Nonsteroidal Estrogens and Estrogen Antagonists: Mechanism of Action and Health Implications

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Endogenous estrogens comprise a family of compounds that have a polycyclic structure and contain a steroid nucleus. These compounds exhibit a wide diversity of biochemical and biological activities. Estrogens both induce and stimulate the cellular proliferation and differentiation of specific cell types in target tissues, a prime example being the critical role of these hormones in sexual differentiation and reproduction. Estrogens also exert a critical role in body fat deposition and in preventing bone resorption in the maintenance of bone structure. Given that these compounds exert such a wide range of activities without requiring absolute structural specificity and that there are in existence a tremendous number of related naturally occurring and synthetic polycyclic compounds, it is highly likely that compounds other than endogenous steroidal estrogens will possess at least some estrogenic properties. This, in fact, is the case. Many of these compounds have been found to inhibit the action of endogenous mammalian steroidal estrogens. Compounds exhibiting this inhibitory activity have been called antiestrogens. Although the terms antiestrogen and antiestrogenic are now widely used in the literature, they do not accurately reflect or describe the properties of these compounds. Antiestrogens, in the strict sense of the word, should be substances that in and of themselves exhibit biological properties opposite to those of estrogens. Typically, what is actually measured is the ability of these substances to inhibit estrogen activity in the presence of estrogens. Therefore the terms estrogen antagonist or estrogen inhibitor would more correctly describe this biological activity. The inhibitory effect is analogous to that which is observed for estrogen receptors (ERs) and to compete with E2 for binding to ER, although this binding was very weak; the IC50 (concentration that causes 50% inhibition of growth) was 23 μM, compared with 0.063 μM for tamoxifen. It has been previously shown that I3C, ICZ, MC, and TCDD bind to the aryl hydrocarbon (Ah) receptor and are considered Ah receptor agonists (4-6). Liu et al. conclude that the induction of CYP1A1 gene expression is not the primary factor in the inhibitory estrogenic properties of ICZ, since the IC50 inhibition is seen at lower concentrations and after a shorter amount of time than is required for CYP1A1 induction. The suggestion that ICZ can inhibit estrogen activity via induction of the cytochrome P450 monooxygenase system comes from studies showing that TCDD and I3C increase CYP1A2-catalyzed 2-hydroxylation of estradiol and, as a consequence, decrease the estrogen response (7). Liu et al. (I) propose that Ah receptor agonists act antagonistically toward estrogens by an as-yet-unknown cellular signal transduction interaction between the Ah

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system and ER system. The direct competitive binding of ICZ to ER does not appear to be a factor, since the concentration required to displace E2 is much higher than that required to inhibit the action of E2.

The mechanism by which Ah agonists interfere with the estrogen cellular signal transduction system is not addressed in this article and remains an important question; therefore new data are needed before this hypothesis can be proven or disproven. There is also the possibility that the inhibition of estrogen-induced cellular proliferation may result from genotoxicity; this explanation is plausible in the case of cells treated with MC or TCDD, since these compounds are known to be genotoxic (8). The possibility of genotoxic effects is, however, not addressed in the Liu et al. study.

The importance of estrogens and their antagonists is derived from evidence that estrogens are a factor in the etiology of cancer at a number of sites, including the breast, the endometrium, and the prostate (9-11). Epidemiological studies have shown that populations that consume high amounts of vegetables, fruits, and soy products have a lower incidence of these cancers (12). High levels of flavonoids, isoflavonoids, lignans, coumestrol, and a number of other classes of relevant compounds are found in dietary plant sources. There are examples in these various classes of compounds that have estrogenic and/or estrogen inhibitory activities. In the past few years, there has been increased interest in the hypothesis that the antagonistic estrogen properties of plant compounds are responsible for the lower incidence of breast cancer in populations that consume high amounts of these substances. Particular attention has been given to isoflavonoids, since they are found predominantly in soy products (which are consumed in low amounts in western countries but in high amounts in Japan). They have also attracted attention because they can be detected at higher levels in the urine and serum of people who consume high amounts of soy products. By contrast, a number of other plant compounds have not been detected in serum. The beneficial effects of consuming a diet containing high levels of phytoestrogens must be weighed against the potential dangers, and understanding this balance at the fundamental level is complicated because of the dual activities—estrogenic versus estrogen antagonistic—of these compounds. In addition, most of these compounds can induce the enzymes that cause hydroxylation of estrogens via the cytochrome P450 monooxygenase enzyme system, resulting in a decrease or total loss of biological activity.

It has been documented that high ingestion of specific phytoestrogens by animals can interfere with reproductive function (13-15). A classic example is the observation of a decrease in the fertility of sheep that have grazed exclusively on subterranean clover pastures in Australia (13). This example is extreme, since the plasma levels of equol and daidzein in these animals were higher than are seen in any human population (16). Daidzein, in the form of its glycoside, is one of the major isoflavonoids found in soy, and equol is formed by intestinal bacterial action on daidzein. In humans, there is no evidence that dietary plant compounds significantly alter reproductive function (16), but this may be explained by dosage considerations or by metabolic inactivation of these compounds. There is also, unfortunately, no compelling evidence in humans of a direct preventive or inhibitory effect of these compounds with regard to cancer of estrogen target tissues. There are data from animal studies showing inhibition of chemically induced mammary tumors in rodents as a result of feeding them soy or genistein (17). The major research challenge in this area is to discover compounds that have much higher estrogen inhibitory activity than estrogenic activity and that can reach the necessary concentrations in target tissues to exert their effects. Tamoxifen (a synthetic compound) has, to some extent, these properties. The search for naturally occurring substances is driven by the hope that side effects can be reduced or eliminated and that safer and more effective chemopreventive and chemotherapeutic agents can be made available. The article by Liu et al. provides some of the methodology necessary for achieving this objective.

References


Notes

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