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SHORT COMMUNICATION

FREE FATTY ACIDS: A POSSIBLE REGULATOR OF THE AVAILABLE OESTRADIOL FRACTIONS IN PLASMA

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Summary—Consumption of dietary fats has been linked to the high incidence of breast cancer found in Western women. *In vitro* studies we have carried out show that unsaturated free fatty acids can increase the biologically available oestradiol fractions in plasma. It is possible therefore that the increased risk for breast cancer associated with a diet high in fats may be related to an elevation in the biologically available oestradiol fractions in plasma.

INTRODUCTION

The incidence of breast cancer is higher in Western women than in Japanese women [1]. As fat consumption is lower in Japan than the West a possible role for fats in the development of breast cancer has been suggested [2]; altered fat consumption might then account for the change in the incidence of breast cancer seen when Japanese women move to America [3]. Several mechanisms by which fat consumption may influence the development of breast cancer have been proposed and include alterations of gut flora [4], secretion of prolactin [5] or increased mass of adipose tissue [6] for oestrogen formation. In a recent study we found that the free fraction of oestradiol was higher in postmenopausal women with breast cancer than in normal postmenopausal women [7], but no difference in the binding capacity of sex hormone binding globulin (SHBG) was detected. Hollander *et al.*[8] using an *in vitro* technique found that free fatty acids (F.F.A.) could increase the free thyroxine levels in serum. In view of the increased free oestradiol fraction found by us and others [9] in breast cancer patients and the correlation between dietary fat consumption and incidence of breast cancer we have examined *in vitro* the ability of F.F.A. to regulate the available fractions of oestradiol in plasma.

EXPERIMENTAL

Methods

The free oestradiol fraction was measured by an equilibrium dialysis technique with a Dianorm dialysis machine using undiluted plasma at 37°C. The fraction of oestradiol not bound to SHBG, i.e. mainly to albumin was measured using a precipitation technique. A full description of these techniques together with a validation of the methods used has been previously published [10]. Linoleic, oleic and palmitic acids were added to a male plasma pool and a postmenopausal plasma pool as their potassium salts in ethanol [8]. Addition of the small volume of solvent had no effect on the free oestradiol fraction. All measurements were carried out in duplicate.

RESULTS

Addition of oleic acid (2 mM) to a male plasma produced a 46% increase in the free oestradiol fraction, while no increase occurred when linoleic or palmitic acids were added at this concentration (Fig. 1a). At higher concentrations (5 mM) both oleic and linoleic acids produced marked increases (89 and 74%, respectively) in the free oestradiol fraction. The effect of palmitic acid was not investigated at a higher concentration owing to its low solubility. Oleic and linoleic acids (2 mM) also produced an increase (25%) in the free oestradiol fraction when added to a postmenopausal plasma pool, whereas palmitic acid had no effect at this concentration (Fig. 1b).

Linoleic acid (0.5–2.0 mM) produced an increase of up to 16% in the non-SHBG-bound oestradiol fraction in the male plasma pool but no increase occurred in the presence of oleic or palmitic acids (Fig. 2a). Linoleic acid (2 mM) resulted in a 25% increase in the non-SHBG-bound oestradiol fraction when added to a postmenopausal plasma pool while the increase resulting from the addition of oleic or palmitic acids was much lower (Fig. 2b).

DISCUSSION

The results of this study suggest another possible mechanism whereby a high fat diet may increase the risk of breast cancer by elevating tissue exposure to biologically active oestradiol. Previous studies have shown that levels of free thyroxine [8] and some drugs [11] are increased when F.F.A. levels are elevated. However little is known about the ability of F.F.A. to influence the binding of steroid hormones to plasma proteins. In the present study the *in vitro* experiments showed that unsaturated F.F.A., at concentrations towards the upper end of the normal physiological range, can interfere with the binding of oestradiol to SHBG or albumin. Although the increase in the non-SHBG-bound oestradiol fraction resulting from the addition of linoleic acid to plasma was similar to the effect of adding the same concentration of oleic acid on the free oestradiol fraction the concentration of albumin-bound oestradiol is much greater than the free steroid concentration. Recent investigations have suggested that steroids bound to albumin may be available to tissues [12]. As it has been reported that women with breast cancer have elevated levels of plasma total lipids and also plasma lipase activity [13], it is possible that the increased risk for breast cancer associated with high fat consumption is related to an elevation in the biologically free oestradiol fraction. Further studies are in progress to investigate the role of F.F.A. in regulating the available fractions of oestradiol *in vivo*.

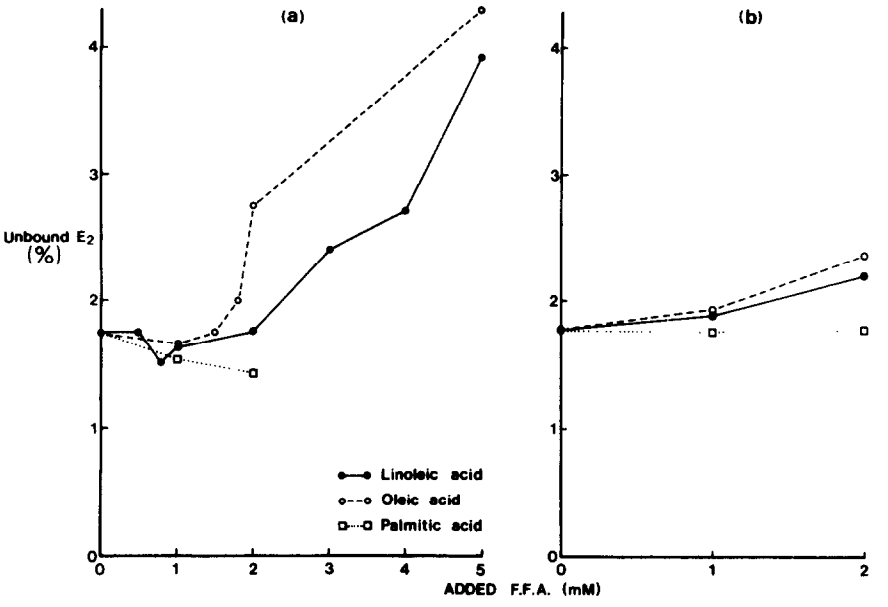

Fig. 1. Effect of adding F.F.A. on the unbound oestradiol (E_2) fraction in: (a) a male plasma pool; and (b) a postmenopausal plasma pool.

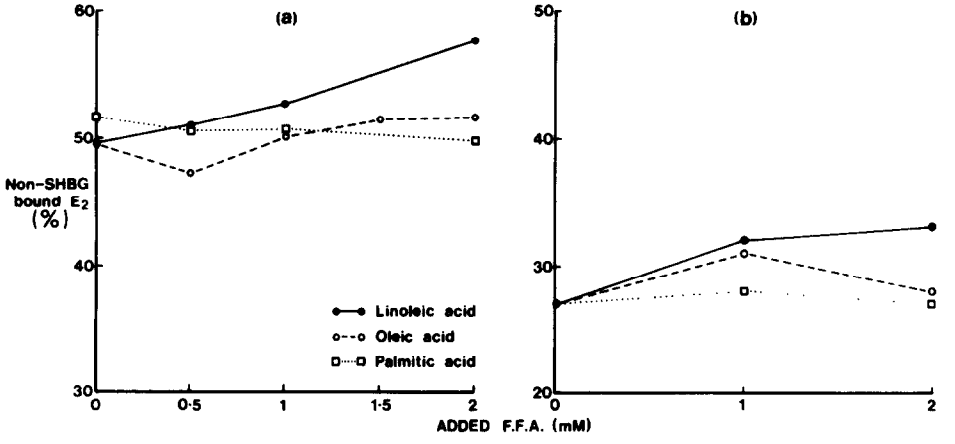

Fig. 2. Effect of adding F.F.A. on the non-SHBG-bound oestradiol (E_2) fraction in: (a) a male plasma pool; and (b) a postmenopausal plasma pool.

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