The Journal of Pain, Vol 11, No 4 (April), 2010: pp 321-329
Available online at www.sciencedirect.com

Differential Roles of Peripheral Metabotropic Glutamate Receptors in Bee Venom-Induced Nociception and Inflammation in Conscious Rats

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Abstract: **Intraplantar injection of bee venom (BV) produces persistent spontaneous nociception (PSN), hyperalgesia, and inflammatory swelling of the injected paw. The present study was designed to determine the roles of peripheral metabotropic glutamate receptors (mGluRs) in BV-induced nociception and inflammation. We determined the effects of the group I mGluR antagonist AIDA, the group II mGluR agonist ADPC, and the group III mGluR agonist L-AP4 on BV-induced PSN, mechanical hyperalgesia, and inflammatory swelling. Pretreatment with intraplantar injections of AIDA, ADPC or L-AP4 at different doses significantly inhibited BV-induced PSN over the 1-hour observational period. The inhibitory effects of ADPC and L-AP4 were completely abolished by pretreatment with the group II mGluR antagonist LY341495 and the group III mGluR antagonist MSOP, respectively. Pretreatment with ADPC prevented the BV-induced decrease in paw-withdrawal mechanical threshold (PWMT) in a dose-dependent manner, while pretreatment with AIDA or L-AP4 had no effect. The antihyperalgesic effect of ADPC was completely abolished by pretreatment with LY341495. Pretreatment with AIDA, ADPC or L-AP4 at different doses had no effect on the BV-induced increase in the paw volume (PV), a measurement of inflammatory swelling. All contralateral drug treatments at the highest doses had no effect on BV-induced PSN, decreases in PWMT or increases in PV, eliminating the possibility of drug-induced systemic effects. These data suggest that the activation of mGluRs in the periphery may play a differential role in BV-induced nociception and inflammation.**

Perspective: ***The present study demonstrated that the intraplantar injection of antagonists or agonists of different mGluRs produced differential effects on bee venom-induced persistent spontaneous nociception and mechanical hyperalgesia. However, no effects on inflammation were observed, suggesting that mGluRs in the periphery have differential roles. Thus, therapies specifically targeting metabotropic glutamate receptors may improve the treatment of patients with persistent spontaneous nociception and hyperalgesia.***

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Key words: *Bee venom, mGluRs, persistent spontaneous nociception, hyperalgesia, inflammation.*

The metabotropic glutamate receptors (mGluRs) are highly expressed in the peripheral and central nervous system and can be divided into 3 groups, based on sequence homology, signal transduction mechanisms, and pharmacological properties. The groups are Group I mGluRs (mGluR1 and 5), Group II (mGluR2 and 3), and Group III mGluRs (mGluR4, 6, 7, and 8).[14] A growing body of evidence supports the role of mGluRs in the transmission and processing of physiological and pathophysiological pain.[13,22,39,50] Since Bhave et al's first preliminary investigations into the key role of peripheral group I mGluRs in pain behavior[3], several studies have demonstrated the effects of peripheral group I-III mGluRs on the modulation and processing of pathological pain signals.[2,29,31,33,34,53,54] The peripheral roles of mGluRs are also supported by additional morphological studies, demonstrating that all 3 groups are expressed in peripheral afferents and dorsal root ganglion neurons.[4-6,35,36,42,49] Despite these and other reports, the underlying mechanisms responsible for the role of peripheral mGluRs in pathological pain are not fully understood.

Received December 22, 2008; Revised June 3, 2009; Accepted July 30, 2009.
Supported by grants from the National Natural Science Foundation of China (30471667) and Postdoctoral Science Foundation of P. R. China (2005037760; both to H.S.C.).
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1526-5900/$36.00
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doi:10.1016/j.jpain.2009.07.013

Many inflammatory pain models, such as the use of formalin, capsaicin, carrageenan, or the complete Freund's adjuvant (CFA), have been widely employed to investigate the mechanisms underlying inflammatory pain. We and others recently show that the bee venom (BV) model also is a suitable model for inflammatory pain.[8,10-12] Furthermore, the behavioral responses and neural mechanisms underlying the BV model are different from those previously reported models.[8,10-12] For example, BV injection induces a mono-phasic persistent spontaneous nociception (PSN), heat and mechanical hyperalgesia, but also inflammatory responses (ie, edema and redness of the injected paw), while formalin injection induces a biphasic PSN and slight inflammatory edema, but not heat and mechanical hyperalgesia. CFA and carrageenan injections result in thermal and mechanical hyperalgesia and inflammatory edema, but not PSN.[8,11] The capsaicin-sensitive neural mechanisms are involved in BV-induced nociception and inflammation, but differentially in formalin-, carrageenan-, and CFA-induced nociception and inflammation.[8,11] Thus, the rat model with intraplantar injection of BV is suitable to simultaneously investigate the underlying mechanisms of PSN, hyperalgesia, and inflammation. Our previous studies have demonstrated that several protein kinases and receptors in the peripheral nervous system are involved in the development of BV-induced nociception and inflammation, including NMDA and nonNMDA receptors,[12,56] protein kinases A and C,[9] and MAP kinases.[7] To our knowledge, there are no published reports detailing the role of peripheral mGluRs in BV-induced nociception and inflammation. The present study was designed to determine the modulatory role of metabotropic glutamate receptors in the physiological response to BV insult.

Methods

Test drugs and Reagents

Lypophylized *Apis mellifera* bee venom (Sigma, St. Louis, MO) was dissolved in 0.9% sterile saline. A total of 50 μL saline containing 0.2 mg BV was used for the entire study. The following drugs were purchased from Tocris Cookson Inc. (Avonmouth, UK): the selective and competitive group I mGluRs antagonist ((RS)-1-Aminoindan-1,5-dicarboxylic acid, AIDA), the selective group II agonist ((2R,4R)-4-Aminopyrrolidine-2,4-dicarboxylate, (2R,4R)-APDC), the selective and competitive group II antagonist ((2S)-2-Amino-2-[(1S,2S)-2-carboxycycloprop-1-yl] -3-(xan th-9-yl) propanoic acid, LY 341495), the selective group III agonist (L-(+)-2-Amino-4-phosphonobutyric acid, L-AP4), and the selective and competitive group III antagonist ((RS)-a-Methylserine-O-phosphate, MSOP). All stock solutions (100 mM) of the test compounds were dissolved in NaOH and diluted with saline to final designated concentrations (pH 7.5).

Animals

Male Sprague–Dawley rats, weighing 250–300 g, were provided by the General Hospital of Shenyang Military Region (Shenyang, China). The animal use and care protocol was reviewed and approved by the Institutional Animal Care and Use Committee of the Hospital and the International Association for the Study of Pain (IASP) guidelines[64] were strictly followed. Animals were housed in plastic cages in groups of 3 in the colony rooms at ambient temperatures with food and water available ad libitum. A 12:12 hour light/dark cycle was maintained and testing was done between the hours of 9:00 am and 6:30 pm. The animals were allowed to acclimate to the testing environment for at least 30 minutes each day for 5 days before testing. At the conclusion of each experiment, rats were sacrificed by saturating, intraperitoneal injections of phenobarbital (200 mg/kg).

Experimental Design

Rats were randomly divided into 5 groups: 1) Ipsilateral drug group: rats received different mGluR antagonists or agonists in the hind paw ipsilateral to BV injection (n = 8 to 10 for each dose/drug); 2) Ipsilateral vehicle group: rats received vehicle in the hind paw ipsilateral to BV injection (n = 8 to 10 for each drug); 3) Contralateral drug group: rats received the highest dose of drugs in the hind paw contralateral to BV injection (n = 8 for each drug); 4) Pretreatment drug group: rats received GluR II or III antagonists prior to GluR II or III agonists in the hind paw ipsilateral to BV injection, respectively (n = 8 to 10 for each drug); and 5) Control drug treatment group: rats received intraplantar injections of 25 nmol of AIDA, 5 nmol of APDC, 10 nmol of L-AP4, 0.2 nmol of LY341495 or 10 nmol of MSOP without BV injection (n = 6 for each drug). To exclude the subjective effect of investigators, all experiments were performed in a blinded manner.

Intraplantar Administration of Different Chemical Agents

Intraplantar injection of AIDA (0.5–25 nmol[33,60]), APDC (0.1–5 nmol, Y[29,54]), L-AP4 (0.1–10 nmol), or vehicle (NaOH/saline) was performed 15 minutes prior to the intraplantar BV injections, given that the drug acts on the peripheral afferents. Additionally, intraplantar injection of LY 341495 or MSOP was performed 15 minutes prior to APDC or L-AP4 injections. To determine whether local injections of these drugs induced nonspecific systemic effects, rats received the highest doses of AIDA, APDC, L-AP4, LY341495 or MSOP into the contralateral hind paws. The injection volume of 50 μL was uniform for all drugs and vehicle treatments for the entire study. All ipsilateral drugs and vehicle treatments were injected into the same site as the bee venom injection. The rats were slightly constrained and injections were given using a 1-mL syringe with a 26-gauge 5/8 inch needle.

Measurement of PSN

A 30×30×30 cm transparent plexiglass test box with a transparent glass floor was placed on a 50-cm-high supporting frame allowing unobstructed observation of the animal's paw. Each rat was placed in the test box for at

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