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Effects of Caffeine and Dietary Fat on Mouse Mammary Development

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ABSTRACT

This study was conducted to examine the effect of caffeine and three dietary levels of fat, i.e., 0%, 5% and 20% on mammary gland development. Mice were assigned to three groups (dietary levels 0%, 5%, 20% fat), and treated caffeine of half within the each group. Caffeine-treated mice with 0% or 20% fat levels significantly increased 4th mammary gland development in comparison with that of no caffeine -treated mice ($P<0.05$). Caffeine-treated mice significantly increased DNA contents of 4th mammary gland in comparison with that of no caffeine-treated mice ($P<0.05$), and DNA contents of mammary gland increased as fat levels increased within caffeine-treated or no caffeine-treated group. nteraction effect was shown between caffeine and 20% fat diet, [(20% fat+caffeine) − (20% fat + no caffeine) vs (0% fat + caffeine) − (0% fat + no caffeine)] ($P<0.01$). Conclusively, caffeine significantly increased mouse mammary gland development possibly by inhibiting phosphodiesterase activity, and dietary fat supplements increased mammary gland development as the fat content of the diet increased from 0 to 20%. The stimulatory effect of caffeine in mammary development interacted with high level of fat diet. (Key words: Caffeine, Dietary fat, Mammary development, Mammary tissue)

Ⅰ. INTRODUCTION

Caffeine (1,3,7-trimethylxanthine), is present in a great variety of dietary sources, such as coffee, tea, beverages and some medications, which are widely consumed by the general population and even during gestational periods. Caffeine consumption by human populations has been associated with an increase risk in the development of benign breast disease (Wolfrom and Welsch, 1990). In addition, caffeine consumption by experimental animals resulted in a significant increase in the normal growth of the mammary glands (Sheffield, 1991; Vander-Pleog et al., 1992). Methylxanthines are capable of increasing intracellular cyclic AMP levels, possibly inhibiting cyclic AMP phosphodiesterase activity (Vernkos-Danellis and Harris, 1968). However, xanthines are able to antagonize both stimulatory and inhibitory adenosine receptors (Daly, 1982). Cholera toxin, prostaglandin (PGE1) and/or isobutylmethylxanthine (IBMX) stimulate mammary epithelial cell growth (Ethier et al., 1987, 1989). In addition, IBMX was found to augment growth when cells were cul-

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tured in the presence of both EGF and linoleate or PGE_2 (Imagawa et al., 1988). Agents that increase intracellular cyclic AMP have been shown to increase mammary development, both *in vivo* and *in vitro* (Stampfer, 1982; Silverstein et al., 1984). Adenylate cyclase and protein kinase A activities increase during pregnancy in mice and rat mammary glands (Rillema, 1976; Sapag-Hagar and Greenbaum, 1973; Sharoni et al., 1984).

It has been known that high levels of dietary fat enhance the mammary development of mammary tumors in rat and mice (Carroll, 1981; Welsch and Aylsworth, 1983). In addition, the level of dietary fat affects in situ mammary development and growth responsiveness to mammogenic hormones (Welsch et al., 1985). It appears that dietary fats rich in polyunsaturated fatty acids, especially those of the 18:2 ω6 and 20:4 ω6 series, activators of protein kinase C, are most effective in the enhancement of mammary tumorigenesis (Chan et al., 1983; Murakami and Routtenberg, 1985; Wooten and Wrenn, 1988; Imagawa et al.1990). In addition, PKC activity in epidermal cells from mice fed the high-fat diet was higher than activity from mice fed the control diet (Birt et al., 1992). Protein kinase C activity in the mammary gland has been shown to remain high in the virgin and during early pregnancy before declining steadily during late pregnancy and lactation (Holladay and Bolander, 1986). Single effect of dietary fat or caffeine consumption on normal mammary growth has been examined by a couple of laboratories, however, the additive or the interactive effect of caffeine with various fat levels in the presence of full ovarian steroids treatment was few. The objective of this study is to examine if caffeine consumption can alters mammary development induced by the dietary fat levels in the presence of estradiol + progesterone and the altered mammary development is subsequently changed in the presence of other mammogenic hormones.

Ⅱ. MATERIALS AND METHODS

1. Animals and Treatments

Three week old female BALB/c mice were obtained from Daehan Experimental Animal Center in Korea. They were housed in a temperature controlled (22℃) and light-controlled (12h/day) room. Mice were divided into two caffeine treatment groups, i.e., 1) no caffeine and 2) caffeine, and each caffeine treatment group subdivided into three dietary fat levels, i.e., 1) 0% fat, 2) 5% fat and 3) 20% fat. Caffeine (methylxanthines) was added to their drinking water at a concentration of 500 mg/L (2.6 mM). Caffeine treatments were for 30 days and drinking water solution (containing caffeine) was made fresh twice per week. Fat was soybean oil and was added to the basal diet. The basal diet was a semipurified fat-free diet obtained from Samyang Oil Feed Company in Korea. The protein content of the basal fat-free diet is 21.7%. The experimental fat diets were fed ad libitum for 30 days. Ten days prior to the last day of caffeine treatment, mice of each group received daily s.c. injection of 17 β-estradiol (1 μg) and progesterone (1 mg). The caffeine, 17 β-estradiol and progesterone were purchased from Sigma Chemical Co., St. Louis, MO, USA. The steroids were mixed with gum Arabic (gum arabic:progesterone, 0.1 : 1.0) (Sigma Chemical Co., St. Louis, MO, USA). The mixture of gum arabic and hormone was dissolved in 0.9% NaCl solution and kept at 4℃ for temporary conservation. At sacrifice, one mammary gland (of each 4th gland pair, inguinal mammary glands) was excised, weighed and prepared for whole-mount evaluation, and the contralateral gland was examined for DNA content measurement.

2. Whole-Mount Mammary Gland Evaluation

One gland from each 4th mammary gland was fixed in glacial acid : 100% ethanol (1 : 3, v/v),

stained with alum carmine (Sigma Chemical Co., St. Louis, MO, USA), and examined by whole-mount evaluation (Banerjee et al., 1976). Mammary development was assessed on a scale of 1 to 6 as previously described (Welsch and Gribler, 1973). Mammary glands were coded and rated for development according to the following criteria: 1, few ducts, few or no end buds; 2, moderate duct growth, moderate number of end buds; 3, numerous ducts and branches, many end buds; 4, numerous ducts and branches, minimal lobuloalveolar growth; 5, numerous ducts and branches, moderate lobuloalveolar growth; and 6, numerous ducts and branches, dense lobuloalveolar growth as in the late pregnancy.

3. DNA Content Measurement

4^{th} mammary glands were homogenized in saline. Protein and nucleic acids were precipitated with an equal volume of 20% trichloroacetic acid. Lipids were removed by sequential washes with methanol :chloroform (2:1, vol:vol) and 100% ethanol (twice each). The DNA was extracted by heating for 45 min in 5% perchloric acid (70℃) and was estimated by the diphenylamine reaction (Burton, 1956).

4. Statistical Analysis

Data were analyzed by analysis of variance using a randomized complete block design model. Interaction effects (non-additive effect) between caffeine and fat diets were evaluated by orthogonal contrasts by comparing DNA contents of 4^{th} mammary glands in mice fed caffeine with or without fat diet. Means were compared using planned comparisons. All comparisons were 2-sided and differences were considered significant at a 5% level, unless stated otherwise (Snedecor and Cochran, 1980).

Ⅲ. RESULTS

1. Influence of Caffeine and Dietary Fat Levels on Average Daily Gain and Mammary Fat Pad Weight

Caffeine treatment significantly decreased average body weight on 30 day after the start of caffeine feeding ($P<0.05$). Within caffeine treatments, mice fed 20% fat diet significantly increased body weight compared to those fed 0 or 5% fat diets on 30 day after the start of fat and caffeine feeding ($P<0.05$), however, fat diet did not affect on body weight without caffeine feeding ($P>0.05$, Fig. 1). Similar results were obtained when average daily gains were compared between caffeine-treated group and no caffeine-treated group. The differences of average daily gains between no caffeine-treated group and caffeine-treated group at 0, 5 and 20% fat diets were 0.72, 1.07 and 0.72g, and the daily gains of caffeine-treated group were less than those of no caffeine-treated group in all fat diet levels ($P<0.05$, Fig. 2). Within caffeine group, 20% fat diet signi-

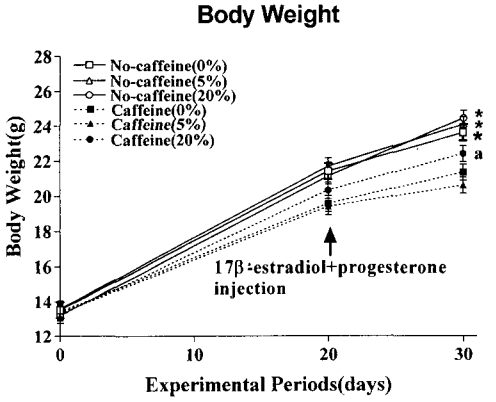

Fig. 1. Influence of caffeine and dietary fat levels on body weight in Balb/c mice. No-caffeine treatment more increased body weight than that of caffeine treatment. *; significantly different from the caffeine-treated mice within each dietary fat level on final mean body weights ($P<0.05$). a; significantly different from 0% or 5% fat diet effect within the caffeine group ($P<0.05$). The data are presented as means ± SE, n = 10.

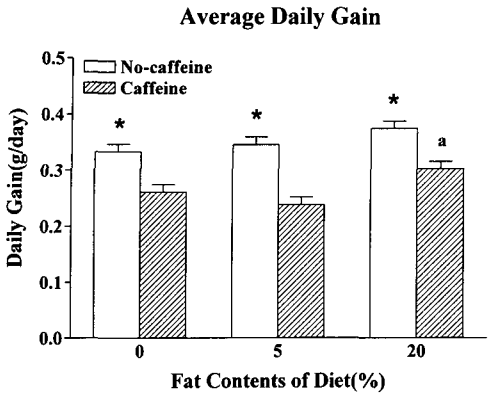

Fig. 2. Influence of caffeine and dietary fat levels on average daily gain in Balb/c mice. No-caffeine treatment more increased average daily gain than that of caffeine treatment. *; significantly different from the caffeine-treated mice within each dietary fat level (P<0.05). a; significantly different from 0% or 5% fat diet effect within the caffeine group. The data are presented as means ± SE, n=10.

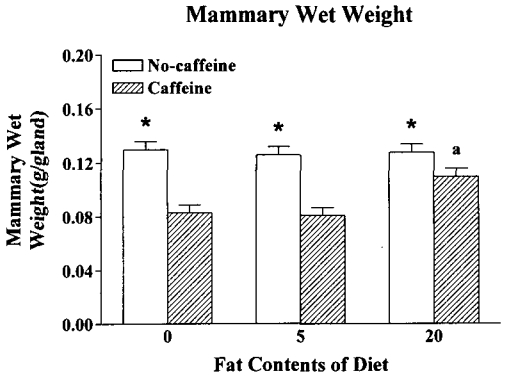

Fig. 3. Influence of caffeine and dietary fat levels on mammary wet weight in Balb /c mice. No-caffeine treatment more increased mammary wet weight than that of caffeine treatment. *; significantly different from the caffeine-treated mice within each dietary fat level (P<0.05). a; significantly different from 0% or 5% fat diet effect within the caffeine group (P<0.05). The data are presented as means ± SE, n = 10.

ficantly increased the average daily gain compared with those of 0 and 5% fat diet groups (P<0.05), however, within no-caffeine group the fat contents of diet did not change the average daily gain (P> 0.05). The average daily feed intakes of mice fed caffeine slightly decreased to those of mice fed no caffeine (data not shown, P<0.1). Caffeine is a bitter-tasting plant alkaloid. Thus, either voluntary feed intake or weight gain should be slightly decreased.

Fig. 3 is to show the change of 4th mammary gland wet weight of mice fed dietary fat with or without caffeine treatment. Caffeine treatments significantly reduced 4th mammary gland wet weights to those of no-caffeine treated groups at 0%, 5% and 20% fat diets levels (P<0.05). There were no significant differences in mammary wet weights among fat diet levels within no-caffeine treated groups, however, mice fed 20% fat diet significantly increased mammary wet weight compared to those fed 0 or 5% fat diet within caffeine group (P<0.05). These results were similar to the change of body weight and average daily gain described in previous results.

2. Influence of Caffeine and Dietary Fat Levels on Mammary Development Score and Mammary DNA Contents

Mammary gland development scores (±SE) for caffeine-treated mice fed 0, 5 and 20% fat diets were 3.28±0.21, 3.55±0.25, and 4.76±0.22, respectively; for no caffeine-treated mice fed 0, 5, and 20% fat diets, mammary gland development scores were 2.61±0.20, 3.70±0.10, and 4.29±0.15, respectively (Fig. 4). Within caffeine treatments, 0% fat diet reduced mammary development score when compared to that of mice fed 20% fat diet, and within no caffeine-treated mice, 0% fat diet also reduced mammary development score when compared to that of mice fed 5 or 20% fat diet (P<

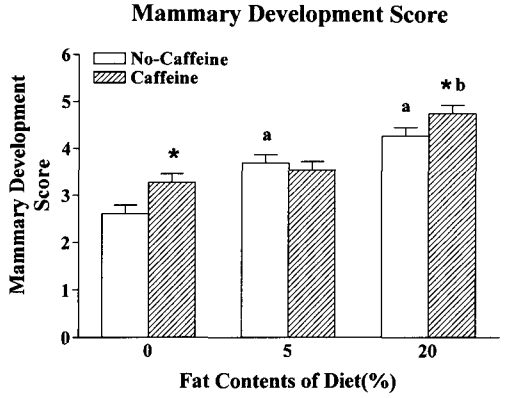

Fig. 4. Effect of caffeine and dietary fat levels on 4th mammary gland development in Balb/c mice. *; significantly different from no-caffeine group within each dietary fat level (P<0.05). a; significantly different from 0% fat diet within no-caffeine group (P<0.05). b; significantly different from 0% or 5% fat diet within caffeine group (P<0.05). The data are presented as means ±SE, n = 10.

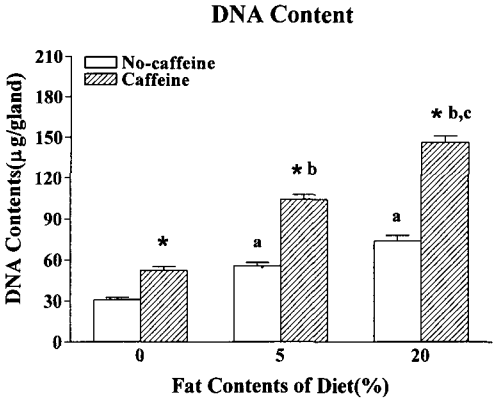

Fig. 5. Effect of caffeine and dietary fat levels on 4th mammary gland DNA contents in Balb/c mice. *; significantly different from no caffeine-treated mice within each dietary fat level (P<0.05). a; significantly different from 0% fat diet within no-caffeine group (P<0.05). b; significantly different from 0% fat diet within caffeine group (P<0.05). c; Interaction effect [(20 % fat + caffeine) − (20% fat + no-caffeine) vs (0% fat + caffeine) − (0% fat+no-caffeine)] (P<0.05). The data are presented as means ± SE, n = 10.

0.05). Mammary development score for caffeine -treated mice (compared to no-caffeine treatment) was significantly increased in mice fed 0 and 20 % fat diet (P<0.05).

Similar results were obtained when mammary developments were measured with DNA contents by colorimetric assay. DNA contents (±SE) for caffeine-treated mice fed 0, 5 and 20% fat diets were 52.38±2.84, 104.38±3.51 and 146.46±4.66 μg/gland, respectively, and those for no caffeine-treated mice fed 0, 5 and 20% fat diet were 30.81±1.52, 55.81±2.45 and 74.31±4.0 μg/gland, respectively. DNA contents of 4th mammary glands in mice fed 5 and 20% fat diet were higher compared to mice fed 0% fat diet both in caffeine-treated mice and in no caffeine-treated mice (P<0.05). In addition, DNA contents in mice fed 20% fat diet were much higher than those in mice fed 5% fat diet in caffeine-treated mice, and DNA contents were significantly increased as diet fat percentages increased in caffeine-treated mice. In interesting, there was significant interaction effect between high fat diet (20%) and caffeine treatment (P<0.01). Without diet fat (0%), caffeine alone increased DNA content from 30.81±1.52 μg/gland to 52.38±2.45 μg/gland. When mice were fed with 20% fat diet, the increase of DNA content was from 74.3±4.0 μg/gland to 146.46±4.66 μg/gland. Thus, caffeine alone increased DNA contents 21.57±1.04 μg/gland, while this magnitude was increased to 73.16±2.9 μg/gland with 20% fat diet (P<0.01).

Ⅳ. DISCUSSION

Caffeine treatment significantly decreased the average daily gain and the final average body weight on 30 day after the start of caffeine feeding. In

addition, the average daily feed intakes of caffeine -treated mice slightly decreased to the no-caffeine -treated mice. These results were similar to those of Jorda et al. (1989), and Li and Hacker (1995) studies that caffeine decreased body weights. Caffeine is a bitter-tasting plant alkaloid. Thus, either feed intake or weight gain should be slightly decreased. Similar results obtained with mammary gland wet weight. Caffeine has previously been shown to affect adipocytes lipolysis and plasma free fatty acids (Bellet et al., 1968), and caffeine excreted significant amounts of calcium in the urine (Massey and Wise, 1984). Whether this mechanism is partially involved in caffeine mediation of the reduced body weight and mammary wet weight is not clear.

The 4^{th} mammary development score and mammary DNA content in caffeine-treated mice was greater than that in no caffeine-treated mice, although the body weight, average daily gain and mammary wet weight of caffeine-treated mice were smaller than those of the others. These results were in accordance with those of pregnant gilts (Li and Hacker, 1995) and mouse (Sheffield, 1991). The higher mammary development score and DNA contents with caffeine treatment were due to greater increase of whole mount mammary size and increase of the proportion of parenchyma to stroma of those of no-caffeine-treated mice. In interesting, caffeine-treated mice fed 20% fat diet showed the synergistic effects in increase of mammary size and were more responsive than those of caffeine alone treatment. These results indicated that caffeine increased mammary tissue sensitivity to fat diet, and the sensitivity might be greater in the stimulation of estradiol+progesterone. In previous studies, the steroid hormones such as estradiol and progesterone, had synergistic effect in the stimulation of mammary development with cAMP active agents or protein kinase A activating pathway (Sheffield, 1989, 1991). Caffeine is known as to increase of intracellular cAMP concentration through at least inhibiting phosphodiesterase activity (Sheffield, 1991).

Thus, the full injection of estradiol+progesterone might be positive stimulator to the mammary growth response of caffeine-treated mice fed 20% fat diet. In the present study, dietary fat source was soybean oil. The general fatty acid compositions and levels of fatty acids of soybean oil were approximately 64% of polyunsaturated fatty acids (PFA), 21% of monounsaturated fatty acids and 15% of saturated fatty acids, and about 56% of PFA was linoleic acids (18:2:ω6, ω9) (Dziezak, 1989; Im, 1993). It has been known that addition of high level of linoleic acid to *in vitro* mammary cell culture significantly increased mammary epithelial cell growth (Bandyopadhyay et al., 1987).

The stimulatory effects of fat diets on mammary development may be explained as follows. First, high fat diet (20%) containing PFA may be transformed to prostaglandin E_1 or E_2 (Bandyopadhyay et al., 1987), and stimulate mammary growth by activation cAMP pathway (Ethier et al., 1989). Second, high fat diet might increase cell membrane phospholipids turn over rate (Imagawa et al., 1989; Williams and Maunder, 1992), and activate protein kinase C (PKC) pathway. It has been known that PKC activity is highly correlated with the unsaturated fatty acids in modifying tumor promoting activity (Craven and DeRubertis, 1988). In our experiments, caffeine as a cAMP active agent, and high fat diet have interaction effect on mammary growth.

This interaction effect between caffeine and high fat diet in mammary growth suggests that the stimulatory effect of caffeine and high fat diet in mammary development may result from different cellular signaling pathway, and one pathway may activate the other side signaling intermediate to maximize the growth response.

In summary, caffeine moderately increased mouse mammary gland development possibly by inhibiting phosphodiesterase activity, and dietary fat supplements increased mammary gland development as the fat content of the diet increased from 0 to 20%.

The stimulatory effect of caffeine in mammary development interacted with high level of fat diet.

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요 약

Caffeine과 지방급여가 생쥐의 유선발달에 미치는 효과

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본 연구는 caffeine과 다불포화 지방산이 다량으로 함유되어 있는 대두유(soybean oil) 급여가 생쥐의 유선발달에 미치는 영향을 검토하였다. 생쥐를 0, 5, 20%의 3개 지방급여 구로 나누고 각 구의 반은 caffeine처리를 하였으며 나머지는 무처리 하였다. Caffeine처리시 무처리구에 비하여 시험종료시 체중, 일당 증체량 및 유선의 무게(wet weight)를 감소시키는 것으로 나타났다($P<0.05$). 그러나 caffeine처리시 무처리구에 비하여, 유의하여 제 4유선의 유선발달 score및 DNA함량/gland을 증가시켰다($P<0.05$). 지방급여 수준효과에 있어서는 caffeine처리구와 무처리구 모두에서 지방함량이 증가할수록 유선발달 score 및 DNA함량/gland이 증가하였다($P<0.05$). Caffeine 급여와 20% 지방급여구 간에는 유선발달에 상호작용 효과가 있었다[(20% 지방 + caffeine) − (20% 지방 + no caffeine) vs (0% 지방 + caffeine) − (0% 지방 + no caffeine)] ($P<0.01$).

Phosphodiesterase 활성 억제인자인 caffeine을 생쥐에 급여할 시 유선의 발달을 증진시키는 것으로 나타났으며, 지방급여에 따른 유선발달은 다불포화 지방산이 다량으로 함유되어 있는 대두유를 0~20%로 증가함에 따라 유선발달이 증가하였다. Caffeine과 대두유를 병행하여 급여할 시 유선발달에 상승효과를 가져오는 것으로 나타났다.

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