Estrogen, Tamoxifen, and the Brain

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With the aging of the population and the increasing numbers of individuals that are being diagnosed with dementia or milder forms of cognitive dysfunction, there is heightened interest in identifying risk factors and protective factors for this important health problem. A series of recent publications (1–6) have called increased attention within the cancer community to the complaints of memory loss and decreased cognitive abilities from patients in active chemotherapy treatment, as well as of those who have received chemotherapy within the previous several years. The results of these studies (1–6) suggest that neurocognitive testing detects clinically significant, but sometimes subtle, abnormalities in a subset of patients who are exposed to both high-dose and standard-dose chemotherapy treatments. In this issue of the Journal, Ernst and colleagues (7) explored the association between the use of tamoxifen therapy in elderly breast cancer patients (mean age = 70.4 years) and patterns of brain metabolism by comparing data from those patients with data obtained from an age-matched sample of healthy older women who had received hormone replacement therapy (HRT), largely as unopposed estrogen, and data from an age-matched sample of healthy older women who had never received HRT or tamoxifen. These investigators made use of a noninvasive neuroimaging tool, proton magnetic resonance spectroscopy, to measure the concentrations of specific biochemical markers in defined areas of the women’s brains.

In this cross-sectional study, the authors hypothesized that the breast cancer patients who had received tamoxifen therapy would have higher cerebral concentrations of myo-inositol (MI), a compound previously implicated in glial metabolism, than would the healthy women who had not received tamoxifen. Thus, the level of MI was used as a marker to detect changes in brain chemistry associated with tamoxifen exposure. They examined three regions of each subject’s brain: the frontal white matter, the basal ganglia, and the left hippocampal region. All subjects were evaluated with physical examinations and laboratory tests to rule out the presence of any serious metabolic, psychiatric, or neurologic disorders. Brief cognitive testing, using a modified mental status examination and two tests of psychomotor speed, detected no statistically significant differences in cognition among the three groups of women. Although the authors did not report on the estimated levels of intellectual functioning in these women, educational attainment was similar for the three groups of women. Ernst and colleagues (7) found a statistically significant difference in cerebral MI concentrations among the three treatment groups ($P = .02$). Whereas the overall concentration of MI was statistically significantly lower in the tamoxifen ($P = .01$) and HRT ($P = .03$) groups than in the control group, the authors found that the most pronounced difference in the MI concentration among the treatment groups occurred in the basal ganglia. In addition, they described an inverse relationship between the length of exposure to tamoxifen and MI concentrations in the basal ganglia and in the hippocampus. Based on these findings, the authors suggested that patients may have received neuroprotective benefits from tamoxifen and HRT, as evidenced by the lowered MI concentrations in their brains. Even if one were to accept the spectroscopy findings at face value, however, it is highly speculative to interpret them as indicative of neuroprotection. In fact, decreases in cerebral MI levels that are measurable by proton magnetic resonance spectroscopy are associated with a variety of processes, including nonspecific cerebral insults that result from exposure to ingested ethanol (8) or cirrhotic hepatic encephalopathy (9), the latter of which is completely reversed following liver transplantation. It is thus not even clear whether the decreased cerebral MI levels observed by Ernst and colleagues in the tamoxifen users are, in fact, a good thing, let alone specifically neuroprotective.

Although the findings of Ernst et al. (7) are provocative and might be reassuring to the millions of women who have taken or are taking tamoxifen, one must be cautious about data that were obtained from a study that included only 16 elderly breast cancer patients who had received tamoxifen therapy. While these authors posit a benefit for study subjects who used either tamoxifen or HRT, it is important to consider alternative explanations for these results that take into account all of what we know about the physiologic effects of estrogen in women, as well as the relationship between lifelong exposure to estrogen and the risk for breast cancer (10–12). First, the observations of lower MI levels in the brains of women on tamoxifen and HRT in this study could reflect the lifelong exposures of these women to endogenous and exogenous estrogens, which may well have reduced the extent of glial cell proliferation in their brains. Specifically, it is well-established that older women who develop breast cancer have higher circulating levels of estrogen after menopause than healthy elderly women who do not have breast cancer (13), they have denser bones and, thus, a lower risk of osteoporosis (14,15), and they have greater breast density (10)—all of which are associations that reflect greater lifelong exposures to endogenous estrogens and, consequently, tissue responsiveness to the effects of estrogen. Thus, one wonders if the brains of the women with breast cancer in the Ernst et al. study were exposed to the beneficial effects of endogenous estrogens long before those women used tamoxifen. Similarly, compared with women who do not take HRT after menopause, those who do take HRT have higher circulating levels of estrogen, and as a result, their bones are protected from the development of osteoporosis, and they have denser breasts (16). These same women are at increased risk of developing breast cancer, such that each year of HRT use is equivalent to an additional year of menstrual life in...
The increased risk of breast cancer in postmenopausal women who use HRT for more than 5 years is also comparable to the risk of postmenopausal breast cancer associated with lifetime weight gain, the latter of which is mediated through the association of higher circulating levels of estrogen after menopause with obesity (10,18). In the Ernst et al. study (7), the women in the HRT group had taken this therapy for a mean of 20.8 years (standard deviation = 10.5 years), which is an extensive exposure. Thus, the HRT and tamoxifen groups in this study may have had comparable exposures to estrogen that could explain their similar brain metabolism findings.

Second, there is much we do not know about the women who were in the control group of this study. We do not know their body mass indices, their reproductive histories, or information about other relevant factors that would allow us to assess their lifetime exposures to endogenous estrogens (17,18). Without controlling for these important exposures, it is difficult to evaluate the suitability of these women as a comparison group for the women with breast cancer who used tamoxifen. Perhaps a more appropriate control group would have consisted of women who were diagnosed with breast cancer and had not taken tamoxifen; such a control group would have allowed a clearer examination of the effect of tamoxifen in women whose lifetime exposures to estrogens were comparable.

Third, the design of this study seemed exploratory rather than hypothesis-driven, without specific focus on the known effects of estrogen on the brain. A body of literature suggests that the effects of estrogen on the brain are most closely associated with verbal memory (19) and that estrogen does not seem to affect other aspects of cognitive functioning (20). Estrogen receptors in the brain are concentrated in the hippocampus (21–23), one of the areas studied in this investigation. Thus, it is surprising that the statistically significant differences in metabolite levels were detected only in basal ganglia. Those differences could be a chance finding, given the multiple statistical tests performed. Furthermore, why did the authors perform specific cognitive tests of psychomotor functioning rather than tests that assess the potential effects of an antiestrogen? An a priori focus on the basal ganglia and psychomotor functioning would not be a primary consideration in the evaluation of tamoxifen or HRT use. Moreover, although the investigators found no difference in brief testing of cognitive function among the three groups of women using a modified version of the Mini-Mental State Examination, it is important to note that this test would not detect very subtle differences in cognitive functioning. Finally, the means and standard deviations for performance on the Digit Symbol Substitution Test task reported by Ernst et al. for the three groups of women in their study would place all three groups in the bottom 2% of the general population (at least using the reference cited in their paper), performances that stand in stark contrast to these same women’s reported performances on the Trail Making Test-part A and on the modified Mini-Mental State Examination (7).

In a recent study of cognitive functioning in younger breast cancer survivors (mean age = 47.6 years, standard deviation = 5.5 years), we found that, at 2–5 years after diagnosis, the women who received local therapy only and were not exposed to any adjuvant chemotherapy or hormonal therapy performed as well as, or slightly better than, healthy women (matched to the breast cancer survivors with respect to age, educational level, and IQ) on several neurocognitive tasks (e.g., verbal memory, visual memory, and visuospatial functioning) (24). These women were initially recruited for a larger cohort study to examine the reproductive health effects of breast cancer treatment in younger women. As part of that larger study, dual energy x-ray absorptiometry (DEXA) whole-body bone density examinations were performed. We have previously reported that these younger breast cancer survivors had bone density measurements that were statistically significantly higher than those of age-matched population control subjects (25). It is interesting that, in the subgroup of breast cancer survivors who participated in our cognitive functioning study (N = 53), there was a positive correlation between whole-body bone density and verbal memory (R = .35, P = .009; Ganz PA, Castellon SA, Petersen L, Abraham L, Greendale GA: unpublished data), which provides some support for an association between lifelong exposure to endogenous estrogens and cognitive functioning.

Finally, one must question what the relationship is between the brain structures (either anatomical or biochemical) and the brain functions reported by Ernst et al. (7). Because the women in that study did not undergo detailed neuropsychological testing, nor were any self-reports of changes in cognitive functioning obtained, it is difficult to interpret the biochemical differences detected by imaging the brains of the women in that study. Specifically, it is not possible, with the available data, to convincingly link the lower MI concentrations observed both in women with breast cancer who were treated with tamoxifen and in healthy women with long-term exposure to HRT to the presumed neuroprotective effects of these agents. Furthermore, to date, there are no prospective, placebo-controlled data available on the effects of tamoxifen on the cognitive functioning in healthy women or in women with breast cancer. As for the potential value of HRT as a neuroprotective agent, we should probably wait for definitive results from the Women’s Health Initiative Memory Study (WHIMS) trial (26), which is prospectively evaluating a sample of older women participating in the HRT trial component of the Women’s Health Initiative. This double-blind, prospective trial will evaluate all of the risks and benefits of HRT and should provide us with conclusive information about the value of HRT for the maintenance of cognitive function and the prevention of dementia. Finally, within the ongoing breast cancer prevention trial—the Study of Tamoxifen and Raloxifene (STAR)—cognitive functioning is being assessed in a special substudy in the two arms of the trial, using the same testing strategy that is being used in the WHIMS trial. Thus, in a few years, we may have reliable information about the neurocognitive effects of estrogen and tamoxifen on the brain.

REFERENCES


Note

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