Regulatory Effect of Inflammatory Reaction by Asiasari Radix

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Mast cells are a potent source of mediators that regulate the inflammatory response in allergic reaction. To evaluate the atopic allergic effect of Asiasari radix(AR), the author investigated a possible effect of AR on mast cell-mediated allergic reaction, cytokines secretion and mRNA expression in vivo and in vitro. In mice orally administered by AR (0.01, 0.1 and 1.0 g/kg) for 1 h, compound 48/80-induced ear swelling was significantly reduced ($P < 0.05$). AR had inhibitory effects on tumor necrosis factor (TNF)-α, interleukin (IL)-8, and IL-6 secretion from HMC-1. Significant reduced levels of TNF-α mRNA was observed in the human mast cell line (HMC-1) with AR (1.0 mg/ml). In addition, AR had no cytotoxic effect on cell viability. These results suggest that AR contributes to the treatment of atopic allergic reactions, and that its action may be due to inhibition of cytokine secretion and mRNA expression in HMC-1.

Key words : Asiasari Radix , mast cell, TNF-α, IL-8, IL-6

Introduction

Asiasari radix (AR) is the dried whole plant, rhizome or root of a number of Asarum species[1]. AR is a traditional herbal medicine widely used to treat various diseases such as aphthous stomatitis, local anesthesia, headache, toothache and inflammatory diseases including gingivitis, in Korea and China[1,2]. Extracts of AR have reported to have analgesic, antipyretic and anti-inflammatory effects[2]. It has been found that AR inhibits immunoglobulin E production in experimental models in vitro and in vivo[3]. It could be suspected that natural products containing anti-inflammatory activity might display some effect. However, it is not known as to whether AR extracts have anti-inflammatory effects in the experimental model.

Mast cells participate in the pathogenesis of several inflammatory disorders. Mast cells are mononuclear, granule-containing secretory cells that reside mostly in the skin, which are increased in number in chronic pathologic lesions[4-6]. One of the well used approaches in the examination of the immunopathological mechanisms of inflammatory disorders is to elicit the formation of edema. Ear swelling test is traditional predictive one for dermal sensitization in humans using mice[7]. Although mast cells have in the past been viewed primarily in the context of immediate-type hypersensitivity reactions, there is recent growing evidence for a role of these cells in tissue homeostasis and in a variety of pathological reactions, including diverse immunological reactions and processes of connective tissue remodelling during rheumatoid arthritis, wound healing, fibrotic diseases and hair growth[8-10]. Support for this view has come with the detection of cytokine production by murine mast cells[11].

Since mast cells are well known to exhibit marked species differences[9], it is of paramount importance to study mast cell cytokine production also in human mast cells. Few such data have been published, and these have been focused on only selected cytokines[13-16].

In recent years, it has been established that activated mast cells synthesize and release a various cytokines and chemokines, of which mast cell-derived tumor necrosis factor (TNF)-α is probably of particular importance in causing allergic inflammation[17]. In addition, mast cells have been also shown to produce interleukin-8 (IL)-8, IL-6, granulocyte-macrophage colony-stimulating factor, and interferon-γ[15,18]. The release of these cytokines may be of major importance in the development of many inflammatory skin disorders[19]. The author investigated whether AR has an effect on the ear swelling response in mice and secretion and mRNA expression of inflammatory cytokines in human mast cell line, HMC-1.

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Materials and Methods

1. Reagents

Compound 48/80, o-phthaldialdehyde (OPA), PMA, and A23187 were purchased from Sigma Chemical Co. (St. Louis, MO, USA). The Iscove's Modified Dulbecco's Medium (IMDM) was purchased from Gibco-BRL, USA (Grand Island, NY, USA). Fetal bovine serum (FBS) was purchased from Life Sciences (Grand Island, NY, USA). Recombinant IL-6 and IL-8, biotinylated IL-6 and IL-8, anti-human IL-6 and IL-8 were purchased from Pharmingen (Torreyana Road, San Diego, CA). Recombinant TNF-α, biotinylated TNF-α, anti-human TNF-α were purchased from R&D systems Inc, USA.

2. Preparation of AR water extract

For all experiments, extract of AR was prepared by decocting the dried prescription of herbs with boiling distilled water (100 g/L). The extraction decocted for approximately 3 h has been filtered, lyophilized and stored at 4℃. The yield of dried extract from starting materials was about 10% (w/w). The dried extract was dissolved in phosphate-buffered saline and filtered with 0.22-μm syringe filter.

3. Cell cultures

The human leukemic mast cell line-1 (HMC-1) was maintained in IMDM with 10% FBS 37℃ in 5% CO_2.

4. Animals

The original stock of ICR mice was purchased from the Damul Experimental Animal Center (Daejeon, Korea). They were housed five to ten per cage in a laminar air-flow room maintained at a temperature of 22 ± 1℃ and relative humidity of 55 ± 10% throughout the study.

5. Ear swelling response

Compound 48/80 was freshly dissolved in saline and injected intradermally into the dorsal aspect of a mouse ear using a microsyringe with a 28-gauge hypodermic needle. Ear thickness was measured with a digital micrometer (Mitutoyo, Japan) under mild anesthesia. Ear swelling response represented an increment in thickness above baseline control values, and was determined 40 min after compound 48/80 or vehicle injection (100 μg/site). AR was administered orally for 1 h before the compound 48/80-injection. The values obtained would appear to represent the effect of compound 48/80 rather than the effect of the vehicle injection (physical swelling), since the ear-swelling response evoked by physiologic saline returned to almost baseline thickness within 40 min.

6. TNF-α, IL-8, and IL-6 assay

TNF-α, IL-8, and IL-6 in supernatants from HMC-1 cells (3×10^5 cells/ml, culture medium IMDM with 10% FBS) were measured by a sandwich enzyme-linked immunosorbent assay (ELISA) according to manufacturers method. Absorption of the avidin-horseradish peroxidase color reaction was measured at 405 nm and compared with serial dilutions of human TNF-α, IL-8 and IL-6 recombinant as a standard.

7. RT-PCR analysis

Total RNA was isolated from HMC-1 cells according to the manufacturers specification using easy-BLUE RNA extraction kit (iNtRON Biotech, Korea). The concentration of total RNA in the final elutes was determined by spectrophotometry. Total RNA (2.5 μg) was heated at 65℃ for 10 min and then chilled on ice. Each sample was reverse-transcribed to cDNA for 90 min at 37℃ using cDNA synthesis kit (AmershamPharmacia, USA). PCR was performed with the following primers for human (h) TNF-α (5′ CGG GAC GTG GAG GCC GAG GAG 3′; 5′ CAC CAG CTG GTT ATC TCT CAG CTC 3′) and IL-8 (5′ CGA TGT CAG TGC ATA AAG ACA 3′; 5′ TGA ATT CTC AGC CCT CTT CAA AAA 3′). The GAPDH (5′CAA AAG GGT CAT CAT CTC TG 3′; 5′CCT GCT TCA CCA CCT TCT TG 3′) was used to verify if equal amounts of RNA were used for reverse transcription and PCR amplification from different experimental conditions. The annealing temperature was 60℃ for TNF-α, IL-8, and GAPDH, respectively. Products were electrophoresed on a 1.5% agarose gel and visualized by staining with ethidium bromide.

8. Statistical analysis

The results were expressed as means ± SEM for the number of experiments. Statistical significance was compared between each treated group and control by the independent t- test. Results with $P < 0.05$ were considered statistically significant.

Results

1. Effect of AR on ear swelling response

The fact that intradermal application of compound 48/80 at the dose of 100 μg/site can induce an ear-swelling response in normal mice has been confirmed in the previous studies20). The author chose a concentration of 100 μg/site for compound 48/80 in 30 min-induced optimal ear-swelling response in this experiment. As shown in Table 1, when mice were pretreated with AR (1 g/kg) for 1 h, the ear-swelling responses derived from compound 48/80 were reduced more significantly by 55.51% ($P < 0.05$).

Table 1. Effect of AR on Compound 48/80-induced Ear Swelling Response in Mice.

AR (g/kg)	Compound 48/80 (100 ㎍/site)	Thickness of ear (㎜)	Inhibition (%)
None (saline)	+	0.254 ± 0.016	
0.01	+	0.167 ± 0.018	34.25*
0.1	+	0.186 ± 0.003	26.77*
1.0	+	0.113 ± 0.003	55.51*

20 ㎕ of compound 48/80 (100 ㎍/site) were applied intradermally. The mice were orally administered with the various concentrations (0.01, 0.1 and 1.0 g/kg) of AR for 1 h prior to the compound 48/80 application. Each datum represents the means ± SEM of three independent experiments. *P < 0.05, Significantly different from the saline value.

2. Effect of AR on TNF-α secretion from HMC-1 cells

To assess the effect of AR in PMA and A23187-induced TNF-α secretion, the cells were pre-treated with various concentrations (0.01, 0.1, and 1.0 ㎎/㎖) of AR for 30 min prior to stimulators. The AR (1 ㎎/㎖) did not affect TNF-α secretion in the absence of PMA and A23187. However, in PMA and A23187-stimulated cells, TNF-α secretion was decreased by treatment of AR. At the 1 ㎎/㎖ of AR, the inhibition rates reached up to 33.89% (Fig. 1).

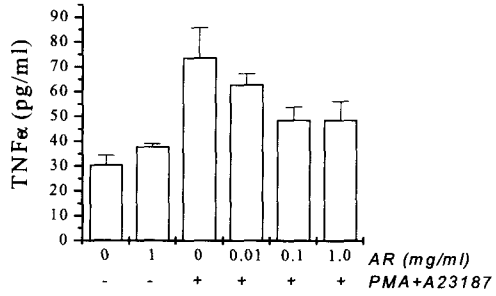

Fig. 1. Effect of AR on TNF-α secretion from HMC-1 HMC-1 cells (3 × 10^5 cells/㎖) were stimulated with PMA (50 nM) and A23187 (1 μM) for 8 h. TNF-α levels in culture supernatant were measured using ELISA. Each point represents the means ± SEM of three independent experiments.

3. Effect of AR on IL-8 secretion from HMC-1 cells

To assess the effect of AR in PMA and A23187-induced IL-8 secretion, the cells were pre-treated with various concentrations (0.01, 0.1 and 1.0 ㎎/㎖) of AR for 30 min prior to stimulators. The AR (1 ㎎/㎖) did not affect IL-8 secretion in the absence of PMA and A23187. However, in PMA and A23187-stimulated cells, IL-8 secretion was decreased by treatment of AR. In the case of IL-8, the effect of AR was dose-dependently inhibited. However, AR (0.01 ㎎/㎖) did not inhibit the IL-8 secretion. Inhibition rate of IL-8 secretion was 17.66% at the treated AR concentration of 1 ㎎/㎖ in the cells (Fig. 2).

4. Effect of AR on IL-6 secretion from HMC-1 cells

To assess the effect of AR in PMA and A23187-induced IL-6 secretion, the cells were pre-treated with various concentrations (0.01, 0.1, and 1.0 ㎎/㎖) of AR for 30 min prior to stimulators. The AR (1 ㎎/㎖) did not affect IL-6 secretion in the absence of PMA and A23187. However, in PMA and A23187-stimulated cell, IL-6 secretion significantly was decreased by treatment of AR in a dose-dependent manner ($P < 0.05$). Maximum effective concentration of AR was 1 ㎎/㎖ for IL-6. IL-6 secretion significantly inhibited by 81.74%, 86.99%, and 93.27% at the treated AR concentrations of 0.01, 0.1, and 1 ㎎/㎖ in the cells, respectively (Fig. 3).

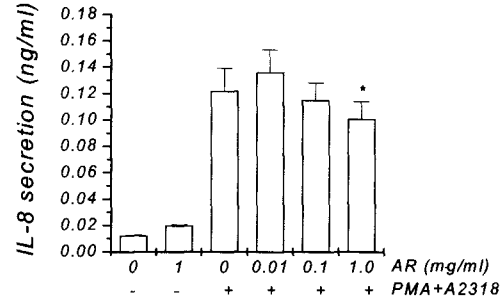

Fig. 2. Effect of AR on IL-8 secretion from HMC-1 HMC-1 cells (3 × 10^5 cells/㎖) were stimulated with PMA (50 nM) and A23187 (1 μM) for 8 h. IL-8 levels in culture supernatant were measured using ELISA. Each point represents the means ± SEM of three independent experiments. *P < 0.05, Significantly different from PMA and A23187 treated value.

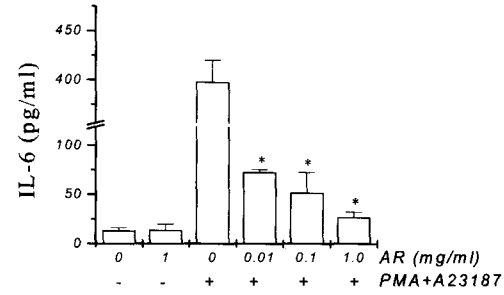

Fig. 3. Effect of AR on IL-6 secretion from HMC-1 HMC-1 cells (3 × 10^5 cells/㎖) were stimulated with PMA (50 nM) and A23187 (1 μM) for 8 h. IL-6 levels in culture supernatant were measured using ELISA. Each point represents the means ± SEM of three independent experiments. *P < 0.05, Significantly different from PMA and A23187 treated value.

5. Effect of AR on TNF-α mRNA expression in HMC-1 cells

To investigate the effect of AR on the change of TNF-α mRNA expression in stimulated HMC-1 (5 × 10^5), the author performed RT-PCR. HMC-1 cells were pre-treated with AR for 30 min at the dose of 1 ㎎/㎖ and then treated with PMA and A23187 for 3 h. As shown in Fig. 4, AR inhibited the TNF-α mRNA expression in the stimulated HMC-1.

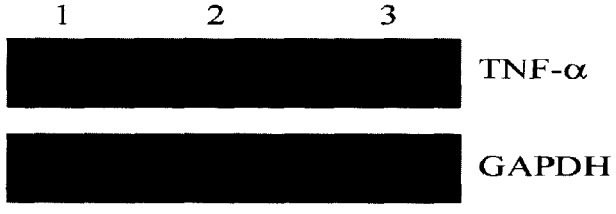

Fig. 4. Effect of AR on TNF-α mRNA expression in PMA and A23187-stimulated HMC-1 cells The total RNA was assayed by RT-PCR. Products were electrophoresed on a 1.5% agarose gel and visualized by staining with ethidium bromide. The GAPDH is loading control. 1. blank; 2. PMA+A23187; 3. PMA+A23187+AR (1 ㎎/㎖)

6. Effect of AR on IL-8 mRNA expression in HMC-1 cells

To investigate the AR can affect on IL-8 mRNA expression in stimulated HMC-1 (5×10^5), the author performed RT-PCR. HMC-1 cells were pretreated AR for 30 min at the dose of 1 ㎎/㎖, and then treated with PMA and A23187 for 3 h. As shown in Fig. 5, induced IL-8 expression was not inhibited by pre-treatment with AR.

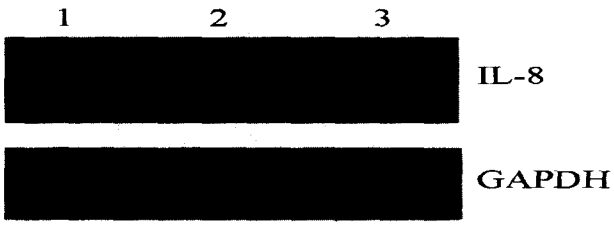

Fig. 5. Effect of AR on IL-8 mRNA expression in PMA and A23187-stimulated HMC-1 cells The total RNA was assayed by RT-PCR analysis. Products were electrophoresed on a 1.5% agarose gel and visualized by staining with ethidium bromide. The GAPDH is loading control. 1, blank; 2, PMA+A23187; 3, PMA+A23187+AR (1 ㎎/㎖)

7. MTT assay to determine cytotoxicity of AR in HMC-1 cells

To test cytotoxic effect of AR, the author performed MTT assay in HMC-1 cells. HMC-1 cells were pre-treated with AR (0.01-1.0 ㎎/㎖) for 24 h. After incubating for 24 h, cell viability was measured by the MTT assay. AR (0.01-1 ㎎/㎖) exerted no cytotoxic effect (Fig. 6).

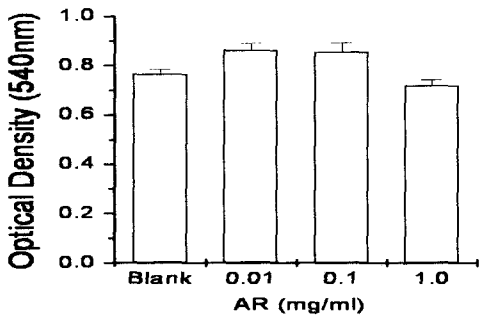

Fig. 6. MTT assay of AR in HMC-1 cells HMC-1 cells (3×10^5) were treated with various concentrations of AR for 24 h. Cell viability was evaluated by MTT colorimetric assay. Values are the mean ± SEM of duplicate determines from three separate experiments.

Discussion

Inflammation is often accompanied by tissue injury and chronic disease state, involved with increased vascular permeability, recruitment of immune cells, and plasma leakage[21]. Mast cells are known to be involved in inflammatory reactions, and mast cell-mediated edema was described in other reports besides induced by compound 48/80. The synthetic compound 48/80 is known to be one of the most potent secretagogues[22]. An appropriate amount of compound 48/80 has been used as a direct and convenient reagent to study the mechanism of systemic anaphylactic reaction[23]. Studies on the compound 48/80-induced ear swelling response and mast cell degranulation have been continuously performed on these theoretical[24]. The activation of proteinase-activated receptor-2, receptor for mast cell tryptase, induced an acute inflammtory response characterized by edema formation, granulocyte infiltration, and increase vascular permeability[25,26]. In recent years, it has been established that activated mast cells synthesize and release a variety of cytokines and chemokines, of which mast cell-derived TNF-α is probably of particular important in causing allergic inflammation[17,27].

After stimulation, HMC-1 cells have been shown to produce TNF-α, IL-8, and IL-6[28]. The regulation of these cytokines secretion from mast cells can provide us with a useful therapeutic strategy for allergic inflammatory disease such as Atopic dermatitis(AD). TNF-α is elevated in patients with AD[29]. TNF-α influences the development of skin inflammation by induction of adhesion molecules, including endothelial E-selectin, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 expression[30-33]. In conjunction with IL-1, TNF-α can induce production of the chemokine IL-8 by a variety of cell types, such as monocytes and epithelial and endothelial cells[34]. IL-8 is a chemoattractant for neutrophils, macrophages and T lymphocytes[35] and facilitates the migration of these cells into inflamed skin[36,37]. IL-8-producing inflammatory cells are found in the dermis of atopic patients[38]. In addition, synthesis of IL-8 has already been described in the human leukemic mast cell line HMC-1, but only after stimulation by chemical compounds such as calcium ionophore and PMA[28]. IL-8 causes inflammation characterized by neutrophilic and lymphocytic infiltration[39]. Lippert et al.[40] observed that monocytes of AD patients secreted IL-8 after antigen stimulation, and the supernatants of these stimulated leukocytes contain factors (presumably cytokines) that trigger skin whealing and itching directly in AD patients, independently of histamine.

Monocytes from patients produced significantly higher levels of IL-8 and IL-6 compared to health non controls[41]. McHugh et al.[41] showed that early and sustained production of large amounts of IL-6 in inflammatory patients. They assumed that IL-6 from monocytes and other cells contributes directly and indirectly (via induction of IL-4) to a predominantly Th2 cytokine environment, which potentiates IgE production and related allergic manifestation. However, in this study, inhibition effect of AR on IL-6 mRNA expression in stimulated HMC-1 is not addressed, further studies are needed.

AR is claimed to be of medicinal value in inflammation. The anti-inflammatory effects of the present study support this

traditional claim. The author demonstrated that AR inhibited ear swelling by compound 48/80 in vivo. The main factors of mast cell-mediated inflammation, TNF-α, IL-8, and IL-6, were investigated in vitro. The AR showed a significant inhibitory effect on the cytokines (TNF-α, IL-8, and IL-6) secretion and TNF-α mRNA expression. The author concluded AR was potential for the treatment of inflammatory diseases by down-modulating the mast cell activation.

Conclusion

The ear-swelling responses derived from compound 48/80 were reduced significantly by treatment of AR. TNF-α secretion was decreased by treatment of AR in the stimulated HMC-1. IL-8 secretion was decreased by treatment of AR in the stimulated HMC-1. IL-6 secretion significantly was decreased by treatment of AR in a dose-dependent manner. TNF-α mRNA expression was inhibited by treatment with AR. IL-8 mRNA expression was not inhibited by treatment with AR.

The authors concluded Asiasari radix(AR) was potential for the treatment of inflammatory diseases.

Acknowledgement

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