Journal of Drug Discovery, Development and Delivery

Austin Publishing Group

Open Access Full Text Article

Letter to the Editor

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

Kania BF[1]* and Wronska D[2]

[1]University of Veterinary Medicine JU-AU, Hugon Kollataj Agricultural University in Cracow, Poland
[2]Department of Physiology and Endocrinology, Hugon Kollataj Agricultural University in Cracow, Poland

***Corresponding author:** Kania BF, University of Veternity Medicine JU-AU, Department of Biotechnology, Hugon Kollataj Agricultural University in Cracow, Poland, 24/28 Al Mickiewicza, 30-059 Cracow, Poland

Received: Aug 01, 2014; **Accepted:** Aug 02, 2014; **Published:** Aug 04, 2014

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^+ and Ca^{2+} 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_1 (increasing Ca^{2+}) and R_5 (activation of Na^+ channels) stimulates activity of phospholipases *via* syntheses of IP_3 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^+ 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 $mGluR_1$ and $mGluR_5$) acting mainly via Gαq phospholipase C were recognized as slow acting excitatory. $mGluR_5$ 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 IIIact *via* Gαi and Gβγ and are classified as slow inhibitory receptors which inhibit adenyl cyclase altering cations flux.

Metabotropic receptors (except subgroup $mGluR_6$) are widely distributed along pain neuraxis and considered for taking part in transmission of analgesic activity. Usage of mGluR agonistsrevealedthat 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 $mGluR_3$ 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 $mGluR_5$ 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 $mGluR_5$ 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.

Citation: Kania BF and Wronska D. The Role of the Glutamate, Metabotropic Glutamate Receptors and their Antagonists in Nociception. J Drug Discov Develop and Deliv. 2014;1(1): 3.

Distension of a colon wall, similarly to duodenum what proved our earlier results [12], caused each time significant inhibition of viscero-visceral inhibitory reflex which was probably caused by sympatho-adrenal system stimulation and adrenal CA release to circulatory system and also significant increase of plasma cortisol concentration what indicated on hypothalamo-pituitary adrenal cortx 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 befor colonal distension - CD) intracerebroventricular premedication (*icv*) DL-AP3 racemate – nonspecific of group I mGluRs antagonist - in dose dep[endent 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 viscero-somatic 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 viscero-somatic 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 tractsis 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 tractsare distinguished bypresence 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 tractwith low excitability treshold which reacts at mechanical impulses of small intensity whereas lumbar visceral tractis 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 phosphonoinositide hydrolysis. The DL-AP3 admnistration 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 hiperalgesia 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 Colonal 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 colonal pain (colic). DL-AP3 can be recommended in alleviating of intestinal colic symptoms in sheep provided that similar effects afetr peripheral usage of the racemate will be confirmed.

References

1. Qi FH, Zhou YL, Xu GY. Targeting voltage-gated sodium channels for treatment for chronic visceral pain. See comment in PubMed Commons below World J Gastroenterol. 2011; 17: 2357-2364.
2. Pin JP, Duvoisin R. The metabotropic glutamate receptors: structure and functions. See comment in PubMed Commons below Neuropharmacology. 1995; 34: 1-26.
3. Perroy J, Raynaud F, Homburger V, Rousset MC, Telley L, Bockaert J, et al. Direct interaction enables cross-talk between ionotropic and group I metabotropic glutamate receptors. See comment in PubMed Commons below J Biol Chem. 2008; 283: 6799-6805.
4. Rosenbrock H, Kramer G, Hobson S, Koros E, Grundl M, Grauert M, et al. Functional interaction of metabotropic glutamate receptor 5 and NMDA-receptor by a metabotropic glutamate receptor 5 positive allosteric modulator. See comment in PubMed Commons below Eur J Pharmacol. 2010; 639: 40-46.
5. Young MR, Fleetwood-Walker SM, Dickinson T, Blackburn-Munro G, Sparrow H, Birch PJ, et al. Behavioral and electrophysiological evidence supporting a role for group I metabotropic receptors in the mediation of nociceptive inputs to the rat spinal cord. Brain Res. 1997; 777: 161-169.
6. Zammataro M, Chiecho S, Montana MC, Traficante A, Copani A, Nicoletti F, et al. mGlu2 metabotropic glutamate receptors restrain inflammatory pain

and mediate the analgesic activity of dual mGlu2/mGlu3 receptor agonists. Molecular Pain. 2011; 7: 6.

7. Foong JP, Bornstein JC. mGluR(1) Receptors Contribute to Non-Purinergic Slow Excitatory Transmission to Submucosal VIP Neurons of Guinea-Pig Ileum. See comment in PubMed Commons below Front Neurosci. 2009; 3: 46.

8. Bonham AC, Chen CY. Glutamatergic neural transmission in the nucleus tractus solitarius: N-methyl-D-aspartate receptors. See comment in PubMed Commons below Clin Exp Pharmacol Physiol. 2002; 29: 497-502.

9. Young MR, Blackburn-Munro G, Dickinson T, Johnson MJ, Anderson H, Nakalembe I, et al. Antisense ablation of type I metabotropic glutamate receptor mGluR1 inhibits spinal nociceptive transmission. J Neurosci. 1998; 18: 10180-10188.

10. Page AJ, Young RL, Martin CM, Umaerus M, O'Donnell TA, Cooper NJ, et al. Metabotropic glutamate receptors inhibit mechanosensitivity in vagal sensory neurons. See comment in PubMed Commons below Gastroenterology. 2005; 128: 402-410.

11. Lu X, Zhang Z, Choy JS, Kassab GS. Role of distension on duodenal and colonic contractility in mice: a novel myograph for intestines. See comment in PubMed Commons below Neurogastroenterol Motil. 2012; 24: 487-493, e220.

12. Kania BF and Sutiak V. Influence of centrally administered Diltiazem on behavioral responses, clinical symptoms, reticulo-ruminal contraction and plasma catecholamine level after experimentally induced duodenal distension in sheep. Res Vet Sci. 2011; 90: 291-297.

13. Kania BF and Wronska D. Supraspinal basis of analgesic and clinical effects of the metabotropic glutamate mGluR1 antagonist during colonic distension in sheep. Small Rum. Res. 2014; 117: 84-93.

14. Kyloh M, Nicholas S, Zagorodnyuk VP, Brookes SJ, Spencer NJ. Identification of the visceral pain pathway activated by noxious colorectal distension in mice. See comment in PubMed Commons below Front Neurosci. 2011; 5: 16.

15. Brierley SM, Jones RC 3rd, Gebhart GF, Blackshaw LA. Splanchnic and pelvic mechanosensory afferents signal different qualities of colonic stimuli in mice. See comment in PubMed Commons below Gastroenterology. 2004; 127: 166-178.

16. Birse EF, Eaton SA, Jane DE, Jones PL, Porter RH, Pook PC, et al. Phenylglycine derivatives as new pharmacological tools for investigating the role of metabotropic glutamate receptors in the central nervous system. See comment in PubMed Commons below Neuroscience. 1993; 52: 481-488.

17. Coderre TJ and Van Empel I. The utility of excitatory amino acid (EAA) antagonists as analgesic agents. I. Comparison of the antinociceptive activity of various classes of EAA antagonists in mechanical, thermal and chemical nociceptive tests. Pain. 1994; 59: 345-352.

18. Meller ST, Dykstra C, Gebhart GF. Acute thermal hyperalgesia in the rat is produced by activation of N-methyl-D-aspartate receptors and protein kinase C and production of nitric oxide. See comment in PubMed Commons below Neuroscience. 1996; 71: 327-335.

J Drug Discov Develop and Deliv - Volume 1 Issue 1 - 2014
ISSN : 2471-0288 | www.austinpublishinggroup.com

Citation: Kania BF and Wronska D. The Role of the Glutamate, Metabotropic Glutamate Receptors and their Antagonists in Nociception. J Drug Discov Develop and Deliv. 2014;1(1): 3.