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Inhibitory effects of atractylone on mast cell-mediated allergic reactions

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ABSTRACT

This study investigated a salutary effect of atractylone (Atr) which is an active constituent of Pyeongwee-San (KMP6) on mast cell-mediated allergic reactions. Our previous report indicated that KMP6 regulated allergic reactions. Thus, this study sought to determine the potential of Atr *in vitro* models, compound 48/80-stimulated rat peritoneal mast cells (RPMCs), phorbol 12-myristate 13-acetate (PMA) plus A23187-stimulated human mast cell line (HMC-1) cells, and stem cell factor (SCF)-stimulated RPMCs as well as *in vivo* models, IgE-mediated passive cutaneous anaphylaxis (PCA), compound 48/80-induced systemic anaphylaxis, and compound 48/80-induced ear swelling. The results showed that Atr inhibited compound 48/80-induced RPMCs degranulation, intracellular calcium level, tryptase release, and histamine release. Atr inhibited the up-regulation of $p56^{lck}$ tyrosine kinase activity by compound 48/80. And Atr reduced tryptase and histamine releases from PMA plus A23187-stimulated HMC-1 cells. In addition, Atr decreased histidine decarboxylase activity and expression in the activated HMC-1 cells. Atr inhibited SCF-induced morphological alteration and filamentous actin formation in RPMCs. Atr improved IgE-induced PCA reaction by decreasing the levels of histamine, IgE, interleukin (IL)-4, IL-5, IL-6, vascular endothelial growth factor, and IL-13 in the serum of PCA-induced mice. Furthermore, Atr mitigated compound 48/80-induced systemic anaphylaxis and ear swelling. Taken together, these results of this study indicate that Atr regulates the degranulation of mast cell, proving its potential in the treatment of mast cell-mediated allergic reactions.

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1. Introduction

Allergic reactions can be common and mild but a life-threatening and serious illness. Allergic reactions have developed from complex interactions, such as dietary factors or environmental factors. Disordered eating habits can influence sensitization to allergens or increase the risk of developing allergic symptoms [1]. Seriously, dyspepsia or *Helicobacter pylori* infection is associated with skin diseases [2,3]. Dyspepsia was manifested in patients with atopic diseases or allergic rhinitis [4].

Mast cells have an inextricable connection with the pathology of allergic disorders including fatal anaphylaxis [5]. Upon exposure to allergens, IgE-bound FcεRI on mast cells becomes crosslinked and leads to mast cell activation via activation of tyrosine kinases [6]. The activated mast cells release tryptase or histamine as well as various inflammatory cytokines, such as interleukin (IL)-1β, IL-4, IL-5, IL-6, IL-13, vascular endothelial growth factor (VEGF), and tumor necrosis factor (TNF)-α [7]. Histamine is a primary mediator of anaphylactic reactions and triggers cascade pathways of inflammatory process [8]. And it was synthesized by histidine decarboxylase (HDC).

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Stem cell factor (SCF) is a main chemotactic factor for mast cells. SCF promotes proliferation, survival, and maturation of mast cells [9]. Also, SCF exacerbates chronic severe allergic responses via the mast cell degranulation and cytokine production [10,11]. SCF results in a change in filamentous actin (F-actin) distribution around the cell rim [12]. F-actin is involved in mast cell degranulation and migration [13].

Our previous report showed that Pyeongwee-San (KMP6) which has been widely used to treat digestive disorders in Korean medicine had anti-allergic effect [14]. Atractylone (Atr, Fig 1A) is a main sesquiterpenic constituent of *Atractylodes japonica* which is a main component of KMP6 [15]. *Atractylodes japonica* was reported to have anti-inflammatory actions [16]. Atr also was reported to have anti-inflammatory effect [17] and anti-hepatotoxic effect [18]. However, the effect of Atr in mast cell-mediated allergic reactions has not been identified. In this study, we investigated the regulatory effect and its mechanism of Atr in the mast cell-mediated allergic reaction using *in vitro* models, compound 48/80 (an inducer of mast cell degranulation, Fig 1B)-stimulated rat peritoneal mast cells (RPMCs), SCF-stimulated RPMCs, and phorbol 12-myristate 13-acetate (PMA) plus A23187 (calcium ionophore)-stimulated human mast cell line (HMC-1) cells as well as *in vivo* models, IgE-mediated passive cutaneous anaphylaxis (PCA), compound 48/80-induced systemic anaphylaxis, and compound 48/80-induced ear swelling.

2. Materials and methods

2.1. Materials

Atr was purchased from ChemFaces Biochemical Co., Ltd. (Hubei, China); Isocove's Modified Dulbecco's Medium (IMDM) and fetal bovine serum (FBS) from Gibco BRL (Grand Island, NY, USA); compound 48/80, percoll®, ketotifen, 1,2-bis(2-aminophenooxy) ethane-N,N,N′,N'- tertraacetic acid-AM (Bapta-AM), Fura-2/AM, damnacanthal (Dam), PMA, A23187 (Calcimycin; $C_{29}H_{37}N_3O_6$), dexamethasone (DEX), anti-dinitrophenyl (DNP)-IgE, DNP-human serum albumin (HSA), and evans blue from Sigma Chemical Co., (St. Louis, MO, USA); HDC and GAPDH antibodies from Santa Cruz Biotechnology (Dallas, Texas, USA); IgE, IL-4, IL-6, and TNF-α antibodies from BD Pharmingen (Torreyana Road, San Diego, CA, USA); IL-1β, IL-5, VEGF, and IL-13 antibodies from R&D Systems (Minneapolis, MN, USA).

2.2. Animals

Male Sprague Dawley rats (7 weeks old) and ICR mice (4 weeks old) were obtained from the Dae-Han Experimental Animal Center (Eumsung, Republic of Korea). The animals were acclimated at 20–23 °C with 50–60% humidity (12 h light-dark cycles). All experimental procedures involving animals followed the ethical regulations of the animal care committee of Kyung Hee University (No. KHUASP(SE)-15-118).

2.3. Preparation of Atr and KMP6

Atr was dissolved in 10% dimethyl sulfoxide. A dose of Atr was determined on the basis of a previous report [15]. KMP6 was obtained from Korea Bio Medical Science Institute (Seoul, Republic of Korea). A prescription of KMP6 consists of *Atractylodes japonica* Koidzumi (13.3 g), *Magnolia officinale* Rehder et Wils (10 g), *Citrus sunki* Hort. ex Tanaka (10 g), *Zingiber officinale* Roscoe (3.3 g), *Glycyrrhiza uralensis* Fisch (3.3 g), and *Zizyphus jujuba var. inermis* (Bunge) Rehder (6.7 g). An extract of KMP6 was prepared by decocting with distilled water (DW) for approximately 3 h according to previous reports [19,20]. The decocted extract has been filtered and lyophilized. The yield of KMP6 was about 21% (w/w). The KMP6 powder was dissolved with DW and filtered through a 0.22 μm syringe filter. A dose (0.1 mg/kg) of KMP6 was determined according to a previous report [14].

2.4. Mast cell culture

Rats were injected with saline buffer (30 mL) including FBS and heparin into the peritoneal cavity. The abdomen was gently massaged for about 3 min. The peritoneal cavity was opened and the fluid was aspirated using a Pasteur pipette. RPMCs were purified by a Percoll density gradient centrifugation as previously described [21]. HMC-1 cells were cultured in IMDM with FBS (10%), penicillin (100 U/mL), and streptomycin (100 μg/mL) at 37 °C in 5% CO_2 with 95% humidity.

2.5. Fluorescent measurements of intracellular calcium levels

To evaluate the intracellular calcium level, purified RPMCs or HMC-1 cells suspensions were pretreated with Fura-2/AM for 30 min and then were harvested. After washing twice with medium containing extracellular calcium chelator EGTA (0.5 mM), the cell suspension (1×10^5 cells) was placed into a 96-well plate and pretreated with Atr, KMP6, ketotifen, or Bapta-AM for 20 min. RPMCs were stimulated with compound 48/80 (6 μg/mL) and HMC-1 cells were stimulated with PMA plus A23187 (PMACI) for 5 min. The intracellular calcium levels were determined at 440 nm (excitation 360 nm) in a spectrofluorometer.

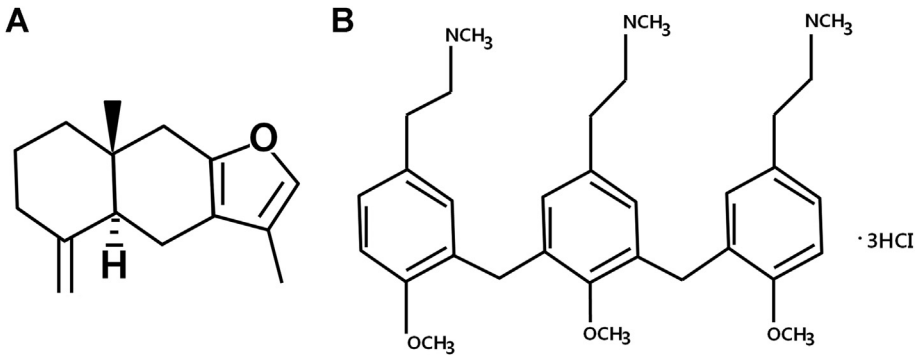

Fig. 1. Structure of (A) Atr and (B) compound 48/80.

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