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Hormonal regulation of the normal breast

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Abstract

The breast is a target organ for reproductive hormones but basic knowledge on hormonal effects is very poor. Available data indicate that the breast is regulated in a specific manner which is distinct from the endometrium and other target organs. It seems clear that the breast undergoes cyclic changes during the menstrual cycle and that *in vivo* there is a direct stimulatory action of progestogens on the breast. In surgically postmenopausal female macaques continuous combined estrogen/progestogen therapy was found to induce greater proliferation than estrogen alone.

Keywords: Estrogen; Progestogen; Mammary profileration

The breast is a target organ for reproductive hormones but basic knowledge on hormonal effects is very poor. In particular the influence of estrogens and progestogens on mammary epithelial proliferation has been a matter of much controversy. When cultured in vitro, both normal and transformed breast epithelial cells seem to behave like the endometrium, i.e. proliferation is stimulated by estrogens and inhibited by progestogen addition [1]. Thus, an antagonistic effect of the two major sex steroids would seem reasonable. On the other hand evidence for a synergistic action comes from in vivo studies of biopsy specimens of 'normal' breast tissue near fibrodenomas fibrocystic disease or breast cancer. In menstruating women maximal epithelial cell proliferation has been demonstrated to occur during the luteal phase when progesterone levels are high [2]. One tentative explanation to the different cell reactions in cultures and in vivo could be that cultured epithelial cells are deprived of their normal complement of blood vessels, adipose tissue, stroma and myoepithelial cells. Surrounding tissue exerts considerable paracrine and hormonal influence in vivo [3].

Measurement of estrogen and progesterone receptors in cytologic smears by the use of monoclonal antibodies provides an accurate and reliable technique that can be performed on isolated cells procured through fine needle aspiration. Using a needle with an outer diameter of 0.6 mm as described by Franzén and Zajicek [4] percutaneous fine needle aspirations were performed in healthy women at different phases of the menstrual cycle. We analysed cytologic samples of breast epithelium obtained by fine needle aspiration

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biopsies from healthy volunteers for estrogen and progesterone receptor content [5]. In women with a hormonally-confirmed ovulation there was a marked decline in detectable estrogen receptors from the follicular to the luteal phase. In contrast, progesterone receptors were detected at high and constant levels during the menstrual cycle. Data indicate that the breast is regulated in a specific and so far incompletely understood manner which is distinct from the endometrium and other target organs.

It seems clear that the breast undergoes cyclic changes during the menstrual cycle and also that in vivo there is a direct stimulatory action of progestogens on the breast. Thymidine kinase, an enzyme of the nucleotide synthesis considered to be an important marker of cell growth is stimulated at physiological progestogen concentrations [6]. Insulin receptor content and insulin stimulation of cell growth is also enhanced by progestogens in human breast cancer cell lines [7]. This observation could also be relevant to the fact that postmenopausal obesity has been demonstrated as a risk factor. The antagonistic action of progestogen on the estrogen induced stimulation of the endometrium has been related to the stimulatory effect of progestogen on the activity of the enzyme 17β-dehydrogenase. This enzyme converts highly active estradiol to less active metabolites in target organs. Recent data indicate the presence of two different genetic types of 17β-HS.D. Genetype I is expressed in breast cancer and favours reductive activity and transformation from estrone into estradiol. The reductive activity is enhanced by progestogens and growth factors like IGF-1 [8].

Combined estrogen/progestogen therapy is used by women all over the world for contraception and postmenopausal replacement. Even in a small country like Sweden (population 8.6 million) more than one million women are treated every day. Hormonal therapies provide a variety of beneficial health effects for women but may also be associated with an increased risk of cancer in target organs [9]. Breast cancer is the most common female cancer and a major cause of death in middle-aged and elderly women. Estrogen is implicated in the development and growth of this malignancy. About 2/3 of the breast cancers are estrogen receptor positive and determination of sex steroid receptors is crucial for the judgement of prognosis and choice of treatment. Early menarche, late menopause, short menstrual cycles, first child birth after the age of 30, postmenopausal obesity and hormone replacement therapy have been defined as risk factors in epidemiological studies [10]. However, it is uncertain whether hormonal risk factors also have a prognostic significance in established disease. Late menarche, early menopause and high parity were recently found to have an adverse effect on breast cancer prognosis [11].

Human and non-human primate mammary glands have many similarities in terms of anatomy, hormonal regulation and cytokeratin immunophenotypes that are not shared by the commonly used laboratory rodents [12]. We believe that the cynomolgus macaque model offers an unique opportunity for study on mammary gland regulation, since it enables evaluation of the effects of long-term HRT on various locations of the breast from healthy subjects. In surgically postmenopausal female macaques continuous combined therapy with conjugated equine estrogens and medroxyprogesterone acetate was compared with estrogen alone with respect to breast proliferation. For a period of two and a half years treatment doses equivalent to those used by women were administered and mammary gland proliferation was assessed by morphometric and stereologic means. In this study continuous combined estrogen/progestogen therapy was found to induce greater proliferation than estrogen alone [13].

Further studies from our group will evaluate sex steroid receptor variation, breast cell proliferation and growth factors in both cycling and estrogen/progestogen treated healthy women and cynomolgus macaques.

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