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IL-1β augments H_2S-induced increase in intracellular Ca^{2+} through polysulfides generated from H_2S/NO interaction

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ABSTRACT

H_2S has excitatory and inhibitory effects on Ca^{2+} signals via transient receptor potential ankyrin 1 (TRPA1) and ATP-sensitive K^+ channels, respectively. H_2S converts intracellularly to polysulfides, which are more potent agonists for TRPA1 than H_2S. Under inflammatory conditions, changes in the expression and activity of these H_2S target channels and/or the conversion of H_2S to polysulfides may modulate H_2S effects. Effects of proinflammatory cytokines on H_2S-induced Ca^{2+} signals and polysulfide production in RIN14B cells were examined using fluorescence imaging with fura-2 and SSP4, respectively. Na_2S, a H_2S donor, induced 1) the inhibition of spontaneous Ca^{2+} signals, 2) inhibition followed by $[Ca^{2+}]_i$ increase, and 3) rapid $[Ca^{2+}]_i$ increase without inhibition in 50% (23/46), 22% (10/46), and 17% (8/46) of cells tested, respectively. IL-1β augmented H_2S-induced $[Ca^{2+}]_i$ increases, which were inhibited by TRPA1 and voltage-dependent L-type Ca^{2+} channel blockers. However, IL-1β treatment did not affect $[Ca^{2+}]_i$ increases evoked by a TRPA1 agonist or high concentration of KCl. Na_2S increased intracellular polysulfide levels, which were enhanced by IL-1β treatment. A NOS inhibitor suppressed the increased polysulfide production and $[Ca^{2+}]_i$ increase in IL-1β-treated cells. These results suggest that IL-1β augments H_2S-induced $[Ca^{2+}]_i$ increases via the conversion of H_2S to polysulfides through NO synthesis, but not via changes in the activity and expression of target channels. Polysulfides may play an important role in the effects of H_2S during inflammation.

1. Introduction

Hydrogen sulfide (H_2S) is a gasotransmitter that is synthesized from cysteine through several enzymatic pathways in mammals (Kamoun, 2004; Miyamoto et al., 2014). H_2S plays important roles in physiological functions such as the modulation of neuronal activity (Abe and Kimura, 1996), the relaxation of smooth muscle (Hosoki et al., 1997; Zhao et al., 2001), and the secretion of hormone and autacoid (Yang et al., 2005; Kaneko et al., 2006; Delgermurun et al., 2016). We previously reported excitatory and inhibitory effects of H_2S on Ca^{2+} signals, i.e., H_2S induces Ca^{2+} influx through transient receptor potential ankyrin 1 (TRPA1) channels, while inhibiting spontaneous Ca^{2+} oscillations through ATP-sensitive K^+ (K_{ATP}) channels, in RIN14B cells, a cell line derived from rat pancreatic δ cells (Ujike et al., 2015). H_2S also increases the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) through TRPA1 activation in TRPA1-expressing CHO cells, HEK293 cells and sensory neurons (Streng et al., 2008; Miyamoto et al., 2011; Ogawa et al., 2012). Moreover, H_2S has inhibitory effects on insulin release and smooth muscle contraction through K_{ATP} channels (Zhao et al., 2001; Yang et al., 2005). TRPA1 and K_{ATP} channels are thought to be important for bidirectional modulation of cellular functions by H_2S.

H_2S also acts as a pathological signaling molecule. The amount of H_2S and expression of H_2S-producing enzymes increases under inflammatory conditions (Li et al., 2005; Wallace et al., 2009; Flannigan et al., 2011). Increased H_2S may be involved in exacerbation or resolution of inflammation (Li et al., 2006; Wallace et al., 2012; Linden, 2014). In addition to H_2S production, TRPA1 channels expression also changes in inflammation. IL-1α and TNF-α, proinflammatory cytokines, upregulate TRPA1 expression and enhance Ca^{2+} responses in synoviocytes and odontoblast-like cells (Hatano et al., 2012; El Karim et al., 2015). TNF-α also promotes transportation of TRPA1 to the plasma membrane in trigeminal ganglion neurons (Meng et al., 2016). In addition to the changes in TRPA1, K_{ATP} channel expression increased in experimental colitis (Mathias and von der Weid, 2013). These changes in H_2S target channels could affect the action of H_2S to control Ca^{2+} signals. Moreover, inflammatory factors, such as neutrophil oxidants and nitric oxide (NO), convert H_2S to polysulfides (Nagy and Winterbourn, 2010; Cortese-Krott et al., 2015; Miyamoto et al., 2017),

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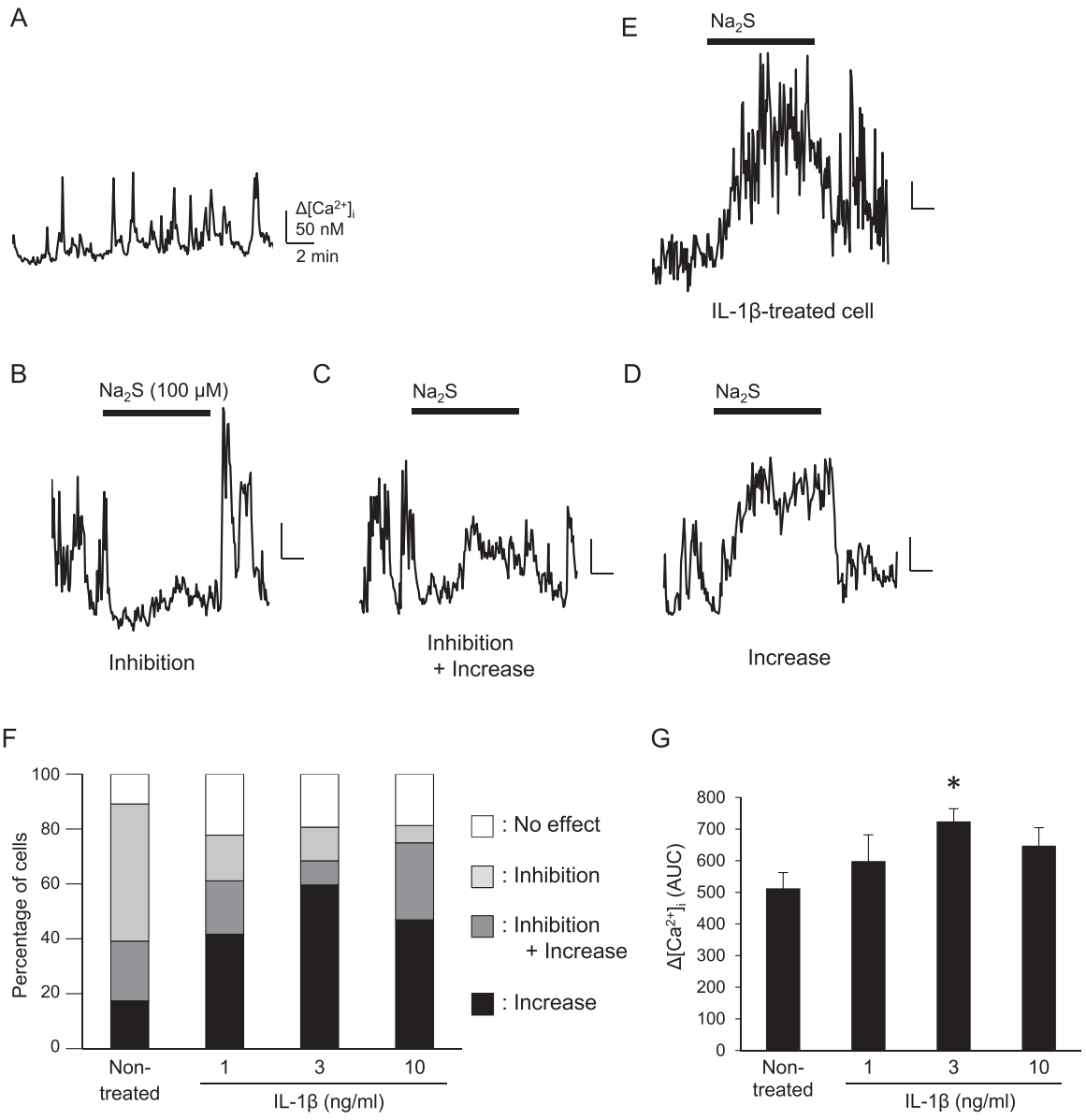

Fig. 1. Effects of IL-1β on $[Ca^{2+}]_i$ responses to H_2S. (A–E) Representative $[Ca^{2+}]_i$ signals with spontaneous Ca^{2+} oscillations under the resting condition (A) and in the presence of Na_2S (100 μM for 10 min, B–E). (B) Spontaneous Ca^{2+} oscillations were inhibited (Inhibition). (C) Inhibition was followed by increased $[Ca^{2+}]_i$ (Inhibition + Increase). (D) $[Ca^{2+}]_i$ immediately increased without inhibition (Increase). (E) $[Ca^{2+}]_i$ increased in IL-1β (3 ng/ml, 24 h)-treated cells. (F) The percentage of cells showing each $[Ca^{2+}]_i$ response to Na_2S (100 μM) in IL-1β (1–10 ng/ml, 24 h, n = 32–57, F). (G) The AUC of $[Ca^{2+}]_i$ responses to Na_2S in IL-1β-treated cells. *$P < 0.05$ vs. non-treated cells (Dunnett's test).

which possess sulfane sulfurs and a higher potency against TRPA1 than H_2S (Kimura et al., 2013; Hatakeyama et al., 2015). The effects of H_2S via TRPA1 may predominate during inflammation. Therefore, it is worth examining the effects of H_2S under inflammatory conditions in RIN14B cells expressing TRPA1 and K_{ATP} channels to reveal the influence of the changes in target channels and the conversion of H_2S described above.

In the present study, we investigated the effects of proinflammatory cytokines on H_2S-induced Ca^{2+} signals in RIN14B cells. We used Na_2S as a H_2S donor and measured $[Ca^{2+}]_i$ and intracellular polysulfide levels using fluorescence imaging with fura-2, a fluorescent Ca^{2+} indicator, and SSP4, a fluorescent sulfane sulfur probe, respectively. The involvement of NO in polysulfide production under inflammatory conditions was also examined.

2. Materials and methods

2.1. Cell culture

RIN14B cells were purchased from DS Pharma Biomedical (Osaka, Japan) and cultured in RPMI1640 medium (Gibco/Thermo Fisher Scientific, Waltham, MA, USA) supplemented with 10% fetal bovine serum, 100 U/ml penicillin, and 100 μg/ml streptomycin (all from Gibco/Thermo Fisher Scientific) at 37 °C in a humidified atmosphere of 5% CO_2 and 95% air.

Cells were placed on coverslips coated with poly-D-lysine (4–5 μg/cm^2, Sigma-Aldrich/Merck, Darmstadt, Germany) for experiments and cultured for 24 h. Cells were then treated with recombinant rat IL-1β, incubated at 37 °C in a humidified atmosphere of 5% CO_2 and 95% air for 24–48 h, and designated as IL-1β-treated cells.

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