Effects of Dietary Essential Fatty Acids on Murine Mammary Gland Development

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Abstract

Removal of unsaturated fatty acids from the diet of female C3H mice resulted in the gradual onset of essential fatty acid deficiency. Upon reaching the deficient state, alveolar components of the mammary gland began to regress as did the ovarian corpora lutea. An increase in the viscosity of microsomal membranes and a decrease in the number of prolactin binding sites also occurred concomitantly as the deficient state increased in severity. Modification of fats within the diet changes the fluidity of cellular membranes. This appears to alter the functionality of the membrane-associated receptors and their subsequent ability to respond to circulating hormones.

Introduction

Animals fed diets containing high concentrations of unsaturated fatty acids develop both spontaneous and carcinogen-induced tumors more rapidly than do those fed diets that contain only saturated fats (3, 10, 12, 13). Since the EFA, linoleic and linolenic acids, are among the polyunsaturated fatty acids and since the essential fatty acid deficiency syndrome includes depressed lactation in addition to suppressed reproductive capacity (2, 11), it was postulated that EFA deficiency might modify the morphology of the mammary gland, thereby altering the number of cells at risk to neoplastic transformation. This might then permit more detailed investigations of the relationship between dietary fats and the pathophysiology of the mammary gland.

Materials and Methods

C3H mice were placed on a diet devoid of essential fatty acids. Fat in this deficient diet was supplied by medium-chain triglycerides at 5% by weight, the medium-chain triglycerides consisting of triglycerides resynthesized from saturated fatty acids of 8- to 14-carbon chain length. The control diet contained 5%, by weight, corn oil in place of the medium-chain triglycerides and was therefore both high in linoleic acid concentration and isocaloric with the deficient diet.

Animals were weaned at 4 weeks of age and placed on either the deficient or control diets 1 to 2 weeks later. The deficient animals gradually began to appear lethargic, developed dermatitis with roughed coats, and showed a marked decrease in the amount of fat within the mammary gland fat pads and i.p. fat deposits, all symptoms of EFA deficiency.

Mammary glands excised after various periods of time on either the control or deficient diets were whole mounted (6), and their morphological characteristics were noted.

Results and Discussion

Alveolar structures gradually appeared in the mammary glands of the control animals, with 85% of the glands possessing alveoli after 22 weeks on this dietary regimen. The rate of alveolar development within the deficient animals was similar to that of the controls and reached a maximum after 17 weeks on the diet (Chart 1). These alveolar structures subsequently involuted until none were detectable after 28 to 32 weeks of exposure to the deficient diet (8).

Loss of alveolar structures within the deficient animals was completely prevented by 3-times-weekly s.c. injections of 11 mg purified linoleic acid, indicating that absence of linoleic acid rather than that of a contaminant or other factor was responsible for the atrophy of the EFA-deficient mammary gland.

Similar results were observed in multiparous mice. No alveolar structures were detectable after they had received the deficient diet from 1 week prepartum through the 32-week postpartum period. Their offspring, which were subsequently maintained on the same diets, developed neither ductal nor alveolar structures, and the mammary glands remained as atrophic organs (8).

The diets fed to the animals in the preceding experiments contained no cholesterol. Diets of other experiments were fortified by the addition of 0.1% cholesterol. This caused the mammary effects of EFA deficiency to become apparent earlier in the course of dietary treatment (Chart 1).

While the histological appearance of the pituitaries remained unaltered by the state of EFA deficiency, the ovaries of EFA-deficient animals were without corpora lutea. This suggests that the morphological deficit within the mammary glands is due to an absence of the appropriate ovarian steroids.

EFA, however, are known to play an integral role in the structure of cell membranes. This prompted the additional thesis that depletion of significant amounts of EFA from the membranes of hormonally responsive tissues might alter the functionality of various membrane-associated receptors. Since prolactin is known to play an integral role in both mammary gland physiology and incidence of rodent mammary carcinomas, prolactin receptors were studied in the hepatic microsomal membrane fraction of animals that had been maintained on either deficient or control diets. Females maintained on the EFA-deficient diets showed a gradual decrease in the prolactin-binding capacity of the target tissue until the value fell to 41% of control after a 32-week feeding period (7). Since prolactin has been shown to be necessary for the induction of the hepatic prolactin receptor in rodents (4), the possibility existed that the loss of detectable receptors might be the result of a change in circulating prolactin levels rather than a primary...
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an altered hormonal milieu. Indeed, fluorescence polarization measurements revealed a 10 to 27% increase in the microviscosity of membranes prepared from the deficient animals when compared to that of controls (5). This EFA deficiency-induced increase in membrane rigidity may be a generalized phenomenon that alters both the response of various tissues to physiological levels of hormones and the ability of endocrine organs to express their differentiated functions (1, 9).

We conclude that essential fatty acids are necessary for the morphological development and maintenance of the murine mammary gland. This may result from modifications within the hormonal milieu and/or changes of the functionality of membrane-associated receptors due to alterations of the microviscosity of these target membranes.

References


alteration in the receptor. Male C3H mice that had been maintained on either the control or deficient diets for 22 weeks were therefore treated with either 100 µg bovine prolactin or the 0.9% NaCl solution carrier every 4 hr for a total of 11 i.p. injections. Animals maintained on the deficient diet did not respond to the exogenous prolactin, whereas the control diet-fed animals exhibited a 4-fold increase in prolactin-binding capacity (7).

This suggests that primary alterations may be either caused by, or intensified by, membrane changes acting in concert with an altered hormonal milieu. Indeed, fluorescence polarization measurements revealed a 10 to 27% increase in the microviscosity of membranes prepared from the deficient animals when compared to that of controls (5). This EFA deficiency-induced increase in membrane rigidity may be a generalized phenomenon that alters both the response of various tissues to physiological levels of hormones and the ability of endocrine organs to express their differentiated functions (1, 9).

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References

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