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Therapeutic potential of group III metabotropic glutamate receptor ligands in pain

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Metabotropic glutamate receptors (mGluRs) modulate neurotransmission all along the pain neuraxis. While the involvement of group I and group II mGluRs in pain is well documented, information has only just started to emerge concerning the role and contribution of group III mGluRs subtypes to pain modulation. Recent data suggest that these receptors reduce symptoms in animal models of chronic pain, as well as regulate neurotransmission at different levels of ascending and descending pain pathway, suggesting that group III mGluRs may be interesting therapeutic targets for the development of analgesics.

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Introduction

Pain is one of the most common symptoms in clinical medicine and represents a permanent medical problem, being an essential component in the therapeutic management of many diseases. Pain can be classified as acute when it is short lasting or chronic when it persists for a long time after the original affection. Acute pain serves the important function of protecting the integrity of the body by detecting actual or potential tissue damage. Chronic pain is among the most debilitating and costly afflictions in North America and Europe, seriously affecting the quality of life of more than 19% of adult Europeans [1–3]. Unfortunately, while acute pain can be correctly managed, chronic pain is not efficiently alleviated by current treatments [4–6]. Therefore, a better understanding of cellular and molecular pathophysiological mechanisms is essential for identifying new pharmacological targets.

Glutamate and pain

Glutamate is the main excitatory neurotransmitter of the mammalian central nervous system and is implicated in many physiological and pathological processes. Glutamate is notably the main neurotransmitter involved in pain transmission. At the synaptic level, glutamate activates two classes of receptors: ionotropic and metabotropic glutamate receptors (mGluRs). Central sensitization of the pain neuraxis is associated with hyperexcitability of the glutamatergic system and leads to the development of the evoked pain symptoms, allodynia (pain due to a stimulus that does not normally provoke pain) and hyperalgesia (increased pain from a stimulus that normally provokes pain) observed in patients with chronic pain [7]. Both iGluRs and mGluRs are involved in the induction and the maintenance of this sensitization. The blockade of increased glutamatergic activity may represent a pivotal mean to reduce chronic pain but awaits a clearer identification of adequate targets.

Metabotropic glutamate receptors

mGluRs are G-protein coupled receptors activated by glutamate, the major excitatory neurotransmitter of the central nervous system (CNS). They are involved in the modulation of synaptic activity. They are thus considered as potential therapeutic targets since less side effects are anticipated compared to essential actors of synaptic transmission.

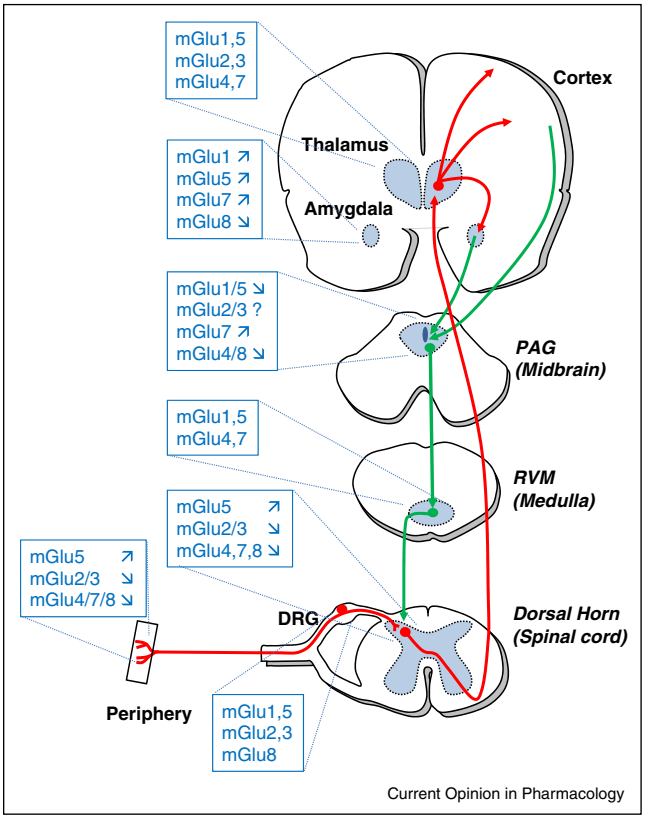
The 8 members of this family are classified into 3 groups: Group I receptors (mGlu1 and 5) are post-synaptic and positively modulate glutamatergic transmission while group II (mGlu2 and 3) and group III receptors (mGlu4, 6, 7 and 8) are predominantly presynaptic and play an inhibitory role on neurotransmission (except for mGlu6, a post-synaptic receptor which is expressed solely in bipolar ON cells in the retina). Group III mGluRs can act either as autoreceptors on glutamatergic terminals or heteroreceptors on GABAergic terminals.mGluRs form constitutive dimers composed of two subunits cross-linked by a disulphide bridge. Dimer formation is mandatory for the function of these receptors [8]. It has long been believed that mGluRs strictly assemble into homodimers but a recent study has shown that certain mGluR subtypes can heterodimerize *in vitro* [9]. Heterodimerization could have consequences notably in terms of pharmacological

profile, signaling response and protein partners. To date, there is no clear evidence of heterodimerization of mGluRs *in vivo*. However, recently, mGlu2/4 heterodimers have been suspected of existing at corticostriatal synapses, based on the detection of a unique pharmacological profile as compared to the mGlu2 or mGlu4 homodimers [10]. Since compatible mGluR subtypes coexist in several regions of the CNS, our comprehension of the regulation of CNS function by mGluRs, including pain, may evolve rapidly in the light of heterodimerization.

The different subtypes of mGluRs are expressed all along the pain neuraxis where they modulate the perception of pain (Figure 1). In general, blocking group-I mGluRs or activating group-II mGluRs alleviates pain (see [11–13] for recent reviews).

The present review will focus on group III mGluRs for which less information is available, mainly due to the lack of selective pharmacological tools. However, the recent progress in the development of subtype selective ligands is opening the way to a better understanding of their modulatory function and therapeutic potential in pain.

Figure 1



Localization and function of mGluRs in the pain neuraxis. The different subtypes of mGluRs are expressed all along the pain neuraxis where they modulate pain perception. Ascending pain pathway is in red and descending pathway in green. Up arrows mean that activation of a particular subtype is proalgesic while down arrows mean that activation is analgesic. PAG: periaqueducal gray; RVM: rostral ventromedial medulla; DRG: dorsal root ganglion.

Group III mGluR pharmacology

As described in Figure 1, mGlu4, 7, 8 receptors of group III are localized all along the pain neuraxis. In order to investigate if these receptors may be novel therapeutic targets to reduce pain symptoms, various ligands were used (Figure 2, Table 1). However, interpretation of these experiments should take into consideration the limitations of these compounds. Most of the drugs that were evaluated are non-selective among the group III subtypes or display solubility issues or metabolic instability (Table 1). Moreover, a 100 ratio of EC50's in cell-based assays does not ensure a selective effect *in vivo* since other factors such as bioavailability, receptor localization and drug concentration may also have an influence.

Both orthosteric ligands and allosteric modulators have been employed. These ligands are listed in this chapter, together with their effects and, when known, their limitations.

Orthosteric ligands

Since mGlu4, 7, 8 receptors are mostly presynaptic, agonists were used to evaluate if down-regulation of neurotransmitter release mediated by their activation may provide any benefit to treat pain symptoms (Figure 2). The most widely applied drug is **L-AP4**, a selective agonist of group III mGlu receptors, which does not discriminate between mGlu4 and 8 receptors, that has been used in inflammatory and neuropathic pain models [14,15,16••,17–21,22••,23,24]. L-AP4 is about 10 times more potent than glutamate, however, it does not cross the blood brain barrier and needs to be injected *in situ*. **L-SOP**, a phosphate analog of L-AP4 with similar properties, has been used in early studies about the contribution of group III mGluRs in the periaqueductal gray to the regulation of nociception [25,26]. ACPT-I is a group III mGluR agonist demonstrating similar selectivity to L-AP4 but is able to be administered systemically [27,28]. The use of **ACPT-I** [27] provided successful results in rat models of inflammatory and neuropathic pain, while leaving acute pain perception unchanged in healthy rats [29]. The weaker agonist, **ACPT-III**, was also used and shown to enhance the antiallodynic action of morphine in a neuropathic pain model in rats [30]. Two compounds **(*S*)-DCPG** [31•] and **LSP4-2022** [32] have been tested as mGlu8 and mGlu4 receptor subtype selective agonists, respectively, in inflammatory or neuropathic pain models [23,33–35,36••,37]. However, a recent study suggests that care must be taken when employing higher concentrations of DCPG since non-selective effects in slices from mice lacking mGlu8 receptors have been observed