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Potential Carcinogens from Steroid Hormones and Diethyl Stilbesterol (DES): Chemical Relationships between Breast, Ovarian and Prostate Cancers

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Abstract

With the exception of certain environmental causes of cancer like sun and occupational exposure (asbestos), many malignancies result from smoking, alcohol or dietary factors and others may be due to endogenous factors. While a large amount of research has focused on exogenous carcinogens both environmental and dietary, much less has been devoted to potential endogenous cancer initiators. In part, this stems from disbelief that naturally-occurring compounds in man are carcinogens. Yet, reactive metabolites of the steroid hormones and related compounds have the potential to transform cellular nucleic acids and thereby initiate precursors to the malignant cell.

An example is a potential metabolite of estradiol, which could lead to catechol estrogens, was shown to be as mutagenic as 3-methylcholantrene in 1980. And yet, no further research has been done to determine whether this proposed metabolite occurs in mammalian systems and if it does, whether it is a causative agent in breast or ovarian malignancies.

Four important questions are: (1) if such metabolites arise *in vivo*, will tests show them to be carcinogenic?, (2) is there a dose-response relationship, in their causation of malignancies?, (3) what are the biological mechanisms, by which these compounds arise?, and (4) are these pathways perturbed in breast and prostate cancer patients, leading to excessive accumulation of these mutagens? These are merely four of many questions that must be addressed when examining potential endogenous carcinogens.

Increasingly, there appears to be a genetic relationship between breast, ovarian and prostate cancers. Could that connection arise from chemical similarities between carcinogenic initiators derived from steroid hormones, their formation, incorporation into nuclear receptors as well as their rate of hydrolysis? These issues in addition to a clarification of the origin of such endogenous carcinogens will be explored. A testable hypothesis is proposed.

Keywords: Endogenous factors; Breast cancer; Ovarian cancer; Prostate cancers; Mutagens

Introduction

There is a dichotomy between the research devoted to examining exogenous chemicals proposed as new drugs by pharmaceutical companies and in use by chemical and energy companies compared with substances created in humans from endogenous sources. Studies of the former have been directed toward identifying the proximate carcinogenic structures and their stereochemistry. An example is the effort in determining how polycyclic aromatic hydrocarbons are causative agents in forming malignancies [1,2]. It is known that some epoxides derived from these compounds are carcinogens. Yet, others are not. Speculation has centered on the possibility that shielding of epoxides [3] may contribute to their longer persistence and thereby their carcinogenicity. Alternatively, the Bay Region theory of carcinogenesis [4], points to a stereoselective reaction at biological receptors such as DNA and RNA. This observation is supported by optically-active enantiomers having different activities. It is known that not all mutagens produce malignancies. That result is dependent upon the rate such compounds are further metabolized to inactive derivatives. The concentration levels of the mutagen/carcinogen may be critical as well as the effectiveness of nucleic acid repair mechanisms.

With endogenously-produced compounds the approach has been more obtuse and less rigorous chemically. There has been an unsubstantiated assumption that compounds produced in humans a priori must not be carcinogenic and even if they are, such as oxygen radicals, peroxides and superoxides they must be weakly so, due to their rapid detoxification enzymatically.

With endogenous malignancies, a greater focus has been on tissue pathology of the malignancy and more recently, on genetic factors implicated in cancer causation. There has been a paucity of research focusing on the chemical initiators of the malignancy's origin.

Steroid Hormones

Steroid hormones are an important class of endogenously-produced compounds, which are implicated in cancer causation. They have been used in preventing contraception, in ameliorating the effects of

menopause, in addressing low testosterone levels in blood, and in cancer treatment. Though widely used, their labile metabolites remain to be isolated, fully characterized chemically, and sought in biological tissues. At the same time, the chemical initiators of breast, ovarian and prostate cancers remain unknown, as does whether there is a chemical connection between these various malignancies.

This is a major limitation in understanding such cancers and their treatment. Could these cancers be caused by labile metabolites of the steroid hormones? And is their formation and biological persistence dependent upon the individual's own unique metabolism?

The formation of reactive metabolites is well documented for a number of drugs which then form less reactive and more readily excreted products after further metabolism and conjugation. In other cases, these reactive metabolites will covalently bind proteins leading to hypersensitivity reactions (phenytoin and carbamazepine) or cause liver damage (acetaminophen and valproic acid).

Steroids are unusual since they are transported into the nucleus of the cell following binding to their receptors and eventually, the steroid-receptor complex interacts with proteins associated with DNA. Reactive metabolites of steroids (possibly epoxides) may bind to their receptors and be carried to the DNA where covalent reaction could result in cancer cell formation.

Only recently, has the comprehensive chemical study of metabolic products been undertaken, a process known as metabolomics [5]. Such research has been spurred by the availability of superior analytical methods and improved synthetic procedures allowing for the isolation and characterization of labile intermediates. Recent focus has been on the various receptors of steroid hormones and the observation that these compounds induce cell proliferation, thus promoting cancer development. Estrogens, androgens and progesterone appear to play a major role in several malignancies such as breast, prostate, ovarian and endometrial carcinomas. For example, removing ovaries in women, a major source of estrogens, reduces significantly the incidence of breast cancer [6].

Estrogens

It was proposed in 1980 [7] that potential endogenous mutagens/carcinogens derived from estradiol may have a greater role to play in breast cancer initiation than believed heretofore. This was substantiated with the synthesis and biological evaluation of various arene oxides derived from estradiol. These epoxides can be viewed as potential precursors of catechol estrogens. Of the three epoxides synthesized and evaluated [8], two were of known stereochemistry. One of the epoxides, Structure A, 4α-5α-epoxyestradiol (Figure 1) transformed Balb/c 3T3 mouse fibroblast cells.

This potential estradiol metabolite is as active in inducing cellular transformations as the highly mutagenic 3-methylcholanthrene and is more active than estradiol itself [8]. The other isomers were inactive at the same concentration levels. Subsequently, the four possible epoxyenones have been synthesized [9] and their stereochemistry characterized. Yet, it remains to be determined whether Structure A or any of the epoxyestradiols are found in mammalian systems and especially in individuals experiencing or prone to breast and ovarian cancers. With its complete characterization, this should now be possible but remains to be accomplished.

The interaction of female sex hormones with biological receptors is based upon their structure, stereochemistry and biochemical function. In their metabolism, the generation of labile, reactive intermediates has the potential of functioning as electrophiles. Such structures can alter native nucleic acids covalently, generating pro-malignant cells with the capacity for continuous self-replication, if the repair process is not initiated.

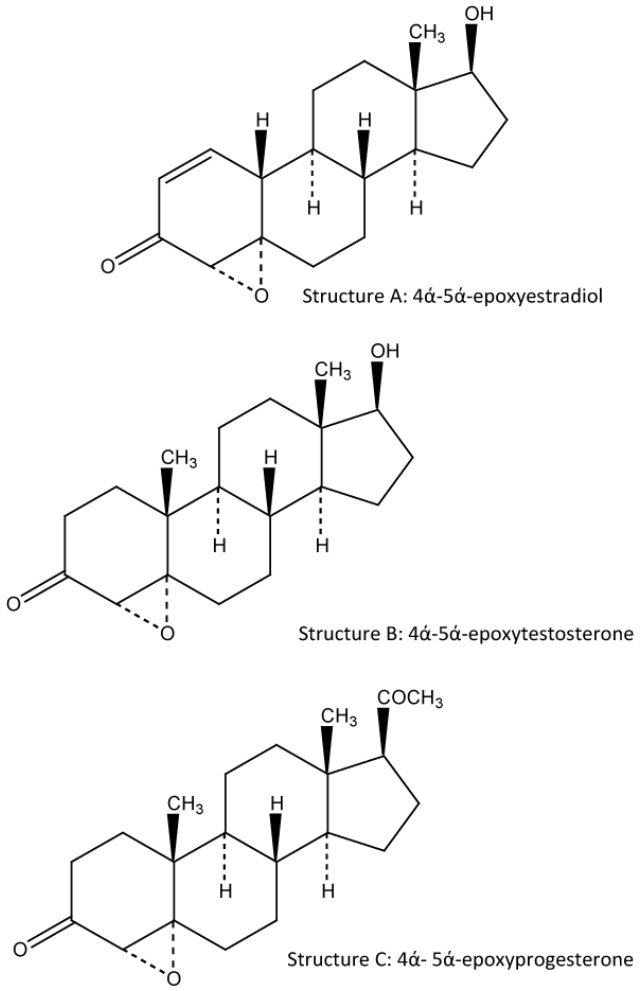

Figure 1: Structures of epoxides.

Endogenous carcinogenesis has become of increasing interest [10,11]. With respect to breast cancer, there has been a focus on the involvement of estrogen metabolism in its causation [12,13]. Two approaches have been suggested, involving the formation of reactive intermediates in the metabolism of the estrogens into the catechol estrogens.

One approach, involves the formation of dienol epoxides as reactive intermediates [14,15] and a second, involves the formation of catechol estrogen quinones [16,17]. In the studies carried out using tritiated estradiol [18], the results are consistent with covalent bond formation at C-4 involving biological nucleophiles. It was observed that the levels of 4-catechol estrogens were nearly four times higher in women with breast carcinoma than in those without this malignancy [16]. This observation is consistent with the possible involvement of Structure A as a causative agent.

Now, with the identification and isolation [19] of a stable benzene oxide from a fungal biotransformation, it should be possible to isolate and characterize Structure A, if it is present in the tissues of individuals with breast and ovarian cancers. As noted, this has not been accomplished as yet.

Androgens

There is increasing evidence that male carriers of BRCA mutations have an elevated risk for prostate cancer [20,21]. An important question is how is that genetic information translated into the chemical initiators for prostate cancer? Loeb [10] has re-emphasized the concept, originally formulated by the Millers [22], that compounds which are electrophiles have the potential of acting as chemical carcinogens by modifying DNA. Epoxides are such electrophiles and can be produced in humans by the action of a large and diverse group of cytochrome P450s [23] whose formation is genetically controlled.

Since epoxides have the potential of acting as carcinogens, another ubiqutous group of enzymes, also genetically determined, are the epoxide hydrolases [24]. Their function is to detoxify these epoxides by converting them to trans-dihydrodiols for conjugation and excretion. It has been noted experimentally with the carcinogen-detoxifying epoxide hydrolase that a threshold exists for carcinogenesis [25]. This must be related to the enzymatic rate of hydrolysis and, by inference, to the residual concentration levels of the epoxide.

As with possible initiators of breast cancer, we do not know the chemical entity/entities that may be responsible for causing prostate and testicular cancers. It was reported anecdotally that eunuch monks who had been castrated prior to puberty don't get prostate cancer. Such an observation, if validated, would strongly implicate testosterone or its metabolites in causing prostate cancer since the removal of the testes guarantees that testosterone would be absent in such individuals. It is known [26] that androgens play an important role in promoting prostate cancer and that castration and drugs that suppress testosterone formation can be beneficial in inhibiting disease progression.

Testosterone is largely metabolized in the skin and prostate to dihydrotestosterone. The latter is one of the primary metabolites of testosterone and would not be expected to be a mutagen or carcinogen from its chemical structure. However, the epoxide derived from testosterone, Structure B in figure 1, might be expected to be a mutagen/carcinogen through its chemical similarity to Structure A.

Comparing Structures A and B, it is apparent that the only difference is an angular methyl group in place of hydrogen at position 10 of the steroid nucleus and a double bond at the 1, 2, position versus no double bond. Therefore, if Structure A is highly mutagenic, one might expect, from its chemical similarity, that the same would apply to Structure B.

When the initial paper was presented [27], Structure B, 4ά, 5ά-epoxytestosterone, had not been synthesized. Though its recent synthesis [28] was not for the purpose of determining whether it is found biologically, nevertheless its current availability and stability offers the potential of determining whether it is carcinogenic and a possible metabolite of testosterone, especially in men with prostate cancer. Even if it were only a minor metabolite, its actual presence, if carcinogenic, should warrant greater concern regarding the use of prescription drugs designed to boost testosterone levels in men with low blood levels of this hormone.

Progesterone

Similarly to breast and prostate cancers, the chemical initiators of ovarian cancer remain unknown. No chemical structures have been proposed as potential initiators. However, since 1982 the International Agency for Research on Cancer (IARC) has indicated that based upon animal experimentation, progesterone is possibly carcinogenic to humans. And since 1988, it has been listed as a human carcinogen. Yet, it is unclear whether the carcinogenicity is due to progesterone itself or one of its metabolites.

Structure C in Figure 1 may be such a potential metabolite. To date, it has not been described in the literature. Nevertheless, 17ά-hydroxy-4, 5-epoxypregnan-3, 20-dione (17ά-hydroxy-4, 5-epoxyprogesterone) has been synthesized [29]. Its preparation was not for the purpose of determining whether it was a metabolite of progesterone or whether it was carcinogenic. Yet, the availability and stability of such epoxides offers the opportunity to determine their carcinogenic potential and to look for their presence in breast and ovarian malignancies.

Diethylstilbestrol (DES)

Related to the steroid hormones but not naturally occurring is the synthetic nonsteroidal estrogen, diethylstilbestrol (DES), an endocrine disruptor. Examining its precise chemical mode of action, as well as its metabolic profile, may provide useful insight as to how the various steroid hormones and their metabolites may be causing malignancies.

DES was prescribed from 1940 through 1970 to pregnant women at risk for miscarriage and related pregnancy complications and has been studied for its long-term health effects. It was shown to cause an increase in breast cancer in women who took DES [30] and to cause adenocarcinoma of the vagina and cervix and an increased incidence in breast cancer together with fertility problems in their daughters exposed to DES during their mother's pregnancy [31]. Studies are underway to examine children whose grandmothers were given DES.

Epoxidation of the double bond in such stilbene derivatives is a major metabolic pathway in their transformation [32]. These epoxides have been examined for their tumor-inhibiting effects and the results to date are equivocal [33]. They do not permit the conclusion that these epoxides are an effective form of cancer therapy or are the responsible entities for the malignancies described above.

Based upon past observations with various alkylating agents used in cancer treatment and the biological effects observed with Compound A (Figure 1), alternate structures will be proposed in the hypothesis section to account for both the carcinogenicity of DES and possible reasons for these entities having anti-cancer activity (Figure 2).

The Hypothesis

Increasingly, there appears to be a connection between some breast, prostate and ovarian cancers. On a cursory examination, one would question how is that possible? First, the incidence of breast cancer largely involve women. Only 1% of all breast cancers occur in men. With respect to prostate cancer, it obviously doesn't occur in women and ovarian carcinomas can only occur in women. A pathological

examination of malignant tissue in each instance would show marked and recognizable differences between the three cancers.

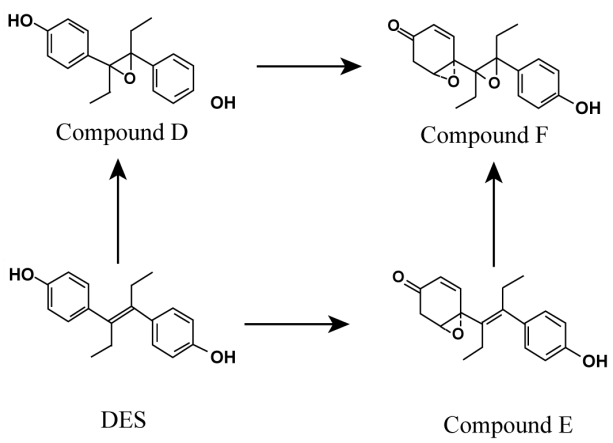

Figure 2: Proposed metabolites of Diethylstilbestrol (DES).

An obvious question is are there genetic mutations that result in the formation of related chemical initiators of these three malignancies? Are there potential electrophiles formed in metabolism that could be the reactive species responsible for initiating DNA alteration? And finally, is there a chemical similarity between the various initiators?

In the case of the female sex hormone, estradiol, it has been shown that Structure A (Figure 1), a possible metabolite in the formation of the catechol estrogens, is comparable in mutagenicity to 3-methylcholanthrene and is at least two orders of magnitude more active than estradiol itself [8].

Structure B, though now synthesized [28], has not been screened for its carcinogenicity. And of course, it has not been sought in the tissues of men with prostate cancer. In fact, there is no evidence presently that this compound is a metabolite of testosterone.

The last structure in Figure 1 is Structure C, 4á- 5á-epoxyprogesterone, which may be derived from the metabolism of progesterone by cytochrome P 450s. However, there is no report of its chemical synthesis to date, even though it should be readily synthesizable by analogy with Structures A and B. The only difference between this compound and Structure A is an angular methyl group at position 10 and the COCH3 at position 17 versus an OH group in estradiol. If this compound is a carcinogen, it would be relevant to look for its presence in breast and ovarian malignancies. The reported synthesis of 17á-hydroxy-4á-5á-epoxyprogesterone [29] eliminates any concern regarding the extreme lability of these steroidal epoxides.

Though these three compounds may be derived chemically from their respective parent compounds through oxidative metabolism by various cytochrome P 450s, a key question would be, are they formed biologically? And under those conditions, would they act as carcinogenic initiators?

In order to probe such questions, it may be relevant to ask how the synthetic female hormone, diethylstilbestrol (DES), has the capability to produce malignancies in women who have taken this compound during their pregnancy. Also, how is this pathology extended to their offspring, exposed to the compound or its metabolites in utero? To explore such questions, it is essential to understand the complete biochemical pathways by which DES and endogenously produced steroid hormones are metabolized, possibly even while bound to hormone receptors.

Such receptors are found on plasma cell membrane, in the cytosol, and in the nucleus of various target cells. What is known is that the steroid hormones are bound initially in non-covalent fashion to nuclear receptor proteins embedded within the cell nucleus. If the compound in this locus exists as the epoxide or can be converted in situ by the cytochrome P450s into an epoxide, this structure would have the potential of reacting covalently as an electrophile with DNA present within a cell. If so, this could be the basis by which the metabolites of steroid hormones transform normal cells into pre-malignant ones. Such a transformation could be the origin by which cancers are caused endogenously, if appropriate repair mechanisms are genetically compromised.

In figure 2 are shown several possible epoxide metabolites of DES. Though the 3, 4- epoxide (compound D) showed very good affinity for the estrogen receptor (32), it showed no significantly different effect on mammary carcinomas than did DES itself. Compounds E and F have not been synthesized. These epoxides may be more reactive chemically than compound D and their synthesis and biological evaluation would determine the validity of this hypothesis. By discovering the carcinogenic metabolite of DES, one may gain greater insight as to how endogenous steroid hormones are instrumental in cancer causation.

Evaluation of the Hypothesis

The hypothesis is that labile, reactive metabolites derived from steroid hormones and DES may bind to the steroid hormone receptor, be carried into the nucleus and act as carcinogenic initiators of breast, prostate and ovarian malignancies. Though the chemical structure of each compound is different, their function in generating a malignant precursor cell may be the same.

To determine the validity of this hypothesis, it would be necessary to first synthesize those compounds which have yet to be prepared. Screen all for their carcinogenic activity and for those which prove to be carcinogenic, examine the appropriate malignancies for possible evidence of these compounds or their further metabolic products in the tumors. The compounds could be generated by the action of the appropriate cytochrome P-450 enzyme prior to their incorporation into the steroid receptor. If the epoxide is retained and not hydrolyzed by the action of the appropriate epoxide hydrolase to inactive derivatives, it would serve as the basis for generating the malignant cell.

Conclusions

Reactive metabolic products derived from steroid hormones have the potential of being bound to steroid receptors in cellular DNA. If the compound, in question, has the potential to act as a mutagen/carcinogen and DNA repair is compromised, then the malignant process may be set in motion.

Possibly in the future, if one knew the specific RNA responsible for the synthesis of the enzymes that are involved in the formation of endogenous carcinogens, gene silencing RNA inhibitors, short interfering RNAs (siRNAs), may be designed for the specific purpose of silencing such genes [34]. The objective would be the actual

prevention of cancer which is derived from steroid hormones. However, much remains to be done before that becomes a viable option. Yet, understanding how malignancies arise biochemically is an important beginning in developing appropriate therapeutic modalities for the prevention of cancer initiation.

Dedication

This paper is dedicated to the Raphaelson family many of whose family members experienced life-threatening malignancies and especially to Mollie (Raphaelson) Soloway, mother of one of the authors, who died of breast cancer at 51.

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