Prolactin and Breast Cancer

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Editor: The onrushing pace of new developments has made the possible relation of prolactin, a single chain polypeptide hormone, and human breast cancer an important experimental subject. What is known about prolactin and breast cancer in animals?

Dr. Sherman: In the C3H strain of mice, which is infected with mammary tumor virus, mammary cancer develops spontaneously in females from hyperplastic alveolar nodules that arise from apparently normal glandular epithelium. The progression of hyperplastic nodules to mammary cancer is at least partially dependent on prolactin. In rats, both prolactin and estrogen seem to be of primary importance in influencing the growth of breast tumors, which are chemically induced. High doses of estrogen stimulate pituitary secretion of prolactin in rats, yet paradoxically result in tumor regression, probably through the peripheral effects on breast tissue. Some of the strongest evidence for the role of prolactin in rodent breast cancer has been obtained by the manipulation of serum levels with L-dopa or the ergot derivatives.

Editor: Do these drugs stimulate or diminish prolactin levels in vivo?

Dr. Sherman: L-dopa and ergot derivatives increase secretion of prolactin-inhibiting factor, thereby inhibiting hormone release and lowering prolactin levels in the blood. Ergot drugs, such as ergocornine and 2-bromo-alpha-ergocryptine, may act directly on the pituitary to restrict prolactin production.

Lowering serum prolactin with ergot drugs or 6-methyl-8-beta-ergoline-acetonitrile, a synthetic ergot, suppresses the development of nodules and decreases the frequency of mammary lesions, but has little effect on established tumors. Welsch and Griebler found that ergot drugs reduced the growth of hyperplastic nodules and the incidence of mammary cancers in both nulliparous and
multiparous mice, although effectiveness was greatest in young virgin mice. Tumors developed in only one of 90 mice treated with ergot for one year and discontinued for 10 months, as compared to 24 of 90 untreated controls. Reduced prolactin levels decreased the rate of mammary tumors in the presence of normal ovarian activity and estrous cycles. A study by Yanai and Nagasawa confirmed that ergot drugs inhibited the growth of hyperplastic alveolar nodules in mice and greatly decreased the number of tumors, if the drugs were started early. Once mammary tumors are established in the mouse system, prolactin does not appear necessary for their maintenance or growth.

Editor: Have the effects of increased serum prolactin been studied?

Dr. Sherman: Yes. In rats, high fat diets raised both prolactin levels and induction rate of mammary tumors by dimethylbenzanthracene (DMBA), implying that prolactin may be a mediating factor in the increased frequency of tumors. Supporting this hypothesis is the observation that 2-bromo-alpha-ergocryptine, which lowers serum prolactin, negates the higher incidence of tumors in rats on high fat diets.

Paradoxically, in female Sprague-Dawley rats, both increases in prolactin (produced by pituitary grafts, drugs, median-eminence lesions, handling, ether anesthesia, or administration of estrogen and progesterone) and decreases in prolactin (caused by hypophysectomy or ovariectomy) inhibit induction of mammary tumors by dimethylbenzanthracene, but only if administered before the carcinogen or soon thereafter. Stimulation of breast tissue by superphysiologic amounts of prolactin apparently "protects" the breast from dimethylbenzanthracene; low levels of prolactin and estrogen may limit tumors because a sufficiency of these hormones may be necessary for tumor development.
In rats, once tumors are established, their size and number continue to be influenced by the hormonal environment. Smaller lesions respond more rapidly and completely to ergocornine than larger ones, suggesting that even induced cancer becomes more hormone independent with age.

Editor: How applicable are these experimental studies to humans?

Dr. Sherman: It has recently been hypothesized that human breast cancer proceeds along lines similar to murine mammary tumors in the progression from hyperplastic nodules to cancer. Wellings and Jensen found hyperplastic lobule-like structures and early foci of ductal carcinoma in situ in the terminal ducts and lobules of human breast tissue. Hyperplastic changes occurred most often, and showed a higher grade of atypia, in cancerous breasts.

However, the hormonal role in breast cancer in humans is much less straightforward than in animals. First, the actual carcinogens (inducers) such as viruses or chemicals are not known; therefore, the time of induction of breast tumors is not ascertainable. Second, prolactin is one of several hormones (including estrogens and growth hormone) that may function as tumor promoters by activating transformed mammary cells. (Figure.) If one looks only at fasting serum levels of prolactin to indicate its role in human breast cancer, one is quickly disappointed. There is no difference in this measurement between patients with breast cancer and matched controls. Yet, Kwa and his coworkers, who noted this, also found higher prolactin levels in 64 members of nine families with a high incidence of breast cancer, defined as more than two first-degree relatives with a history of breast cancer. This suggests that prolactin may be a factor in certain high-risk populations.

Editor: Does the inability to demonstrate fasting elevated prolactin levels in patients with breast cancer rule out its possible importance?

Dr. Sherman: No. It must be remembered that absolute levels of prolactin may not be the essential element. The ability of prolactin to stimulate mammary tumor growth may depend more on the number of receptor sites in the tumor tissue that are able to react with the hormone. In turn, the number of these sites may be influenced by other hormones including estrogens. In fact, it was recently shown that prolactin stimulates estrogen receptor binding capacity in explants of rat DMBA-induced tumors. The growth of such estrogen-responsive tumors may therefore depend in part on the number and functional integrity of prolactin receptor sites in breast tumor tissue.

Editor: Has manipulation of prolactin by drugs been studied in man?

Dr. Sherman: L-dopa has been found to produce objective and subjective remissions in only a few patients and for a very short time. Frantz and his colleagues found it necessary to treat some patients as often
Figure. Hypothetical role of hormones and environmental carcinogens in the biochemical transformation and later neoplastic degeneration of human breast cells.

Route A shows possible fates of an alveolar cell transformed to one with malignant potential. Route B shows fate of an alveolar cell protected by early hormonal stimulation. Open triangles indicate onset of menopause.

as every two hours to maintain low serum prolactin. Since prolactin levels peak during sleep and early in the morning, continuous control is extremely difficult.

A study of 30 patients by Minton evaluated the ability of L-dopa not only to ease bone pain in metastatic breast cancer, but more importantly, its potential role in predicting response to endocrine ablation. Three of his 10 patients with relief of pain were operated upon. One had an oophorectomy and subsequent remission for eight months. Twenty months after adrenalectomy, another patient was tumor free, and following hypophysectomy, a third responded but only for one month. Unfortunately, this study cannot substantiate the value of L-dopa in predicting response, since only a small number of patients, and only those with relief of pain, underwent surgery.

Editor: What is the effect of increased prolactin levels in humans?
Dr. Sherman: Women living in countries with high fat consumption, which raises prolactin levels, do have a greater risk of breast cancer. However, in a study by Turkington and colleagues, previously undetectable prolactin was subsequently found in very high concentration in some patients who had an objective remission after pituitary stalk section, which increases serum prolactin. Herein lies a seeming inconsistency with the prolactin hypothesis of human breast cancer.

Editor: Can this be explained?

Dr. Sherman: The perplexing effects of stalk section are possibly explained by the varying prolactin dependence of tumors. Hormonal requirements of breast tumor tissue obtained by biopsy and cultured in vitro have been studied by the Tumour Biology Group at Westminster Hospital in London. Prolactin was needed to maintain cell viability in 32 percent of the tumors, as measured by continued high activity of the pentose-shunt pathway, which is essential for cancer tissue survival. Later, it was reported that preservation of viability was found in eight percent of cultured tumors with a low-normal concentration of prolactin in tissue-culture fluid (6 ng. per millimeter). Such concentrations are difficult to achieve with hypophysectomy alone, perhaps explaining the failure of this operation in some patients who may have prolactin-dependent tumors.

Editor: Why might some tumors be prolactin dependent and others not?

Dr. Sherman: I wish I knew. Prolactin receptors have been identified in both mouse and rat mammary tissue and tumors, and their number has been correlated with the prolactin responsiveness of tumors. However, these receptors have not yet been detected in human breast cancer cells. Cytoplasmic estrogen receptors have been found in human breast tumor cells; their presence correlates with tumor regression after endocrine ablation, while their absence correlates with refractoriness to such ablation. The hormone responsiveness of breast tumors, therefore, seems linked to the presence of their specific hormone receptors in the tumor tissue.

Editor: Can the prolactin dependency of a tumor be exploited clinically?

Dr. Sherman: Evidence indicates that some prolactin-dependent tumors can survive on low levels of prolactin, but when zero serum levels are approached, breast tumor regression can occur. Further work, particularly on tumors demonstrated to be prolactin dependent in vitro, is necessary in order to evaluate the effect of low serum prolactin levels in patients with breast cancer. By determining the dependence and responsiveness of breast tumors to serum prolactin and growth hormone, it may be possible to predict the eventual therapeutic effects of hypophysectomy, other endocrine ablation or drugs.
Editor: Will drugs be used in the future to control prolactin secretion and induce tumor regression?

Dr. Sherman: L-dopa and ergot derivatives only reduce prolactin secretion; less toxic and more effective substances will probably be required before the drugs become useful in long-term treatment. New ergot alkaloids, causing less vasoconstriction, and ergoline derivatives are currently being tested in animals. It may be necessary to use combinations of drugs that simultaneously lower serum prolactin concentration and antagonize the hormone’s effects on the breast. I must add a caveat here. Just a year ago, the group at Westminster Hospital reported that there was in vitro dependence on growth hormone in the same human breast cancers that demonstrated prolactin dependence. This may explain in part why prolactin inhibition alone can fail to induce complete regression of tumor growth. It certainly re-emphasizes the interrelation of hormones that promote breast tumor growth.

Editor: Might prolactin be utilized to predict the occurrence of breast cancer?

Dr. Sherman: Because prolactin may be an important factor in certain populations, its measurement in peripheral blood may help identify those at high risk before cancer develops. It may even be possible to prevent breast cancer in women by suppressing the development of hyperplastic nodules—if they are proven to be forerunners of cancer in women, as in animals.

Furthermore, the hormonal responsiveness of atypical nodules in humans must be determined. Because responsiveness to hormone therapy is usually lost once frank breast cancer develops, and because remissions are temporary, suppressing atypical precancerous lesions hormonally would offer the best chance of preventing breast cancer. Continued work on the relationship of prolactin and breast cancer should help answer some of these questions and realize some of these hopes.

Editor: Thank you, Dr. Sherman.