Journal of Pharmacological Sciences 130 (2016) 139–142

HOSTED BY

Contents lists available at ScienceDirect

Journal of Pharmacological Sciences

journal homepage: www.elsevier.com/locate/jphs

Short communication

Peripheral HMGB1-induced hyperalgesia in mice: Redox state-dependent distinct roles of RAGE and TLR4

Daichi Yamasoba [a], Maho Tsubota [a], Risa Domoto [a], Fumiko Sekiguchi [a], Hiroyuki Nishikawa [a], Keyue Liu [b], Masahiro Nishibori [b], Hiroyasu Ishikura [c], Tetsushi Yamamoto [d], Atsushi Taga [d], Atsufumi Kawabata [a, *]

[a] Laboratory of Pharmacology and Pathophysiology, Faculty of Pharmacy, Kindai University (formerly Kinki University), Higashi-Osaka 577-8502, Japan
[b] Department of Pharmacology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan
[c] Department of Emergency and Critical Care Medicine, Fukuoka University Hospital, Fukuoka 814-0180, Japan
[d] Laboratory of Pathological and Biomolecule Analyses, Faculty of Pharmacy, Kindai University (formerly Kinki University), Higashi-Osaka 577-8502, Japan

ARTICLE INFO

Article history:
Received 23 November 2015
Received in revised form
25 December 2015
Accepted 12 January 2016
Available online 23 January 2016

Keywords:
High mobility group box 1
Pain
Redox state

ABSTRACT

Nuclear HMGB1 that contains 3 cysteine residues is acetylated and secreted to the extracellular space, promoting inflammation via multiple molecules such as RAGE and TLR4. We thus evaluated and characterized the redox state-dependent effects of peripheral HMGB1 on nociception. Intraplantar (i.pl.) administration of bovine thymus-derived HMGB1 (bt-HMGB1), all-thiol HMGB1 (at-HMGB1) or disulfide HMGB1 (ds-HMGB1) caused long-lasting mechanical hyperalgesia in mice. The hyperalgesia following i.pl. bt-HMGB1 or at-HMGB1 was attenuated by RAGE inhibitors, while the ds-HMGB1-induced hyperalgesia was abolished by a TLR4 antagonist. Thus, nociceptive processing by peripheral HMGB1 is considered dependent on its redox states.
© 2016 Japanese Pharmacological Society. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

High mobility group box 1 (HMGB1), a DNA binding protein, is passively released from necrotic cells and actively secreted by certain cells such as macrophages, playing a pro-inflammatory role as damage-associated molecular patterns (DAMPs) (1). In macrophages, nuclear HMGB1 is acetylated by histone acetyltransferases (HATs) and deacetylated by histone deacetylases (HDACs), and the acetylated HMGB1 is translocated to the cytoplasm and then packaged to secretory lysosomes, followed by its active secretion to the extracellular space (2). The extracellular HMGB1 targets multiple molecules including Toll-like receptor 4 (TLR4), TLR2 and the receptor for advanced glycation endproducts (RAGE), and also forms a heterocomplex with two CXC chemokine ligand 12 (CXCL12) molecules which accelerates the activation of CXC-chemokine receptor 4 (CXCR4) through the receptor dimerization, playing a pro-inflammatory role (3). HMGB1 contains 3 cysteine residues, C23, C45 and C106, and the redox modification of them affects the potency of HMGB1 in activating distinct receptors; all-thiol-HMGB1 (at-HMGB1) is capable of activating RAGE and also CXCL12/CXCR4 signals, while disulfide-HMGB1 (ds-HMGB1) that has an intramolecular disulfide bond between C23 and C45 preferentially interacts with TLR4 (3–5). Intracellular HMGB1 is present in the all-thiol form and released to the extracellular space, and the released at-HMGB1 may be oxidized to ds-HMGB1 by reactive oxygen species (ROS) during inflammation (3). There is plenty of evidence for the pro-nociceptive role of HMGB1 in the spinal cord or dorsal root ganglion (DRG) (5,6). Recent independent studies have shown that intrathecal administration of ds-HMGB1, but not at-HMGB1, causes hyperalgesia in mice (6,7), while at-HMGB1 and ds-HMGB1 cause excitation of acutely dissociated rat DRG neurons via activation of RAGE and TLR4, respectively (5). On the other hand, we have reported that peripheral HMGB1 plays a pro-nociceptive role in somatic inflammatory hyperalgesia (8) and also in cystitis-related bladder pain/referred hyperalgesia (9), whereas the redox state-dependence of peripheral HMGB1-induced hyperalgesia remains unclear. Thus, we examined and characterized the effects of peripheral HMGB1 in distinct redox states on somatic nociception in mice.

Male ddY mice (3 weeks old) were purchased from Kiwa Laboratory Animals Co., Ltd (Wakayama, Japan) and housed in a room

* Corresponding author. Laboratory of Pharmacology and Pathophysiology, Faculty of Pharmacy, Kindai University, 3-4-1 Kowakae, Higashi-Osaka 577-8502, Japan. Tel.: +81 6 4307 3631; fax: +81 6 6730 1394.
E-mail address: kawabata@phar.kindai.ac.jp (A. Kawabata).
Peer review under responsibility of Japanese Pharmacological Society.

http://dx.doi.org/10.1016/j.jphs.2016.01.005
1347-8613/© 2016 Japanese Pharmacological Society. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

kept at 22–24 °C under a 12-h day/night cycle with free access to food and water at least for 1 week before experiments. All animals were used with approval by the Committee for the Care and Use of Laboratory Animals at Kindai University, and all procedures employed in the present study were in accordance with the guidelines of the Committee for Research and Ethical Issues of IASP [www.iasp-pain.org/Education/Content.aspx?ItemNumber=1217]. Bovine thymus-derived HMGB1 (bt-HMGB1) was purchased from Shino-Test Corp. (Tokyo, Japan), and recombinant all-thiol-HMGB1 (at-HMGB1) and disulfide-HMGB1 (ds-HMGB1) were from HMGBiotech (Milan, Italy). Trichostatin A (TSA), suberoylanilide hydroxamic acid (SAHA) and AMD3100 were purchased from Sigma–Aldrich (St. Louis, MO, USA), and lipopolysaccharide from *Rhodobacter sphaeroides* (LPS-RS) was from InvivoGen (San Diego, CA, USA). Low molecular weight heparin (LMWH) was a gift from Fuso Pharmaceutical Industries, Ltd. (Osaka, Japan). TSA and SAHA were dissolved in DMSO and then diluted with saline (the final DMSO concentration was 0.3%), and all other chemicals were dissolved in saline. An anti-human HMGB1 neutralizing rat monoclonal antibody and the control IgG were produced by Dr. Nishibori (Okayama University Graduate School of Medicine, Okayama, Japan), and dissolved in 0.01 M phosphate-buffered

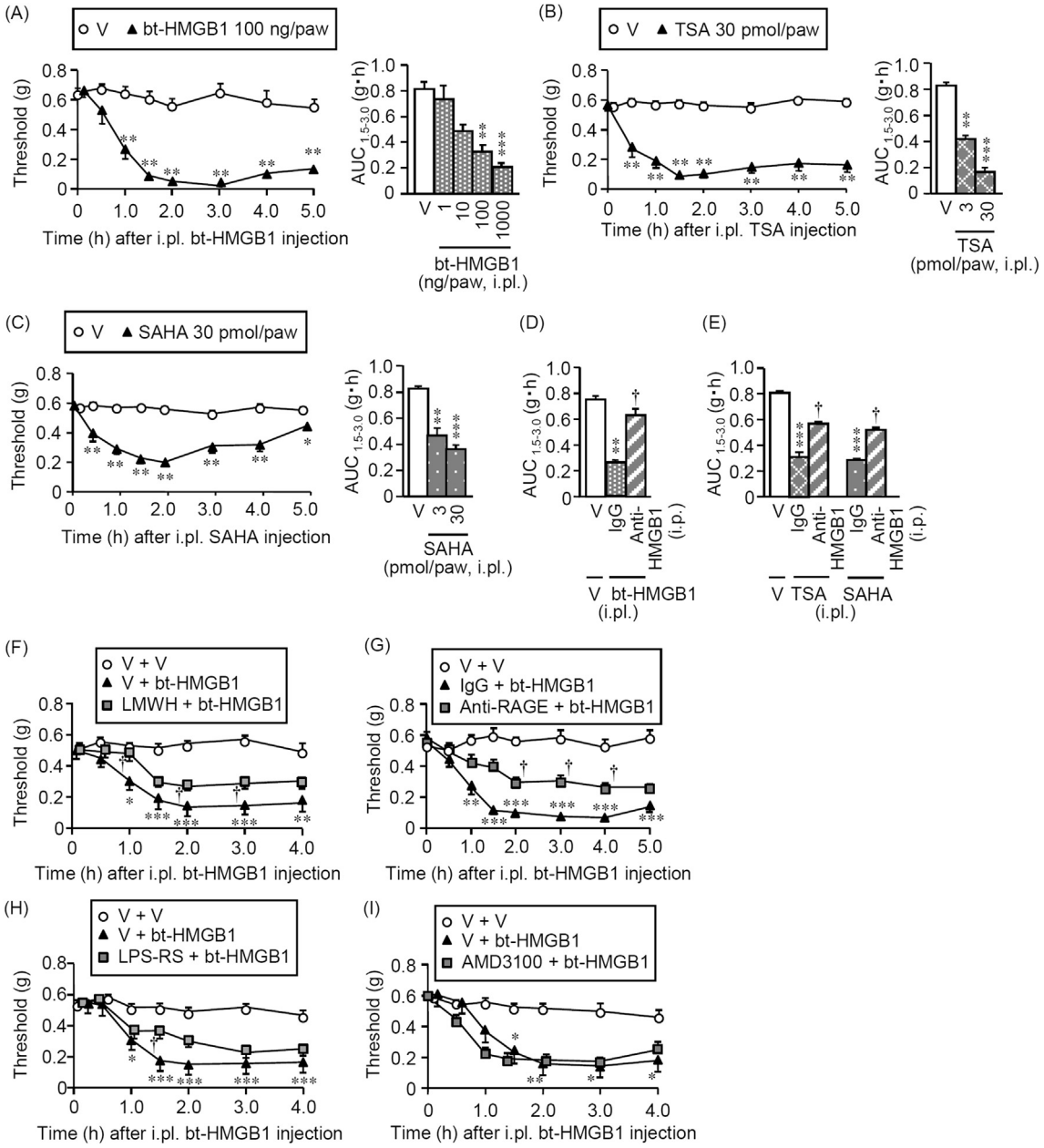

Fig. 1. The mechanical hyperalgesia following intraplantar administration of bovine thymus-derived HMGB1 or HDAC inhibitors in mice. Mice received intraplantar (i.pl.) administration of bovine thymus-derived HMGB1 (bt-HMGB1) at 1–1000 ng/paw (A, D, F–I) or of TSA and SAHA, HDAC inhibitors, 3 or 30 pmol/paw (B, C, E) in a volume of 10 μl. The anti-HMGB1 neutralizing antibody or the control IgG at 1 mg/kg (D, E), LMWH, known to inhibit RAGE, at 2.5 mg/kg (F), LPS-RS, a TLR4 antagonist, at 0.5 mg/kg (H) or AMD3100 at 5 mg/kg (I) was administered i.p. 30 min before i.pl. bt-HMGB1 at 100 ng/paw and before i.pl. TSA or SAHA at 30 pmol/paw. The anti-RAGE neutralizing antibody or the control IgG at 100 ng/paw was administered i.pl. 1 h before i.pl. bt-HMGB1 at 100 ng/paw (G). Data show the mean ± SEM of the nociceptive threshold or of the AUC of the time–threshold curve between 1.5 and 3 h after challenge with bt-HMGB1 or HDAC inhibitors. The number of mice: 4–6 (A), 5–10 (B), 6–12 (C), 5 (D), 7–9 (E), 5–9 (F), 6–8 (G), 6–7 (H) and 4 (I). *P < 0.05, **P < 0.01, ***P < 0.001 vs. vehicle (V) (A–C) or V + V (D–I); †P < 0.05, ††P < 0.01 vs. IgG + bt-HMGB1 (D, G), V + TSA or SAHA (E), and V + bt-HMGB1 (F, H, I).

Download English Version:

https://daneshyari.com/en/article/2548783

Download Persian Version:

https://daneshyari.com/article/2548783

Daneshyari.com