Biology of aromatase inhibitors: pharmacology/endocrinology within the breast

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Abstract
Both mammary adipose tissue and breast cancers have the ability to aromatize androgens into oestrogens. Such potential may maintain the growth of hormone-dependent tumours. It has therefore been important to determine the effects of new aromatase inhibitors such as formestane, exemestane, anastrozole and letrozole on oestrogen biosynthesis and concentrations of endogenous hormones within the breast. Studies based on in vitro incubations of breast cancer and cultures of mammary adipose tissue fibroblasts demonstrate that these drugs are highly effective inhibitors, with IC_{50} values ranging between 1 and 50 nM (although the relative efficacy varies between tissues and test systems). Despite this potential, in vitro incubations of breast tissues from patients treated with type II inhibitors such as aminogluthethimide and letrozole can display paradoxically high aromatase activity; this appears to be caused by the reversible nature of the inhibition, coupled with induction/stabilization of the aromatase enzyme. To assess in situ effects within the breast, postmenopausal women with large primary breast cancers have been treated neoadjuvantly with aromatase inhibitors using a protocol that included (i) breast biopsy before treatment, (ii) definitive surgery after 3 months of treatment and (iii) infusion of [3H]androstenedione and [14C]oestrone in the 18 h immediately before biopsy and surgery. With this study design, it has been shown that drugs such as letrozole profoundly inhibit in situ aromatase activity and reduce endogenous oestrogens within the breast.

Introduction
Oestrogen deprivation therapy is a major treatment for breast cancer (Miller 1996a). In postmenopausal women, this is most commonly achieved by the use of drugs that either block oestrogen action (Jordan et al. 1993) or inhibit its synthesis (Miller 1997a). In the latter case, there has been a resurgence of interest because of the development of highly specific and potent agents that are capable of inhibiting the aromatase enzyme (Miller 1996b), catalysing the conversion of androgens to oestrogens. Although there are substantial data relating to the general endocrinology of these new aromatase inhibitors (Geisler et al. 1996, Lonning 1996), observations of direct effects on breast tissue are relatively scarce. This represents an important gap in knowledge because aromatase activity has been demonstrated within the breast, both in mammary adipose tissue and breast cancers (Perel & Killinger 1979, Miller et al. 1997). Although its clinical and physiological relevance is controversial (Miller 1986), oestrogen biosynthesis might be responsible for determining endogenous oestrogen concentrations and maintaining the growth of some hormone-dependent tumours (Miller 1997b). Because of this, the present paper reports on the potential of aromatase inhibitors to block oestrogen biosynthesis by breast tissues as determined by ex vivo and in situ assays.

Materials and Methods
Breast tissues
Breast cancers were obtained either by biopsy or at mastectomy from patients with histologically confirmed malignancy of the breast and who had given their informed consent to participate in the studies (which had been approved by the Hospital Trust Ethics Committee). Adipose tissue was derived at operation from the breasts of women presenting with either benign or malignant conditions of the breast. Specimens from which cells were to be cultured were immediately transferred aseptically into sterile phosphate-buffered saline (PBS). All remaining tissues were put on ice in the operating theatre and transported to the laboratory.
Aromatase activity in particulate fractions

Tumours were homogenized by hand in a glass-to-glass homogenizer in phosphate buffer and centrifuged at 800 g for 5 min. The resultant supernatant was separated from the upper layer of fat and lower pellet of cell debris using a Pasteur pipette and was centrifuged at 100 000 g for 1 h. The pellet was resuspended in buffer and used as a particulate fraction in the aromatase assay.

The determination of aromatase activity in adipose tissue was based on the measurement of \( ^3 \text{H} \) water after incubation with \( [\text{\( ^1\text{H} \)}] \text{A}-4 \)-androstenedione. Particulate fractions were incubated for 5 h at 37 °C in phosphate buffer with \( [\text{\( ^1\text{H} \)}] \text{A}-4 \)-androstenedione (1 µCi, 100 nM) and an NADPH-generating system. Blank incubations were performed with bovine serum albumin (1.5 mg/ml) in place of the particulate fraction. Aliquots of each incubated system were dispensed into ice-cold chloroform, shaken and centrifuged. The aqueous phases were then mixed with 5% charcoal in phosphate buffer and centrifuged at 2000 g for 15 min. The resultant supernatant was decanted into a counting vial containing NE260 scintillant (10 ml) (Nuclear Enterprises, Edinburgh, UK) and counted.

Aromatase activity in fibroblast cell cultures

Gross fat was teased from breast adipose tissue and the stromal-enriched fraction was chopped into small pieces. Aliquots (2 g) were then placed into universal containers and minced. Collagenase was added to each vial and incubated for 30 min at 37 °C in a shaking bath. The contents were allowed to settle for 10 min and the liquid phase was aspirated from below the surface lipid layer and centrifuged at 3000 r.p.m. for 10 min. The supernatant was washed twice in PBS and resuspended in \( \alpha \)-minimal essential medium (\( \alpha \)-MEM) supplemented with penicillin, streptomycin and heat-inactivated fetal calf serum (FCS) (15%). The cell suspension was then transferred to 60 mm Petri dishes (4 ml aliquot per dish) and grown as monolayer cultures in an atmosphere of 5% CO\(_2\)-95% air. After 48 h, cultures were washed twice with PBS and fresh media added. Cells were then allowed to grow to confluency. Before being assayed for aromatase activity, cell lines were incubated with dexamethasone (1 µM) in the presence of FCS (15%) for 18 h.

Measurement of aromatase activity involved removing ‘spent’ tissue culture media and washing dishes with PBS. To each dish, \( [\text{\( ^1\text{H} \)}] \text{A}-4 \)-androstenedione (2 µCi; 100 nM) in \( \alpha \)-MEM was added and incubation was carried out at 37 °C for 5 h under an atmosphere of 5% CO\(_2\)-95% air. Blank incubations consisted of dishes containing media but no cells. After incubation, all dishes were placed on ice for 15 min and the medium was aspirated, transferred to ice-cold chloroform (5 ml), shaken vigorously and centrifuged. The radioactivity in the aqueous phase was measured after charcoal extraction as described above.

Neoadjuvant treatment with letrozole - \textit{in situ} oestrogen biosynthesis

Postmenopausal patients with large (>3 cm) oestrogen receptor-positive (>20 fmol/mg cytosol protein) primary breast cancers (stages T2, T3, N0 or N1) were entered into the study. None had previously received treatment with hormonal agents for breast cancer or were taking hormone preparations at the time of study. All patients received primary endocrine therapy comprising letrozole (2.5 or 10 mg daily) for 3 months. Tumour material was taken by surgical biopsy on the day before treatment and 3 months later, at the time of definitive local-regional surgery (comprising wide local excision), which was performed on the last day of treatment. Infusion with radioactively labelled steroid hormones was performed immediately preceding biopsy and wide local excision of the tumour.

The infusion consisted of 20 MBq \([\text{\( ^{1,2,6,7-\text{H}} \)}] \text{A}-4 \)-androstenedione (85 Ci/mmol, Amersham, Little Chalfont, Bucks, UK) and 1 MBq \([\text{\( ^{4,14}\text{C} \)}] \text{O}-\text{estrone} (56 mCi/mmol, Amersham) in 50 ml 95% plasma protein solution and 5% ethanol. An initial 10 ml bolus injection was given, followed by an 18-h infusion at 2 ml/h, delivered via a 50 ml syringe attached to Teflon-coated tubing and transmitted through a 21 gauge venflon into a peripheral vein. At the end of the infusion, breast cancer tissue and plasma were taken for purification of radioactively-labelled steroids. The method was essentially that described by James \textit{et al.} (1987) and Reed \textit{et al.} (1989). Briefly, a portion of each tumour was pulverized in liquid nitrogen using a microdismembrator (Braun). The resultant powder was vortexed in phosphate buffer and left at room temperature for 30 min. The extract was then added to ethanol:acetone (1:1) containing radio-inert oestrone (500 µg) and centrifuged. The supernatant was evaporated, reconstituted in methanol (70% in water) and left overnight at −20 °C. The mixture was then centrifuged and the supernatant decanted off and evaporated. The residue was partitioned between acetate buffer and ether. Either extracts were evaporated to dryness and reconstituted in toluene:methanol (92:8) and subjected to chromatography on lipidx 5000 columns (Reed \textit{et al.} 1986). Oestrone fractions were further purified by thin layer chromatography on silica gel (HF 254+360) plates using cyclohexane:ethyl acetate (1:1 v/v) as solvent. Procedural losses were monitored by measuring the OD\(_{282}\) of the oestrone fractions. The radioactivity in the fractions was measured by liquid scintillation counting on a 1900 CA tricarb analyser (Packard), the oestrone being dissolved in NE260 scintillant (Nuclear Enterprises).
Peripheral plasma was extracted with ether and purified by column chromatography on Lipidex 5000 and thin layer chromatography as described above.

*In situ* oestrone synthesis was calculated on the basis of $[^3H]$oestrone being formed from $[^3H]$androstenedione. As the aromatase enzyme complex may be present in both the breast and other peripheral tissues, it is possible that some of the $[^3H]$oestrone found in the breast may be formed peripherally, secreted into the circulation and then taken up by breast tissues. To compensate for this, $[^14C]$oestrone was also infused, to determine uptake of oestrone from blood into the breast. Any $[^3H]$oestrone present in breast tissues in excess of that expected from uptake was taken to represent *in situ* oestrone synthesis, thus:

$$[^3H]\text{oestrone}_{\text{tumour}} - \frac{[^{14}C]\text{oestrone}_{\text{tumour}} \times [^3H]\text{oestrone}_{\text{plasma}}}{[^{14}C]\text{oestrone}_{\text{plasma}}}$$

Endogenous oestrogens in breast tissues were measured by radioimmunoassay using essentially a method based on that described by Thijssen *et al.* (1991). In brief, tumour was pulverized in liquid N$_2$ and delipidized as described above, except that radiolabelled oestrogens were added, to monitor procedural losses, and oestrogens were purified on calibrated Sephadex LH-20 columns, which were eluted with toluene:methanol (92:8 v/v). Fractions corresponding to oestrone and oestradiol were collected separately and subject to specific radioimmunoassays. Because patients had been exposed to $[^14C]$oestrone, aliquots of each purified steroid fraction were counted for carbon-14 by liquid scintillation counting and identical amounts of $^{14}$C-labelled oestrogens were also included in assays as samples. Values were corrected for these measurements.

The radioimmunoassay for oestradiol was performed using anti-oestradiol BW 26.9.80 and oestradiol 3-CME iodohistamine as tracer, that for oestrone using an

![Figure 1](https://example.com/figure1.png)

*Figure 1* Effects of inhibitors on aromatase activity (as a percentage of control systems without inhibitor) in particulate fractions of breast cancer (a) and culture of mammary adipose tissue fibroblasts (b). Columns are means and bars are standard errors of the means of three different systems.
antiserum supplied by Dr J Moore (ICRF) and [2,4,6,7-^3^H]oestrone as tracer.

**Results**

**In vitro sensitivity to aromatase inhibitors**

The effects of adding aminoglutethimide, letrozole, anastrozole, formestane or exemestane to particulate fractions derived from breast cancers are shown in Fig. 1a. All drugs inhibited aromatase activity in a dose-related fashion. However, whereas concentrations of aminoglutethimide were required in the µM range, effects could be elicited at nM concentrations with the other drugs. Approximate IC$_{50}$ values were 20 µM for aminoglutethimide, 2 nM for letrozole, 8 nM for anastrozole, 15 nM for exemestane and 30 nM for formestane.

The corresponding data for the same drugs added to cultured fibroblasts derived from mammary adipose tissue are shown in Fig. 1b. Again, all drugs produced a dose-related inhibition of aromatase activity, µM concentration being required for aminoglutethimide and nM concentrations for the remaining inhibitors. Approximate IC$_{50}$ values were 10 µM for aminoglutethimide, 0.8 nM for letrozole, 15 nM for anastrozole, 5 nM for exemestane and 30 nM for formestane.

**Ex vivo studies**

Aromatase activity was measured *in vitro* in paired samples of either breast cancers or non-malignant breast from the same patients taken before and after 3 months of treatment with letrozole. The results are shown in Table 1. Treatment was associated with a decrease in aromatase activity in all three breast cancers studied. In the same patients, a reduced activity after therapy was also seen in the non-malignant breast; however, the effect was less than that in the tumours. In other cases of normal breast, particularly when activity was low before treatment, a paradoxical increase in aromatase activity was seen after 3 months of therapy.

**Effects of inhibitors on aromatase in cultured fibroblasts**

Data on the effects of inhibitors on aromatase in fibroblasts derived from mammary adipose tissue have already been presented in Fig. 1b. The inhibitory results were obtained from experiments in which aromatase was induced by dexamethasone in fibroblasts grown in the absence of inhibitors, the latter being added to the cultures only during the assay for aromatase. However, this model is the reverse of conditions in the neoadjuvant study, described above, in which the inhibitor was present *in vivo*, but absent during the *ex vivo* assay of aromatase. Because of this, cultures of fibroblasts were set up in which aromatase inhibitors were added during the ‘preincubation’ induction period (18 h) with dexamethasone, but were absent during the assay for aromatase. These results are compared with those from the standard aromatase assay, using aminoglutethimide and letrozole as examples, in Fig. 2a and b respectively. In contrast to the inhibitory effects observed when aminoglutethimide was included at the aromatase assay stage, preincubation with aminoglutethimide was associated with enhanced aromatase activity at all concentrations tested ($10^{-7}$ to $10^{-5}$ M). Similarly, whereas letrozole markedly decreased aromatase activity when included in the aromatase assay, preincubation with letrozole at concentrations of 2 and 20 nM caused an increase in aromatase activity; although inhibition was observed at 200 nM, the effect was markedly less than that seen when the same concentration was present in the assay.

<p>| Table 1: In vitro aromatase activity (pmol/g per hour) in paired samples of either breast cancer or non-malignant breast from patients before (pre) and after 3 months of treatment with letrozole |
|-----------------------------------------------|-----------------------------------------------|</p>
<table>
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<th>Non-malignant</th>
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<td></td>
<td>Pre</td>
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<tr>
<td>B</td>
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phase. Interestingly, enhanced aromatase activity was also produced by preincubation with anastrozole, whereas formestane was associated with inhibitory effects whether the drug was included in the preincubation or the incubation phase (data not shown).

Effects of neoadjuvant treatment with letrozole on in situ aromatase and endogenous oestrogens in the breast

A total of 24 women (12 treated with 2.5 mg letrozole daily and 12 treated with 10 mg daily) were studied but, because one individual experienced a complete pathological response and tumour was therefore not available for assay at 3 months, tumour pairs were available for only 23 of them. Results on the relative contribution of in situ synthesis and uptake are shown in Fig. 3. Evidence for in situ synthesis was obtained in 20 tumours (varying from 25 to 75% of the total contribution to the oestrogen concentration); in the remaining three patients, radioactive oestrogen within the tumours could be completely accounted for by uptake from the circulation both before and during treatment. The effects of treatment with letrozole on in situ synthesis in the 20 tumours displaying activity is shown in Fig. 4. Nine of the patients treated with 2.5 mg letrozole displayed a marked decrease in in situ synthesis with therapy, whereas the 10 mg dose was associated with a decrease in in situ synthesis in all cases. The difference between paired pretreatment and 3-month values was statistically significant by sign test (P=0.022

**Figure 2** Effect on aromatase activity (expressed as % of control systems without inhibitors) of either preincubating with drug but assaying in its absence, or preincubating in the absence of drug but assaying in its presence with aminogluthimide (a) and with letrozole (b).
for 2.5 mg and \( P=0.004 \) for 10 mg doses). No significant qualitative or quantitative differences were apparent between doses.

The effects of treatment on endogenous oestrogens (oestradiol plus oestrone) are shown in Fig. 5. Concentrations decreased with the 2.5 mg dose in all cases (although when concentrations of either oestrone or oestradiol were already low before treatment, it was not always possible to detect a decrease for the individual oestrogen). A similar decrease with treatment was also evident in 11 of 12 patients after the 10 mg dose (in the single patient showing no change with therapy, lack of effect was evident for both oestrone and oestradiol). The decrease in total oestrogen was statistically significant for both the 2.5 mg and 10 mg doses (\( P=0.002 \) in each case). However, there were no significant qualitative or quantitative differences between doses.

**Discussion**

Traditionally, aromatase inhibitors have been screened in model systems such as placental microsomes before being tested in phase I trials in which the endpoints are, generally, toxicity and effects on circulating oestrogens. However, because breast cancers in postmenopausal women have a distinctive endocrinology in terms of their oestrogen profiles and their sensitivity to such hormones, it is important to monitor the effects of endocrine agents on the breast and its tumours.

Results have been presented that demonstrate the potential of new drugs such as anastrozole, exemestane and letrozole to inhibit aromatase activity in breast tissues. This is most readily shown *in vitro*, aromatase activity being effectively inhibited in both particulate fractions of breast cancers and cultures of mammary adipose tissue fibroblasts. The sensitivity to individual inhibitors in these systems is similar to that previously reported in placental microsomes (di Salle *et al.* 1992, Plourde *et al.* 1994, Bhatnagar *et al.* 1998), with the newer inhibitors being at least 100-fold more potent than aminoglutethimide and having IC\(_{50}\) values at nM concentrations (compared with \( \mu \)M values for the older drug). Some differences between
test systems were noted. Thus, in breast cancers, the two type II inhibitors, anastrozole and letrozole, were more potent than the two type I drugs, exemestane and formestane (as is the case in placental microsomes) (Miller 1997a), but, in cultured fibroblasts, letrozole and exemestane seemed to have increased potency. The reason for this is not immediately apparent - it could be one of differences either between malignant and non-malignant tissues or between disrupted and whole-cell preparations. Interestingly, letrozole seems to have increased potency in other whole-cell systems, and it has been postulated that the drug accumulates to a greater extent in such systems (Bhatnagar & Miller 1998).

Because of the potential to inhibit aromatase within the breast and the promising results of the newer drugs in the treatment of advanced breast cancer (Buzdar 1999, this issue), we have embarked upon a series of studies in which the new generation of aromatase inhibitors have been used as neoadjuvant endocrine therapy in patients with large primary cancers. These investigations have allowed us not only to study the clinical effects of the drug by measuring the change in size of the primary tumour (Dixon et al. 1999), but also to determine endocrinological effects within the breast by biopsying breast tissue before and after 3 months of treatment with inhibitors.

We initially studied the effects of letrozole by comparing in vitro assays of aromatase activity in paired specimens of both malignant and non-malignant breast tissue before and after treatment. The results showed the expected inhibition in malignant tissue, but in non-malignant breast the degree of decrease with treatment was less marked, and paradoxical increases in activity were seen in cases in which aromatase activity was initially low. We have reported similar paradoxical increases in aromatase activity in tumours from patients treated with aminoglutethimide (Miller & O'Neill 1987); this activity was shown to be still sensitive to aminoglutethimide, by demonstrating inhibition after in vitro incubation with the drug. To explore further the nature of these effects, cultures of mammary fibroblasts were preincubated with aromatase inhibitors (to simulate patient treatment) and then assayed in the absence of drugs (as were the breast tissues from treated patients). Interestingly, under these conditions all three type II inhibitors (aminoglutethimide, letrozole and anastrozole) failed to realize their full inhibitory potential and, at certain concentrations, were associated with enhanced activity. The lack of full inhibition and the enhanced activity is likely to reflect the reversible nature of these inhibitors and the ability of the inhibitors to induce aromatase mRNA/stabilize aromatase protein which has been reported by Harada et al. (1999) and Chen et al. (1999). In contrast to these effects, the type I inhibitor, formestane, was always associated with decreased aromatase activity; indeed, inclusion in the 18-h preincubation period tended to produce greater effects than were achieved in the 5-h assay. This probably reflects the irreversible 'suicide' mechanism of action of this inhibitor (Brodie et al. 1981). These observations may have clinical relevance in that, although in the short-term type II inhibitors may effectively cause oestrogen

Figure 5 Effects of 3 months of treatment with letrozole (either 2.5 or 10 mg daily) on endogenous oestrogens within the breasts. Values are combined concentrations of oestrone (E1) and oestradiol (E2).
blockade (see below), chronic administration might increase the aromatase enzyme to such an extent that the drugs may no longer be efficient. Compatible with this, there is the suggestion that oestrogen concentrations may increase at relapse in patients treated with aminoglutethimide (Dowsett et al. 1984). Under these circumstances, it might be expected that type I inhibitors such as formestane may produce beneficial effects in patients relapsing while receiving type II drugs, as has been observed clinically (Coombes et al. 1984). Such non-cross-resistance to aromatase inhibitors points to a role for type I inhibitors following type II inhibitors, despite the inherently lower potency of the former in experimental systems.

The other important point to derive from the in vitro studies of tissues from inhibitor-treated patients is that in vitro assays probably do not accurately reflect the degree of inhibition produced in situ by type II agents. Thus, whereas the in vitro studies yield results in which inhibition is incomplete or activity may be increased, other endocrinological data on circulating oestrogens or whole-body perfusion studies suggest that inhibition of peripheral aromatase is almost total (Lonning 1996). Because of this, we considered it essential to measure the effects of treatment using a protocol that could measure events occurring in situ within the breast. To achieve this, patients were infused with radioactively labelled androgen and oestrogen before and after treatment with letrozole.

These studies confirmed that breast tumours obtained oestrogen both by uptake from the circulation and by local biosynthesis from androgen precursors. The relative contribution of uptake and synthesis varied between different tumours, but in situ production was evident in 20 of the 23 cancers examined and, in many tumours, local biosynthesis seemed to be the major source of oestrogen. In situ aromatase activity was also reduced after letrozole treatment in 19 of the 20 patients with the potential for in situ production of oestrogen. The reason for a failure to demonstrate a decrease with treatment in the remaining patient is not apparent. It may be that the aromatase activity within the tumour was inherently insensitive to aromatase inhibitor and, interestingly, pretreatment in situ synthesis was the lowest amongst the tumours. Nevertheless, treatment produced a marked decrease in amounts of ‘whole-body’ conversion of androgen to oestrogen (as measured by $[3^H]$oestrone in plasma), a suppression of endogenous concentrations of oestrogen within the breast, and a clinical response that would be compatible with inhibition of aromatase.

Measurements of tumour ‘total’ oestrogens showed that letrozole was capable of reducing local concentrations within the breast in all but a single patient. This effect was also seen in the three tumours that failed to demonstrate in situ synthesis; presumably, in these patients, endogenous oestrogens are entirely accounted for by peripheral aromatase (interestingly, whole body aromatase, as measured by $[3^H]$oestrone in plasma, was markedly reduced by treatment). Whereas inhibitory effects were seen in total oestrogen, it was not always possible to show a decrease in both oestrone and oestriadiol, especially when pretreatment values were already low. However, this may have been because patients received $^{14}C$-labelled oestrone in the 18 h immediately before surgical removal of breast tissue, and all tumours contained radioactive oestrogen which contributed to the total oestrogen pool within the tumour; although an appropriate correction was made, this may be inaccurate when endogenous concentrations of oestrogen are low.

In the single patient in whom total oestrogen failed to decrease with treatment, the lack of effect was apparent for both oestrone or oestradiol. However, letrozole inhibited in situ and total body aromatase and the patient also experienced a clinical response to treatment. The reason for these inconsistent effects is not apparent, and should not cloud the observation that letrozole generally produced a marked inhibition of aromatase activity and decrease in endogenous oestrogens. These actions are compatible with the clinical benefits, in terms of tumour shrinkage, that were achieved with letrozole treatment (Dixon et al. 1999).

In conclusion, the new generation of aromatase inhibitors, which include anastrozole, letrozole, exemestane and formestane, are extremely potent agents capable of profoundly influencing endocrine events within the breast. They merit a place within the armament of hormone deprivation therapies.

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