

## Chapter 2

# Supraspinal Metabotropic Glutamate Receptors: An Endogenous Substrate for Alleviating Chronic Pain and Related Affective Disorders

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**Abstract** Metabotropic glutamate receptors (mGluRs) are key players in modulating excitatory transmission and important regulators of synaptic plasticity. mGluRs are G-protein-coupled receptors (GPCRs) that have been subdivided into three groups (mGluR1–mGluR8) based on sequence homology, intracellular pathways, and pharmacological profile. mGluRs are widely localized all along the nociceptive neuroaxis, including brain circuits controlling pain often overlapping those controlling affective/cognitive behaviors which prove deeply altered in several neurological disorders including chronic pain.

This chapter summarizes current outcomes related to the supraspinal mGluRs in chronic pain states. Due to their wide expression within the pain descending system, a particular highlighting will be given to the pharmacological manipulation of mGluRs in PAG-RVM pathway, a key circuitry of the pain descending system. The current development of novel subtype-selective mGluR positive and negative allosteric modulators will allow a more stringent assessment of each mGluR subtype role in controlling chronic pain and pain-related affective cognitive behavior.

**Keywords** Metabotropic glutamate receptors • Chronic pain • Antinociceptive descending pathway • Positive and negative allosteric modulators • Pain-related affective and cognitive disorders

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## Abbreviations

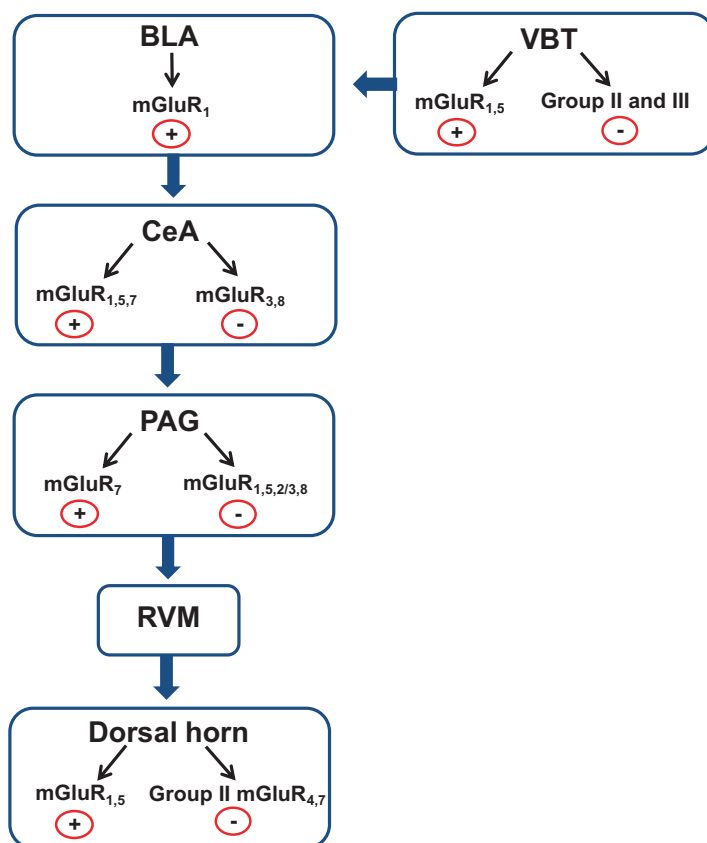
|              |                                                                 |
|--------------|-----------------------------------------------------------------|
| BLA          | basolateral amygdala                                            |
| CeA          | central nucleus of the amygdala                                 |
| CNS          | central nervous system                                          |
| CPCCOEt      | 7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxylate ethyl ester |
| (S)-3,4-DCPG | (S)-3,4-dicarboxyphenylglycine                                  |
| GPCRs        | G-protein coupled receptors                                     |
| iGluR        | ionotropic glutamate receptor                                   |
| IL           | infra-limbic                                                    |
| mGluR        | metabotropic glutamate receptor                                 |
| MPEP         | 2-methyl-6-(phenylethynyl)pyridine                              |
| mPFC         | medial prefrontal cortex                                        |
| NAAG         | N-acetylaspartylglutamate                                       |
| NMDA         | N-methyl-D-aspartate                                            |
| NTS          | nucleus tractus solitarius                                      |
| PAG          | periaqueductal gray                                             |
| PL           | pre-limbic                                                      |
| PLC          | phospholipase C                                                 |
| RVM          | rostral ventromedial medulla                                    |
| TRPV1        | transient receptor potential vanilloid 1                        |

## 2.1 Introduction

As the most abundant excitatory neurotransmitter in the central nervous system (CNS), glutamate plays a pivotal role in main physiological brain functions. Glutamate exerts its effects through the activation of ligand-gated ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs). iGluRs are ion channel receptors, divided into N-methyl-D-aspartate (NMDA),  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), and kainate (KA) receptors, which mediate fast responses, associated with long-lasting modifications in synaptic transmission (Bleakman and Lodge 1998; Yamakura and Shimoji 1999), while mGluRs are G-protein-coupled receptors (GPCRs) subdivided into three groups (mGluR1–mGluR8) based on sequence homology, intracellular pathways, and pharmacological profile. Group I mGluRs, consisting of mGluR<sub>1</sub> and mGluR<sub>5</sub>, are postsynaptically located and positively coupled to phospholipase C, and their activation leads to the intracellular calcium mobilization. Group II mGluRs, consisting of mGluR<sub>2</sub> and mGluR<sub>3</sub>, and group III mGluRs, consisting of mGluR<sub>4</sub>, mGluR<sub>6</sub>, mGluR<sub>7</sub>, and mGluR<sub>8</sub>, are mainly presynaptic and coupled to the inhibition of adenylyl cyclase activity and to other signaling pathway, including the activation of mitogen-activated protein kinase cascade (Tian et al. 2010). mGluRs, by modulating ion channel activity and neurotransmitter release, play a modulatory role on

CNS synaptic excitability (Maione et al. 1998a; Cartmell and Schoepp 2000). Thus, signaling via these receptors is slower and longer-lasting driving to a fine-tuning of glutamate transmission.

Hyperexcitability of glutamatergic system is the main event occurring in central sensitization associated to chronic pain. Apart from classical symptoms, such as allodynia (pain experience following a not-painful stimulus) and hyperalgesia (increased pain perception from a painful stimulus), chronic pain presents comorbidity with affective and cognitive impairments. mGluRs are suitable pharmacological substrate for producing a fine modulation of glutamate transmission, whose hyperactivity or altered functioning is often associated with neurodegenerative, neurological, and psychiatric diseases. The effects of mGluRs stimulation in supraspinal areas of the pain pathway are summarized in Fig. 2.1. By this subject, mGluRs



**Fig. 2.1** Scheme indicating the effect of mGluRs in supraspinal areas of the pain pathway. + indicates a facilitatory effect on pain transmission, while – indicates an inhibitory effect on pain transmission. *VBT* ventrobasal thalamus

pharmacological manipulation may represent an optimal strategy to treat chronic pain, including untreatable forms such as neuropathic pain, and associated affective and cognitive impairments.

## 2.2 mGluRs and Pain Processing

Increasing evidence supports a crucial role of mGluRs in nociceptive transmission, given their extensive expression all along the nociceptive neuroaxis, such as the peripheral sensory terminals, dorsal root ganglia, spinal cord dorsal horn, rostral ventromedial medulla (RVM), periaqueductal gray (PAG), thalamus, amygdala, and cortex. The large variety and different synaptic distribution of mGluR subtypes determine their diverse role in pain transmission. Group I mGluRs are mainly expressed in the postsynaptic membrane, whereas group II and III mGluRs are localized presynaptically where they serve as auto- or hetero-receptors (Ohishi et al. 1995). Generally, stimulation of group I mGlu receptors facilitates pain (Hama 2003; Chiechio and Nicoletti 2012; Palazzo et al. 2014a, b). Conversely, activation of presynaptic mGluRs on glutamatergic terminals leads to a decrease in glutamate release (Attwell et al. 1995; Battaglia et al. 1997) correcting hyperactivity of glutamatergic system associated with chronic pain (Gerber et al. 2000). Within the pain descending pathway, high glutamate levels are associated with antinociception throughout a facilitation of the descending pain system functioning (Behbehani and Field 1979). In fact, the activation of group I or groups II and III mGluRs exerts antinociceptive or pronociceptive opposite effects (Marabese et al. 2005, 2007a, b) depending on the mGluR subtype signaling and its location on glutamatergic or GABAergic terminals.

Over the last decade, accumulating evidence has strengthened the evidence that dysfunction of the glutamate system is linked with the pathophysiological mechanisms responsible for chronic pain development (Neugebauer 2001). Neuropathic or inflammatory injury triggers structural and functional changes in the peripheral or central sensory circuits, resulting in altered nociceptive signal processes, such as spontaneous pain, allodynia, and hyperalgesia (Neugebauer et al. 2009; Goudet et al. 2008; Byrnes et al. 2009). Under neuropathic pain conditions, enhanced glutamate release and overactivation of glutamate receptors have been observed in cortical areas involved in pain-related responses, including the anterior cingulate (ACC), insular, and prelimbic-infralimbic (PL-IL) cortex (Giordano et al. 2012; Hung et al. 2014). Furthermore, chronic pain interferes with specific limbic brain areas affecting neuropsychological processes which are glutamate-dependent, such as cognition, memory, and decision-making. mGluRs are supraspinally expressed within limbic system thus controlling negative affective disorders associated with chronic pain (Ferraguti and Shigemoto 2006; Latremoliere and Woolf 2009).

## 2.3 Group I mGluRs

The difficulty to develop selective agonists or antagonists for specific mGluR subtype arises from the sequence homology of mGluRs within the ligand binding site, which presents a hydrophilic moiety which makes the compound too hydrophilic to penetrate the blood-brain barrier for brain exposure. The identification, in the last years, of novel compounds acting as PAMs or NAMs, has guaranteed selectivity and lipophilicity since allosteric binding sites proved less conserved among the other mGluRs and do not require hydrophilic molecules. Activation of group I mGluRs generally facilitates nociception (Bhave et al. 2001) and mediates the development of inflammatory hyperalgesia (Walker et al. 2000; Palazzo et al. 2004). The role of supraspinal group I mGluRs in controlling pain responses has been investigated in the ventrobasal thalamus, periaqueductal gray, rostral ventromedial medulla, and amygdala.

**Thalamus** Ventrobasal thalamus is a crucial relay point processing the somatosensory information which from the spinal cord reach the cerebral cortex. At this level, mGluR1, mGluR5, and NMDA receptor stimulation enhances neuronal responses to nociceptive stimuli. Conversely, NMDA receptor, mGluR1, or mGluR5 blockade reduced the neuronal responses (Salt and Binns 2000).

**Amygdala and Cortex** Basolateral (BLA) and central nucleus (CeA) of the amygdala are deeply involved in the emotional consequences of pain, such as pain-related anxiety and depression-like behaviors. While the electrical manipulation of CeA activity does not modify the spontaneous nociceptive behaviors (Carrasquillo and Gereau 2008; Veinante et al. 2013), chronic pain leads to increased synaptic transmission in the CeA, associated with the induction or maintenance of hypersensitivity observed in different pain models.

The activation of group I mGluRs in the amygdala is generally associated with pronociceptive effects (Neugebauer et al. 2003a, b; Kolber et al. 2010). Conversely, the blockade of mGluR1 inhibits pain stimuli-induced audible and ultrasonic vocalizations (Han and Neugebauer 2005) and decreases excitatory postsynaptic currents in neurons within the CeA in arthritic rats (Neugebauer et al. 2003a; Ren and Neugebauer 2010). It has been recently shown that group I mGluRs are involved in the plastic changes that develop in the BLA and medial prefrontal cortex (mPFC) circuitry in chronic pain states (Ji and Neugebauer 2011; Guida et al. 2015). Later on, Luongo et al. (2013) have showed that intra-BLA microinjection of (S)-3,5-dihydroxyphenylglycine (DHPG), a group I mGluR agonist, reverted neuronal phenotypical changes occurring in the mPFC, under chronic pain condition. The 7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxylate ethyl ester, CPCOOEt, a selective mGluR1 antagonist, but not 2-methyl-6-(phenylethynyl)-pyridine, MPEP, a selective mGluR5 antagonist, prevented alteration in mPFC under chronic pain condition, suggesting that mGluR1, but not mGluR5, plays a role in the modulation of BLA-mPFC circuitry, which is thought to be a key substrate for affective/cognitive impairments associated with chronic pain.

Group I mGluRs may control inflammation and chronic pain state also through a functional cross talk with transient receptor potential vanilloid type 1, TRPV1 (Hu et al. 2002; Palazzo et al. 2002), a sort of a polymodal pain transducer, activated by chemical and thermal stimuli which open a cationic influx driving to action potentials. mGluR5 activation sensitizes TRPV1 through the PLC activation and protein kinase A pathway (Hu et al. 2002). Reciprocally, brain TRPV1 stimulation induces glutamate release through depolarization and intracellular  $\text{Ca}^{2+}$  mobilization (Hu et al. 2002; Kim et al. 2009). The spared nerve injury (SNI) of the sciatic nerve, a model of neuropathic pain in rodents (Decosterd and Woolf 2000), increased extracellular level of glutamate in the PL/IL portion of the mPFC. Blockade of mGluR5 by MPEP microinjection in the PL/IL worsened mechanical allodynia in the SNI mice, possibly by braking the enhancement of the antinociceptive descending pathway played by glutamate outflow, an effect which requires mGluR5 receptor stimulation (Giordano et al. 2012).

*Periaqueductal Gray (PAG)/Rostral Ventromedial Medulla (RVM)* The presence of mGluRs within the PAG has a strategic importance for modulating pain processing, since it is a key station in the pain descending pathway. Indeed, its electrical or chemical stimulation produces deep analgesia in rats (Reynolds 1969; Behbehani 1995). The PAG-mediated analgesia is correlated with the modulation of neuron firing activity within the nucleus raphe magnus, the adjacent reticular formation, and the nucleus gigantocellularis, which constitute the RVM (Behbehani and Fields 1979). RVM neurons, in turn, project to the spinal cord dorsal horn (Fields and Basbaum 1999), thus inhibiting the nociceptive neuronal response to noxious stimuli. Stimulation of group I mGluRs at the PAG level triggers glutamate-induced analgesia. It has been shown that selective activation of mGluR1 in the PAG prevents nocifensive behavior in formalin-induced persistent pain (Maione et al. 2000). mGluR5, at supraspinal level, contributes to hypersensitivity following peripheral neuropathy. Indeed, shown that MPEP, the selective mGluR5 antagonist, dose-dependently reduces the neuropathy-induced cold hypersensitivity, when microinjected directly into the RVM (Urban et al. 2003). Conversely, groups II and III mGluR stimulation facilitated nociceptive responses by depressing PAG-RVM activity within the antinociceptive descending pathway (Maione et al. 1998b). The mechanism through which mGluRs mediate analgesia at the PAG level remains not fully understood. Activation of group I mGluRs produces antinociception via pre-synaptic inhibition of GABA release (Maione et al. 1998a, b, 2000), which in turn enhances pain descending system activity. Moreover, several studies have shown that activation of group I mGluR promotes the production of endocannabinoids, which in turn diffuse out of postsynaptic neurons in a retrograde way to presynaptic terminals. Endocannabinoids bind to cannabinoid type 1 receptor (CB1R) and reduce neurotransmitter release. A functional cross talk between CB1R and group I mGluRs in the PAG-RVM circuitry has also been shown in healthy (Palazzo et al. 2001) and in neuropathic pain condition induced by chronic constriction injury (CCI) of the sciatic nerve. In this study, the effects of intra-ventrolateral (VL) PAG microinjection of WIN 55,212-2, a nonselective cannabinoid receptor agonist,

evaluated as behavioral analgesia and electrophysiological RVM neuronal responses, were prevented by MPEP, a selective mGluR5 antagonist (Palazzo et al. 2012), supporting a role for mGluR5 in cannabinoid-induced analgesia at PAG level in neuropathic pain conditions.

## 2.4 Group II mGluRs

Group II agents have shown being involved in a number of animal models of psychiatric, neurological, and neurodegenerative disorders, associated with glutamate overexcitation. Group II mGluRs are located on the preterminal regions of primary afferent nerve endings and in supraspinal pain-regulatory centers such as the thalamus, amygdala, and PAG. They negatively regulate glutamate and other neurotransmitter release and inhibit TRPV1 and sodium channel activities (Yang and Gereau 2002, 2003; Carlton et al. 2009). mGluR2 agonists produce analgesia in models of inflammatory and neuropathic pain, but their use is limited by the development of tolerance, usually occurring after 4–5 days of repeated doses (Jones et al. 2005). Their supraspinal involvement in pain processing has been investigated in the amygdala, PAG, and ventrobasal and reticular thalamus.

*Amygdala* In contrast to group I, group II mGluR stimulation inhibits nociceptive processing in CeA neurons. In anesthetized rats, the increased function and endogenous activation of group II mGluRs reduces the ongoing, as well as, evoked cell activity, in the knee-joint kaolin-/carrageenan-induced arthritis (Li and Neugebauer 2006). Further and more recent studies have indicated that mGluR2 is more important in controlling pain transmission than mGluR3 (Zammataro et al. 2011). In the amygdala, mGluR2 and mGluR3 stimulation inhibits GABA release at the BLA-CeA synapse leading to an increased activity of GABAergic interneurons in the CeA which in turn reduces the output of the medial central amygdala to the brain regions mediating the autonomic, motor, and endocrine features of anxiety (Linden et al. 2005, 2006). By this subject group II mGluRs in the amygdala are well positioned to inhibit both pain responses and the pain-related anxiety behavior.

*Ventrobasal Thalamus and Reticular Thalamus* Group II mGluRs in the ventrobasal thalamus inhibit GABAergic interneuron responses evoked by sensory stimulation in vivo (Salt and Eaton 1995; Salt and Turner 1998). Conversely, their blockade in the reticular thalamic nucleus produced antinociception in monoarthritic rats, probably by disinhibiting local GABAergic inhibitory neurons (Neto and Castro-Lopes 2000; Neto et al. 2000).

*PAG-RVM Circuitry* The effects of supraspinal group II mGluRs on pain responses have been recently carried out exploiting the compound ZJ43, a peptidase inhibitor degrading N-acetylaspartylglutamate (NAAG) which acts as a selective mGluR3 agonist. The microinjection of ZJ43 into the PAG and RVM reduced both phases of the nocifensive reaction induced by the peripheral injection of formalin into the

hind paw. The effect of ZJ43 was antagonized by LY341495, a group II mGluR antagonist. However, ZJ43 did not affect the thermal withdrawal response in the hot plate test in healthy animals when microinjected into the same brain sites (Yamada et al. 2012). This study is consistent with previous studies showing that the intra-PAG microinjection of a group II mGluR agonist, L-CCG-I, or the intracerebroventricular administration of NAAG peptidase inhibitors reduced nocifensive behavior in the formalin test (Maione et al. 2000; Yamamoto et al. 2000) and with those which conversely show that intra-PAG L-CCG-I decreased the thermal threshold in the hot plate test, possibly by depressing the activity of the pain descending system at PAG level (Maione et al. 1998b). These studies suggest that group II mGluR stimulation within the PAG produces analgesia in chronic pain conditions, but proved ineffective (or even facilitated pain responses) in acute pain conditions (Maione et al. 1998b; Palazzo et al. 2001).

## 2.5 Group III mGluRs

Group III is the largest mGluR group which remains the less investigated due to the lack of selective ligands. Fortunately, selective compounds have been developed recently thus permitting a clarification of group III mGluR roles in the CNS diseases (Acher and Goudet 2015). Apart from mGluR6 which mediates responses of ON bipolar cells at retinal synapses (Vardi et al. 2000), mGluR4, mGluR7, and mGluR8 are extensively distributed throughout the CNS. Group III mGluR activation in the presynaptic active zone of transmitter release leads to glutamate and GABA release inhibition (Niswender and Conn 2010). Low release of excitatory transmitters results in the presynaptic inhibition of transmission. On the other hand, the decrease of release of GABA may indirectly have excitatory effects on neuronal excitability (disinhibition). Thus, the overall effect of group III mGluR activity may be a balance between pain facilitation and inhibition. Moreover, glutamate shows high affinity for mGluR4 and mGluR8 and very low affinity for mGluR7 (Schoepp 2001) suggesting that mGluR7 may be recruited under pathological conditions characterized by excessive glutamate transmission activity. mGluR4 proved to be highly expressed in the cerebellum where it inhibits glutamate release at the synapses between granule cell axons and Purkinje cells. mGluR4 expression has been also found in the thalamus, basal ganglia, and olfactory bulb. mGluR7 is the most widely distributed among the presynaptic mGluRs. High expression of mGluR7 has been found in locus coeruleus, hippocampus, septum, frontal cortex, amygdala, cingulate cortex, bed nucleus of the stria terminalis, PAG, nucleus accumbens, thalamus, hypothalamus, and pituitary gland (Kinzie et al. 1995; Kinoshita et al. 1998). The mGluR8 is also widely distributed in brain areas such as the amygdala, pontine gray, lateral septum, lateral reticular nucleus of the thalamus, olfactory bulb, piriform cortex, cerebral cortex, hippocampus, hypothalamus, and cerebellum (Saugstad et al. 1997; Ferraguti et al. 2006). Notwithstanding the wide distribution information regarding group III mGluR, the role and contribution to pain modulation has

only just started to emerge owing to the limitations of the ligands used until recently. The majority of the drugs which have been applied until the last years are nonselective among the group III mGluR subtypes and display scarce solubility or metabolite instability. The recent progress in the selective ligand development has driven the investigations toward a better understanding of their modulatory function and their therapeutic potential in neurological and psychiatric disorders.

*Thalamus* The thalamus shows a relevant expression for group III mGluRs (Neto and Castro-Lopes 2000). In the corticothalamic synapses, broad-spectrum group III mGluR agonists inhibited excitatory postsynaptic potentials, showing that glutamate released at this level depresses cortical control of thalamic function (Turner and Salt 1999).

*Amygdala* L-AP4 is a broad-spectrum group III mGluR agonist which does not discriminate between mGluR4 and mGluR8 and shows scarce affinity for mGluR7. In the CeA, L-AP4 inhibits neuron sensitization in chronic pain conditions induced by the knee-joint injection of kaolin/carrageen which develops in arthritic pain. The inhibition of neuron plasticity by L-AP4 within the CeA involves a presynaptic mechanism. L-AP4 slightly changed CeA neuronal responses under normal conditions (Han et al. 2004). The N,N'-bis(diphenylmethyl)-1,2-ethanediamine dihydrochloride, AMN082, has been introduced as the first selective PAMs toward mGluR7 (Mitsukawa et al. 2005). In the CeA, AMN082 perfusion throughout reverse microdialysis facilitated nociception, whereas the selective activation of mGluR8 with (S)-3,4-DCPG (Thomas et al. 2001) produced the opposite effect driving to antinociception (Palazzo et al.). mGluR7 and mGluR8 in the CeA also changed pain-related affective responses conversely. AMN082 increased audible and ultrasonic vocalizations, which reflect supraspinally organized nocifensive and affective responses to aversive stimuli (Borszcz and Leaton 2003) and reduced the open-arm preference, a positive indicator of anxiolytic-like effect, in the elevated plus maze in healthy rats, whereas it was devoid of activity in the model of arthritic inflammatory pain. In contrast, (S)-3,4-DCPG had no effect in normal animals, but inhibited audible and ultrasonic vocalizations and enhanced the open-arm access in the arthritic animals. It seems like under normal conditions, mGluR7, but not mGluR8, facilitates pain and anxiety responses, whereas mGluR8 can inhibit pain response and affective behavior in chronic pain conditions such as arthritic pain (Palazzo et al.). The effect of mGluR8 activation at CeA level in chronic pain condition only has also investigated in inflammatory pain conditions induced by the intraplantar injection of carrageenan (Palazzo et al.). Intra-CeA (S)-3,4-DCPG decreased GABA and simultaneously increased serotonin and glutamate release in carrageenan-given rats, while it did not change neurotransmitter levels in control animals. Intra-CeA (S)-3,4-DCPG also increased the thermoceptive threshold and modify the activity of RVM pain-responding neurons: the ON cells which are activated and the OFF cells which are inhibited by nociceptive stimuli (Fields et al. 1983; Heinricher et al. 1989). Consistently with behavioral analgesia, intra-CeA (S)-3,4-DCPG inhibited the ON cell activity and enhanced the OFF cell activity in rats treated with carrageenan. (S)-3,4-DCPG was instead ineffective on pain responses and ON and OFF

cell activity in control rats. Thus, it seems like a pain-related plasticity in the CeA is required for mGluR8 stimulation being effective. An increase in mGluR8 expression on vesicular GABA transporter (vGAT)-positive profiles has been found in the CAA of carrageenan-given rats thus providing a functional target for inhibiting pain through the disinhibition of the descending facilitatory system (Maione et al. 2000; Berrino et al. 2001).

**PAG/RVM** Being PAG a crucial area within the antinociceptive descending pathway, whose stimulation induces analgesia (Reynolds et al. 1969; Behbehani 1995), mGluR expression at this level (Catania et al. 1994; Leyva et al. 1995) has a strategic importance. First evidence that group III mGluRs at PAG level modulate pain threshold came from a study in which L-SOP, a phosphate analog of L-AP4 with the same group III mGluR agonist property, microinjected into the PAG facilitated pain response under normal conditions (Maione et al. 1998b) and in the late phase of the formalin pain test, possibly by inhibiting descending pain inhibition (disinhibition) or by activating the descending facilitatory system (Maione et al. 2000; Berrino et al. 2001). Later on, by using more selective compounds, it has been shown that the individual roles of mGluR7 and mGluR8 in the regulation of pain threshold within the PAG were not univocal as in the CeA. The intra-PAG administration of (S)-3,4-DCPG alleviated pain responses, an effect which proved to depend from the time of administration with respect to the peripheral injection of formalin and carrageenan. Interestingly, the intra-PAG microinjection of MSOP, a group III receptor antagonist, antagonized the analgesic response of systemically administered (S)-3,4-DCPG suggesting that the analgesic effect of systemic (S)-3,4-DCPG requires mGluR8 within the PAG (Marabese et al. 2007a). The analgesic effect of intra-PAG (S)-3,4-DCPG was also associated with simultaneous changes in the RVM activity (Marabese et al. 2007b). Indeed, it increased the ongoing and tail flick-related activity of OFF cells and reduced that of ON cells. Conversely, the mGluR7 stimulation in the PAG by AMN082 increased the activity of ON cells and reduced that of OFF cells and consistently decreased tail flick latency (Marabese et al. 2007b). mGluR7 and mGluR8 stimulation within the PAG produced opposite effect on GABA and glutamate release too. Indeed, intra-PAG (S)-3,4-DCPG increased glutamate and decreased the GABA levels, whereas AMN082 reduced the glutamate concentration and increased GABA release, conversely (Marabese et al. 2007b). The role of mGluR7 at PAG level has been recently deepened by microinjecting into the PAG the novel selective negative allosteric modulator for mGluR7, the 6-(4-methoxyphenyl)-5-methyl-3-pyridin-4-ylisoxazolo[4,5-c]pyridin-4(5H)-one, MMPIP (Suzuki et al. 2007; Nakamura et al. 2010). Intra-VL PAG MMPIP inhibited pain responses in formalin and neuropathic pain models remaining ineffective in healthy rats. MMPIP also modulated RVM cell activity by increasing the activity of the antinociceptive OFF cells and decreased that of the pronociceptive ON cells, consistently with antinociception only in neuropathic rats and proved to be ineffective in healthy controls (Palazzo et al. 2012). The context-

dependent MMPIP effect was later on confirmed in a recent study where systemic MMPIP has proved to revert pain and pain-related affective and cognitive responses in the SNI model of neuropathic while remaining ineffective in control mice (Palazzo et al. 2015).

*Nucleus Tractus Solitarius (NTS)* Interestingly and accordingly to the opposite effects on pain modulation played by mGluR7 and mGluR8 stimulation in the PAG and amygdala, opposite roles of these receptors have also been reported in the NTS. However, the function played by mGluR7 (pain facilitation) and mGluR8 (pain inhibition) on cardiac somatic reflex induced by pericardial capsaicin was exactly the opposite to those played in the amygdala and PAG. Indeed, mGluR7 has an inhibitory, whereas mGluR8 has a facilitatory role in modulating cardiac nociception in the NTS (Liu et al. 2012). The effects of intra-NTS stimulation of mGluR7 and mGluR8 were antagonized by intra-NTS MSOP, a selective group III mGluR antagonist. The reason of the discrepancy among mGluR7 and mGluR8 stimulation effect within the NTS and PAG/amygdala may originate from the fact that NTS has a pronociceptive action and the stimulation of mGluR8 on GABAergic terminals by disinhibiting NTS-descending activity increases nociceptive information at the spinal cord level. The stimulation of mGluR7 on glutamatergic terminals would have the opposite effect (Liu et al. 2012). It has been also recently shown that group III mGluR blockade in NTS prevents sensitization of neural firing response to intratracheal application of capsaicin in both naïve- and allergen-sensitized rats (Spaziano et al. 2015).

*Dorsal Striatum (DS)* The role of the mGluR8 in modulating pain responses in neuropathic pain conditions has been recently investigated also in the dorsal striatum (DS). mGluR8 stimulation did not modify the nociceptive behavior and RVM neural activity in control rats but increased the mechanical withdrawal threshold and the activity of the OFF cells while decreasing that of the ON cells in the SNI model of neuropathic pain. The effect of mGluR8 manipulation (and of other group III mGluRs) being analgesic in chronic pain conditions only is consistent with previous reports (2011b, 2014a,b, 2015). AZ12216052, a mGluR8 PAM, has shown an effect similar to that of (S)-3,4-DCPG. An increase in tail flick latency and in the OFF cell activity and a decrease in the ON cell activity have been observed in SNI rats only. However, the effect of AZ12216052 was less potent than that of (S)-3,4-DCPG. Differently from mGluR8, the mGluR4 stimulation by VU0155041, a selective mGluR4 PAM, was ineffective in changing pain responses in both shams and SNI rats thus confirming the specificity of (S)-3,4-DCPG effect was due by mGluR8 stimulation (Thomas et al. 2001). mGluR8 protein expression was increased in the DS and associated with vesicular glutamate transporter vGAT-positive profiles in SNI rats suggesting that disinhibition of the DS inhibits pain transmission throughout the descending pain pathway activation at RVM level in chronic pain condition (Rossi et al. 2014).

## 2.6 Conclusion

Altogether the potential and the variety of the effects which may be obtained by mGluR manipulation on CNS functioning are unlimited. A large number of neurological and psychiatric diseases are associated with glutamate transmission dysregulation; thus, its modulation by mGluR fine-tuning appears strategic. The mGluR-wide expression in nervous tissue of the pain pathway suggests that multiple avenues exist to exploit mGluRs for designing pain-killers. In particular, pain-controlling supraspinal sites often overlap those controlling affective and cognitive behaviors which are seriously compromised in chronic pain suffering subjects. Moreover, their expression in supraspinal structures such as those belonging to the endogenous antinociceptive descending pathway, including PAG and RVM, whose task is to counteract pain, offers an endogenous substrate for evoking analgesia. Taken as a whole, the mGluR ligand effects on pain and pain-related affective/cognitive responses depend not only from their selectivity for a particular mGluR subtype and the transduction cascades to which they are coupled but also from the neuron type (glutamate or GABA) and the brain site which can be pronociceptive or antinociceptive on which they are located. The recent increasing development of NAMs and PAMs which have shown selectivity toward a specific mGluR subtype offers a large variety of pharmacological tools for investigating mGluR potential on psychiatric and neurological diseases including chronic pain and its emotional and cognitive consequences. Moreover, these allosteric modulators present better lipophilicity and selectivity than their orthosteric counterparts. While preliminary studies investigating the effect of mGluR8 PAMs and mGluR7 NAMs on chronic pain and related affective cognitive consequences appear encouraging, further studies will be needed to clarify the precise contribution of each mGluR subtype and its therapeutic potential.

## References

- Acher F, Goudet C (2015) Therapeutic potential of group III metabotropic glutamate receptor ligands in pain. *Curr Opin Pharmacol* 20:64–72
- Attwell PJE, Kaura S, Sigala G, Bradford HF, Croucher MJ, Jane DE et al (1995) Blockade of both epileptogenesis and glutamate release by (1S,3S)-ACPD, a presynaptic glutamate receptor agonist. *Brain Res* 698(1–2):155–162
- Battaglia G, Monn JA, Schoepp DD (1997) In vivo inhibition of veratridine-evoked release of striatal excitatory amino acids by the group II metabotropic glutamate receptor agonist LY354740 in rats. *Neurosci Lett* 229(3):161–164
- Behbehani MM (1995) Functional characteristics of the midbrain periaqueductal gray. *Prog Neurobiol* 46(6):575–605
- Behbehani MM, Fields HL (1979) Evidence that an excitatory connection between the periaqueductal gray and nucleus raphe magnus mediates stimulation produced analgesia. *Brain Res* 170(1):85–93
- Berrino L, Oliva P, Rossi F, Palazzo E, Nobili B, Maione S (2001) Interaction between metabotropic and NMDA glutamate receptors in the periaqueductal grey pain modulatory system. *Naunyn Schmiedeberg Arch Pharmacol* 364(5):437–443

- Bhave G, Karim F, Carlton SM, Gereau RW (2001) Peripheral group I metabotropic glutamate receptors modulate nociception in mice. *Nat Neurosci* 4(4):417–423
- Bleakman D, Lodge D (1998) Neuropharmacology of AMPA and kainate receptors. *Neuropharmacol* 37(10–11):1187–1204
- Borszcz GS, Leaton RN (2003) The effect of amygdala lesions on conditional and unconditional vocalizations in rats. *Neurobiol Learn Mem* 79(3):212–225
- Byrnes KR, Stoica B, Loane DJ, Riccio A, Davis MI, Faden AI (2009) Metabotropic glutamate receptor 5 activation inhibits microglial associated inflammation and neurotoxicity. *Glia* 57(5):550–560
- Carlton SM, Du J, Zhou S (2009) Group II metabotropic glutamate receptor activation on peripheral nociceptors modulates TRPV1 function. *Brain Res* 1248:86–95
- Carrasquillo Y, Gereau RW (2008) Hemispheric lateralization of a molecular signal for pain modulation in the amygdala. *Mol Pain* 4:24
- Cartmell J, Schoepp DD (2000) Regulation of neurotransmitter release by metabotropic glutamate receptors. *J Neurochem* 75(3):889–907
- Catania MV, De SH, Penney JB, Young AB (1994) Metabotropic glutamate receptor heterogeneity in rat brain. *Mol Pharmacol* 45(4):626–636
- Chiechio S, Nicoletti F (2012) Metabotropic glutamate receptors and the control of chronic pain. *Curr Opin Pharmacol* 12(1):28–34
- Decosterd I, Woolf CJ (2000) Spared nerve injury: an animal model of persistent peripheral neuropathic pain. *Pain* 87(2):149–158
- Ferraguti F, Shigemoto R (2006) Metabotropic glutamate receptors. *Cell Tissue Res* 326(2):483–504
- Fields HL, Basbaum AI (1999) Central nervous system mechanisms of pain modulation. In: Wall PD, Melzack R (eds) *Textbook of pain*. Churchill Livingstone, New York, pp 243–257
- Fields HL, Bry J, Hentall I, Zorman G (1983) The activity of neurons in the rostral medulla of the rat during withdrawal from noxious heat. *J Neurosci* 3(12):2545–2552
- Gerber G, Zhong J, Youn D, Randic M (2000) Group II and group III metabotropic glutamate receptor agonists depress synaptic transmission in the rat spinal cord dorsal horn. *Neurosci* 100(2):393–406
- Giordano C, Cristino L, Luongo L, Siniscalco D, Petrosino S, Piscitelli F et al (2012) TRPV1-dependent and-independent alterations in the limbic cortex of neuropathic mice: impact on glial caspases and pain perception. *Cereb Cortex* 22(11):2495–2518
- Goudet C, Chapuy E, Alloui A, Acher F, Pin JP, Eschaliere A (2008) Group III metabotropic glutamate receptors inhibit hyperalgesia in animal models of inflammation and neuropathic pain. *Pain* 137(1):112–124
- Guida F, Luongo L, Marmo F, Romano R, Iannotta M, Napolitano F, Belardo C, Marabese I, D'Aniello A, Bellini G, Rossi F, Piscitelli F, Lattanzi R, de Bartolomeis A, Usiello A, Di Marzo V, de Novellis V, Maione S (2015) Palmitoylethanolamide reduces pain-related behaviors and restores glutamatergic synapses homeostasis in the medial prefrontal cortex of neuropathic mice. *Mol Brain* 8:47
- Hama AT (2003) Acute activation of the spinal cord metabotropic glutamate subtype-5 receptor leads to cold hypersensitivity in the rat. *Neuropharmacology* 44(4):423–430
- Han JS, Neugebauer V (2005) mGluR1 and mGluR5 antagonists in the amygdala inhibit different components of audible and ultrasonic vocalizations in a model of arthritic pain. *Pain* 113(1–2):211–222
- Han JS, Bird GC, Neugebauer V (2004) Enhanced group III mGluR-mediated inhibition of pain-related synaptic plasticity in the amygdala. *Neuropharmacology* 46(7):918–926
- Heinricher MM, Barbaro NM, Fields HL (1989) Putative nociceptive modulating neurons in the rostral ventromedial medulla of the rat: firing of on- and off-cells is related to nociceptive responsiveness. *Somatosens Mot Res* 6(4):427–439
- Hu H-J, Bhave G, Gereau RW (2002) Prostaglandin and protein kinase A-dependent modulation of vanilloid receptor function by metabotropic glutamate receptor 5: potential mechanism for thermal hyperalgesia. *J Neurosci* 22(17):7444–7452

- Hung KL, Wang SJ, Wang YC, Chiang TR, Wang CC (2014) Upregulation of presynaptic proteins and protein kinases associated with enhanced glutamate release from axonal terminals (synaptosomes) of the medial prefrontal cortex in rats with neuropathic pain. *Pain* 155(2):377–387
- Ji G, Neugebauer V (2010) Reactive oxygen species are involved in group I mGluR-mediated facilitation of nociceptive processing in amygdala neurons. *J Neurophysiol* 104(1):218–229
- Ji G, Neugebauer V (2011) Pain-related deactivation of medial prefrontal cortical neurons involves mGluR1 and GABAA receptors. *J Neurophysiol* 106(5):2642–2652
- Jones CK, Eberle EL, Peters SC, Monn JA, Shannon HE (2005) Analgesic effects of the selective group II (mGlu2/3) metabotropic glutamate receptor agonists LY379268 and LY389795 in persistent and inflammatory pain models after acute and repeated dosing. *Neuropharmacology* 49(Suppl):206–218
- Kim H, Cui L, Kim J, Kim SJ (2009) Transient receptor potential vanilloid type 1 receptor regulates glutamatergic synaptic inputs to the spinothalamic tract neurons of the spinal cord deep dorsal horn. *Neuroscience* 160(2):508–516
- Kinoshita A, Shigemoto R, Ohishi H, van der Putten H, Mizuno N (1998) Immunohistochemical localization of metabotropic glutamate receptors, mGluR7a and mGluR7b, in the central nervous system of the adult rat and mouse: a light and electron microscopic study. *J Comp Neurol* 393(3):332–352
- Kinzie JM, Saugstad JA, Westbrook GL, Segerson TP (1995) Distribution of metabotropic glutamate receptor 7 messenger RNA in the developing and adult rat brain. *Neuroscience* 69(1):167–176
- Kolber BJ, Montana MC, Carrasquillo Y, Xu J, Heinemann SF, Muglia LJ et al (2010) Activation of metabotropic glutamate receptor 5 in the amygdala modulates pain-like behavior. *J Neurosci* 30(24):8203–8213
- Latremoliere A, Woolf CJ (2009) Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain* 10(9):895–926
- Leyva J, Maione S, Pallotta M, Berrino L, Rossi F (1995) Metabotropic and ionotropic glutamate receptors mediate opposite effects on periaqueductal gray matter. *Eur J Pharmacol* 285(2):123–126
- Li W, Neugebauer V (2006) Differential changes of group II and group III mGluR function in central amygdala neurons in a model of arthritic pain. *J Neurophysiol* 96(4):1803–1815
- Linden AM, Shannon H, Baez M, Yu JL, Koester A, Schoepp DD (2005) Anxiolytic-like activity of the mGlu2/3 receptor agonist LY354740 in the elevated plus maze test is disrupted in metabotropic glutamate receptor 2 and 3 knock-out mice. *Psychopharmacology* 179(1):284–291
- Linden A-M, Baez M, Bergeron M, Schoepp DD (2006) Effects of mGlu2 or mGlu3 receptor deletions on mGlu2/3 receptor agonist (LY354740)-induced brain c-Fos expression: specific roles for mGlu2 in the amygdala and subcortical nuclei, and mGlu3 in the hippocampus. *Neuropharmacology* 51(2):213–228
- Liu XH, Han M, Zhu JX, Sun N, Tang JS, Huo FQ et al (2012) Metabotropic glutamate subtype 7 and 8 receptors oppositely modulate cardiac nociception in the rat nucleus tractus solitarius. *Neuroscience [Internet]* 220:322–329
- Luongo L, De Novellis V, Gatta L, Palazzo E, Vita D, Guida F et al (2013) Role of metabotropic glutamate receptor 1 in the basolateral amygdala-driven prefrontal cortical deactivation in inflammatory pain in the rat. *Neuropharmacology* 66:317–329
- Maione S, Palazzo E, de Novellis V et al (1998a) Metabotropic glutamate receptors modulate serotonin release in the rat periaqueductal gray matter. *Naunyn Schmiedeberg's Arch Pharmacol* 358(4):411–417
- Maione S, Marabese I, Leyva J, Palazzo E, De Novellis V, Rossi F (1998b) Characterisation of mGluRs which modulate nociception in the PAG of the mouse. *Neuropharmacology* 37(12):1475–1483
- Maione S, Oliva P, Marabese I, Palazzo E, Rossi F, Berrino L et al (2000) Periaqueductal gray matter metabotropic glutamate receptors modulate formalin-induced nociception. *Pain* 85(1–2):183–189

- Marabese I, de Novellis V, Palazzo E, Mariani L, Siniscalco D, Rodella L et al (2005) Differential roles of mGlu8 receptors in the regulation of glutamate and gamma-aminobutyric acid release at periaqueductal grey level. *Neuropharmacology* 1:157–166
- Marabese I, de Novellis V, Palazzo E, Scafuro MA, Vita D, Rossi F et al (2007a) Effects of (S)-3,4-DCPG, an mGlu8 receptor agonist, on inflammatory and neuropathic pain in mice. *Neuropharmacology* 52(2):253–262
- Marabese I, Rossi F, Palazzo E, de Novellis V, Starowicz K, Cristino L et al (2007b) Periaqueductal gray metabotropic glutamate receptor subtype 7 and 8 mediate opposite effects on amino acid release, rostral ventromedial medulla cell activities, and thermal nociception. *J Neurophysiol* 98(1):43–53
- Mitsukawa K, Yamamoto R, Ofner S, Nozulak J, Pescott O, Lukic S, Stoeckl N, Mombereau C, Kuhn R, KH MA, van der Putten H, Cryan JF, Flor PJ (2005) A selective metabotropic glutamate receptor 7 agonist: activation of receptor signaling via an allosteric site modulates stress parameters in vivo. *Proc Natl Acad Sci USA* 102:18712–18717
- Nakamura M, Kurihara H, Suzuki G, Mitsuya M, Ohkubo M, Ohta H (2010) Isoxazolyridone derivatives as allosteric metabotropic glutamate receptor 7 antagonists. *Bioorganic Med Chem Lett* 20(2):726–729
- Neto FL, Castro-Lopes JM (2000) Antinociceptive effect of a group II metabotropic glutamate receptor antagonist in the thalamus of monoarthritic rats. *Neurosci Lett* 296(1):25–28
- Neto FL, Schadrack J, Berthele A, Zieglgänsberger W, Tölle TR, Castro-Lopes JM (2000) Differential distribution of metabotropic glutamate receptor subtype mRNAs in the thalamus of the rat. *Brain Res* 854(1–2):93–105
- Neugebauer V (2001) Metabotropic glutamate receptors: novel targets for pain relief. *Expert Rev Neurother* 1(2):207–224
- Neugebauer V, Li W, Bird GC, Bhawe G, Gereau RW (2003a) Synaptic plasticity in the amygdala in a model of arthritic pain: differential roles of metabotropic glutamate receptors 1 and 5. *J Neurosci* 23(1):52–63
- Neugebauer V, Galhardo V, Maione S, Mackey SC (2009) Forebrain pain mechanisms. *Brain Res Rev* 60(1):226–242
- Niswender CM, Conn PJ (2010) Metabotropic glutamate receptors: physiology, pharmacology, and disease. *Annu Rev Pharmacol Toxicol* 50:295–322
- Ohishi H, Akazawa C, Shigemoto R, Nakanishi S, Mizuno N (1995) Distributions of the mRNAs for L-2-amino-4-phosphonobutyrate-sensitive metabotropic glutamate receptors, mGluR4 and mGluR7, in the rat brain. *J Comp Neurol* 360(4):555–570
- Palazzo E, Marabese I, De Novellis V, Oliva P, Rossi F, Berrino L et al (2001) Metabotropic and NMDA glutamate receptors participate in the cannabinoid-induced antinociception. *Neuropharmacology* 40(3):319–326
- Palazzo E, De Novellis V, Marabese I, Cuomo D, Rossi F, Berrino L et al (2002) Interaction between vanilloid and glutamate receptors in the central modulation of nociception. *Eur J Pharmacol* 439(1–3):69–75
- Palazzo E, Genovese R, Mariani L, Siniscalco D, Marabese I, De Novellis V et al (2004) Metabotropic glutamate receptor 5 and dorsal raphe serotonin release in inflammatory pain in rat. *Eur J Pharmacol* 492(2–3):169–176
- Palazzo E, Marabese I, Soukupova M, Luongo L, Boccella S, Giordano C et al (2011b) Metabotropic glutamate receptor subtype 8 in the amygdala modulates thermal threshold, neurotransmitter release, and rostral ventromedial medulla cell activity in inflammatory pain. *J Neurosci* 31(12):4687–4697
- Palazzo E, Luongo L, Bellini G, Guida F et al (2012) Changes in Cannabinoid Receptor Subtype 1 Activity and Interaction with Metabotropic Glutamate Subtype 5 Receptors in the Periaqueductal Gray-Rostral Ventromedial Medulla Pathway in a Rodent Neuropathic Pain Model. *CNS Neurol Disord Drug Targets* 11(2)
- Palazzo E, Marabese I, de Novellis V, Rossi F, Maione S (2014a) Supraspinal metabotropic glutamate receptors: a target for pain relief and beyond. *Eur J Neurosci* 39(3):444–454

- Palazzo E, de Novellis V, Rossi F, Maione S (2014b) Supraspinal metabotropic glutamate receptor subtype 8: a switch to turn off pain. *Amino Acids* 46(6):1441–1448
- Palazzo E, Romano R, Luongo L, Boccella S, De Gregorio D, Giordano ME et al (2015) MMPIP, an mGluR7-selective negative allosteric modulator, alleviates pain and normalizes affective and cognitive behavior in neuropathic mice. *Pain* 156(6):1060–1073
- Ren W, Neugebauer V (2010) Pain-related increase of excitatory transmission and decrease of inhibitory transmission in the central nucleus of the amygdala are mediated by mGluR1. *Mol Pain* 6:93
- Reynolds DV (1969) Surgery in the rat during electrical analgesia induced by focal brain stimulation. *Science* 164(878):444–445
- Rossi F, Marabese I, De Chiaro M, Boccella S, Luongo L, Guida F et al (2014) Dorsal striatum metabotropic glutamate receptor 8 affects nocifensive responses and rostral ventromedial medulla cell activity in neuropathic pain conditions. *J Neurophysiol* 111(11):2196–2209
- Salt TE, Binns KE (2000) Contributions of mGlu1 and mGlu5 receptors to interactions with N-methyl-D-aspartate receptor-mediated responses and nociceptive sensory responses of rat thalamic neurons. *Neuroscience* 100(2):375–380
- Salt TE, Eaton SA (1995) Modulation of sensory neurone excitatory and inhibitory responses in the ventrobasal thalamus by activation of metabotropic excitatory amino acid receptors. *Neuropharmacology* 34(8):1043–1051
- Salt TE, Turner JP (1998) Modulation of sensory inhibition in the ventrobasal thalamus via activation of group II metabotropic glutamate receptors by 2R,4R-aminopyrrolidine-2,4-dicarboxylate. *Exp Brain Res* 121(2):181–185
- Saugstad JA, Kinzie JM, Shinohara MM, Segerson TP, Westbrook GL (1997) Cloning and expression of rat metabotropic glutamate receptor 8 reveals a distinct pharmacological profile. *Mol Pharmacol* 51(1):119–125
- Saugstad JA, Marino MJ, Folk JA, Hepler JR, Conn PJ (1998) RGS4 inhibits signaling by group I metabotropic glutamate receptors. *J Neurosci* 18(3):905–913
- Schoepp DD (2001) Unveiling the functions of presynaptic metabotropic glutamate receptors in the central nervous system. *J Pharmacol Exp Ther* 299(1):12–20
- Spaziano G, Luongo L, Guida F, Petrosino S, Matteis M, Palazzo E et al (2015) Exposure to allergen causes changes in NTS neural activities after intratracheal capsaicin application, in endocannabinoid levels and in the glia morphology of NTS. *Biomed Res Int* 2015:980983
- Suzuki G, Tsukamoto N, Fushiki H, Kawagishi A, Nakamura M, Kurihara H et al (2007) In vitro pharmacological characterization of novel isoxazopyridone derivatives as allosteric metabotropic glutamate receptor 7 antagonists. *J Pharmacol Exp Ther* 323(1):147–156
- Thomas NK, Wright RA, Howson PA, Kingston AE, Schoepp DD, Jane DE (2001) (S)-3,4-DCPG, a potent and selective mGlu8a receptor agonist, activates metabotropic glutamate receptors on primary afferent terminals in the neonatal rat spinal cord. *Neuropharmacology* 40(3):311–318
- Tian Y, Liu Y, Chen X, Kang Q, Zhang J, Shi Q et al (2010) AMN082 promotes the proliferation and differentiation of neural progenitor cells with influence on phosphorylation of MAPK signaling pathways. *Neurochem Int* 57(1):8–15
- Turner JP, Salt TE (1999) Group III metabotropic glutamate receptors control corticothalamic synaptic transmission in the rat thalamus in vitro. *J Physiol* 519:481–491
- Urban MO, Hama AT, Bradbury M, Anderson J, Varney MA, Bristow L (2003) Role of metabotropic glutamate receptor subtype 5 (mGluR5) in the maintenance of cold hypersensitivity following a peripheral mononeuropathy in the rat. *Neuropharmacology* 44(8):983–993
- Vardi N, Duvoisin R, Wu G, Sterling P (2000) Localization of mGluR6 to dendrites of ON bipolar cells in primate retina. *J Comp Neurol* 423(3):402–412
- Veinante P, Yalcin I, Barrot M (2013) The amygdala between sensation and affect: a role in pain. *J Mol Psychiat* 1(1):9
- Walker K, Reeve A, Bowes M, Winter J, Wotherspoon G, Davis A et al (2000) mGlu5 receptors and nociceptive function II. mGlu5 receptors functionally expressed on peripheral sensory neurones mediate inflammatory hyperalgesia. *Neuropharmacology* 40(1):10–19

- Yamada T, Zuo D, Yamamoto T, Olszewski RT, Bzdega T, Moffett JR, Neale JH (2012) Peptidase inhibition in the periaqueductal gray and rostral ventromedial medulla reduces flinching in the formalin model inflammation. *Mol Pain* 12:8–67
- Yamakura T, Shimoji K (1999) Subunit- and site-specific pharmacology of the NMDA receptor channel. *Prog Neurobiol* 59(3):279–298
- Yamamoto T, Kozikowski A, Zhou J, Neale JH (2000) Intracerebroventricular administration of N-acetylaspartylglutamate (NAAG) peptidase inhibitors is analgesic in inflammatory pain. *Mol Pain* 81:4–31
- Yang D, Gereau RW (2002) Peripheral group II metabotropic glutamate receptors (mGluR2/3) regulate prostaglandin E2-mediated sensitization of capsaicin responses and thermal nociception. *J Neurosci*. 22(15):6388–6393
- Yang D, Gereau RW (2003) Peripheral group II metabotropic glutamate receptors mediate endogenous anti-allodynia in inflammation. *Pain*:411–417
- Zammataro M, Chiechio S, Montana MC, Traficante A, Copani A, Nicoletti F et al (2011) mGlu2 metabotropic glutamate receptors restrain inflammatory pain and mediate the analgesic activity of dual mGlu2/mGlu3 receptor agonists. *Mol Pain* 7:6

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