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Lack of chemopreventive effects of α-eleostearic acid on 7,12-dimethylbenz[*a*]anthracene (DMBA) and 1,2-dimethylhydrazine (DMH)-induced mammary and colon carcinogenesis in female Sprague–Dawley rats

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Abstract

α-Eleostearic acid is one of the conjugated linolenic acids from tung oil, which is obtained from the seeds of *Aleurites fordii*. The effects of dietary α-eleostearic acid (18:3, n-5) on the post-initiation period of 7,12-dimethylbenz[*a*]anthracene (DMBA) and 1,2-dimethylhydrazine (DMH)-induced mammary and colon carcinogenesis were examined using female Sprague–Dawley (SD) rats. For initiation, rats were given subcutaneous injections of 40 mg/kg body weight (5 times) and 20 mg/kg body weight (3 times) of DMH during the age of 6–8 weeks and a single intragastric administration of 50 mg/kg body weight of DMBA at 9 weeks. Then, the animals were treated with 0%, 0.01%, 0.1% or 1.0% α-eleostearic acid for 34 weeks. Control rats received the basal diet alone or 1.0% α-eleostearic acid without prior initiation treatment. All surviving animals were killed at week 37 of the experiment. There were no statistically significant alterations in any of the parameters for either mammary or colon tumors. These results thus indicate that α-eleostearic acid does not exert clear modification effects on DMBA and DMH-induced mammary and colon carcinogenesis, at least under the present experimental conditions.
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Keywords: α-Eleostearic acid; Tung oil; Conjugated linolenic acid; 7,12-Dimethylbenz[*a*]anthracene (DMBA); 1,2-Dimethylhydrazine (DMH); Mammary carcinogenesis; Colon carcinogenesis

1. Introduction

α-Eleostearic acid (9*c*, 11*t*, 13*t*-octadecatrienoic acid, 18:3, n-5), constitutes approximately 80% of total fatty acids of tung oil, obtained from the seeds of *Aleurites fordii* (Holmes et al., 1954). It also accounts for approximately 30–50% of the fatty acids in snake gourd (*Trichosanthes diocia*) and bitter gourd (*Momordica charantia*) oils (Dhar and Bhattacharyya, 1998).

Conjugated fatty acids are a general term for polyunsaturated fatty acids, which exist as positional geometric

Abbreviations: ACF, aberrant crypt foci; AOM, azoxymethane; CLA, conjugated linoleic acid; CLNA, conjugated α-linolenic acid; COX, cyclo-oxygenase; DHA, docosahexaenoic acid; DMBA, 7,12-dimethylbenz[*a*]anthracene; DMH, 1,2-dimethylhydrazine; EPA, _eicosapentaenoic acid; H&E, hematoxylin and eosin; IQ, 2-amino-3-methylimidazo[4,5-*f*]quinoline; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine; SD, Sprague–Dawley.

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isomers with several double bonds. One form, conjugated linoleic acid (CLA; a mixture of mainly 9*c*, 11*t*-octadecadienoic acid, 18:2, n-6), abundant in beef, cheese and butterfat, is known to have bioactivity in humans. For instance, effects on cancer, atherosclerosis, body fat mass and diabetes have been demonstrated in experimental animals (Belury, 2002). In the two-stage mammary carcinogenesis model, CLA inhibited both initiation and post-initiation stages (Ip et al., 1994; Ip et al., 1996) in rats initiated with 7,12-dimethylbenz[*a*]anthracene (DMBA). It also reduced induction of rat colon aberrant crypt foci (ACF) by 2-amino-3-methylimidazo[4,5-*f*]quinoline (IQ) in the initiation stage (Liew et al., 1995). In contrast, the non-conjugated linoleic acid has been found to consistently enhance mammary (Fischer et al., 1992; Ip et al., 1985; Welsch, 1992) and colon (Minoura et al., 1988; Reddy and Sugie, 1988; Reddy et al., 1991) carcinogenesis in rodents.

Focusing on trienoic fatty acids, a perilla oil-supplemented diet, rich in α-linolenic acid (18:3, n-3), has been demonstrated to inhibit DMBA and 1,2-dimethylhydrazine (DMH)-induced rat mammary and colon carcinogenesis (Hirose et al., 1990). Dietary perilla oil may also suppress the development of ACF (Onogi et al., 1996) and colon tumors in rats (Narisawa et al., 1994). In addition, a diet rich in conjugated α-linolenic acid (CLNA) derived from perilla oil was found to decrease 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP)-induced rat mammary carcinogenesis in the post-initiation period, with parallel inhibition of cell proliferation (Futakuchi et al., 2002). Moreover, CLNA isolated from the seeds of bitter gourd inhibited azoxymethane (AOM)-induction of rat ACF in the colon when given in the initiation period (Kohno et al., 2002).

Comparing three types of conjugated fatty acids prepared with alkaline treatments, Igarashi and Miyazawa (2000) could demonstrate that the trienoic fatty acids, α-eleostearic acid and CLNA (prepared from α-linolenic acid), are both more cytotoxic to human tumor cells than CLA. Therefore, α-eleostearic acid might be expected to be a potent candidate dietary factor for cancer chemoprevention.

In the present experiment, the effects of dietary α-eleostearic acid extracted from tung oil on DMBA and DMH-induced mammary and colon carcinogenesis when given in the post-initiation period were, therefore, examined in female Sprague–Dawley (SD) rats.

2. Materials and methods

2.1. Chemicals

DMBA and DMH were obtained from Sigma Chemical Co. (St. Louis, USA) and Nacalai Tesque, Inc. (Kyoto, Japan), respectively. α-Eleostearic acid, approximately 70.7% purity, was kindly supplied by Asahi Denka Co., Ltd. (Tokyo, Japan). It was obtained by purifying tung oil without addition of antioxidants. The chemical structure of α-eleostearic acid is shown in Fig. 1.

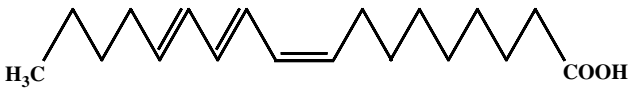

Fig. 1. Chemical structure of α-eleostearic acid.

2.2. Animals and diets

One hundred female Crj:CD(SD) rats were obtained from Charles River Japan Inc. (Tokyo, Japan) at 5 weeks of age and acclimatized for approximately 1 week before being assigned to 6 groups. They were housed in plastic cages (5 rats/cage) with soft chips for bedding in a room with a barrier system and maintained under the following conditions: temperature (23 ± 2), relative humidity ($60 \pm 5\%$), ventilation frequency (18 times per hour) and a 12-h illumination. Normal powder diet (CRF-1, Oriental Yeast Co., Tokyo, Japan) and tap water were available ad libitum. The Animal Care and Utilization Committee for the National Institute of Health Sciences, Japan, approved the protocols for this study.

2.3. Experimental design

The experimental design is shown in Fig. 2. The animals were randomly divided to give equal weight distributions into 4 groups (groups 1–4) consisting of 20 animals each and 2 groups (groups 5 and 6) consisting of 10 animals each. From the age of 6 weeks, groups 1–4 received subcutaneous injections of 40 mg DMH/1 ml saline/kg body weight (the days 0, 2, 4, 7 and 9) for initiation. Dose level of DMH was selected according to the report that 5 times injections of this dose level could not induce colon tumor (Kimoto et al., 2001). Therefore, we planed additional 3 times injections of 40 mg/kg DMH before the start of this experiment. However, this dose level was found to be excessively toxic. Then, the dose level of DMH was lowered to 20 mg/1 ml saline/kg body weight thereafter (the days 15, 18 and 21). In addition, they were given a single intragastric administration of 50 mg DMBA/5 ml sesame oil/kg body weight at the age of 9 weeks. Some animals undergoing treatment died or became moribund during the initiation period. Therefore, the number of animals on each initiated group was reduced to 17 at the beginning of the post-initiation period. From week 4, the four groups of rats received basal diet containing 0%, 0.01%, 0.1% or 1.0% α-eleostearic acid (groups 1–4, respectively) for 34 weeks. The remaining two groups

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