

Letter to the Editor

# The Role of the Glutamate, Metabotropic Glutamate Receptors and their Antagonists in Nociception

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## Abstract

Presence of metabotropic receptors in dorsal horns of the spinal cord neurons stated that after intraventricular intrathecal use of specific antagonists for mGluR1 receptors reveals analgetic activity both in rodents and large mammals. Knockdown of spinal mGluR1 receptors soothes pain and restores effectiveness of opioids activity after damage of the nerve in rats. Recently published researches proved that mice which were deprived of endothelin-3 in rectum on Hirschprung disease model lose selectively the ability to feel visceral pain. Qi and co-workers, suggest special participation of tension-dependent Na<sup>+</sup> and Ca<sup>2+</sup> channels in visceral pain feeling whereas use of these channels antagonists can contribute to new possibilities in visceral pain therapy.

Results of our research interchangeably indicate that used centrally non-specific mGluRgroup I receptor antagonist – which is racemic form of DL-AP3 – impedes transmission of nocifensive impuls induced by 5 min mechanical distension of descending colon wall in sheep. It also prevents from cascade of behavioural, clinical and neuroendocrine phenomena released in sharp visceral pain by mechanical impuls. DL-AP3 can be recommended in soothing of intestines colic symptoms in sheep provided that similar effects after peripheral usage of that racemate will be confirmed.

**Keywords:** Glutamate; mGluRs and antagonists; Nociception

## Introduction

Glutamate (glutamic acid – Glu) is one of the major excitatory neurotransmitters in central (CNS) and autonomic nervous system (ANS) acting *via* two classes of receptors: on ligand gated ion channels (ionotropic receptors – iNMDA) or G-protein coupled receptors (metabotropic receptors – mGluRs). mGluR receptors existing primarily in CNS belong to subfamily C of G-protein coupled receptors divided into three distinct groups (I-III) and eight subgroups. They were classified into subgroups based on neuroanatomical distribution, pharmacological profile, specific signal transduction and agonist selectivity [1,2]. Group I mGluR with subclasses R<sub>1</sub> (increasing Ca<sup>2+</sup>) and R<sub>5</sub> (activation of Na<sup>+</sup> channels) stimulates activity of phospholipases *via* syntheses of IP<sub>3</sub> and DAG as second messengers. Protein G bound to the intracellular region of mGluR causes its phosphorylation and wide range of effects *via* modulation of K<sup>+</sup> activity channels. It can cause both increase and decrease of postsynaptic neuronal cell excitability. The same neurotransmitter may evoke excitation (fast or slow) or inhibition, often within the same group of CNS neurons. Group I (subgroup mGluR<sub>1</sub> and mGluR<sub>5</sub>) acting mainly *via* Gαq phospholipase C were recognized as slow acting excitatory. mGluR<sub>5</sub> receptors are coupled to N-methyl-D-aspartate ionotropic receptors and their specific modulators cause appearance of NMDA mediated responses [3,4]. Receptors belong to group II and III act *via* Gαi and Gβγ and are classified as slow inhibitory receptors which inhibit adenyl cyclase altering cations flux.

Metabotropic receptors (except subgroup mGluR<sub>6</sub>) are widely distributed along pain neuraxis and considered for taking

part in transmission of analgesic activity. Usage of mGluR agonists revealed that activation of these receptors in the dorsal horn and finally facilitates pain transmission. Group I receptors are important in hyperalgesia, persistent pain and central post injury sensitization [5]. Activation of group II metabotropic receptors proved to be analgesic and subgroup mGluR<sub>3</sub> was found to play predominant role in transmission of inflammatory pain [6].

Group I receptors are primarily localized as postsynaptic neural cells in brain structures (cerebral cortex, dorsal and ventral striatum, septal area, hippocampus). Metabotropic receptors exist in CNS as well as in enteric nervous system [7] including sensory neurons projecting to the CNS [8] Studies of [5,9] showed that *i.c.v.* infusion of 2-Methyl-6-Phenylethynyl-Pyridine (MPEP), which is mGluR<sub>5</sub> antagonist, reduces mechanosensitivity of ferret tension receptors activated by gastric distension. Sensory neurons that occur in vagal sensory ganglia innervate gastrointestinal tract. Expression of all kinds of mGluRs has been demonstrated in vagal afferent cells [10]. Several behavioral studies have demonstrated that mGluR<sub>5</sub> in the dorsal horn of the spinal cord play crucial role in visceral, inflammatory and neuropathic pain.

Physiopharmacology of visceral pain was proved on a model of mechanical nocifensive impuls emitted by duodenum and/or colon distension in rodents Lu et al. [11]. The results indicate interchangeably that stretching of an intestine wall is correlated with contraction amplitude of both duodenum and colon. It is also an important impuls for intestines contractility. In Lu et al. [11]. opinion contractility reaction of mice intestine wall for mechanic impulses nervous regulation is involved.

Distension of a colon wall, similarly to duodenum what proved our earlier results [12], caused each time significant inhibition of viscerovisceral inhibitory reflex which was probably caused by sympathoadrenal system stimulation and adrenal CA release to circulatory system and also significant increase of plasma cortisol concentration what indicated on hypothalamo-pituitary adrenal cortex activation [13]. The action of mechanical pain impuls in the intestine may be concern as strong general stressor which initiated classical defensive reactions of the organism. Such reaction was prevented by previous (10 min before colonic distension - CD) intracerebroventricular premedication (*icv*) DL-AP3 racemate - nonspecific of group I mGluRs antagonist - in dose dependent manner. This premedication also prevented from tachycardia, hyperventilation as well as behavioural symptoms of pain demeanour. It proves that DL-AP3 can not only reveal its peripheral actions as well as central ones, mainly by retardation of mGluR activity in motivation structures and nociceptive afferent ways that transmit mechanical impulses, such as distension of intestines walls, from periphery to higher structures of nervous system.

Kyloh and co-workers [14] marked out tracts of visceral pain by means of activity of mechanical nocifensive factor which was rectum/colon distension in mice. It can be presumed that irritable bowel syndrome in men which is connected with it visceral pain, what is probably caused by colorectum distension. External nervous afferent routes which receive impulses and transmit visceral pain from colorectum to spinal cord are still not well recognized. On the basis of viscerosomatic reaction in mice, the fact that visceral pain evoked by final colorectum segment extension, which was released by damaged mechanical impuls, is conducted through afferent spinal colorectum, fibres cell bodies which are localised mainly in lumbo-sacral part of spinal cord, was stated [14]. There is lack of reasons to suppose that visceral afferents are necessary for detection and conduction of nocifensive mechanical impulses from that colorectum region. Lesions of visceral nervous fibres that approach colon as well as intersection of right or left hypogastric nerves did not inhibit viscerosomatic reaction as a result of colorectum distension [14]. On the other hand, damages of both left and right branches of pelvic nerves neutralized visceral-somatic impuls regardless of the fact whether fibers approaching from visceral part to colon or hypogastric nerves were damaged. Malfunction of rectal nerves neutralized visceral-somatic impuls caused by colon distension. By means of backward marking with fluorescence method with use of Dil there was stated that sensory neurons are localized mainly in ganglions of dorsal root of the lumbar spinal cord (L6 - S1) in mice [14].

In mammals there are two independent afferent nervous tracts that can potentially transmit sensory information from rectum and (sigmoid) pelvic colon to spinal cord. It is known that lumbar colon nerves (LCN)/lumbar visceral ones and rectal-colonic sacral ones / pelvis nerves [15]. There was not stated interchangeably up till now which of these tracts is more important for detection and transmission of visceral pain from colon and/or rectum. Latest results of Feng et al. [16] revealed that in mice these two separate sensory nervous tracts are distinguished by presence of at least 5 different types of afferent fibres every of which reacts selectively and independently at activity of various impulses. Principle, there is not certain whether nervous rectal-colonic tract (pelvis nerve) is first of all nervous

tract with low excitability threshold which reacts at mechanical impulses of small intensity whereas lumbar visceral tracts mainly the one which involve at impulses of high intensity which possesses only small amount (10%) of afferent fibres sensitive to distension [15].

DL-AP3, the racemate phosphono analog of aspartate, is a non-competitive antagonist of trans-ACPD-activated phosphoinositide hydrolysis. The DL-AP3 administration did not decrease nociceptive behaviors caused by formalin injection [17]. On the other hand it was shown only weak antagonistic activity against mGluR of group I [18]. However, the effect of mGluR antagonists administration on pain behaviors depends on experimental model which they it was tested.

Behavioral evidence supporting differential role of metabotropic glutamate receptors (mGluRs) in spinal nociception in normal sheep and rodents was confirmed in earlier research. It is particularly apparent in neuropathic, inflammatory hyperalgesia produced by unilateral intradermal injection of carrageenan into the lower forelimb and mechanical hypersensitivity following abdominal surgery in sheep. Intrathecal blockade of mGluRs group I antagonists inhibits this phenomenon [17].

The our study examined contribution of group I mGluRs in development and maintenance changes in behavioral and clinical symptoms, and cortisol and catecholamines blood concentrations caused by visceral pain produced by Colonic Distension (CD) in sheep [13]. Intracerebroventricular (*icv*) administration of the group I mGluRs non-selective antagonist DL-2-Amino-3-phosphonopropionic acid (DL-AP3, 4.0, 8.0 and/or 12.0 mg *in toto*), blocked development of visceral pain symptoms and neuroendocrinological changes in the blood of sheep. This data demonstrated that development and maintenance of visceral pain symptoms of CD is dependent on activation of group I mGluRs in Central Nervous System (CNS) in our opinion these receptors play a crucial role in modulating of acute colonic pain (colic). DL-AP3 can be recommended in alleviating of intestinal colic symptoms in sheep provided that similar effects after peripheral usage of the racemate will be confirmed.

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