Study on Anti-allergic Effects of Electroacupuncture in Allergic Mouse Model

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Electroacupuncture(EA) is commonly used in various diseases. In the present study, the effect of EA in the allergic mouse model was examined. Allergy is generated via immunological mechanism and non-immunological mechanism. Mast cells activated by those mechanisms get to release various substances such as histamine, leukotrienes, prostaglandin, TNF-α, IL-4, IL-6, etc. which induce allergic reactions and the following inflammatory responses. To evaluate the anti-allergic effects of EA, mortality, ear swelling response, vascular permeability and cytokine secretion were investigated in EA group and non-EA group of which mice were compound 48/80-induced allergy model or PCA model. Compound 48/80 induces allergic reaction via non-immunological mechanism and PCA model is generated through the same mechanism with immediate-type(Type1) allergic reaction, one of immunological allergic reactions. EA inhibited compound 48/80-induced ear swelling response but did not inhibit the systemic anaphylaxis. EA also inhibited passive cutaneous anaphylaxis(PCA) activated by anti-dinitrophenol IgE. In addition, EA inhibited IL-6 and TNF-α secretion from 48 h PCA in mice. These results indicate that EA may be used for the treatment of mast cell-mediated allergic diseases, especially immediate-type(Type 1) allergy and non-immunologically mediated allergy.

Key words : allergy, electroacupuncture(EA), compound 48/80, passive anaphylaxis(PCA)

Introduction

Acupuncture has been performed for prevention and care of the various diseases including allergy by stimulating each specific acupoints. Electroacupuncture(EA) is commonly used to regulate the frequency and intensity of acupuncture stimulation efficiently[1].

In recent report, Tracey suggested that acupuncture may have anti-inflammatory effect due to Ach(acetylcholine) and norepinephrine release which acts on macrophage[2]. And Cho et al. hypothesized that acupuncture action on immune effects is carried out by autonomic and endocrine system controlled through hypothalamus[3]. Also, there are some EA studies coming up about allergy and asthma[4-6]. As recently reported, the low frequency EA inhibits carrageenan induced plantar edema through the opioid-independent pathway[7]. EA was turned out to work for delayed-type allergy through the excitatory pathway of neuroendocrine system by Kasahara et al.[8]. But there is no report referring to the EA effect on immediate-type allergy.

Allergic reaction is generated via immunological mechanism and non-immunological mechanism. Mast cell stimulated in different manners depending on the type and mechanism of allergy plays a major role in the reactions.

Anti-allergic effects of EA was evaluated through systemic anaphylactic shock, ear swelling reaction induced by compound 48/80 and passive cutaneous anaphylaxis(PCA) induced by anti-DNP IgE antibody in ICR mouse. Also the change of IL-6 and TNF-α secretion in tissue in the dorsum of PCA mice model was observed.

Materials and Methods

1. Reagents and devices

Compound 48/80, anti-DNP(dinitrophenol) IgE, DNP-HSA(human serum albumin), o-phthaldialdehyde, evans blue, fetal bovine serum, α-minimum essential medium(Sigma, St. Louis, MO, USA). Anti-mouse IL-6 antibody, biotinylated anti-mouse IL-6 antibody, recombinant mouse IL-6(BD PharMingen, San Diego, CA, USA). Anti-mouse TNF-α antibody, biotinylated anti-mouse TNF-α

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antibody, recombinant mouse TNF-α(R&D systems, Minneapolis, MN, USA). Acupuncture needle was 20mm length, 0.18mm diameter stainless steel(DongBang Acupuncture Inc., Korea). Electroacupuncture stimulator was PG-306(YoungMok, Japan).

2. Animals

ICR male mice(4week old, 18-22g) were from Daehan Biolink Co., Ltd.(EumSung-Gun, Korea). Mice had continuous access to food and water and were housed in suspended steel cages in a colony room on a timer controlled 12 L:12 D cycle.

3. Group

9 ICR male mice were divided into 4 groups.

1) Blank group

Mice were injected with DNP-HSA and put under stress for 10 mins in a holder.

2) Control group

Mice were put under stress for 10 mins(same with EA stimulating time) in a holder just after ear swelling response, systemic anaphylactic shock and passive cutaneous anaphylaxis.

3) 2Hz group

2Hz EAwas performed at right Zusanli(ST36) just after induction of those allergy responses above.

4) 120Hz group

120Hz EA was performed at right Zusanli just after induction of those allergy responses above.

4. Systemic anaphylactic shock

ICR male mice were kept for 24 hours after enough food intake before the experiment. Compound 48/80 dissolved in PBS(phosphate-buffered saline) was injected intraperitoneally(8 mg/kg) and EA was performed at 2Hz and 120Hz. EA effect was measured by mortality after 18 mins(mean time to death for systemic anaphylactic shock induced mice without EA).

5. Ear swelling responses

A mouse was anesthetized to be measured the ear's thickness and compound 48/80(100 μg/site) was injected intradermally into the dorsal aspect of the mouse ear using a microsyringe. EA at 2Hz and 120Hz was performed for 10 mins and ear thickness was measured to determine the change in the ear thickness after 30 mins.

6. Passive cutaneous anaphylaxis(PCA)

Dorsal skins of mice were shaved and injected intradermally with 100ng of anti-DNP IgE at four spots marked with a water-soluble red pen. 48 hours later, mice received into the vein an injection of 200μl of PBS containing 100μg DNP-HSA with 4% of Evans blue followed by 2Hz and 120Hz. At 40 mins after challenge with DNP-HSA, mice were sacrificed and Evans blue dye extravasation was measured in accord with the method of Katayama et al.[9]. In other words, a piece of the skin containing extravasated dye was soaked for 12 hours in a glass tube containing 0.5ml of 1 N KOH at 37℃. Then, 9ml of mixed solution of 0.6 N phosphoric acid and acetone(5:13) was added to the tube. The tube was centrifuged at 3,000 rpm for 15 mins and then colorimetry was done at 620nm.

7. Measurement of IL-6 and TNF-α

After PCA and EA as reported earlier, sample soaked in 1ml of homogenization buffer was grinded on the ice. Grinded sample was centrifuged at 12,000 rpm at 30 minsand supernatant was shifted into an EP tube. After quantifying the total protein amount, IL-6 and TNF-α amount was measured by modified ELISA(enzyme-linked immunosorbent assay) in accord with the method of Scuderi et al.[10]. In other words, a 96-well plate was precoated with 1μg/ml of anti-mouse IL-6 antibody and anti-mouse TNF-α antibody at 4℃ 12 hours prior to the add of blocking buffer which consists of PBS and 2% BSA(bovine serum albumin) for blocking the non-specific binding site. The plate was kept at 37℃ for 2 hours. Then the plate was rinsed with PBS containing 0.05% tween 20 for 4 times and each well was added 100μl mixture of recombinant mouse IL-6, TNF-α standard solution and culture solution of each samples. After being kept at 37℃ for 2 hours, the plate was rinsed with PBS containing 0.05% tween 20 for 4 times and each well was treated by 0.05μg/ml mixture of bitinylated anti-mouse IL-6 and TNF-α diluted by PBS containing 1% BSA to be kept at 37℃ for 2 hours. The plate was rinsed with washing buffer for 7 times and each well was treated by 2.5μg/ml of avidin-conjugated enzyme. After being kept at 37℃ for 40 mins and washed for 7 times. Color development was induced by adding 100μl of ABTS substrate solution to each well. Each amount of IL-6 and TNF-α was measured at 405nm using ELISA reader.

8. Statistical Analysis

Data are represented the mean±S.E.M and statistical analysis was carried out using SPSS 11.0. Significance was examined by Student's t-test.

Results

1. Suppressive effect of EA on systemic anaphylactic shock

In vivo model representing systemic anaphylaxis and compound 48/80, a lethal allergic reaction inducer via mast cell degranulation, were used for the study. Compound 48/80 was injected intraperitoneally and EA was just followed in 2Hz group and 120Hz group for 10 mins. 18 mins after the injection, the mortality was checked. All the group showed 100% mortality(Table 1).

Table 1. Mortality in each group

Hz (EA)	Compound 48/80 (8 mg/kg)	Mortality (%)
None	+	100.0
2	+	100.0
120	+	100.0

2. Suppressive effect of EA on ear swelling response

Compound 48/80(100μg/site) was injected intradermally on the dorsal aspect of a mouse ear and the ear thickness before and after the injection was measured. 2Hz EA tended to suppress the ear swelling response but it wasn't significant enough. Ear thickness was 0.6535±0.05450 in control group, 0.5880±0.01002 in 2Hz group and 0.6527±0.00441 in 120Hz group.

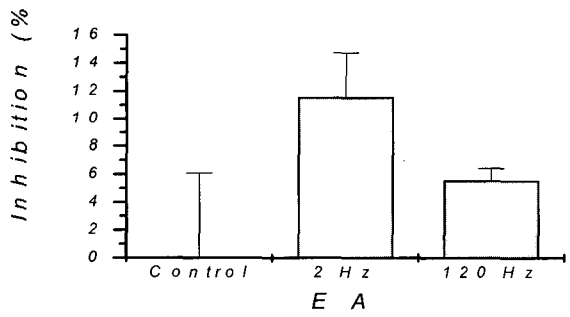

Fig. 1. Effect of EA on compound 48/80-induced ear swelling response in mice. EA tended to suppress the ear swelling response but it wasn't significant enough. Each datum represents the mean±S.E.M..

3. Suppressive effect of EA on Passive cutaneous anaphylaxis

PCA was induced by injecting anti-DNP IgE and 48h later the mouse was challenged intravenously with DNP-HSA in Evans blue. Change in vascular permeability induced by PCA was assessed by measuring Evans blue dye extravasation and it indicates immediate-type allergic reaction in localized skin area. PCA reaction was suppressed in both EA group, especially in 2Hz group in statistic(Fig. 2). The amount of dye (μg/ml) was 0.5742±0.03824 in control group, 0.4006±0.05408 in 2Hz group and 0.4986±0.04073 in 120Hz group.

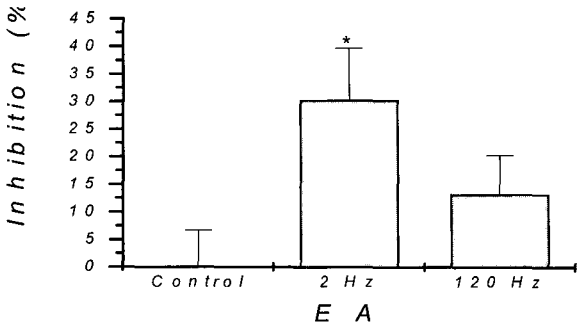

Fig. 2. Effect of EA on 48 h PCA in mice. EA suppressed PCA reaction and especially it was significant enoughin 2Hz group. Each datum represents as mean±S.E.M.. *P<0.05; significantly different from the control value.

4. Suppressive effect of EA on IL-6 release in PCA model

The amount of IL-6 in tissue of a PCA-induced mouse was measured. 2Hz EA stimulation suppressed IL-6 release (Fig. 3) significantly. The amount of IL-6 was 0.0318±0.00413 in blank group, 0.401±0.00084 in control group and 0.0342±0.00123 in 2Hz group.

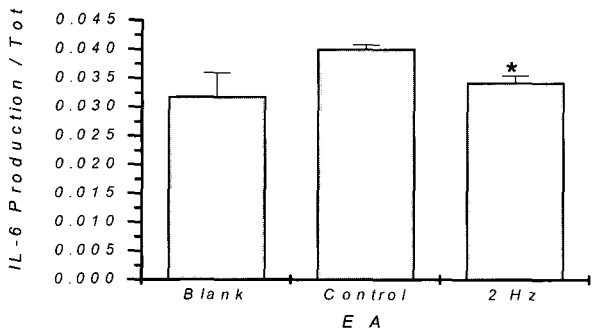

Fig. 3. Effect of EA on IL-6 secretion in PCA mice. EA suppressed IL-6 secretion markedly. Each datum represents the mean±S.E.M.

5. Suppressive effect of EA on TNF-α release in PCA model

The amount of TNF-α in tissue of a PCA-induced mouse was measured. 2Hz EA stimulation tended to suppress TNF-α release(Fig. 4). The amount of TNF-α was 1.0667±0.05544 in blank group, 1.3910±0.02845 in control group and 1.3538±0.05877 in 2Hz group.

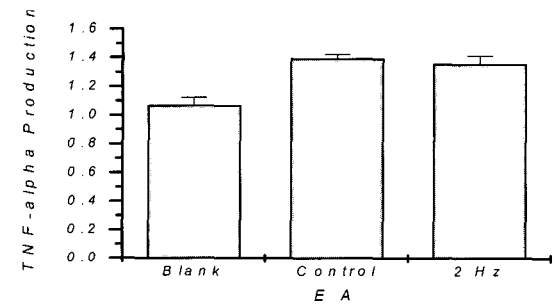

Fig. 4. Effect of EA on TNF-α secretion in PCA mice. EA tended to suppress TNF-α secretion but not significantly. Each datum represents the mean±S.E.M.. *P<0.05

Discussion

Electroacupuncture(EA), which is convenient to control the frequency and intensity of acupuncture stimulation efficiently.

Zusanli(ST36) is a common acupoint used for gastroenteropathy such as gastritis, enteritis conventionally. Also, it has been recently reported that Zusanli is effective for stress-induced immunodeficiency[11], immune-mediated disorders[12] and immunologic function of cells[13].

Allergic reaction is generated via either immunological mechanism or non-immunological mechanism. Through these mechanisms, mast cell gets activated to release histamin, leukotrienes, prostaglandin and cytokines like TNF-α, IL-4, IL-6, etc. which produce allergic reactions and the following inflammatory responses.

In this study, 2Hz and 120Hz EA was performed at Zusanli on allergic mouse model to evaluate its anti-allergic effects. This experiment convinced that EA suppresses the acute allergic reaction owing to the activation of mast cell via either specific immune mechanism or non-specific immune mechanism. Compound 48/80 is a well-known mast cell degranulator and plays a major role in physiological change induced by allergy[14]. Intracellular calcium, cAMP and histamin release are induced effectively in mast cells of the rat by substances such as compound 48/80, NaF[15]. Compound 48/80 is known to facilitate the histamin release non-immunologically[16]. It is easy to handle and works directly on anaphylactic reaction[17]. In this report, the study about degranulation of mast cell and ear swelling response induced by compound 48/80 were performed based on the theory of Kim et al.[18-22]. Compound 48/80 activates G protein[23-24] and its treatment lowers the number of mast cell. EA tended to suppress ear swelling response induced by injection of compound 48/80 in the experiment. This result means that EA can be used as a suppressor for non-immunologically mediated allergic reaction. EA effect on systemic anaphylactic shock induced by compound 48/80 was also observed but mortality was same as 100% in all the groups. It is presumed that the mean survival time of systemic anaphylactic shock-induced mouse was too short for EA to exert its influence on systemic reaction.

Binding of allergens with IgE to the IgE receptors on mast cell results in its secretion[14,25-26]. Anti-DNP IgE antibody is used to induce passive cutaneous anaphylaxis(PCA), a typical model for mast cell-mediated allergic reaction. The skin of mice is the most suitable one for PCA study[27-28]. PCA is an appropriate method to study skin allergic reaction[31] and it was used to evaluate the EA effect on localized allergic reaction mediated by IgE. Mice in 2Hz EA group were turned out to be protected from localized allergic reaction mediated by IgE. From this, we saw that EA could be used as a suppressor for immediate-type(Type 1)allergic reaction mediated by IgE, although the mechanism of protection couldn't be explained in detail only with this experiment.

Activated mast cells release many kinds of inflammatory factor, proinflammatory and chemotaxic cytokines like TNF-α, IL-1, IL-6, IL-8, IL-13[29-32]. How to control the cytokines secretion from mast cell could be the fundamental solution for allergic disease. Recently, it has proved that IL-6 heightens the histamin level[33], which also happens in human mast cell from peripheral blood, reported by Kikuchi[34]. TNF-α is reported to contribute to the development of allergic rhinitis in mice[35] and is observed increased in alveolar wash fluid of mice under allergic reaction in the bronchi[36]. IL-6 plays a major role in inflammation and immune response as proved in rheumatoid arthritis model or multiple sclerosis model[37-38]. TNF-α is an important initiator of cell-activating substance release related to inflammation and promotes leukocyte infiltration, inflammatory responses and granuloma formation[39]. 2Hz EA tended to suppress TNF-α release and suppress IL-6 in the experiment thus it is convinced that EA can be used for the suppression of allergic inflammatory responses.

This experimental results indicates that EA may be used as a suppressor for non-immunologically mediated allergic reaction and immediate-type(Type 1) allergic reaction. And EA also prevents the inflammatory responses following the allergic reaction.

Conclusions

Some conclusions were derived from the study on the effect of EA on mast cell-mediated allergic reactions.

Both 2Hz and 120Hz EA didn't make a difference compared with control group in mast cell-mediated systemic anaphylactic shock induced by compound 48/80. Both 2Hz and 120Hz EA tended to suppress mast cell-mediated ear swelling response induced by compound 48/80. Both 2Hz and 120Hz EA suppressed PCA reaction. Especially, 2Hz EA suppressed the reaction significantly in statistic. 2Hz EA suppressed IL-6 release in a PCA mouse model markedly. 2Hz EA tended to suppress TNF-α release in a PCA mouse model. These results indicate that EA may be used for the treatment ofmast cell-mediated allergic diseases, especially immediate-type(Type 1) allergy and non-immunologically mediated allergy.

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