MECHANISMS OF GENOTOXIC EFFECTS OF HORMONES

Ninoslav ĐELIĆ

Department of Biology, Faculty of Veterinary Medicine, University of Belgrade, 11000 Belgrade, Yugoslavia

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A concept that compounds commonly present in biological systems lack genotoxic and mutagenic activities is generally in use, hence a low number of endogenous substances have ever been tested to mutagenicity. Epidemiological and experimental analyses indicated, however, that sexual steroids could contribute to initiation and/or continuation of malign diseases. Detailed studies using methods of biochemistry, molecular biology, cytogenetics and other branches, showed that not only epigenetic mechanisms, such as a stimulation of cell proliferation, but also certain hormones, that can express genotoxic effects, such as covalent DNA modification, then chromosomal lesions and chromosomal aberrations, are in the background of malign transformation under activities of hormones. In the case of oestrogens, it was shown that excessive hormonal stimulation led to a metabolic conversion of these hormones to reactive intermediates with formation of reactive oxygenic derivates, so that cells were virtually under conditions of oxidative stress. Individual and tissue susceptibility to occurrence of deterioration of DNA and other cell components generally results from the differences in efficiency of enzymic and non-enzymic mechanisms of resistance against oxidative stress. Besides, steroid, thyeroid hormones and catecholamine (dopamine, noradrenaline/norepinephrine and adrenaline) can express genotoxic effects in some test-systems. It is interesting that all above mentioned hormones have a phenolic group. Data on possible genotoxic effects of pep-

Corresponding author: Ninoslav Đelić, Katedra za Biologiju, Fakultet veterinarske medicine, Univerzitet u Beogradu, Bul. JNA 18, Beograd;
e-mail: ndjelic@vet.bg.ac.yu

tide and protein hormones are very scarce, but based on the available literature it is considered that this group of hormones probably lacks mutagenic activities. The possibility that hormones, as endogenous substances, express mutagenic activities results from the fact that DNA is, regardless of chemical and metabolic stability, susceptible, to a certain extent, to changeability compatible with the processes of the biological evolution.

Key words: hormones, toxic effects

INTRODUCTION

Two essential organic systems - nervous and endocrine - contributing to regulation of physiological processes and integration of an organism as an entity were developed during the evolution of animals. Concerning the fact that hormones are included into regulation of a number of living processes and a generally accepted concept that hormones are phylogenetically elder than functions that are under their control, it is necessary to ask a question whether hormones can, by their impacts, contribute to the formation of mutations at the level of the genetic material. Although sufficiently efficient mediators and endocrine regulators selected during the evolution of animals do not disturb genetic integrity, experimental and epidemiological analyses indicate that previously stated possibility could be real.

At present, it is clear that beside a great number of environmental genotoxic chemical agents some substances, ordinarily present in the animal or human organism, can express genotoxic and mutagenic effects. Considering that these substances are compounds, normally included into regulation of biochemical and physiological processes, intermediates and metabolic products, they are called endogenous mutagenes.

It is known that a relatively good correlation between mutagenesis and carcinogenesis exits. Therefore, data indicated associations between some types of cancer and the application of hormones could point out to a certain mutagenic potential. Hence, data of experiments with cultured cells, certain species of rodents, as well as, results on extensive epidemiological and endocrinological studies in humans, pointed to an effect of hormones in originating and/or maintenance of malignly transformed cells (HENDERSON *et al*., 1982). According to some authors (KEY and BERAL, 1992), hormonal effects in originating of malign diseases signify effects at the level of carcinogenesis processes promotion, which is in conformity with negative results obtained by tests of hormones for genotoxicity in certain systems (BRAUN, 1977; BARRET *et al*., 1981; HERZOG and LEUSCHNER, 1995; ĐELIĆ, 2001). On the other hand, there are literature data on genotoxic effects of hormones (MCQUARRIE *et al*., 1970; VAN ASWEGEN *et al*., 1989; BALI *et al*., 1990; TSUTSUI *et al*., 1990; ĐELIĆ and ĐELIĆ, 2002) that stimulated researchers to consider a possible role of hormones in carcinogenesis initiation.

The differences in obtained test results on hormones for genotoxicity can be caused by limitations of test-systems themselves, different reactivity under *in*

vitro and *in vivo* conditions, possibilities of existence of tissue and species-specificities in expressing of genotoxic effects.

The studies on mutagenic effects of hormones were performed in different *in vitro* and *in vivo* systems, form bacteria to mammals. The selection of hormones encompassed mainly steroids due to an obvious correlation between occurrences of certain types of malignity and the use of natural and synthetic hormones in the therapy. The present paper displays in detail a mechanism of genotoxic effects of oestrogenic hormones, since they are observed best, while literature data on non-steroid hormones are very modest.

MECHANISM OF GENOTOXIC EFFECTS OF OESTROGENS

The application of the current methods of biochemistry and molecular biology has opened a new field that contributed to highlighting molecular mutagenesis and carcinogenesis under effects of steroids. According to today's available literature data, oestrogens have been studied to the highest degree.

A greater number of substances of different chemical structures expresses the activity of oestrogenic hormones. Estradiol (E_2) and estron are the major natural oestrogens produced in ovaries. Synthetic oestrogens can be steroidal, such as 17α ethynil estradiol - an oestrogenic component of many contraceptives, or non-steroidal, such as diethylstilbestrol and hexestrol (Fig. 1).

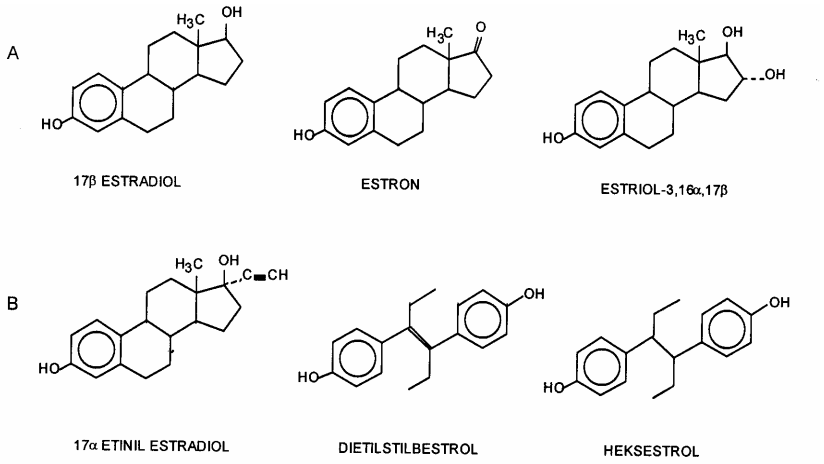

Figure 1. Structural formulae of the most important natural (A) and synthetic (B) oestrogens

Besides, phenols with a certain oestrogenic activity were either discovered in plants or were chemically synthesised (DODDS *et al.*, 1983; BRADBURY and WHITE, 1954). Hormonal effects of this large group of substances are revealed by either the affinity for oestrogenic receptors or biological responses characteristic for oestrogens.

Normal physiological responses are achieved by means of E_2 or potential synthetic estrogens at very low concentrations. At higher dosages, however, estrogens induce tumours in experimental animals (WALKER, 1983), i.e. result in carcinogenic effects in humans (IARC, 1979).

Even though effects of hormones in formation of neoplasms mainly occur at the level or promotion process (KEY and BERAL, 1992), data obtained from various tests for genotoxicity indicate to a possible role of carcinogenesis initiation.

The greatest number of studies on oestrogen-induced carcinogenesis has been performed on a model of renal tumour in hamsters. Although spontaneous initiation of renal cancer is a very rear phenomenon in this species, predisposition to oestrogen-induced carcinogenesis of kidney cortex was observed (KIRKMAN, 1959). It is also interesting that there is no correlation between the hormonal activity strength of oestrogens and their ability to induce tumours (LI and LI, 1984). Therefore, it was assumed that beside effects induced by oestrogenic receptors, that could be the base of the epigenetic mechanisms, there are certain processes regulating mutagenic activities of oestrogenic hormones (METZLER and MCLACHLAN, 1978).

The presently actual apprehension is that metabolic reactions at significantly higher concentrations of oestrogens, in which free radicals are generated, become predominant biochemical processes that overlays their hormonal effects. Forasmuch as oestrogens are phenols, metabolism of their phenolic groups can, at higher concentrations of oestrogens, express harmful effects in cells, including damaging of DNA molecules (LIEHR and ROY, 1990).

Redox cycling, generating free radicals, is base of genotoxic effects of oestrogens and similar compounds. Prior to its involvement into redox cycling, estradiol is converted to catecholestrogen by the activity of the enzyme oestrogen hydroxylase (Fig. 2). In contrast, diethylstilbestrol (DES) presents hydroquinone capable to be directly involved into redox reactions.

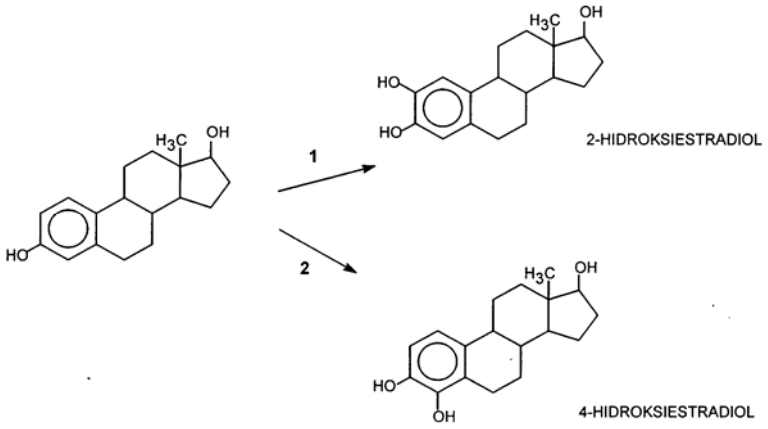

Figure 2. Conversion of estradiol to catecholestrogen (CE)
1 - estrogen 2-hidoxilase; 2 - estrogen 4-hydroxylase

Catecholestrogens (CE) and DES can be oxidised to the appropriate quinones by means of peroxidases and H_2O_2 (LIEHR *et al*., 1983) or cytochrome P-450 oxidase and organic hydroperoxids (LIEHR *et al*., 1986). It is assumed that semiquinones represent intermediates in this process, but this cannot be yet proven by available techniques. Superoxide radical (O_2^-), formed during conversion of semiquinone to quinone in the presence of molecular oxygen (O_2) (ROY and LIEHR, 1988), can be, under appropriate conditions, further transformed into hydroxyl radical ($^{\cdot}OH$). The completion of redox cycling is provided by the reduction of quinones over semiquinones to DES and CE (i.e. hydroquinones by the activity of NADPH dependent cytochrome P-450 reductases) (POWIS and APPEL, 1980). Besides, quinone reductase (DT-diaphorase) reduces DES Q directly to Z-DES by the transfer of two electrons, without formation of semiquinonic intermediate (Fig. 3 and 4).

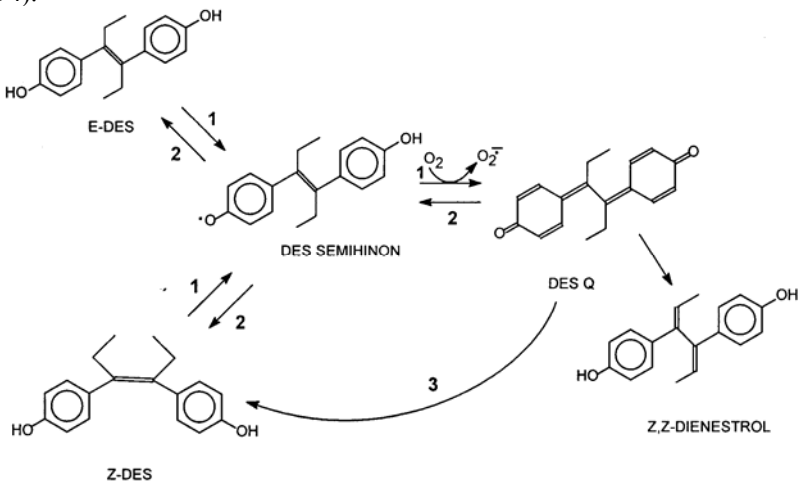

Figure 3. Redox cycling between DES and DES Q (DES quinone) and generation of free radicals; 1-cytochrome P 450 oxidase, 2-NADPH dependent cytochrome P450 reductase; 3-quinone reductase; E-DES and Z-DES present stereoizomeric DES forms; Z,Z-dienestrol is spontaneously formed from DES Q; DES Q - diethylstilbestrol-4', 4" quinone

It is known that generation of reactive radicals results in damages of DNA molecule (SMITH *et al*., 1985). The formation of covalent DNA additive products (adducts) is a key step in the initiation of carcinogenesis (BROKKES and LOWLEY, 1964). Therefore, different experimental approaches were used in order to contribute to a better understanding of interactions between metabolic products of oestrogenic hormones and DNA molecules. A ^{32}P-postlabelling method (RANDERATH and RANDERATH, 1994) greatly contributed to a detection of covalently modified nucleotides. The enzymic hydrolysis of DNA to 3'-mononucleotides is the first step in this method. Then, these 3'-mononucleotides are converted to 5-^{32}P-labelled 3'5'-biphosphate derivetes by the action of T4 polynucleotide kinase in the presence of [γ-^{32}P]-ATP. Separation of labelled nucleotides can be performed by the ion ex-

change thin layer chromatography (TLC). The detection of DNA adducts is then done by autoradiography. In such a way, it is possible to detect 1 aromatic adduct in ≈ 10^9 normal DNA nucleotides (approximately 10 adducts in the mammalian genome, RANDERATH *et al*., 1985). The existence of three different groups of DNA covalent modifications was determined by the application of the ^{32}P-postlabelling method and other methods for analysing DNA isolated from animals treated with oestrogens (LIEHR *et al*., 1993).

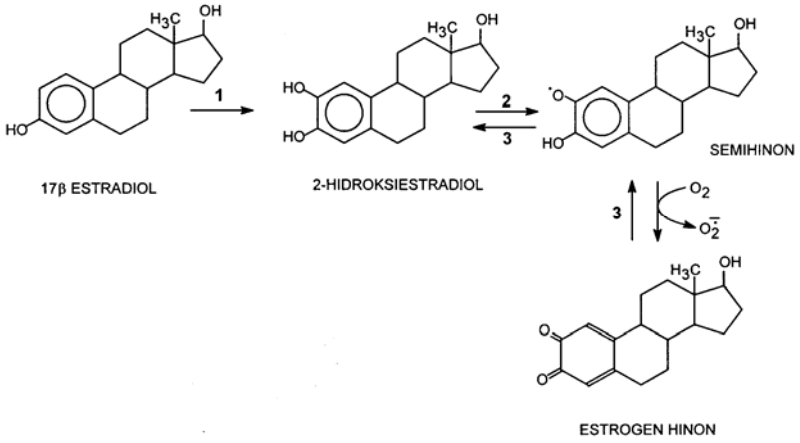

Figure 4. Metabolic conversion of estradiol to CE and redox cycling; 1-estradiol, 2-hydroxylase; 2-cytochrome P 450 oxidase; 3-NADPH dependent cytochrome P 450 reductase

The first group consists of nucleotides covalently bound to reactive derivates of hormones themselves. In such a way, it was detected that a single high dosage of DES produced a specific set of DNA adducts in liver, kidney and uterus of hamsters (GLADEK and LIEHR, 1989). The identical set of modified bases can be obtained if purified DNA or dGMP are incubated with DES quionone (DES Q), a major DES metabolite under *in vitro* and *in vivo* conditions. Accordingly, DES is metabolically activated *in vitro* to DES Q, which can be then bound to DNA. The investigation of the intensity of covalent binding of DES Q to different DNA fragments showed a high level of base modification in oligonucleotides rich in guanine and c-*myc* protooncogene, while a significantly lower level of DNA addition products was registered in c-*fos* protooncogenes (Bhat *et al*., 1992).

LIEHR *et al*. (1993) classified so-called oestrogen-induced endogenous DNA adducts into the second group of modified nucleotides. These DNA adducts occur in kidneys of hamsters chronically treated with oestrogens for several months. The occurrence of these modifications of DNA molecules precedes morphologically detectable malign cells. The fact that structurally different oestrogens induce the occurrence of the identical set of modified nucleotides is especially interesting. Therefore, it is considered that oestrogens, in fact, induce the formation of electrophylic reactants capable to damage the DNA molecule. Chemical nature

of endogenous substances has not been determined yet, although there are some indications (on the basis of chromatographic motility of modified nucleotides) that they can be derivates of lipids or lipid peroxides (WANG and LIEHR, 1995).

The third group of modification in DNA is initiated due to covalent damages caused by oxygenic free radicals that are released during redox cycling of oestrogens. Semiquinone intermediates are free radicals promoting the formation of superoxide radical (O_2^-) out of oxygen (O_2) that can be converted to H_2O_2 by the action of superoxide dismutase (SOD). Although both, O_2^- and H_2O_2 are sufficiently reactive to cause damages to biomolecules, hydroxyl radical ($^{\cdot}OH$) that can be generated form H_2O_2 by means of metal cations, is even more reactive (IMLAY and LINN, 1988). In terms of the experimental data that the level of 8-hydroxydeoxyguanosine (8-OH-dGuo) significantly increases with incubation of DNA, microsomes, NADPH and DES Q in the presence of $FeCl_3$, ROY *et al*. (1991) assumed that $^{\cdot}OH$ regulated hydorxilation of guanine (Fig. 5). The same authors showed that the level of 8-OH-dGuo elevated in Syrian hamsters treated by diethylstilbestrol (DES). The elevated level of 8-OH-dGuo requires the increase of metabolic activities that maintain redox cycling and generation of free radicals and/or decrease activity of DNA reparation mechanisms.

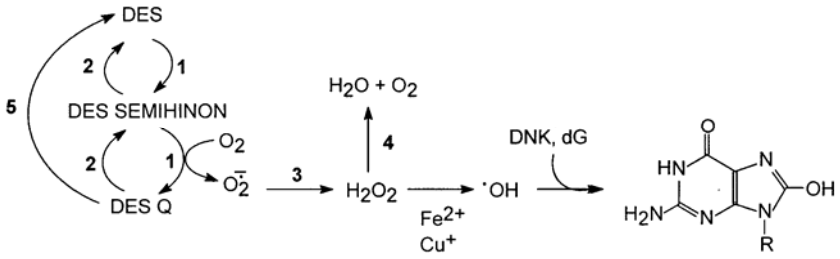

Figure 5. Suggested mechanism of hydroxylation of guanine base due to DES redox cycling; dG-deoxyguanosine; Enzymes: 1-cytochrome P 450 oxidase, 2-cytochrome P 450 reducase; 3- superoxide dismutase (SOD); 4-catalase; 5-quinone reductase (ROY *et al*., 1991)

The Figure 6 shows the principal processes controlling genotoxicity of oestrogens. However, it is necessary to mention that realisation of genotoxic potential of oestrogenic hormones depends, to a great extent, on a level of activities of enzymes involved into conversion of steroidal oestrogens to EC, enzymes that perform detoxication of free radicals and non-enzymic mechanisms of free radicals elimination.

Mechanisms of protection that can decrease occurrence of semiquinoines and quinones imply the elimination of catecholestrogens (CE) by methylation with catechol-O-methyltransferase (COMT, Fig. 7) or by other reactions of conjugation with glutathione, glucuronide and sulphate (LIEHR, 1990). It was shown that 4-hydroxyestradiol mainly occurs as a product of hydroxylation of oestrogens in organs prone to oestrogen-induced carcinogenesis (LIEHR and RICCI, 1996).

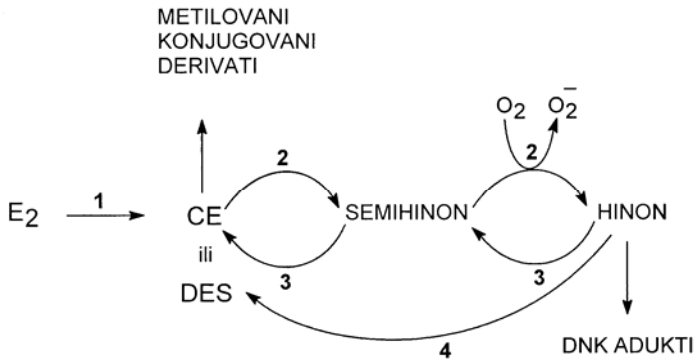

Figure 6. Suggested mechanism of genotoxicity of oestrogens (LIEHR, 1990). Steroidal oestrogens convert to catecholestrogens (CE) by means of 2- and 4-hydroxylase(1). Free radicals generate in redox cycling between CE or DES and their quinone. Cytochrome P 450 oxidase catalyses oxidation (2), while cytochrome P 450 reductase (3) or quinone reductase (4) catalyse reduction.

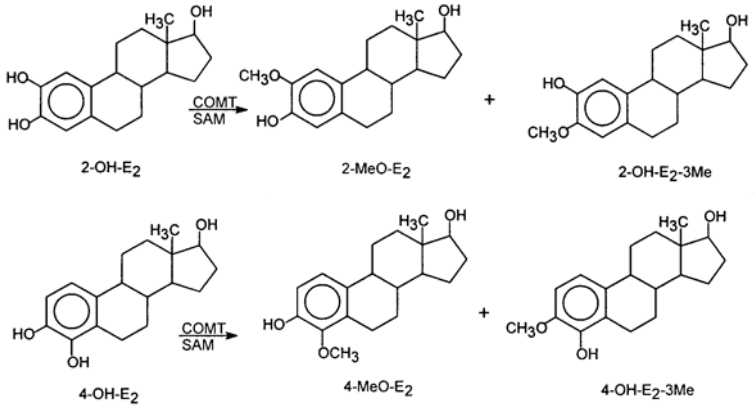

Figure 7. Methylation of catecholestrogens with catechol-O-methyltransferase (COMT) in the presence of S-adenosylmethionine (SAM) (ROY *et al*., 1990); 2-OH-E_2 - 2-hydroxyestradiol; 4-OH-E_2 4-hydroxyestradiol; 2-MeO-E_2 - 2-methoxyestradiol; 2-OH-E_2 - 3Me - 2-hydroxyestradiol 3-methyl ether; 4- MeO-E_2 - 4-methoxyestradiol; 4-OH-E_2 -3Me - 4-hydroxyestradiol 3-methyl ether

Chronic administration of estradiol to Syrian hamsters reduces renal oestrogen 4-hydroxylase activity by about 25%, while the level of 2-hydroxylase decreases by 75% in relation to control values. The elevated level of 4-hydroxyestradiol (4-OH-E_2) is a final result. Besides, it is important to emphasise that 2-OH-E_2 (ROY *et al*., 1990) and catecholamines (ZHU and LIEHR, 1993) inhibit methylation of 4-OH-E_2 by which physiological inactivation by COMT is reduced. Enzymic changes that facilitate the initiation of DNA covalent damages also include a temporary decrease in renal quinone reductase and catalase activity with the increase

of glutathione peroxidase activity. In such a way, estradiol disturbs the balance of enzymic mechanisms of protection against oxidative stress (ROY and LIEHR, 1989).

The effect of vitamin C as a non-enzymic mechanism that reduces genotoxicity of oestrogens is very interesting. The DES Q concentration in hamsters excessively treated with vitamin C reduces by approximately 50% following DES activity, which corresponds to the reduction of renal tumour incidence by 50% (LIEHR *et al*., 1989). The effect of vitamin C is attributed to non-enzymic mechanisms of DES Q reduction, as well as, to capability to remove superoxide radical (LIHER, 1991).

A special significance for maintenance of redox cycling of oestrogens belongs to lipid peroxidation. Lipid peroxides, formed under effects of free radicals (probably $^{\cdot}$OH), can then serve as cofactors for CE of DES oxidation to semquinones and quinones. Furthermore, discovered oestrogen 2/4-hydroxylasedependent on organic hydroperoxides induce CE formation by oxidation of oestrogens. As a result of all these processes, redox cycling of oestrogens is a self-preservative process in which free radicals are generated and are capable to form lipid peroxides, which will support redox cycling itself until steroid hormones enter the cell (KAPPUS, 1985; LIEHR and ROY 1990).

In the end, the question on whether reactions in redox cycling of oestrogens have any physiological role or no arises. It is well-known that almost all biochemical phenomena occurring during carcinogenesis have, at least during a certain period of the individual development, important and necessary roles in cell cycling and in the organism generally. Unfortunately, the information on possible physiological significance of redox cycling of CE and generation of free radicals today is inferior to knowledge on pathophysiological modifications that are the base of malign transformation.

However, there are some indications that catecholestrogens (CE) can function as local mediators in physiological and pathophysilogical responses to oestrogenic hormones (WEISZ, 1991). For instance, it was suggested that CE assisted in the maturation of phyllocula (SPICER and HAMMOND, 1989) and implantation of blastocysts (PARIA *et al*., 1990). One of possible roles of free radicals could be related to their participation in parturition inducements. There are evidences that prostaglandins are involved in the parturition (NOVY and LIGGINS, 1980) and that hydrogen peroxide supports uterus contractions by stimulation of the prostaglandin production (CHEROUNY *et al*., 1988). These processes are possibly amplified by CE over stimulation of prostaglandin synthesis in the uterus (PAKRASI and DEY, 1983). Further studies are necessary for more accurate and detailed determinations of a possible physiological importance of redox cycling.

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MEHANIZMI GENOTOKSIČNIH EFEKATA HORMONA

Ninoslav ĐELIĆ

Katedra za Biologiju, Fakultet veterinarske medicine, Univerzitet u Beogradu, 11000 Beograd, Jugoslavija

I z v o d

Često se polazi od shvatanja da jedinjenja koja su normalno prisutna u biološkim sistemima nemaju genotoksične i mutagene efekte, tako da je mali broj endogenih supstanci testiran na mutagenost. Epidemiološke i eksperimentalne analize ukazale su, me|utim, da seksualni steroidi mogu da doprinesu nastanku i/ili održavanju malignih oboljenja. Podrobnija ispitivanja primenom metoda biohemije, molekularne biologije, citogenetike i drugih disciplina otkrila su da se u osnovi maligne transformacije pod dejstvom hormona ne nalaze samo epigenetički mehanizmi poput stimulacije deobe ćelija, već neki hormoni mogu da ispolje genotoksične efekte kao što su kovalentne modifikacije DNK, oštećenja hromozoma i hromozomske aberacije. U slučaju estrogena, pokazano je da prekomerna hormonska stimulacija vodi ka metaboličkoj konverziji ovih hormona do reaktivnih intermedijera uz nastanak reaktivnih kiseoničnih derivata, tako da se ćelije praktično nalaze u uslovima oksidativnog stresa. Individualna i tkivna osetljivost ka nastanku oštećenja DNK i drugih komponenti ćelije, uglavnom proisitče iz razlika u efiksanosti enzimskih i neenzimskih mehanizama odbrane od oksidativnog stresa. Pored steroidnih, tieroidni hormoni i kateholamini (dopamin, noradrenalin i adrenalin) mogu da ispolje genotoksične efekte u nekim test-sistemima. Interesanto je da svi gore navedeni hormoni imaju fenolnu grupu. Podaci o mogućim genotoksičnim efektima peptidnih i proteinskih hormona veoma su oskudni, ali se na osnovu raspoložive literature smatra da ova grupa hormona verovatno nema mutagene efekte. Mogućnost da hromoni kao endogene supstance ispolje mutagene efekte proističe iz toga što je DNK pored hemijske i metaboličke stabilnosti podložna izvesnom stepenu promenljivosti kompatibilnom sa procesima biološke evolucije.

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