

Preventive Effects of (-)-Epigallocatechin-3-O-gallate on Mouse Type IV Allergy Induced by Oxazolone and its Antiinflammatory Activities

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(Received June 3, 2010; Accepted June 18, 2010)

Abstract

We investigated the mechanisms underlying the inhibitory effects of (-)-epigallocatechin-3-O-gallate (EGCG) on oxazolone-induced type IV allergy in male ICR mice and two simple inflammation mouse models. Serum levels of interleukin-12 (IL-12) and γ -interferon (γ -IFN) were significantly increased in mice with severe ear edema induced by type IV allergy in comparison with normal mice. The oral administration of EGCG at a dose of 50 mg/kg body weight prevented the elevations of these levels. Lowering of serum levels of IL-2, spleen natural killer NK cell activity and serum antioxidant activity in mice with allergic symptoms were also prevented by oral administration of EGCG. Furthermore, the oral administration of EGCG at the same dose prevented mouse ear edema induced by arachidonic acid and tended to prevent mouse ear edema induced by croton oil. These results suggested that the antiallergic mechanism of action of EGCG involves inhibition of the fluctuations in cytokines and chemical mediators, and maintenance of antioxidant status in allergic mice.

Keywords: Tea catechin, Type IV allergy, Inflammation, Mouse

1. Introduction

Recently, the increase in incidence rates of allergic diseases has become an important medical problem around the world. Allergies can be classified into four types, designated type I to type IV, based on their mechanisms[1]. Type IV allergy, such as delayed type contact hypersensitivity and tuberculosis, is a common type of allergic disease similar to type I allergy, such as anaphylaxis. Type IV allergy involves cell-mediated immunity controlled by some proinflammatory cytokines, such as interleukin-12

(IL-12), secreted by antigen presenting cells (APC) such as macrophages and dendritic cells and stimulates naive T cells; IL-2, which is secreted by type 1 T helper (Th1) cells and mononuclear cells (MNC) and stimulates cytotoxic T lymphocytes (CTL) and natural killer (NK) cells; and γ -interferon (γ -IFN) and tumor necrosis factor- α (TNF- α), which are secreted by Th1 cells and macrophages and stimulate macrophages. IL-12, γ -IFN, and TNF- α are known as potent proinflammatory cytokines. Severe inflammation is a key process in the development of

type IV allergy.

Tea (*Camellia sinensis* L.) is one of the most popular beverages around the world. The content of catechins in green tea leaves is up to 15% dry weight, and (-)-epigallocatechin-3-O-gallate (EGCG) is a specific and major flavan-3-ol derivative included in tea leaves[2]. The chemical structure of EGCG is shown in Figure 1. It was reported that extracts of green tea as well as some catechins present in tea leaves could prevent picryl chloride-induced mouse ear edema[3] and ultraviolet-B radiation-induced edema[4]. We also reported that the extract of green tea, some catechins, and their O-methylated derivatives present in tea leaves could prevent oxazolone-induced mouse ear edema[5,6]. Lin *et al.*[7] suggested that the galloyl moiety of catechins was essential for the potent antiinflammatory activities. Therefore, daily intake of tea as a beverage could be beneficial in the prevention of allergic disorders.

In this study, we investigated the effects of EGCG on serum cytokine levels, spleen NK cell activities, and serum antioxidant activities in mice with type IV allergy induced by oxazolone and on arachidonic acid or croton oil-induced mouse ear edema to study the mechanisms underlying the preventive effects of EGCG on mouse type IV allergy induced by oxazolone.

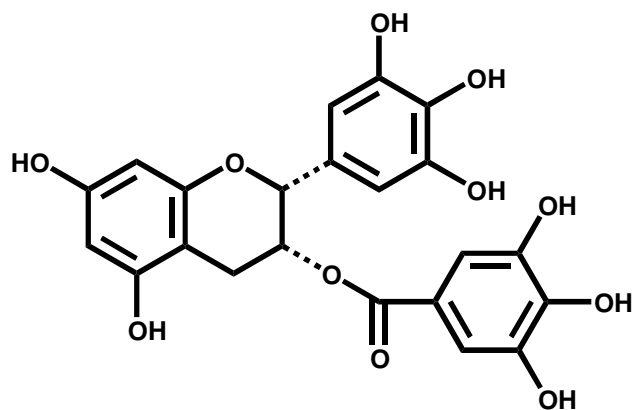


Figure 1 Chemical Structure of EGCG.

2. Materials and Methods

2.1 Materials and animals

Oxazolone (4-ethoxymethylene-2-phenyl-2-oxazolin-5-one) was purchased from Sigma-Aldrich Chemical Co. (Milwaukee, WI, USA) and used as a sensitizer for type IV allergy. EGCG was purchased from Kurita Co. (Tokyo, Japan). Other chemicals used were of reagent grade. Male ICR mice, 4 weeks old, were purchased from Japan SLC Inc. (Shizuoka, Japan). Throughout the experiment, the animals were handled in accordance with “*The Guide for the Animal Experiments in Numazu National College of Technology.*”

2.2 Determination of mouse type IV allergic response

Oxazolone-induced edema of the ear in mice was used as a model of type IV allergy[8,9]. The hair of the abdominal region of male ICR mice was carefully shaved off, and 0.1 mL of 0.5% oxazolone solution in ethanol was applied to the skin (sensitization). Five days after sensitization, 20 μ L of 0.5% oxazolone solution in acetone was applied to both sides of each animal's right ear (challenge). Twenty-four hours after the challenge, the mice were sacrificed under ether anesthesia, and circular plugs 5.0 mm in diameter were removed from both ears using a punching apparatus. Mouse blood was taken and centrifuged at $1500 \times g$ for 10 min, and the supernatant was used as the serum. The spleen was also taken for determination of natural killer cell activities. The weights of the right and left ears (WR and WL, respectively) were measured and the ear swelling ratio was calculated using the following equation:

$$\text{Ear swelling ratio (\%)} = \frac{\{(WR_{\text{sample}} - WL_{\text{sample}}) / WL_{\text{sample}}\}}{\{(WR_{\text{control}} - WL_{\text{control}}) / WL_{\text{control}}\}} \times 100.$$

EGCG was dissolved in 0.5% tragacanth gum solution

and administered orally to mice 1 h prior to the challenge at a dose of 50 mg/kg body weight. A control experiment was performed with 0.5% tragacanth gum solution. The number of mice in each group was 8.

2.3 Determination of cytokines in mouse serum

The levels of IL-12, γ -IFN, and IL-2 in mouse serum were determined by enzyme-linked immunosorbent assay (ELISA) with a Murine IL-12 ELISA Development Kit (Pepro Tech EC, Ltd., London, UK), Chemikine™ Mouse IFN γ Sandwich ELISA Kit (Chemicon International Inc., Temecula, CA, USA), and TiterZyme EIA (mouse Interleukin-2 assay) kit (Assay Designs, Inc., Ann Arbor, MI, USA), respectively.

2.4 Determination of natural killer cell activities in mouse spleen cells

The cytolytic function of NK cells in mouse spleen was determined by a Cr⁵¹ release assay with YAC-1 target cells, murine lymphoma cells, labeled with Cr⁵¹. The assay was performed at Mitsubishi Kagaku Bio-Clinical Laboratories, Inc., Tokyo, Japan.

2.5 Determination of antioxidative activities in mouse serum

Male ddY mice, 6 weeks old, were purchased from Japan SLC, Inc. The supernatant of 5% mouse brain homogenate in 0.04 M phosphate buffer (pH 7.4) was prepared and 0.25 mL was added to 0.5 mL of phosphate buffer. The mixture with or without 3 mL of serum obtained from mice used in the allergy experiment was autooxidized at 37°C for 60 min[10]. The level of lipid peroxide in the reaction mixture was determined by the thiobarbituric acid method[11] and the inhibitory activities of mouse serum against lipid peroxidation were evaluated.

2.6 Two mouse models for simple

inflammatory response

Two simple inflammation models, *i.e.*, arachidonic acid and croton oil-induced edema of the ear in mice, were used[12 – 14]. Briefly, aliquots of 20 μ L of a 12.5-mg/mL solution of arachidonic acid (Sigma-Aldrich Chemical Co.) and/or 20 mg/mL of croton oil solution (Wako Pure Chemical Ind., Osaka, Japan) in 20% ethanol/acetone were applied to both sides of the right ear of 5-week-old male ICR mice (Japan SLC Inc.). One hour after treatment, the mice were sacrificed under ether anesthesia, and circular plugs 5.0 mm in diameter were removed from both ears using a punching apparatus. Ear swelling ratios were determined by the same method as in the model of type IV allergy. EGCG and hydrocortisone, a well-known steroid-type antiinflammatory agent, were dissolved in 0.5% tragacanth gum solution and administered orally to mice 1 h prior to treatment with arachidonic acid and/or croton oil as a dose of 50 mg/kg body weight. A control experiment was performed with 0.5% tragacanth gum solution. The number of mice in each group was 5.

2.7 Statistical Analysis

Differences between the appropriate experimental groups were analyzed by Student's *t* test, and *P* < 0.05 was considered statistically significant.

3. Results and Discussion

3.1 Effects of EGCG on serum cytokine levels in mice with type IV allergy

When administered orally at a dose of 50 mg/kg body weight, EGCG exhibited significant antiallergic activities, as described in our previous report[6]. In the present study, ear swelling ratios of allergic mice and EGCG-administered allergic mice were 100% \pm 18.6% and 56.7% \pm 24.6%, respectively. The rate of inhibition of type IV allergy was 43.3%. The effects of

oral administration of EGCG on the serum levels of IL-12, γ -IFN, and IL-2 in mice with oxazolone-induced type IV allergy are shown in Figure 2. These cytokines are known to be important for the allergic process. Serum IL-12 levels of allergic mice were significantly higher than those of normal controls. This increase was significantly prevented by the oral administration of EGCG at 50 mg/kg body weight. IL-12 is a cytokine secreted by APC and induces the differentiation of native T cells into Th1 cells. Serum γ -IFN levels were also significantly higher in allergic mice than in normal controls. This increase was also significantly prevented by the oral administration of EGCG at 50 mg/kg body weight. The proinflammatory cytokines γ -IFN and TNF- α have multiple actions, such as the stimulation of macrophages, Th1 cells, and CTL, and the suppression of type 2 T helper cells. Serum IL-2 levels in allergic mice were significantly lower than those of normal controls. This decrease was significantly prevented by

the oral administration of EGCG at 50 mg/kg body weight. IL-2 produced by Th1 cells and MNC stimulated CTL and NK cell activities. These results indicated that EGCG has some modulatory effects on the immune responses in mice with oxazolone-induced type IV allergy. Particularly, the production and/or release of IL-12 from APC and γ -IFN from Th1 cells and macrophages were efficiently inhibited by EGCG. These suppressive effects of EGCG on the induction of proinflammatory cytokines were thought to contribute to the preventive effects against type IV allergy in mice.

It was reported in some studies using cultured cells and/or gene-deficient mice that catechins inhibited the activation of nuclear factor-kappa B in macrophages and Th1 cells, which is a transcription factor associated with the expression of some proinflammatory cytokines, including IL-12, γ -IFN, and TNF- α , as well as inducible nitric oxide synthase (iNOS)[15 – 17]. In the present study, the same functions of catechins were observed in the type IV allergic mouse model. In addition, inhibitory effects of green tea extract on hyaluronidase are thought to contribute to its antiinflammatory effects[18].

3.2 Effects of EGCG on spleen NK cell activities in mice with type IV allergy

The spleen NK cell activities in mice with oxazolone-induced type IV allergy are shown in Figure 3. The activities were significantly lower in allergic mice than in normal controls. This lowering of spleen NK cell activities was significantly prevented by oral administration of EGCG at 50 mg/kg body weight. In general, IL-2 and NK cell activities are thought to play important roles in cell-mediated immunity. As NK cell activities could be stimulated by IL-2, the changes in NK cell activities associated with changes in serum IL-2 levels are reasonable. It

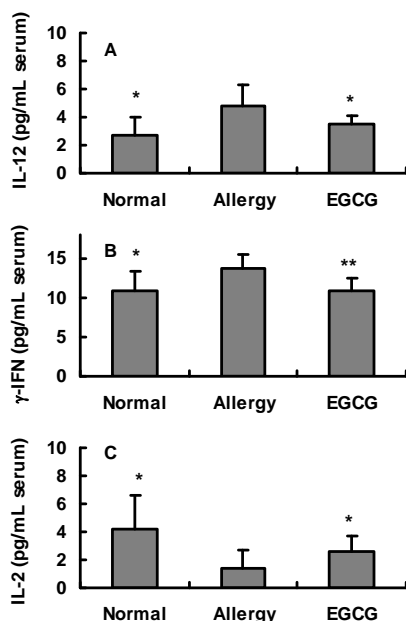


Figure 2 Effects of the oral administration of EGCG on levels of several cytokines in the sera of 5-week-old male ICR mice with oxazolone-induced type IV allergy. A, IL-12; B, γ -IFN; C, IL-2. Mean \pm SE. *n* = 8. Dose: 50 mg/kg body weight. Significant differences from “Allergy” group; * *P* < 0.05, ** *P* < 0.01.

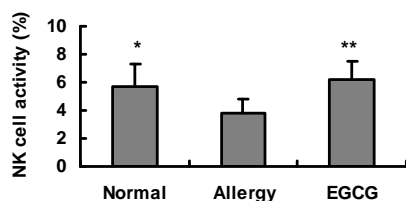


Figure 3 Effects of oral administration of EGCG on NK cell activities in the spleen cells of 5-week-old male ICR mice with oxazolone-induced type IV allergy. Mean \pm SE. $n = 8$. Dose: 50 mg/kg body weight. Significant differences from "Allergy" group; * $P < 0.05$.

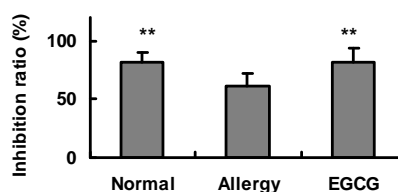


Figure 4 Effects of the oral administration of EGCG on antioxidative activities in the sera of 5-week-old male ICR mice with oxazolone-induced type IV allergy. Mean \pm SE. $n = 8$. Dose: 50 mg/kg body weight. Significant differences from "Allergy" group; * $P < 0.05$, ** $P < 0.01$.

was reported that the changes in NK cell activities had little effect on the degree of delayed type hypersensitivity, such as mouse arthritis[19,20], and the lowering of NK cell activities was not related to the severity of inflammation in oxazolone-induced ear edema[21]. These data suggest the complexity of type IV allergic responses, such as oxazolone-induced ear edema.

3.3 Effects of EGCG on serum antioxidative activities in mice with type IV allergy

The antioxidative activities in the serum of mice with oxazolone-induced type IV allergy are shown in Figure 4. The activities were significantly lower in allergic mice than in normal controls. The lowering of serum antioxidative activities was significantly prevented by oral administration of EGCG at 50 mg/kg body weight. The excess production of superoxide anion radicals and nitric oxide by macrophages and neutrophils is thought to provoke inflammation in the neighboring tissues[22,23]. It is well known that tea catechins, including EGCG, exhibit strong antioxidative activities[24,25]. Nitric oxide produced by iNOS would be converted to DNA-damaging and carcinogenic peroxynitrite and nitrite. EGCG inhibits lipopolysaccharide and γ -IFN-induced nitrite production by mouse peritoneal cells[26]. The enhancement of serum antioxidant activities in mice administered EGCG was also

thought to contribute to the antiallergic effects observed in this study.

3.4 Effects of EGCG on simple inflammation models in mice

It was reported that the inflammation caused by oxazolone sensitization could be mediated by the metabolites of arachidonic acid obtained with 5-lipoxygenase (5-LOX) and cyclooxygenase (COX)[27]. The enzymatic oxidation of arachidonic acid is important to produce chemical mediators of inflammation, such as leukotrienes and prostaglandins. Catechins were reported to inhibit the activities of LOX and COX [28 – 30].

The inhibitory effects of EGCG on two simple inflammation models of mouse ear edema induced by arachidonic acid or croton oil are shown in Figure 5. Some inhibitors of COX are effective in the arachidonic acid-induced model, whereas some inhibitors of LOX and/or COX are effective in the croton oil-induced model. Oral administration of EGCG at a dose of 50 mg/kg body weight significantly suppressed ear edema induced by arachidonic acid. Ear edema induced by croton oil also tended to be prevented by the oral administration of EGCG, although the effect was not significant. In a previous study, tea polyphenols were shown to suppress phorbol ester-induced mouse dermal inflammation by inhibiting the activities of LOX and

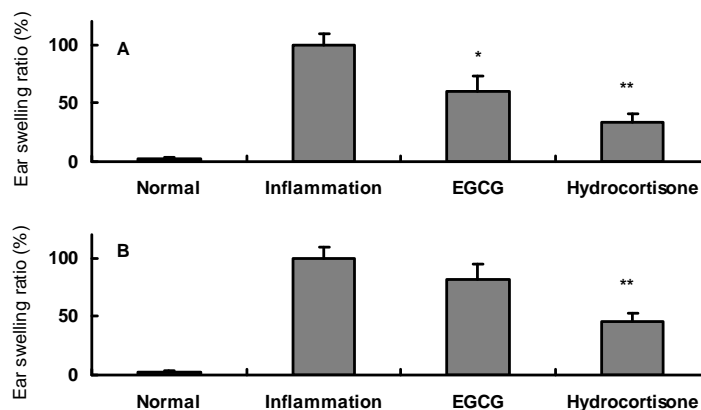


Figure 5 Effects of the oral administration of EGCG on simple inflammatory models in 5-week-old male ICR mice. A, Arachidonic acid-induced edema; B, Croton oil-induced edema. Mean \pm SE. $n = 5$. Dose: 50 mg/kg body weight. Significant differences from “Allergy” group; * $P < 0.05$, ** $P < 0.01$.

COX[28]. Croton oil generally includes phorbol esters. Hydrocortisone significantly suppressed both types of edema at the same dose as EGCG. The positive effects of EGCG on serum antioxidative activities in mice may also help inhibit the enzymatic oxidation of arachidonic acid.

4. Conclusions

In summary, the effects of EGCG on serum cytokine levels, spleen NK cell activities, and serum antioxidant activities in mice with type IV allergy induced by oxazolone and on two simple inflammation models in mice were investigated. We propose a scheme of possible preventive effects of EGCG against mouse type IV allergy induced by oxazolone and the inflammation in Figure 6. EGCG is thought to play a prominent role in the anti-allergic effects mainly *via* the following four functions: (1) inhibition of production and/or release of IL-12 secreted from APC, resulting in suppression of Th1 cell production; (2) inhibition of production and/or release of γ -IFN secreted from Th1 cells and macrophages, resulting in suppression of stimulation of Th1 cells and macrophages; (3) suppression of oxidative stress induced by active oxygen species; and

(4) inhibition of the activities of LOX and COX, resulting in decreases in the levels of proinflammatory chemical mediators. In addition, EGCG showed immunomodulatory effects on the decreases in serum IL-2 levels and spleen NK cell activities in mice with type IV allergy. Further investigations of the absorption, distribution, and metabolism of EGCG

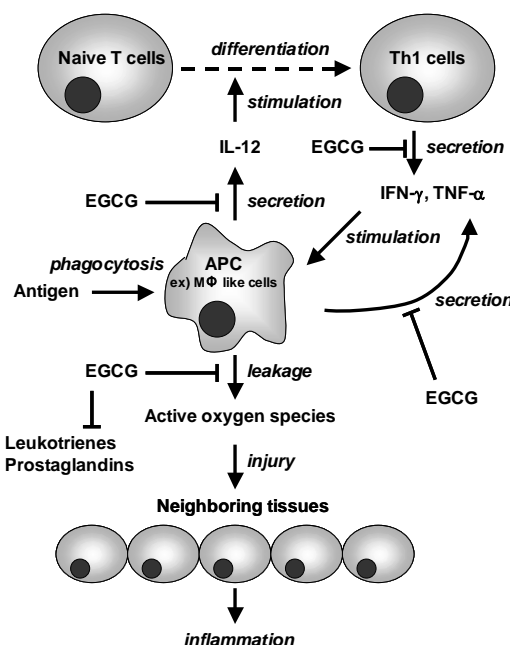


Figure 6 Preventive effects of EGCG against mouse type IV allergy induced by oxazolone. —| The symbols show the expected active points of EGCG for suppression of type IV allergy in this study.

after oral administration are necessary to clarify the mechanisms of the antiallergic effects.

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オキサゾロン誘発マウスIV型アレルギーに対する(-)-エピガロカテキン

-3-O-ガレートの抑制作用とその抗炎症作用

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要旨

雄性ICR系マウスにおけるオキサゾロン誘発IV型アレルギーと2種類の単純炎症マウスモデルに対する(-)-エピガロカテキン-3-O-ガレート(EGCG)の抑制作用を検討した。インターリューキン-12 (IL-12)および γ -インターフェロン(γ -IFN)の血清レベルは、健常マウスに比較してIV型アレルギーによる激しい耳介浮腫を起こしたマウスで有意に上昇した。EGCGの経口投与は、50 mg/kg体重の投与量でこれらのレベルの上昇を抑制した。アレルギーを発症したマウスで見られた血清IL-2レベル、脾臓ナチュラルキラーNK細胞活性および血清抗酸化活性の低下も、EGCGの経口投与によって予防された。さらに、同用量のEGCGの経口投与は、アラキドン酸誘発のマウス耳介浮腫を抑制し、ハズ油誘発のマウス耳介浮腫に対しても抑制する経口を示した。これらの結果は、EGCGの抗アレルギー作用機序が、アレルギー誘発マウスにおけるサイトカインとケミカルメディエーター量の変動と抗酸化状態の保持によるものであることを示唆している。

キーワード：茶カテキン, IV型アレルギー, 炎症, マウス