selective pharmacological tools and elucidate their respective roles in the processing of nociceptive information. From electrophysiological studies, it has not yet become clear if activation of spinal kainate receptors will have pro- or antinociceptive effects. However, behavioral studies consistently report antinociceptive actions of kainate receptor antagonists. While application of mixed AMPA/kainate receptor antagonists as analgesic drugs is limited by side effects, such as ataxia, kainate receptor antagonists seem to have more specific antinociceptive actions at least in rats [51].

Some kainate receptors exhibit permeability to Ca^{2+} and thus may translate nociceptive excitation into cellular Ca^{2+} entry. Elevated intracellular Ca^{2+} concentrations are able to evoke a wealth of reactions, among them excitotoxicity and synaptic plasticity. DRG neurons express Ca^{2+} permeable kainate receptors in embryonic and early postnatal rats but seem to be impermeable to Ca^{2+} from P4 [31]. It remains to be investigated if kainate receptors on intrinsic dorsal horn neurons exhibit Ca^{2+} conductance and what role they play in central sensitization.

References

[1] S.G. Agrawal, R.H. Evans, The primary afferent depolarizing action of kainate in the rat, Br. J. Pharmacol. 87 (1986) 345–355.
[2] B. Ault, L.M. Hildebrand, Activation of nociceptive reflexes by peripheral kainate receptors, J. Pharmacol. Exp. Ther. 265 (1993) 927–932.
[3] J.A. Bennett, R. Dingledine, Topology profile for a glutamate receptor: three transmembrane domains and a channel-lining reentrant membrane loop, Neuron 14 (1995) 373–384.
[4] A. Bernard, L. Ferhat, F. Dessi, G. Charton, A. Represa, Y. Ben-Ari, M. Khrestchatisky, Q/R editing of the rat GluR5 and GluR6 kainate receptors in vivo and in vitro: evidence for independent developmental, pathological and cellular regulation, Eur. J. Neurosci. 11 (1999) 604–616.
[5] B. Bettler, J. Boulter, I. Hermans-Borgmeyer, A. O'Shea-Greenfield, E.S. Deneris, C. Moll, U. Borgmeyer, M. Hollmann, S. Heinemann, Cloning of a novel glutamate receptor subunit, GluR5: expression in the nervous system during development, Neuron 5 (1990) 583–595.
[6] B. Bettler, J. Egebjerg, G. Sharma, G. Pecht, I. Hermans-Borgmeyer, C. Moll, C.F. Stevens, S. Heinemann, Cloning of a putative glutamate receptor: a low affinity kainate-binding subunit, Neuron 8 (1992) 257–265.
[7] D. Bleakman, B.A. Ballyk, D.D. Schoepp, A.J. Palmer, C.P. Bath, E.F. Sharpe, M.L. Woolley, H.R. Bufton, R.K. Kamboj, I. Tarnawa, D. Lodge, Activity of 2,3-benzodiazepines at native rat and recombinant human glutamate receptors in vitro: stereospecificity and selectivity profiles, Neuropharmacology 35 (1996) 1689–1702.
[8] D. Bleakman, D.D. Schoepp, B. Ballyk, H. Bufton, E.F. Sharpe, K. Thomas, P.L. Ornstein, R.K. Kamboj, Pharmacological discrimination of GluR5 and GluR6 kainate receptor subtypes by (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)ethyl]decahydroisoquinoline-3 carboxylic-acid, Mol. Pharmacol. 49 (1996) 581–585.
[9] A. Bonnot, M. Corio, G. Tramu, D. Viala, Immunocytochemical distribution of ionotropic glutamate receptor subunits in the spinal cord of the rabbit, J. Chem. Neuroanat. 11 (1996) 267–278.
[10] Z.A. Bortolotto, V.R. Clarke, C.M. Delany, M.C. Parry, I. Smolders, M. Vignes, K.H. Ho, P. Miu, B.T. Brinton, R. Fantaske, A. Ogden, M. Gates, P.L. Ornstein, D. Lodge, D. Bleakman, G.L. Collingridge, Kainate receptors are involved in synaptic plasticity, Nature 402 (1999) 297–301.
[11] N. Burnashev, A. Villarroel, B. Sakmann, Dimensions and ion selectivity of recombinant AMPA and kainate receptor channels and their dependence on Q/R site residues, J. Physiol. 496 (1996) 165–173.
[12] N. Burnashev, Z. Zhou, E. Neher, B. Sakmann, Fractional calcium currents through recombinant GluR channels of the NMDA, AMPA and kainate receptor subtypes, J. Physiol. 485 (1995) 403–418.
[13] S.M. Carlton, R.E. Coggeshall, Inflammation-induced changes in peripheral glutamate receptor populations, Brain Res. 820 (1999) 63–70.
[14] S.M. Carlton, G.L. Hargett, R.E. Coggeshall, Localization and activation of glutamate receptors in unmyelinated axons of rat glabrous skin, Neurosci. Lett. 197 (1995) 25–28.
[15] V.R. Clarke, B.A. Ballyk, K.H. Hoo, A. Mandelzys, A. Pellizzari, C.P. Bath, J. Thomas, E.F. Sharpe, C.H. Davies, P.L. Ornstein, D.D. Schoepp, R.K. Kamboj, G.L. Collingridge, D. Lodge, D. Bleakman, A hippocampal GluR5 kainate receptor regulating inhibitory synaptic transmission, Nature 389 (1997) 599–603.
[16] R.E. Coggeshall, S.M. Carlton, Ultrastructural analysis of NMDA, AMPA, and kainate receptors on unmyelinated and myelinated axons in the periphery, J. Comp. Neurol. 391 (1998) 78–86.
[17] J. Egebjerg, S.F. Heinemann, Ca^{2+} permeability of unedited and edited versions of the kainate selective glutamate receptor GluR6, Proc. Natl. Acad. Sci. USA 90 (1993) 755–759.
[18] I. Everts, R. Petroski, P. Kizelsztein, V.I. Teichberg, S.F. Heinemann, M. Hollmann, Lectin-induced inhibition of desensitization of the kainate receptor GluR6 depends on the activation state and can be mediated by a single native or ectopic N-linked carbohydrate side chain, J. Neurosci. 19 (1999) 916–927.
[19] I. Everts, C. Villmann, M. Hollmann, N-Glycosylation is not a prerequisite for glutamate receptor function but is essential for lectin modulation, Mol. Pharmacol. 52 (1997) 861–873.
[20] T. Furuyama, H. Kiyama, K. Sato, H.T. Park, H. Maeno, H. Takagi, M. Tohyama, Region-specific expression of subunits of ionotropic glutamate receptors (AMPA-type, KA-type and NMDA receptors) in the rat spinal cord with special reference to nociception, Mol. Brain Res. 18 (1993) 141–151.
[21] P. Gregor, B.F. O'Hara, X. Yang, G.R. Uhl, Expression and novel subunit isoforms of glutamate receptor genes GluR5 and GluR6, Neuroreport 4 (1993) 1343–1346.
[22] Z.Q. Gu, D.P. Hesson, J.C. Pelletier, M.L. Maccecchini, L.M. Zhou, P. Skolnick, Synthesis, resolution, and biological evaluation of the four stereoisomers of 4-methylglutamic acid: selective probes of kainate receptors, J. Med. Chem. 38 (1995) 2518–2520.

[23] A. Herb, N. Burnashev, P. Werner, B. Sakmann, W. Wisden, P.H. Seeburg, The KA-2 subunit of excitatory amino acid receptors shows widespread expression in brain and forms ion channels with distantly related subunits, Neuron 8 (1992) 775–785.

[24] J.E. Huettner, Glutamate receptor channels in rat DRG neurons: activation by kainate and quisqualate and blockade of desensitization by Con A, Neuron 5 (1990) 255–266.

[25] S.J. Hwang, S. Pagliardini, A. Rustioni, J.G. Valtschanoff, Presynaptic kainate receptors in primary afferents to the superficial laminae of the rat spinal cord, J. Comp. Neurol. 436 (2001) 275–289.

[26] D.E. Jane, K. Hoo, R. Kamboj, M. Deverill, D. Bleakman, A. Mandelzys, Synthesis of willardiine and 6-azawillardiine analogs: pharmacological characterization on cloned homomeric human AMPA and kainate receptor subtypes, J. Med. Chem. 40 (1997) 3645–3650.

[27] K.A. Jones, T.J. Wilding, J.E. Huettner, A.M. Costa, Desensitization of kainate receptors by kainate, glutamate and diastereomers of 4-methylglutamate, Neuropharmacology 36 (1997) 853–863.

[28] G.A. Kerchner, G.D. Wang, C.S. Qiu, J.E. Huettner, M. Zhuo, Direct presynaptic regulation of GABA/glycine release by kainate receptors in the dorsal horn: an ionotropic mechanism, Neuron 32 (2001) 477–488.

[29] G.A. Kerchner, T.J. Wilding, P. Li, M. Zhuo, J.E. Huettner, Presynaptic kainate receptors regulate spinal sensory transmission, J. Neurosci. 21 (2001) 59–66.

[30] M. Köhler, N. Burnashev, B. Sakmann, P.H. Seeburg, Determinants of Ca^{2+} permeability in both TM1 and TM2 of high affinity kainate receptor channels: diversity by RNA editing, Neuron 10 (1993) 491–500.

[31] C.J. Lee, H. Kong, M.C. Manzini, C. Albuquerque, M.V. Chao, A.B. MacDermott, Kainate receptors expressed by a subpopulation of developing nociceptors rapidly switch from high to low Ca^{2+} permeability, J. Neurosci. 21 (2001) 4572–4581.

[32] J. Lerma, A.V. Paternain, A. Rodriguez-Moreno, J.C. Lopez-Garcia, Molecular physiology of kainate receptors, Physiol. Rev. 81 (2001) 971–998.

[33] P. Li, T.J. Wilding, S.J. Kim, A.A. Calejesan, J.E. Huettner, M. Zhuo, Kainate-receptor-mediated sensory synaptic transmission in mammalian spinal cord, Nature 397 (1999) 161–164.

[34] D. Lodge, M.G. Jones, A.J. Palmer, Excitatory amino acids: new tools for old stories or pharmacological subtypes of glutamate receptors: electrophysiological studies, Can. J. Physiol. Pharmacol. 69 (1991) 1123–1128.

[35] J.J. Mitchell, K.J. Anderson, Quantitative autoradiographic analysis of excitatory amino acid receptors in the cat spinal cord, Neurosci. Lett. 124 (1991) 269–272.

[36] K.A. Moore, H. Baba, C.J. Woolf, Synaptic transmission and plasticity in the superficial dorsal horn, in: J. Sandkühler, B. Bromm, G.F. Gebhart (Eds.), Nervous System Plasticity and Chronic Pain, Progress in Brain Research, Vol. 129, Elsevier, Amsterdam, 2000, pp. 63–80.

[37] K.M. Partin, D.K. Patneau, C.A. Winters, M.L. Mayer, A. Buonanno, Selective modulation of desensitization at AMPA versus kainate receptors by cyclothiazide and concanavalin A, Neuron 11 (1993) 1069–1082.

[38] A.V. Paternain, M.T. Herrera, M.A. Nieto, J. Lerma, GluR5 and GluR6 kainate receptor subunits coexist in hippocampal neurons and coassemble to form functional receptors, J. Neurosci. 20 (2000) 196–205.

[39] A.V. Paternain, M. Morales, J. Lerma, Selective antagonism of AMPA receptors unmasks kainate receptor-mediated responses in hippocampal neurons, Neuron 14 (1995) 185–189.

[40] A.V. Paternain, A. Rodriguez-Moreno, A. Villarroel, J. Lerma, Activation and desensitization properties of native and recombinant kainate receptors, Neuropharmacology 37 (1998) 1249–1259.

[41] A.V. Paternain, A. Vicente, E.O. Nielsen, J. Lerma, Comparative antagonism of kainate-activated kainate and AMPA receptors in hippocampal neurons, Eur. J. Neurosci. 8 (1996) 2129–2136.

[42] M.J. Procter, A.K. Houghton, E.S. Faber, B.A. Chizh, P.L. Ornstein, D. Lodge, P.M. Headley, Actions of kainate and AMPA selective glutamate receptor ligands on nociceptive processing in the spinal cord, Neuropharmacology 37 (1998) 1287–1297.

[43] C. Rosenmund, Y. Stern-Bach, C.F. Stevens, The tetrameric structure of a glutamate receptor channel, Science 280 (1998) 1596–1599.

[44] Y. Sahara, N. Noro, Y. Iida, K. Soma, Y. Nakamura, Glutamate receptor subunits GluR5 and KA-2 are coexpressed in rat trigeminal ganglion neurons, J. Neurosci. 17 (1997) 6611–6620.

[45] J. Sandkühler, Learning and memory in pain pathways, Pain 88 (2000) 113–118.

[46] C.N. Sang, M.P. Hostetter, R.H. Gracely, A.S. Chappell, D.D. Schoepp, G. Lee, S. Whitcup, R. Caruso, M.B. Max, AMPA/kainate antagonist LY293558 reduces capsaicin-evoked hyperalgesia but not pain in normal skin in humans, Anesthesiology 89 (1998) 1060–1067.

[47] K. Sato, H. Kiyama, H.T. Park, M. Tohyama, AMPA, KA and NMDA receptors are expressed in the rat DRG neurones, Neuroreport 4 (1993) 1263–1265.

[48] H.H. Schiffer, G.T. Swanson, S.F. Heinemann, Rat GluR7 and a carboxy-terminal splice variant, GluR7b, are functional kainate receptor subunits with a low sensitivity to glutamate, Neuron 19 (1997) 1141–1146.

[49] P.H. Seeburg, The TINS/TiPS Lecture. The molecular biology of mammalian glutamate receptor channels, Trends Neurosci. 16 (1993) 359–365.

[50] S. Sequeira, J. Nasstrom, Low-affinity kainate receptors and long-lasting depression of NMDA-receptor-mediated currents in rat superficial dorsal horn, J. Neurophysiol. 80 (1998) 895–902.

[51] R.M. Simmons, D.L. Li, K.H. Hoo, M. Deverill, P.L. Ornstein, S. Iyengar, Kainate GluR5 receptor subtype mediates the nociceptive response to formalin in the rat, Neuropharmacology 37 (1998) 25–36.

[52] B. Small, J. Thomas, M. Kemp, K. Hoo, B. Ballyk, M. Deverill, A.M. Ogden, A. Rubio, C. Pedregal, D. Bleakman, LY339434, a GluR5 kainate receptor agonist, Neuropharmacology 37 (1998) 1261–1267.

[53] B. Sommer, N. Burnashev, T.A. Verdoorn, K. Keinanen, B. Sakmann, P.H. Seeburg, A glutamate receptor channel with high affinity for domoate and kainate, EMBO J. 11 (1992) 1651–1656.

[54] S.L. Stegenga, R.G. Kalb, Developmental regulation of *N*-methyl-D-aspartate- and kainate-type glutamate receptor expression in the rat spinal cord, Neuroscience 105 (1902) 499–507.

[55] J.L. Sutton, M.L. Maccecchini, K.C. Kajander, The kainate receptor antagonist 2S,4R-4-methylglutamate attenuates mechanical allodynia and thermal hyperalgesia in a rat model of nerve injury, Neuroscience 91 (1999) 283–292.

[56] G.T. Swanson, D. Feldmeyer, M. Kaneda, S.G. Cull-Candy, Effect of RNA editing and subunit co-assembly single-channel properties of recombinant kainate receptors, J. Physiol. 492 (1996) 129–142.

[57] G.T. Swanson, T. Green, S.F. Heinemann, Kainate receptors exhibit differential sensitivities to (S)-5-iodowillardiine, Mol. Pharmacol. 53 (1998) 942–949.

[58] G.T. Swanson, S.F. Heinemann, Heterogeneity of homomeric GluR5 kainate receptor desensitization expressed in HEK293 cells, J. Physiol. 513 (1998) 639–646.

[59] L.E. Ta, R.A. Dionne, J.R. Fricton, J.S. Hodges, K.C. Kajander, SYM-2081, a kainate receptor antagonist reduces allodynia and hyperalgesia in a freeze injury model of neuropathic pain, Brain Res. 858 (2000) 106–120.

[60] F.A. Taverna, L.Y. Wang, J.F. MacDonald, D.R. Hampson, A transmembrane model for an ionotropic glutamate receptor predicted

on the basis of the location of asparagine-linked oligosaccharides, J. Biol. Chem. 269 (1994) 14159–14164.
[61] T.R. Tölle, A. Berthele, W. Zieglgänsberger, P.H. Seeburg, W. Wisden, The differential expression of 16 NMDA and non-NMDA receptor subunits in the rat spinal cord and in periaqueductal gray, J. Neurosci. 13 (1993) 5009–5028.
[62] T.A. Verdoorn, T.H. Johansen, J. Drejer, E.O. Nielsen, Selective block of recombinant glur6 receptors by NS-102, a novel non-NMDA receptor antagonist, Eur. J. Pharmacol. 269 (1994) 43–49.
[63] P. Werner, M. Voigt, K. Keinanen, W. Wisden, P.H. Seeburg, Cloning of a putative high-affinity kainate receptor expressed predominantly in hippocampal CA3 cells, Nature 351 (1991) 742–744.
[64] T.J. Wilding, J.E. Huettner, Antagonist pharmacology of kainate- and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-preferring receptors, Mol. Pharmacol. 49 (1996) 540–546.
[65] T.J. Wilding, J.E. Huettner, Functional diversity and developmental changes in rat neuronal kainate receptors, J. Physiol. 532 (2001) 411–421.
[66] Z.G. Wo, R.E. Oswald, Unraveling the modular design of glutamate-gated ion channels, Trends Neurosci. 18 (1995) 161–168.
[67] L.A. Wong, M.L. Mayer, Differential modulation by cyclothiazide and concanavalin A of desensitization at native alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid- and kainate-preferring glutamate receptors, Mol. Pharmacol. 44 (1993) 504–510.
[68] L.A. Wong, M.L. Mayer, D.E. Jane, J.C. Watkins, Willardiines differentiate agonist binding sites for kainate- versus AMPA-preferring glutamate receptors in DRG and hippocampal neurons, J. Neurosci. 14 (1994) 3881–3897.
[69] K.K. Yung, Localization of glutamate receptors in dorsal horn of rat spinal cord, Neuroreport 9 (1998) 1639–1644.