Oleate Activates Phosphatidylinositol 3-Kinase and Promotes Proliferation and Reduces Apoptosis of MDA-MB-231 Breast Cancer Cells, Whereas Palmitate Has Opposite Effects

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ABSTRACT

Epidemiological studies and experiments using animal models and cultured breast cancer cells have suggested that a high intake of dietary fat could increase breast cancer risk. Little is known about the biochemical pathways by which various free fatty acids (FFAs) influence breast cancer cell proliferation and apoptosis. The present study was designed to investigate the effects of the two most abundant circulating FFAs, oleate and palmitate, on established human breast cancer cell lines after a short period of serum starvation. The unsaturated FFA oleate (C:18:1) stimulated cell proliferation, whereas the saturated FFA palmitate (C:16) dose dependently inhibited it. The half maximal effective concentrations of oleate and palmitate in the presence of albumin were 5 and 25 μM, respectively. The growth-inhibitory effect of palmitate in MDA-MB-231 cells was related to the induction of apoptosis as indicated by morphological and biochemical criteria. Moreover, oleate protected cells against the proapoptotic action of palmitate. Oleate and palmitate increased and decreased phosphatidylinositol 3-kinase (PI3-K) activity, respectively, and the actions of the two FFAs on the enzyme were antagonistic. The PI3-K inhibitors wortmannin and 1Y294002 completely blocked the proliferative action of oleate. 2-Bromopalmitate, a nonmetabolizable analogue, did not affect MDA-MB-231 cell proliferation, suggesting that palmitate must be metabolized to exert its effect. Thus, various types of fatty acids are not equivalent with respect to their actions on breast cancer cell proliferation and apoptosis. The results support the concept that PI3-K is implicated in the control of breast cancer cell growth by FFAs and that PI3-K may provide a link between fat and cancer. The data are also consistent with the view that the type of FFA and their ratios in the diet in addition to the total amount of fat influence mammary carcinogenesis.

INTRODUCTION

Breast cancer affects a growing number of women around the world. Unfortunately, almost all that is known with certainty about its causes are factors over which no preventive action can be easily taken, such as genetics and the age at which a woman has a child. Epidemiological studies indicate that women in countries with high-fat diets have a risk of breast cancer that can be 5-fold higher than those of women in countries with low fat consumption (1–3). From these observations, it has been postulated that a high intake of dietary fat could increase breast cancer risk (3). The dietary fat hypothesis has been supported by a meta-analysis of case-control studies and by a large number of studies using animal models and cultured breast cancer cells (4). In contrast, recent prospective epidemiological studies failed to confirm the hypothesis (5), and, moreover, a recent large study showed a small but significant inverse correlation (6).

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2 The abbreviations used are: FAS, fatty acid synthase; FBS, fetal bovine serum; FFA, free fatty acid; PARP, poly(ADP-ribose) polymerase; PI3-K, phosphatidylinositol 3-kinase.

The question of why epidemiological studies have not been as consistent as animal studies in relating fat intake and breast cancer risk is a complex one. On one hand, nutritional epidemiology suffers from profound imprecision of exposure measurements. It has been argued that this imprecision leads to substantial underestimation of disease-exposure associations, such as relative risk and dose response. Also, all cohort studies focused on fat consumption during adulthood, whereas it is possible that fat intake during adolescence may be of greater importance for subsequent breast cancer development. On the other hand, inconsistencies also exist in experimental studies. A recent meta-analysis of about 100 rodent studies indicated that n-6 polyunsaturated fatty acids have a strong tumor-enhancing effect, whereas saturated fatty acids have a weaker effect (7). Monounsaturated fatty acids and n-3 polyunsaturated fatty acids have no statistically significant effects (7). However, as reviewed by Hardy et al. (8), many studies reported contradictory conclusions with respect to the respective actions of the different types of fatty acids, particularly for oleic acid, in the animal mammary tumor models. Because the ratio, type, and amount of fatty acids may influence tumor development in different ways in animals, conflicting results may be explained in part by the fact that fat is generally administered as a mixture of several different fatty acids and not as individual fatty acids (8, 9). Different effects of saturated and unsaturated fatty acids on cell proliferation and promotion have also been documented in breast cancer cell culture studies (10–14). These inconsistencies could be related to differences in culture conditions or to the use or nonuse of albumin-bound fatty acids (15, 16). Thus, several in vitro studies tested the action of fatty acids unbound to BSA at concentrations far above their critical micellar concentrations. This raises doubts about the results obtained with such nonphysiological conditions.

In an effort to clarify these problems, we based our works on the premise that assessing the effects of individual major dietary fatty acids on cell proliferation will help us to understand the mechanisms by which fatty acids may influence tumor cells and therefore be helpful in the design of future epidemiological studies and, eventually, dietary counseling. Relatively little information exists on the biochemical pathways by which fatty acids influence tumor cell proliferation and metabolism. The discovery that FAS,3 an enzyme essential to fatty acid metabolism, is a prognostic indicator of breast cancer progression strengthens the hypothesis that fatty acids are involved in the regulation of tumor cell growth (17–20). Also, consistent with this view is the observation that troglitazone, a ligand for peroxisome proliferator-activated receptor γ, a nuclear receptor that also binds various fatty acids, markedly influences the growth and apoptosis of various cancer cells (21–25). We recently proposed that fatty acids could influence insulinoma cell growth through the induction of proto-oncogenes like c-fos via Ca2+ and protein kinase C signaling (26). Thus, much...
remains to be learned about the primary target of fatty acids in relation to oncogenesis. PI3-K phosphorylates inositol lipids that act as second messengers for several pathways related to cell proliferation and apoptosis (27–30). Whether long-chain fatty acids influence cell proliferation via PI3-K is unknown.

In the present study, the actions of the two most abundant circulating fatty acids, oleate and palmitate, were investigated in established human breast cancer cell lines after a short period of serum starvation. We found that oleate (C:18:1; unsaturated fatty acid) stimulates cell proliferation, whereas palmitate (C:16; saturated fatty acid) promotes apoptosis. Moreover, oleate protects cells against palmitate-induced apoptosis. Evidence that PI3-K may be implicated in the mode of action of these fatty acids is also provided.

**MATERIALS AND METHODS**

**Cell Lines and Culture Conditions.** The human breast cancer cell lines MCF-7, ZR-75-1, T-47-D, and MDA-MB-231 were obtained from the American Type Culture Collection. Cells were cultured at 37°C and 5% CO₂ in phenol red-free MEM with nonessential amino acids supplemented with 2 mM glutamine, 10 μg/ml insulin, and 10% heat-inactivated FBS. Albumin-bound fatty acids were prepared by stirring fatty acid sodium salts (≥99% purity; Sigma) at 37°C with 5% fraction V essentially fatty acid-free BSA (Sigma) as described previously (26). After being adjusted to pH 7.4, the solution was filtered through a 0.22 μm filter, and the fatty acid concentration was measured using a NEFAC kit (Wako Chemicals GmbH). When BSA-bound fatty acids were added to serum-free culture medium, the final concentration of BSA was always adjusted to 0.5%.

**[3H]Thymidine Incorporation.** Cells were seeded at 5000 cells/well in 96-well plates and incubated for 24 h in standard medium. After a 24-h starvation period in media without insulin and serum but with 0.5% fatty acid-free BSA, cells were incubated without or with BSA-bound fatty acids for 24 h. DNA synthesis was then assayed with a pulse of [3H]thymidine (1 μCi/well; specific activity, 71 Ci/mmol) during the last 4 h of incubation. Cells were harvested with a PHD cell harvester from Cambridge Technology (Watertown, MA), and the radioactivity retained on the dried glass fiber filters was counted using a Packard scintillation spectrophotometer (31).

**Apoptosis Assay.** Cells were seeded in 100-mm Petri dishes at 1 × 10⁶ cells/dish and treated as described in the figure legends. To determine the percentage of apoptotic cells, the detached cells present in the culture medium and in a 5-ml PBS wash of the dish were centrifuged at 1000 × g for 5 min, resuspended in PBS, and counted with a hemocytometer. The attached cells were trypsinized and counted. The percentage of apoptotic cells in triplicate dishes was evaluated by dividing the number of detached cells by the total number of cells (detached cells + attached cells). This method for quantification of apoptotic cells gave results that were similar within 5% to a direct counting of cells with apoptotic morphology (cell rounding and blebbing) in randomly selected fields using a Nikon Diaphot inverted photomicroscope (×200).

**Analysis of DNA Laddering by Agarose Gel Electrophoresis.** Cellular DNA was extracted from detached cells by the salting out procedure described by Miller et al. (32). Electrophoresis was done in 1.5% agarose gels in Tris-borate buffer (pH 8.0). DNA was visualized under UV illumination after staining with ethidium bromide.

**Protein Extraction and Analysis.** Total protein extracts were prepared by lysing cells in protein extraction buffer [65 mM Tris (pH 6.8), 6 mM urea, and 2% SDS] followed by sonication to shear the DNA. After determination of protein concentration using the Bio-Rad DC (detergent compatible) colorimetric assay with BSA as a standard, DTT was added to a concentration of 5% (v/v), and the samples were boiled for 5 min before performing SDS-PAGE and Western blotting. After incubation with PARP/Ab-2, a mouse monoclonal antibody (Calbiochem) directed against PARP, the membrane was incubated with horse-radish peroxidase-conjugated goat antiamouse antibody (Amersham Corp.), and the bound peroxidase was revealed using the SuperSignal (Pierce) detection kit.

**PI3-K Activity Measurements.** MDA-MB-231 cells were grown in 150-mm Petri dishes. After a 5-min incubation period in the presence of various test substances, PI3-K was assayed as described previously (33). In brief, PI3-K was immunoprecipitated from 5 mg of total protein extracts with an anti-p85PI3-K antibody (Santa Cruz Biotechnology, Santa Cruz, CA) and resuspended in 50 μl of a buffer containing 20 mM Tris-HCl (pH 7.5), 100 mM NaCl, and 100 mM EGTA. After incubation for 10 min with 10 μg of l-α-phosphatidylinositol, 10 μCi of [γ-32P]ATP were added with 10 mM MgCl₂. The reaction was stopped after 4 min at room temperature with a mixture of CHCl₃-methanol-HCl (100:200:2), and the lipids were extracted and separated by TLC on silica gel plates. PI3-K activity was quantified through phosphatidylinositol 3-phosphate formation.

**RESULTS**

**Opposite Effects of Oleate and Palmitate on the Proliferation of Various Breast Cancer Cell Lines.** The effects of oleate and palmitate on the proliferation of one hormone-independent (MDA-MB-231) and three hormone-dependent (MCF-7, ZR-75-1, and T-47-D) human breast cancer cell lines were studied. These fatty acids were chosen because they constitute the two most abundant fatty acids in the plasma (34). Oleate stimulated [3H]thymidine incorporation in serum-starved MDA-MB-231, MCF-7, and ZR-75-1 cells by 2–4-fold but had little effect in T-47-D cells (Fig. 1A). In contrast, palmitate had a drastically different effect because it decreased the [3H]thymidine incorporation to 5% of the respective control (Fig. 1B).

![Fig. 1. Effects of oleate and palmitate on the incorporation of [3H]thymidine in various breast cancer cell lines. After 24 h of serum starvation in the presence of 0.5% BSA in MEM without insulin, cells were incubated for 24 h with 0.5% BSA (Control) or BSA-bound oleate (A) and palmitate (B). During the last 4 h of incubation, cells were labeled with [3H]thymidine as described in “Materials and Methods.” The results represent the means ± SE of three independent experiments performed in triplicate. All values with oleate or palmitate are significant (P < 0.01) versus their respective control situations, except for the action of oleate on the tritiated thymidine incorporation in T-47-D cells (not significant).](image-url)
incorporation in the four cell lines by 30–90% (Fig. 1B). The T-47-D cells, which were insensitive to oleate, exhibited sensitivity to palmitate to an extent similar to that of MCF-7 and ZR-75-1 cells. Interestingly, the opposite effects of both fatty acids were most pronounced in hormone-independent MDA-MB-231 cells. The results indicate that whereas DNA replication was stimulated by oleate in the majority of the tested breast cancer cells, it was inhibited by palmitate in all of them.

Due to the profound effectiveness of both fatty acids in MDA-MB-231 cells, this cell line was used for most of the subsequent experiments. As shown in Fig. 2, the effects of oleate and palmitate on \(^{3}\)H thymidine incorporation were dose dependent. The stimulation of DNA synthesis by oleate, which was detectable at a concentration of 1 \(\mu\)M, reached a plateau at 10 \(\mu\)M that was sustained up to 400 \(\mu\)M, the highest tested concentration (Fig. 2A). The cell proliferation-inhibitory effects of palmitate occurred in the 10–100 \(\mu\)M range. The microscopic observation of palmitate-treated cells revealed that this fatty acid caused a dose-dependent rise in the percentage of cells exhibiting morphological signs of apoptosis (cell blebbing, rounding, and detachment) that paralleled the decreased \(^{3}\)H thymidine incorporation (Fig. 2B). Similar results were obtained with oleate and palmitate purchased from two other companies (data not shown). It should be noted that on the basis of recent estimates of the free concentrations of fatty acids in the blood (35) and at different albumin: fatty acid ratios (36), the free concentrations of both palmitate and oleate in the cell culture medium should be in the nanomolar range.

To better assess the growth-stimulatory effect of oleate, MDA-MB-231 cells were incubated after a 1-day period of serum starvation in media containing either BSA alone, BSA-bound oleate, or FBS, and the attached cells were counted over a 6-day period (Fig. 3). The growth of control cells stopped after 1 day of culture, and at 3 days after serum starvation, the number of attached cells had dropped considerably. Microscopic observations revealed that most cells that detached from the dishes exhibited apoptotic morphological changes (data not shown). In sharp contrast, the number of oleate-treated cells increased 2-fold during the same 3-day period and remained constant over the next 2 days. However, the growth of these cells was less rapid than that of serum-treated cells, and a plateau was attained at a much lower density. Although the majority of oleate-treated cells did not exhibit morphological signs of apoptosis, they differed somewhat from serum-treated cells by exhibiting a higher content of dark inclusions in their cytoplasm (Fig. 4A). Taken together, the data indicate that the death process induced in MDA-MB-231 cells by serum starvation is counteracted by oleate. Conversely, palmitate considerably promotes the death of serum-starved cells.

**Oleate Is Antiapoptotic and Impairs the Proapoptotic Action of Palmitate.** The morphological changes seen in serum-starved MDA-MB-231 cells that were dramatically amplified by palmitate treatment were typical of apoptosis. To obtain direct evidence that palmitate promotes an apoptotic process, we examined whether the proteolysis of PARP and the cleavage of DNA into nucleosomal fragments, two hallmark features of apoptosis, also occurred in these cells. To minimize apoptosis in the control BSA-treated dishes, the period of serum starvation before the addition of fatty acids was shortened to 12 h. Under these conditions, in which about 10% of the control cells exhibited morphological signs of apoptosis (Fig. 4A), a small amount of the M, 89,000 PARP degradation product was detected (Fig. 4B).

**Fig. 2.** Dose dependence of the effects of oleate and palmitate on the incorporation of \(^{3}\)H thymidine in MDA-MB-231 cells. Cells were cultured for 24 h as described in the Fig. 1 legend with 0.5% BSA (Control) or various concentrations of BSA-bound oleate (A) and palmitate (B). \(^{3}\)H thymidine incorporation values (\(\bullet\)) are expressed as a percentage of the control. The percentage of apoptosis (\(\checkmark\)) was assessed as described in “Materials and Methods.” The results represent the means ± SE of three independent experiments performed in triplicate. All test values are significant (\(P < 0.01\)) versus their respective control situations.

**Fig. 3.** Effects of oleate and FBS on MDA-MB-231 cell growth. Cells were plated in 60-mm dishes in MEM with 5% FCS at \(4 \times 10^{4}\) cells/dish. After 24 h of incubation (time 0), they were serum starved as described in the Fig. 1 legend. On day 1, cells were refed with MEM containing 0.5% BSA alone (Control), BSA-bound oleate (0.1 mM), or 5% FCS. At the indicated times, attached cells were trypsinized and counted. Values are the means of two separate experiments.
Oleate almost completely prevented PARP cleavage, whereas palmitate increased it. When DNA degradation was analyzed on the entire cell populations, typical DNA laddering was barely visible (data not shown). However, when the DNA was extracted only from cells floating in the medium, laddering that was faintly visible in the control situation was apparent in the palmitate condition. Oleate nearly completely prevented DNA degradation (Fig. 4C). These results establish that oleate exerts an antiapoptotic effect on serum-starved MDA-MB-231 cells, whereas palmitate is proapoptotic.

To determine whether oleate may protect cells against death triggered by palmitate, the level of apoptosis induced by palmitate (100 μM) in the presence of an increasing concentration of oleate was evaluated (Fig. 5). Fifty % protection was already attained at the lowest tested concentration of oleate (1 μM). At 10 μM, the percentage of apoptosis was similar to that of controls (9%). Thus, a 1:10 molar ratio of oleate versus palmitate was sufficient for full protection. The cells protected by oleate against palmitate had a morphological appearance similar to that of cells treated with oleate alone (Fig. 4A). Moreover, cells incubated in presence of palmitate (100 μM) plus oleate (30 μM) exhibited as little PARP cleavage and DNA fragmentation as control cells (Fig. 4B and C). The proapoptotic action of palmitate was also observed in the estrogen-dependent cell line T-47-D. As shown in Fig. 4D, palmitate induced qualitatively similar changes in PARP cleavage in T-47-D cells and in the estrogen-independent cell line MDA-MB-231, and PARP cleavage could be counteracted by oleate. The morphological changes caused by both fatty acids, alone or in combination, were also similar in both cell lines (data not shown).

**Effect of Fatty Acids on PI3-K Activity.** To assess a possible role of PI3-K in the action of oleate, the effect of two PI3-K inhibitors was tested. Wortmannin and LY294002 completely blocked the proliferative action of oleate (Fig. 6). Because PI3-K inhibitors had only a weak effect (~20% decrease) on the proliferation of control cells (data not shown), these results suggested that PI3-K plays an important role in the proliferative effect of oleate. To confirm that PI3-K is involved in the action of oleate, PI3-K activity was measured in extracts of cells incubated for 5 min with the fatty acid (Fig. 7). In each of six separate experiments, oleate stimulated PI3-K activity by a factor that averages to 2-fold. For comparison, 5% FBS also activated PI3-K by 2-fold (n = 2; data not shown). In contrast, palmitate caused a 60% reduction of PI3-K activity, whereas the mixture of the two fatty acids had no effect. These results provide supporting evidence that PI3-K is implicated in the mode of action of oleate and palmitate on breast cancer cell proliferation and apoptosis, respectively.

**DISCUSSION**

Human breast cancer cell proliferation involves a complex interaction between genes, growth factors, hormones, and calorigenic nutrients. Numerous studies have documented both in vivo and in vitro that long-chain FFAs influence the proliferation of these cells. However,
little is known about the mechanism of such effects. When the action of selected fatty acids bound to albumin on the proliferation of four different human breast cancer cell lines was assessed in a defined serum-free medium, oleate stimulated proliferation, whereas palmitate inhibited it. The growth inhibition of palmitate was related to the induction of apoptosis. The proapoptotic effect of palmitate is counteracted by oleate. Thus, surprisingly, the two major circulating fatty acids present in the diet have opposite effects on breast cancer cell proliferation. Moreover, because the nonmetabolizable analogue 2-bromopalmitate (200 μM) had no effect on the incorporation of [3H]thymidine in MDA-MB-231 cells (data not shown; n = 3), we conclude that palmitate has to be metabolized to exert its proapoptotic action.

Stimulation of MDA-MB-231 cell proliferation by oleate has also been observed by others in the presence of 5% FBS (37) or in serum-free medium (15). Provided that these observations may be extended to the in vivo situation, it can be postulated that a diet rich in oleate may favor mammary tumor progression. Thus, obesity is characterized by elevated circulating FFAs, as well as insulin resistance (38) and an increase in the risk of breast (39) and colorectal cancer (40). Furthermore, a positive correlation exists between these pathological diseases (40–43).

In contrast, palmitate decreased the proliferation of MDA-MB-231 cells. Other groups have also observed that saturated fatty acids diminish the proliferation rate of human breast cancer cells (14, 15); however, to our knowledge, this is the first time it has been shown to be associated with the induction of apoptosis. Palmitate also induces apoptosis in isolated pancreatic islets (44), hematopoietic precursor cell line LyD9 (45), and neonatal rat cardiomyocytes (46). The mechanism of the proapoptotic action of palmitate is uncertain. Palmitate is a precursor of ceramide, whereas oleate is not (47). Evidence has been provided that palmitate might induce apoptosis via ceramide production in isolated pancreatic islets (44) and in the hematopoietic precursor cell line LyD9 (45). Whether de novo synthesis of ceramide is causally linked to the proapoptotic action of palmitate in MDA-MB-231 cells remains to be evaluated. Another possibility is the inhibition of FAS, the enzyme responsible for the endogenous synthesis of fatty acids. Thus, palmitate inhibits FAS activity and gene expression in various cell types (48), and the inhibition of this enzyme by cerululin has been reported to induce apoptosis in breast cancer cells (17).

The effect of palmitate on MDA-MB-231 apoptotic cell death is reversed by oleate. Moreover, the combination of the two fatty acids at 100 μM resulted in an increased proliferation of MDA-MB-231 cells (data not shown). An antiapoptotic action of oleate against palmitate has also been observed in neonatal rat cardiomyocytes in which equimolar amounts of both fatty acids were necessary for full protection (46). The opposite action of different fatty acids on breast cancer cell growth may explain why the results of epidemiological and animal studies using different diets are often conflicting. In vivo animal studies always used oils that were rich in particular fatty acids but also contained other fatty acids that may have influenced tumor promotion in a markedly different manner.

PI3-K activation after growth factor stimulation is closely associated with increased proliferation and survival (27, 28). Oleate appears to act like a growth factor because it stimulates cell proliferation at a very low concentration and activates PI3-K in MDA-MB-231 cells. In contrast, palmitate reduced basal PI3-K activity in this cell line. To our knowledge, this provides the first evidence of changes in PI3-K activity by various fatty acids for any cell type. The very rapid response to treatment renders an effect involving changes in protein synthesis unlikely. It rather suggests signaling via membrane receptors such as receptor tyrosine kinases or G protein-coupled receptors, which are known to act via PI3-K activation (49, 50). Interestingly, it has recently been shown that oleate, but not palmitate, can activate the epithelial growth factor receptor in endothelial cells (51). PI3-K activation could also occur via CD36, a cell surface protein that can interact with fatty acids (52) and activate members of the src protein tyrosine kinase family (53).

Taken together our results support the view that the type of fatty acids (saturated, monounsaturated, and polyunsaturated) and their ratios in the diet in addition to the total amount of fat influence mammary carcinogenesis. It will be of interest to determine the detailed mechanisms of palmitate and oleate action on breast cancer cell growth, particularly upstream and downstream of PI3-K. Because the activity of PI3-K, a key signal transduction protein implicated in cell growth control, is modulated by exogenous fatty acids (the present study) and glucose (31), the possibility should be considered that PI3-K provides a link between excessive calorigenic nutrient

Fig. 6. Effect of PI3-K inhibitors on MDA-MB-231 cell proliferation induced by oleate. Cells were serum starved for 24 h as described in the Fig. 1 legend and subsequently incubated for 24 h with 0.5% BSA (Control) or BSA-bound oleate (0.1 mM) in the absence or presence of 50 μM wortmannin or 50 μM LY294002. Proliferation was evaluated by [3H]thymidine incorporation. Values are the means ± SE of three independent experiments performed in triplicate. ∗, P < 0.01 versus control.

Fig. 7. Effect of oleate and palmitate on PI3-K activity. After 24 h of serum starvation, cells were treated for 5 min with the same medium containing 0.5% BSA alone (Control), BSA-bound oleate (100 μM), or palmitate (100 μM). The results represent the means ± SE of six independent experiments. ∗, P < 0.05 versus control; **, P < 0.01 versus control.
intake and cancer. The results may also explain the contradictions in the literature by pointing out that different fatty acids are not equivalent as far as cell growth and tumor promotion are concerned.

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