Chapter 21

Pain transmission and peripheral group III metabotropic glutamate receptors (mGluRs)

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Abbreviations

AC	adenylyl cyclase
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
cAMP	cyclic adenosine monophosphate
Cav	(N-type) voltage-gated Ca^{2+} channels
CFA	complete Freund's adjuvant
CGRP	calcitonin gene-related peptide
CNS	central nervous system
DAG	diacylglycerol
DRG	dorsal root ganglia
EAAT	excitatory amino acid transporter
EC_{50}	half maximal effective concentration
eEPSCs	evoked excitatory postsynaptic currents
EPSPs	excitatory postsynaptic potentials
GDNF	glial-derived neurotrophic factor
GLS	glutaminase
IB4	isolectin B4
iGluRs	ionotropic glutamate receptors
IP3	1,4,5-triphosphate
mEPSC	miniature excitatory postsynaptic current
mGluRs	metabotropic glutamate receptors
mRNA	messenger ribonucleic acid
NAAG	*N*-acetyl-aspartyl-glutamate
NGF	nerve growth factor
NMDA	*N*-methyl-D-aspartate receptor
NTS	nucleus tractus solitarius
PAG	periaqueductal gray
PAM	positive allosteric modulator
PLC	phospholipase C
PNS	peripheral nerve system
RET	rearranged during transfection
SCs	Schwann cells
SGCs	satellite glial cells
SP	substance P
TG	trigeminal ganglia
TrkA	tropomyosin receptor kinase A
TRPV1	transient receptor potential cation channel subfamily V member 1
VGLUTs	vesicular glutamate transporters

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Introduction

Pain is a critical symptom in clinical medicine. Nociceptive pain serves to warn living organism of protecting the body against an actual or potential tissue damage. Since pain is a perception mainly mediated by the nervous system, nociceptors present in terminals of peripheral nerve system (PNS) can transduce noxious stimuli to electrochemical information that is transmitted to central nervous system (CNS).

Small and medium diameter cell bodies of dorsal root ganglia (DRG) or the trigeminal ganglia (TG) neurons exhibit two general types of nociceptors (Basbaum, Bautista, Scherrer, & Julius, 2009). Unmyelinated C fibers nociceptor with slowly conducting velocity mediate a delayed and dull pain, and thinly myelinated Aδ fibers nociceptor with more rapidly conducting velocity mediate a rapid and sharp pain. DRG (for body) and TG (for face) have pseudo-unipolar morphology. Peripheral terminals of axon innervating peripheral tissues are responsible for transducing noxious stimuli and initiating action potential, and central terminals of axon extend into the superficial dorsal horn in the spinal cord and form the first presynaptic circuit. The first relay neurons project to periaqueductal gray (PAG), reticular formation of brain stem and thalamus, finally transferring the nociceptive information to cerebral cortex including the somatosensory cortex, insular cortex, and cingulate cortex. Nociceptive information from the face is relayed into thalamus and somatosensory cortex by the trigeminal system. Most of all, this ascending information of pain delivers into neurons of the rostral ventral medulla and PAG to engage descending pathway to regulate the spinal cord output.

Glutamatergic transmission or signaling play a crucial role in initiating and maintaining pain. Nociceptive Aδ and C fibers are glutamatergic, and several types of glutamate receptors capable of binding with glutamate are abundantly distributed in the pain pathway of nervous system. The hyperexcitability of the glutamatergic system induces the augmented glutamate release and upregulation (or phosphorylation) of glutamate receptor in axon terminal and cell bodies of nervous system. For this reason, the glutamatergic action can be highly associated with the sensitized response of nociceptor in animal and human with acute or chronic pain (Bleakman, Alt, & Nisenbaum, 2006). Multiple studies have identified that the activation of ionotropic or metabotropic glutamate receptors (iGluRs or mGluRs) localized in nervous system can regulate nociceptive processing. Importantly, the role of glutamatergic signaling in PNS is essential in the first phase of nociceptive processing (Carlton, 2001). Accumulated evidences are emerging that NMDA receptor and group I mGluRs in cell bodies and peripheral afferent fibers of PNS can potentiate the nociceptive processing (Bhave, Karim, Carlton, & Gereau, 2001; Cairns et al., 2003; Zhang et al., 2009); however, much attention has been less drawn into the function of peripheral group III mGluRs. Therefore, the present review will target peripheral group III mGluRs of PNS which can provide a better understanding of modulatory role and therapeutic potential in pain processing.

Glutamate metabolism in peripheral nervous system

Plasma glutamate concentration maintain in a low-level range of 20–50 μM. Systemic absorption of glutamate from colonic lumen to portal circulation is poor owing to the first pass metabolism in the splanchnic bed and extensive energy production for lumen function (Julio-Pieper, Flor, Dinan, & Cryan, 2011). Since blood barrier restrict the entry of glutamate and glutamine into PNS and CNS (Hawkins, 2009; Reinhold & Rittner, 2020), glutamate as the main neurotransmitter can be produced (or reuptaked) in primary neuron, transported, and released from peripheral terminals.

The production of endogenous glutamate in PNS is implicated in mitochondrial glutaminase (GLS; the conversion of glutamine into glutamate), excitatory amino acid transporter (EAAT; glutamate reuptake), and the degradation of *N*-acetyl-aspartyl-glutamate (NAAG; *N*-acetyl-aspartyl-glutamate into glutamate and *N*-acetyl-aspartate) in DRG neurons and glia (Miller, Hoffman, Sutharshan, & Schechter, 2011). The synthesized glutamate in DRG cells is packed in vesicular glutamate transporters (VGLUTs) and is transported to peripheral terminals. Intense noxious stimuli, tissue damage, and inflammation causes augmented glutamate to be released from peripheral afferent nerve terminals. Extensive analysis in mice has revealed that mRNA and protein of VGLUT1 are mostly shown in medium-to-large diameter DRG neurons, whereas those of VGLUT2 and VGLUT3 are present in small-to-medium diameter DRG neurons (Malet & Brumovsky, 2015). Especially, VGLUT2 DRG neurons are colocalized with peptidergic calcitonin gene-related peptide (CGRP) and nonpeptidergic isolectin B4 (IB4) (Rogoz, Lagerstrom, Dufour, & Kullander, 2012; Scherrer et al., 2010) and VGLUT2-expressed nerve terminals are abundantly expressed in hindlimb skin and viscera (Brumovsky et al., 2013).

Glutamate release and pain

Glutamatergic transmission is required for both physiological and pathological condition in nervous system. Under a sensitization in the pain pathways, the glutamatergic system is strongly hyperexcitable in response to noxious or innocuous

stimuli. Hyperalgesia (increased pain by a stimulus that usually provokes pain) and allodynia (pain by a stimulus that does not usually provoke pain) can be accompanied in animals and patients with inflammatory or chronic pain (Basbaum et al., 2009; Woolf & Ma, 2007). Increased glutamate release in axon terminals of PNS leads to the development of these evoked pain response (Alfredson & Lorentzon, 2002; Schizas et al., 2010).

Besides endogenous glutamate release in pain processing, the exogenous application of glutamate can induce pain response. In a glabrous hindpaw skin of rat, intraplantar application of L-glutamate causes the excitation response of Aδ and C fibers and lowers a temporal threshold of these fibers to heat stimulation (Du, Koltzenburg, & Carlton, 2001). Intraplantar injection of L-glutamate causes both mechanical allodynia and mechanical hyperalgesia (Carlton, Hargett, & Coggeshall, 1995). In a human study, subcutaneous injection of glutamate to forehead reduces pressure pain threshold, causes secondary hyperalgesia, elevates skin temperature by about 1°C (Gazerani, Wang, Cairns, Svensson, & Arendt-Nielsen, 2006). Similar to skin, there are sensitized effects of glutamate on muscle and joint of humans (Castrillon et al., 2008; Svensson et al., 2003).

Glutamate can also play an action into substance P (SP), CGRP, adenosine, and TRPV1 to initiate pain processing. The release of CGRP in bovine dental pulp is found after the treatment of L-glutamate (Jackson & Hargreaves, 1999). Subcutaneous injection of L-glutamate into rat hindlimb dose-dependently evokes adenosine release; however, systemic preadministration of capsaicin to desensitize primary afferents fibers does not induce adenosine release of L-glutamate (Liu, White, & Sawynok, 2002). Subcutaneous application of glutamate with SP into hairy skin of rats increases mean spikes firing of Aδ and C fibers compared to either glutamate or SP alone (Carlton, Zhou, & Coggeshall, 1998).

Glutamate receptor signaling: iGluR and mGluR

Augmented glutamate action is mediated through two different types of receptors: ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs). It has been known that iGluRs (NMDA, AMPA, and kainate receptors) play roles to mediate fast excitatory transmission, whereas mGluRs modulate neuronal excitability via G-protein-dependent or G-protein-independent signaling pathways (Neugebauer, 2002; Niswender & Conn, 2010).

The topology of mGluRs comprises seven hydrophobic transmembrane domains with extracellular loops and intracellular loops, a large extracellular N-terminal domain and a cytoplasmic C-terminal domain. Subtypes of mGluRs can be divided into three different groups according to their sequence similarity, pharmacology, and intracellular signal transduction pathways. Group I mGluRs—mGluR1 and 5—are coupled to $G_{aq/11}$proteins and activate phospholipase C (PLC). A signal transduction of PLC leads to activate protein kinase C and mobilize Ca^{2+} from intracellular storage. On the other hand, group II (2 and 3) and group III (4, 6, 7, and 8) mGluRs are negatively coupled to adenylate cyclase and decrease cAMP levels, regulating K^+ and Ca^{2+} channels. This different signal pathways of mGluRs can explain different roles of mGluRs (Fig. 1).

Localization of peripheral group III mGluR

Except for mGluR6 restrictedly localized within the retina, the presence of mGluR4, mGluR7, and mGluR8 is widely identified in PNS associated with nociception (Neugebauer, 2002) (Fig. 2).

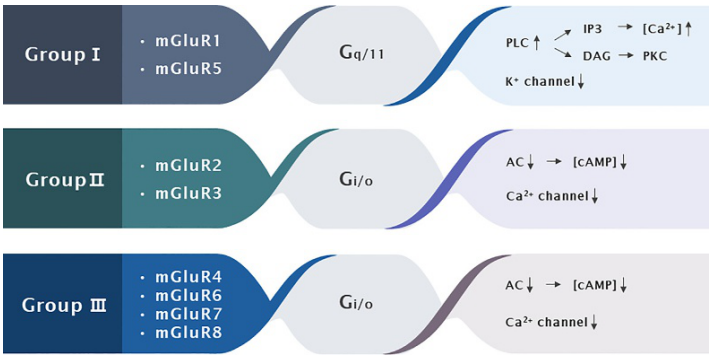


FIG. 1 Classification and signal transduction of mGluRs. mGluRs are classified into three family. Group I induces PLC hydrolysis with formation of IP3 and DAG, whereas groups II and III induce a decrease of intercellular levels of cAMP through negatively coupling to AC.

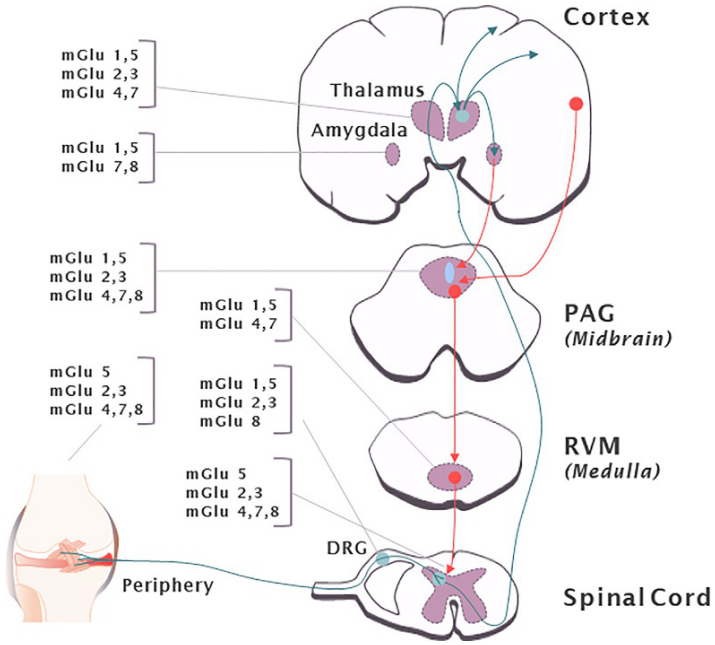


FIG. 2 Localization of mGluRs in pain pathways. Subtypes of mGluRs are widely expressed in pain pathways of nervous system. *Green line* symbolizes ascending pathway and *red line* symbolizes descending pathway.

The immunoreactivity of mGluR4 is found particularly in small-to-medium diameter DRG neurons, and in the axon terminal of laminar II in spinal dorsal horn of rats. In detail, a few studies reveal that mGlu4 are expressed in both the inner lamina II of mice spinal dorsal horn and unmyelinated C afferent fibers expressing VGLUT3 (Azkue et al., 2001; Vilar et al., 2013). A small proportion of mGlu4 receptor staining (<10%) are colocalized with both peptidergic SP/CGRP and nonpeptidergic IB4 (Vilar et al., 2013). It is also reported that mGluR4 mRNA in DRG is downregulated after sciatic nerve ligation of rats (Xiao et al., 2002).

The immunoreactivity of mGluR7 is shown in terminals or cell bodies of DRG and TG neurons of rats (Li et al., 1996, 1997). It is found that mGluR7 is highly immunolabeled in DRG (85%) of rats where the double-labeled proportion with SP, CGRP, and TRPV1 are expressed in 86%, 92%, and 71%, respectively. However, there is a relatively low double-labeling (22%) of mGluR7 with nonpeptidergic IB4 (Li et al., 2012). Interestingly, mGluR7 is accumulated at the proximal site to DRG neurons after sciatic nerve ligation, whereas the expression level of mGluR7 mRNA and protein in DRG neurons is downregulated after this ligation (Li et al., 2012), thus implicating the transportation of this receptor into peripheral and central terminal.

Immunoreactive and stereological study shows that mGluR8 is highly expressed (75%) in small, medium, and large diameter DRG cells, and the double-labeled proportion of mGluR8 with mGluR2/3 have a considerable population (21%) (Carlton, Hargett, & Coggeshall, 2001). The labeling of mGluR8 within digital nerves is shown in unmyelinated (22%) and myelinated (19%) axons, and mGluR8-labeled L4 DRG neurons display double-labeling (25%) for TRPV1 (Govea, Zhou, & Carlton, 2012). In the TG, a high proportion (56%) of the neurons are positive for mGluR8 of which the immunolabeling is distributed as small (6%), medium (41%), and large (53%) diameter neurons (Boye Larsen et al., 2014).

Negative modulation of pain transmission

As with the contribution of group III mGluRs to neuronal excitability in presynaptic location of CNS, these receptors on primary afferent terminal of PNS are also thought to inhibit neuronal excitability by negatively modulating the glutamatergic transmission.

Some behavioral and electrophysiological studies present evidences to identify that group III mGluR located in peripheral terminal of PNS can reduce nociceptive inputs before transmission to the spinal cord (Table 1). Intraplantar

TABLE 1 Summary of the function of peripheral group III mGluRs on pain processing.

Location	Drugs (route)	Receptors	Experimental model	Effects	References
Peripheral terminal of primary DRG neurons	UBP1112 (intraplantar)	Group III antagonist	Capsaicin-injected hindpaw (extracellular recording)	The increased firings of primary afferent C fiber	Carlton, Zhou, Govea, and Du (2011)
	LY341495 (intraplantar)	Group II/III antagonist	Capsaicin- or excess glutamate-injected hindpaw (extracellular recording)	The increased firings of primary afferent C fiber	
				The increased pain behavior (flinching, lifting, licking, and paw withdrawal)	
			Capsaicin-injected primary DRG neurons (calcium imaging)	The increased calcium influx	
	L-AP4 (intraarticular)	Group III agonist	Carrageenan-injected knee joint	The decreased pain behavior (dynamic weight load and paw withdrawal)	Lee, Park, Cho, Kim, and Han (2013)
	L-AP4 (intraarticular)	Group III agonist	CFA-injected knee joint (extracellular recording)	The decreased firings of mechanosensitive afferent fiber	Park et al. (2019)
			CFA-injected knee joint	The decreased pain behavior (dynamic weight load)	
	MSOP (intraplantar)	Group III mGluR antagonist	Capsaicin-injected hindpaw	No effect (paw withdrawal)	Jin et al. (2009)
Central terminal of primary DRG neurons	L-AP4 (intrathecal)	Group III agonist	Spinal nerve-ligated injury	The decreased pain behavior (paw withdrawal and cold water)	Fisher, Lefebvre, and Coderre (2002)
	L-AP4 (intrathecal)	Group III agonist	Capsaicin-injected hindpaw	The decreased pain behavior (paw withdrawal and hot water)	Soliman, Yu, and Coderre (2005)
	L-AP4 (intrathecal)	Group III agonist	Spinal nerve-ligated injury	The decreased pain behavior (paw withdrawal and radiant heat)	Chen and Pan (2005)
			Single unit in dorsal spinal cord (extracellular recording)	The decreased firings of mechanosensitive afferent fiber	
	ACPT-I (intrathecal)	Group III mGluR agonist	Capsaicin-injected hindpaw or CFA-induced ankle	The decreased pain behavior (paw pressure)	Goudet et al. (2008)
			Spinal nerve-ligated injury or Vincristine-injected neuropathy	The decreased pain behavior (paw pressure)	
	PHCCC (intrathecal)	mGlu4 positive allosteric modulator	Capsaicin-injected hindpaw or Spinal nerve-ligated injury	The decreased pain behavior (paw pressure)	

Continued

TABLE 1 Summary of the function of peripheral group III mGluRs on pain processing—cont'd

Location	Drugs (route)	Receptors	Experimental model	Effects	References
	AMN082 (intrathecal)	mGluR7-positive allosteric modulator	Capsaicin-injected or incision hindpaw	The decreased pain behavior (paw withdrawal and radiant heat)	Dolan, Gunn, Biddlestone, and Nolan (2009)
	L-AP4 (intrathecal)	Group III agonist	Spinal nerve-ligated injury	The decreased pain behavior (paw withdrawal)	Wang, Jiang, Yang, and Li (2011)
	VU0155041 (intrathecal)	mGluR4-positive allosteric modulator	Spinal nerve-ligated injury	The decreased pain behavior (paw withdrawal)	
	LSP4-2022 (intrathecal)	mGlu4 agonist	Whole neuron in sliced dorsal spinal cord (intracellular recording)	The inhibition of evoked excitatory postsynaptic current	Vilar et al. (2013)
			Carrageenan-injected hindpaw or Spinal nerve-ligated injury	The decreased pain behavior (paw withdrawal and lifting)	
			Knowdown-mGlu4	The decreased pain behavior (paw lifting and licking, tail withdrawal)	
	AMN082 (intrathecal)	mGluR7-positive allosteric modulator	Spinal nerve-ligated injury	No effect (paw withdrawal)	Wang et al. (2011)

application of UBP1112, selective group III mGluRs antagonist, shows an increased neuronal firings (250%) of primary afferent C fiber in capsaicin-injected hindpaw of rats, and the application of group II and III mGluRs antagonist LY341495 significantly enhance capsaicin-induced calcium influx in primary DRG culture (Carlton et al., 2011). Intraarticular applications of group III mGluR agonist LAP4 dose-dependently inhibit pain behavior (reduced dynamic weight load) and decrease mechanosensitive firings (40%–50% from baseline) of primary afferent fibers in inflamed knee joint of rat (Lee et al., 2013; Park et al., 2019).

In central terminal of PNS, intrathecal pretreatment with L-AP4 increases a mechanical or thermal threshold of capsaicin-injected hindpaw in rats (Soliman et al., 2005). It is also revealed that intrathecal treatments with L-AP4 or mGluR4-positive allosteric modulator VU0155041 reduce mechanical thresholds in rats with neuropathic pain (Fisher et al., 2002; Wang et al., 2011). Intrathecal application with mGluR7 allosteric agonist AMN082 inhibits mechanical and thermal hyperalgesia in rats with inflammatory or incision pain (Dolan et al., 2009). Intrathecal application of LAP4 dose-dependently decreases neuronal firings of dorsal horn neuron evoked by mechanical stimulation (tough, pressure, and pinch) in rats having neuropathic pain, and intrathecal injection of group III mGluR antagonist MAP4 blocks this inhibitory effect of LAP4 (Chen & Pan, 2005). Administration of mGluR4 agonist LSP4-2022 to lumbar spinal slices of mice decreases the amplitude of evoked excitatory postsynaptic current (eEPSC) to an electrical stimulation on the dorsal root, possibly through coupling to Cav2.2. channel (Vilar et al., 2013).

The key comment is that peripheral group III mGluRs can play a modulatory role on glutamatergic neurotransmission through activity-dependent inhibition, rather than simply tonic inhibition. That is to say, the reaction of group III mGluRs is silent to a noxious stimulation in naïve or healthy environment; however, their ability to inhibit excitatory transmission is reinforced when inflammation or tissue damage occur. For instance, intrathecal applications of positive allosteric mGluR4 modulator, PHCCC, dose-dependently increase mechanical thresholds in rats with inflammatory and nerve-injured pain; however, there is no effect of PHCCC on a mechanical threshold of healthy rat (Goudet et al., 2008) (Fig. 3). In addition, depressant effects of LSP4-2022 on eEPSC amplitude of mice lumbar spinal slices remarkably enhance by 68% under an

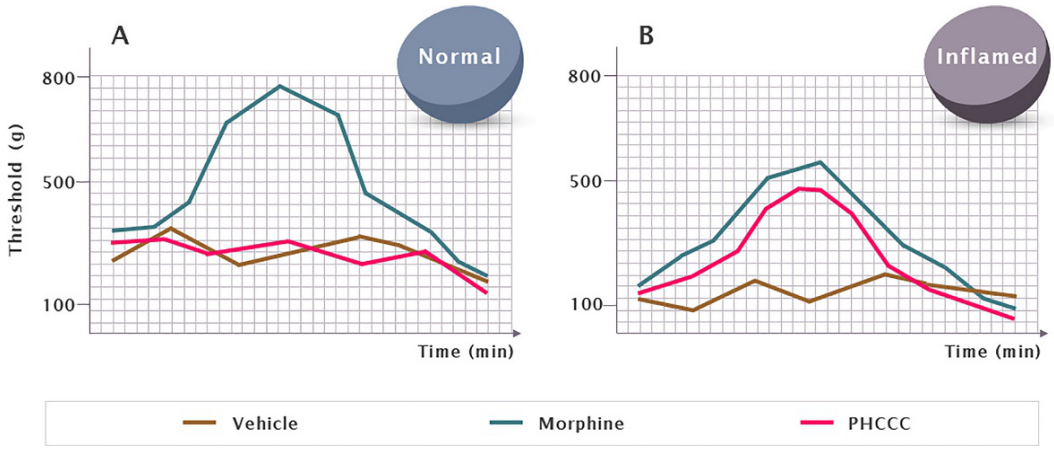


FIG. 3 Negative modulation of peripheral group III mGluRs on pain behavior. (A) Intrathecal application of mGlu4 positive allosteric modulator PHCCC has no effect on mechanical threshold of naïve animals. (B) Intrathecal application of PHCCC leads to an increased mechanical threshold in animals with inflammation or nerve injury. However, intrathecal application of morphine tonically has increased effects on mechanical threshold. *(From Goudet, C., Chapuy, E., Alloui, A., Acher, F., Pin, J. P., Eschalier, A. (2008). Group III metabotropic glutamate receptors inhibit hyperalgesia in animal models of inflammation and neuropathic pain.* Pain, 137(1), *112–124, https://doi.org/10.1016/j.pain.2007.08.020.)*

inflammatory condition, compared to by 53% under a normal condition. In parallel, mGlu4-knockout mice show higher mechanical thresholds and licking/biting behavior in response to noxious mechanical stimulation to tail and formalin injection to hindpaw (Vilar et al., 2013). Intraplantar applications of LY341495, group II/III mGluRs antagonist, produce both enhanced firing rates (400%) and lowered thermal threshold (about 1°C) to heat stimulation of primary afferent C fiber under the presence of excess exogenous glutamate (1 mM) into hindpaw preparation of rat, compared to under the condition of vehicle-control (Carlton et al., 2011). The activated mGluRs via LAP4 have no influence on mechanosensitive responses of primary afferent fibers under saline-injected knee joint (Park et al., 2019) (Fig. 4).

Although both group II and III mGluRs in PNS are known to be responsible for pain modulation, there are actually inconsistent effects of these receptors. Intraplantar applications of MCCG or MSOP, group II or group III mGluR antagonist, in rat have no effects on capsaicin-induced thermal hypersensitivity (Jin et al., 2009). Intrathecal treatment with mGluR7-positive allosteric modulator AMN082 does not reduce a mechanical threshold in rat model of neuropathic pain (Wang et al., 2011). In addition, the activation of group II mGluR via intrathecal treatment with DCG-IV has a pronociceptive effect on the sham control rats, implicating the involvement of NMDARs in spinal cord (Zhou, Chen, Chen, & Pan, 2011).

Group III mGluRs in non-neuronal glial cells

The cell bodies (DRG and TG) and axons fibers of PNS are in close contact with two types of glial cells such as satellite glial cells (SGCs) and myelinating/nonmyelinating Schwann cells (SCc). The morphology of satellite glial cells (SGCs) tightly envelops cell bodies of primary afferent neurons and creates an extracellular space of 15–20 nm. Myelinating Schwann cells wrap around axons of neurons to generate the myelin sheath and shape the axonal activity in peripheral nerves. It can be possible to extensively communicate with neurons and glial cells (Ji, Chamessian, & Zhang, 2016). In fact, glial cells can maintain neuronal homeostasis and glutamate recycling, thus regulating glutamate neurotransmission. However, after nerve or tissue injury SGCs can proliferate and initiate aberrant excitability via the coupling among SGC to SGC or neuron to SGC, therefore, contributing to developing chronic pain (Kim et al., 2016; Takeda, Takahashi, & Matsumoto, 2009).

Glutamate receptors including iGluRs and group I mGluRs in SGCs seem to contribute to glutamatergic signaling (Ferrari et al., 2014; Kung et al., 2013). For example, the application of glutamate into DRG cultures induces calcium influx only in satellite cells, which are suppressed by preadministration of NMDAR antagonist D-AP5 (Ferrari et al., 2014). Most of all, a few evidences implicate possible roles of group III mGluRs of SGCs on pain although there is no precise mechanism of these receptors toward SGCs (Fig. 5). A study reveals that group III mGluR8 is very highly expressed in SGCs of rats, with only minimal expression of group I (mGluR1) and group II (mGluR2/3) (Carlton & Hargett, 2007; Govea et al., 2012). In parallel, mGluR8 and mGluR1α, but not mGluR2/3, are found on SGCs in TG of rats (Boye Larsen et al., 2014).

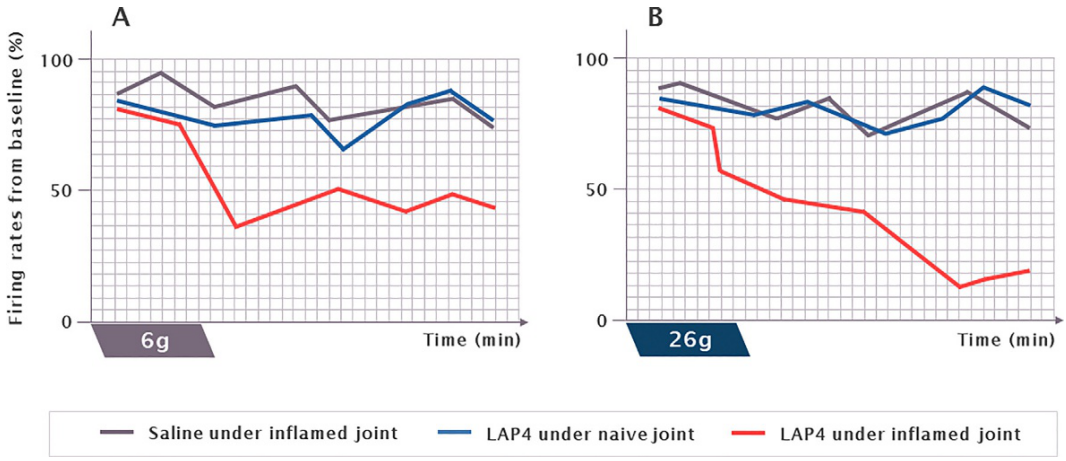
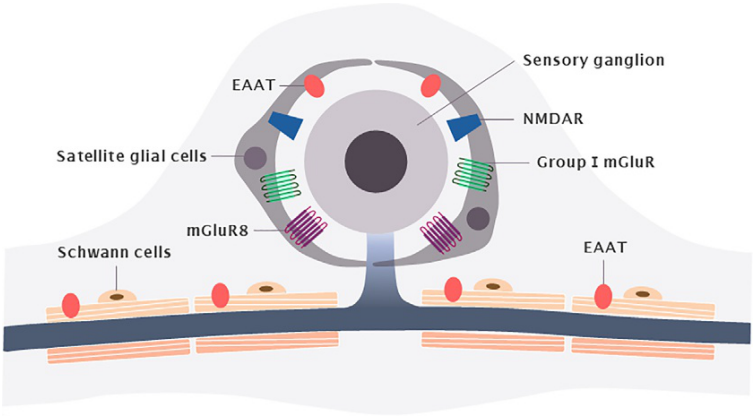


FIG. 4 Negative modulation of peripheral group III mGluRs on excitability of primary afferent fibers. The activation of peripheral group III mGluRs through L-AP4 has inhibitory effect on neuronal excitation evoked by 6 g (A) and 26 g (B) mechanical stimulations under inflamed knee joint. However, there is no effect of these receptors on mechanosensitive neuronal excitation under saline-injected knee joint. *(From Park, E. H., Lee, S. W., Moon, S. W., Suh, H. R., Kim, Y. I., Han, H. C. (2019). Activation of peripheral group III metabotropic glutamate receptors inhibits pain transmission by decreasing neuronal excitability in the CFA-inflamed knee joint*. Neuroscience Letters, 694*, 111–115. https://doi.org/10.1016/j.neulet.2018.11.033.)*

FIG. 5 Peripheral group III mGluRs in satellite glial cells. Non-neuronal glial cells are essential for maintaining neuronal homeostasis and glutamate recycling in peripheral nervous system. Especially, satellite glial cells (SGCs) can contribute to developing chronic pain. Group III mGluR8, as well as NMDA receptor and group I mGluRs, has a possible action for glutamatergic signaling in pain processing.



Applications to other areas

Group III mGluR4 in taste sensation. Glutamate deriving from dietary protein and food additive elicits umami taste. An umami-related sensory inputs are delivered to the rostral division of nucleus tractus solitarius (NTS) through facial, glossopharyngeal, and vagus nerves, which are transmitted to thalamus and gustatory cortex. The blockade of mGlu4 with a pharmacological antagonist or mGluR4 knock-out mice reduces the response of the umami taste stimulation (Pal Choudhuri, Delay, & Delay, 2016; Yasumatsu et al., 2015).

Group III mGluR7 and mGluR8 in colonic motor or secretory response. Colonic mGluRs can regulate intestinal mucosal function by acting on enteric neurons or epithelial cells. The activation of mGluR8 using (RS)PPG in the guinea pig colon dose-dependently increases the rate of propulsion (Tong & Kirchgessner, 2003). In addition, selective mGlu7 receptor agonist AMN082 increases water content and remarkably amplifies the bethanechol (acetylcholine analog)-induced electrolyte transport (Julio-Pieper, Hyland, Bravo, Dinan, & Cryan, 2010).

Group III mGluR4 in reward. These glutamatergic inputs of nucleus accumbens originated from the medial prefrontal cortex, hippocampus and amygdala contribute to reward-related perception and memory. The electrophysiological study indicates that group III receptor agonists such as L-SOP and LAP4 decrease the amplitude of cortically evoked

EPSPs in a dose-dependent manner (Pisani, Calabresi, Centonze, & Bernardi, 1997). In addition, a selective mGluR4 agonist LSP1-3081 not only inhibits cortically evoked EPSPs in a dose-dependent manner, but also reduces the frequency of miniature excitatory postsynaptic current (mEPSC) (Cuomo et al., 2009).

Other agents of interest

N-Phenyl-7-(hydroxyamino)cyclopropa[b]chromen-1a-carboxamide (PHCCC). PHCCC is the first selective positive allosteric modulator of mGluR4. Allosteric modulator increases or decreases the affinity of agonists through the binding to allosteric site of target receptor. PHCCC displays a micromolar potency for mGluR4 (EC_{50}, 4.1 μM) (Niswender et al., 2008), and has inhibitory effects on animals with inflammatory and neuropathic pain. However, PHCCC is also known as a partial antagonist (30%) of mGluR1.

Mini-dictionary of terms

Peripheral sensitization. Hyperexcitability or reduced threshold of the nociceptors in peripheral afferent neuron terminals and cell bodies after the occurrence of injury or inflammation.

Peptidergic nociceptor. Peptidergic nociceptor releases the neuropeptide such as substance P and calcitonin-gene-related peptide (CGRP) and also expresses a large proportion of TrkA receptor to bind with nerve growth factor.

Nonpeptidergic nociceptor. Nonpeptidergic nociceptor expresses the c-Ret neurotrophin receptor to respond to glial-derived neurotrophic factor (GDNF), and a large percentage of the c-Ret-positive population also binds with the IB4 isolectin (A lectin from the plant *Griffonia simplicifolia*).

Allosteric modulator. Allosteric modulators positively or negatively regulate receptor activity by binding at a site distinct from the orthosteric pocket of endogenous natural ligands.

Excitatory postsynaptic current. Excitatory neurotransmitters induce the opening of cationic channels in postsynaptic neurons, leading to the depolarizing phase capable of generating an action potential. These electrical events are called as excitatory postsynaptic currents (EPSCs) and excitatory postsynaptic potentials (EPSPs).

Key facts of *activity-dependent inhibition*

- Activity-dependent inhibition mechanism of peripheral group III mGluRs plays a role in negatively regulating glutamatergic neurotransmission.
- It can be recruited in peripheral or central terminals of PNS after the nociceptor is activated through excess glutamate release or inflammation/injury.
- The activation of peripheral group III mGluRs generates both decreased firing rates and increased threshold in primary afferent C fibers of hindpaw to heat stimulation under excess glutamate condition. However, these receptors do not inhibit neuronal excitability evoked by thermal stimulation under vehicle-control condition.
- The activation of peripheral group III mGluRs decreases mechanosensitive neuronal firings of primary afferent fibers innervating inflamed knee joint. However, there are no inhibitory effects of these receptors on mechanosensitivities under saline-injected knee joint.
- In the central terminal of primary afferent neuron, the activation of peripheral mGluR4 produces stronger effects on the reduction of eEPSC amplitude under CFA-induced inflammatory condition, compared to under normal condition.

Summary points

- This review focuses on the localization and function of the peripheral group III mGluRs with regard to glutamatergic transmission.
- After glutamate is produced (or reuptaked) in primary neurons and glia, it is transported through VGLUTs and released from peripheral terminals.
- The increased glutamate release from terminals of PNS involves the sensitization of nociceptor after tissue injury and inflammation occur.
- Glutamatergic transmission can be positively or negatively modulated by peripheral mGluRs.
- The expression and function of mGluR4, mGluR7, and mGluR8 among group III mGluRs are widely identified in PNS associated with nociception.

- Peripheral group III mGluRs of PNS have the ability to play an autoinhibitory role on excitatory neurotransmission under inflammation or tissue injury or excess glutamate.
- Peripheral group III mGluRs in SGCs have a feasible role to communicate with primary neurons for regulating pain.

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