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*Guest editorial**

Hormonal Steroids Act as Tumour Promoters by Modulating Oncogene Expression**

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Summary. Recent advances in the molecular action of steroid hormones and in the role of oncogenes in cell transformation are considered in defining, at the molecular level, the involvement of steroid hormones in tumour formation. In the context of the generally accepted three-stage model of carcinogenesis, it is proposed that the hormonal steroids act as tumour promoters by modulating oncogene expression. It is postulated that the hormonal steroids act on cells in which the initiating carcinogen has either induced mutations in protooncogenes normally hormonally regulated or has induced changes in gene architecture, aligning protooncogenes to hormone-responsive elements, thus placing these genes under non-physiological hormonal control. In contrast to the defined action of solitary carcinogens on the genetic material, tumour promoters appear to act by various molecular pathways, one of which, as hypothesized for hormonal steroids, could be a direct effect on oncogene expression.

Key words: Hormonal steroids – Tumour promotors – Oncogenes

Introduction

Clinical studies suggested effects of steroid hormones on tumour growth first in the classical observations by Beatson (1886), who showed a beneficial effect of ovariectomy on patients with inoperable breast cancer. Similar observations were made much later by Huggins (Huggins and Hodges 1941; Huggins et al. 1941) regarding the positive effects of castration or of diethylstilbestrol administration on prostatic carcinoma. A period of intense experimentation, both in animal models and in cells in culture, followed the isolation, determination of structure and synthesis of natural and synthetic hormonal steroids. Lacassagne in the early thirties was able to induce mammary tumours in male mice by administering oestradiol. Prolonged administration of oestrogens induced mammary tumours also in rats (Dunning et al. 1947), the degree of susceptibility to induction being strain-dependent. Kaufmann et al. (1949) demonstrated the appearance of mammary tumours in female mice after application of natural and synthetic oestrogens, the interval between application of oestrogen and appearance of tumour being shorter, the larger the dose. In males, tumour appearance was much lower; however, high doses of hormones led to feminization of the animals, which then, as regards time of appearance and number of mammary tumours, behaved as females. Polycyclic-aromatic-hydrocarbon-induced mammary tumours in rats were introduced as an in vivo model by Huggins (Huggins et al. 1959, 1961): breast cancers appeared only in intact female animals but not in oophorectomized ones. Ovarian grafting, however, at the time of administration of the carcinogen, restored the capacity of tumour formation.

Various in vitro cell models have been introduced in studies relating the effects of hormones to cell transformation, the MCF-7 breast cancer cell line (Soule et al. 1973) being one of the most extensively exploited. The growth of these cells is arrested by antioestrogens, which induce a mid G-1 block.This effect is reversed by oestrogens, and growth is restored. No growth of transplanted MCF-7 cells in ovariectomized nude mice is observed, the cells remaining viable. However, the administration of oestrogens restores the capacity for growth and tumour formation in these animals.

In all these studies the nature of steroid involvement in the process of tumour formation was the focus of interest. In contrast to the initially prevailing view of steroids as solitary carcinogens, Butenandt (1950) and Kaufmann et al. (1949) characterized oestrogens as „bedingt krebs-

* The "Journal of Cancer Research and Clinical Oncology" publishes in loose succession "Editorials" and "Guest editorials" on current and/or controversial problems in experimental and clinical oncology. These contributions represent exclusively the personal opinion of the author The Editors

** This paper is gratefully dedicated to Professor A. Butenandt on the occasion of his 88th birthday

auslösende Faktoren", i.e. "conditional carcinogens", mainly substances that are not carcinogenic per se but induce the increased appearance of tumours in organisms showing an increased susceptibility for tumour formation.

Stages in carcinogenesis and involvement of steroid hormones

In recent years, particularly in the example of skin carcinogenesis, a model of tumour formation has been clearly formulated comprising three operationally defined stages (Hecker 1987). The first stage, initiation, is induced by the solitary carcinogen, which can be a chemical or a physical agent, but also a virus. It damages the genetic material, in the form of a point mutation or a deletion or by even more drastic changes, such as gene rearrangement, insertion or chromosomal translocation. The change is sudden and persists for long time. The initiated cell remains in a condition of latency, unless subjected to the action of promotors, whose main, but not sole, effect is to stimulate cell proliferation. In the case of skin carcinogenesis, the well-characterized promotor, 12-*O*-tetradecanoylphorbol 13-acetate, binds specifically to cell receptors. By way of phosphokinase C stimulation and the inositol/phopholipid/diacylglycerol system, it acts as a tissue-specific mitogen, but does not damage DNA (Hecker 1987). During this stage benign tumours appear, and occasionally also a few malignant ones. Exposure of the benign tumours to another single dose of the solitary carcinogen increases significantly the proportion of the malignant tumours (progression phase) and the tumour cells acquire more and more aberrant characteristics. Thus, the solitary carcinogen acts as both an initiator as well as a progressor.

Considering a general multistage concept of carcinogenesis and the described effects of steroids on tumour formation, the question arises as to the stage of tumorigenesis that is affected by the hormonal steroids. There are no indications of a chemical modification of DNA by the steroids, i.e. they are not mutagenic. This excludes them from the category of initiators of carcinogenesis. Rather the fact that in the various animal models they must act for a long period of time with repeated exposures, in order to induce carcinogenesis, and the demonstration that both androgens and oestrogens are powerful mitogens promoting cell division in their target organs, e.g. prostate, breast and cervix, place them in the category of promotors, or „bedingt krebsauslösende Faktoren", according to Butenandt. However, in contrast to the progressively increasing knowledge of the molecular mechanism of action of the classical skin-tumour promotors, such as 12-*O*-tetradecancylphorbol 13-acetate (Hecker 1987), our concepts regarding the molecular action of steroid hormones as promotors of carcinogenesis are still rudimentary.

Taking into account the major advances in the molecular mechanisms of hormone action and the remarkable progress in our understanding of the role of oncogenes in cell transformation, the hypothesis that the promoting effects of steroids in tumorigenesis are mediated through modulation of oncogene expression will be supported.

Molecular action of steroid hormones

It is now well established that steroid hormones exert their physiological functions by way of gene activation and induction of protein synthesis as postulated by Karlson (1961). The hormone specifically and with high affinity binds to the respective receptor protein, which then acts as a *trans*-acting transcription modulator (Evans 1988; Green and Chambon 1988; Beato et al. 1989) by binding to specific DNA sequences, the hormone-responsive elements (HREs). Cloning of the various steroid receptor genes has led to the demonstration of common structural features in these molecules, important for their intreaction with the steroid ligand, with the DNA, as well as with other regulatory macromolecules (Fig. 1).

The DNA-binding domain of the receptors is highly conserved, consisting of 66–68 amino acids rich in cysteines and basic amino acids, showing similarity with the "zinc finger" motif characteristic of TFIIIA, the transcription factor of the 5S-RNA gene and of other DNA-binding proteins.

The HREs represent palindromic, 15-base-pair structures, showing a dyad symmetry (Fig. 2) suggesting that the receptor binds to these sequences as a dimer. The receptors for glucocorticoids, mineralocorticoids, progesterone and androgen recognize a common HRE, the oes-

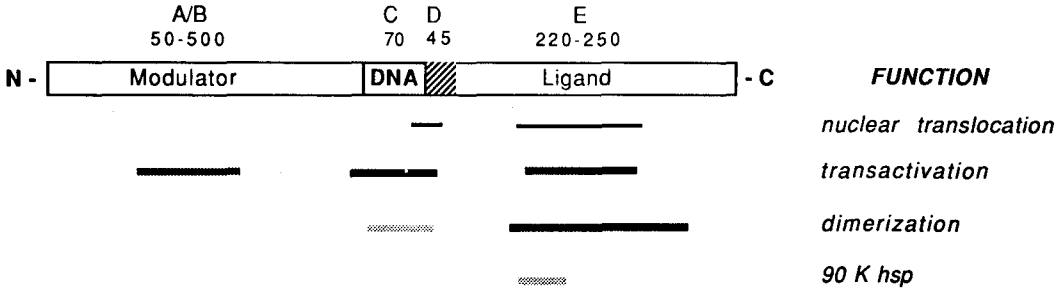

Fig. 1. Schematic representation of a steroid receptor. All steroid receptors examined exhibit (a) a variable N-terminal region (*A/B*) believed to have a modulatory effect on *trans*-activation (b) a central domain (*C*), well conserved and rich in cysteines responsible for DNA binding, and (c) a C-terminal domain (*E*), responsible for binding of the hormonal steroid. Regions involved in additional functions, such as nuclear translocation, transactivation and binding of the 90-kDa heat-shock protein, are also indicated (from Beato et al. 1989)

Fig. 2. Consensus-responsive elements (RE) for nuclear receptors. *GRE*, glucocorticoid RE; *PRE*, progesterone RE; *ARE*, androgen RE; *MRE*, mineralocorticoid RE; *ERE*, oestrogen RE; *EcRE*, ecdysone RE; *TRE*, thyroid hormone RE; *RRE*, retinoic acid RE. (From Beato et al. 1989)

trogens a different one (Fig. 2). The HREs are distributed at various positions of the hormone-regulated genes, near the promoter, at various distances in the 5'-upstream region or within the gene itself.

Some genes contain more than one HRE, which in receptor-binding experiments and transfection studies with chimaeric genes make variable contributions as hormone-inducible enhancer elements and act synergistically. In some cases, even sequences that are half-palindromic but in multiple copies can confer hormone inducibility to the respective gene. A series of other regulatory sequences interacting with general and tissue-specific factors serve to modulate the hormonal effects.

Oncogenes and human cancer

Protooncogenes affect cellular regulation, growth and developmental processes through their respective encoded proteins, which belong to various categories of regulatory macromolecules, such as growth factors, growth-factor receptors, GTP-binding proteins and nuclear proteins involved in transcription regulation (Weinberg 1985). The realization that the expression of a mutated protooncogene product or the overexpression or untimely expression of an otherwise normal protooncogene is a major causal factor in cell transformation was a major breakthrough in our concept of carcinogenesis. This resulted in a series of studies dealing with the role of increased expression of normal or of mutated protooncogenes in the pathogenesis of human tumours. An increased expression of protooncogenes has been noted in a series of human tumours (Table 1). In many cases, amplification of several oncogenes has also been observed (Table 2).

A possible causal relationship between oncogene expression and tumorigenesis in humans will be illustrated on the paradigm of the *HER*-2 gene. A detailed study of the expression of this protooncogene in human breast cancer has recently appeared (Slamon et al. 1989). The *HER*-2 (c-*erb*B2) is the human homologue of the c-*neu* gene, cloned from a rat neuroglioblastoma, coding for a transmembrane protein, with extra- and intracellular domains, and partially homologous to the tyrosine kinase family of growth-factor receptors. In 25%–30% of human primary breast cancers this protooncogene is amplified, the degreee of amplification being negatively correlated to disease-free and overall survival. It was also shown that amplification was accompanied with increased expression of the corresponding mRNA and protein products. The expressed protein is identical to the one expressed in normal tissues, with the exception of a neutral substitution (isoleucine for valine) at position 655 of the transmembrane domain. The *HER*-2 gene is amplified and overexpressed also in human ovarian tumours, with a similar negative correlation between over-

Table 2. Amplification of oncogenes in various human and animal tumours

Oncogene	Tumour
c-*myc*	Breast carcinoma Promyelocytic leukemia, colon carcinoma, small-cell lung carcinoma
N-*myc*	Neuroblastoma, retinoblastoma, small-cell lung carcinoma
c-Ki-*ras*-2	Lung carcinoma, bladder carcinoma
N-*ras*	Mammary carcinoma
c-*erb*B2	Breast carcinoma, ovarian carcinoma
c-*abl*	Chronic granulocytic leukemia
c-*myb*	Colon carcinoma
int-2	Breast carcinoma

Table 1. Increased expression of oncogenes in human neoplasms

Oncogene	Cellular function	Tumour
N-*ras*	GTP-binding protein	Neuroblastoma
H-*ras*-1	GTP-binding protein	Wilm's tumour
K-*ras*-2	GTP-binding protein	Chronic lymphoblastic leukemia
neu (*erb*B2, *HER*-2)	Growth factor receptor	Mammary carcinoma
int-2	Growth-factor-like	Mammary carcinoma
abl	Membrane-associated Tyr kinase	Chronic myelogenous leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia
c-*myc*	Nuclear transcription factor	Burkitt's lymphoma
mos	Cytoplasmic threonine kinase	Acute myelogenous leukemia
sis	Platelet-derived growth factor 2	Chronic myelogenous leukemia Burkitt's lymphoma

expression and disease – free interval. Amplification of the protooncogene proved to be a prognostic factor superior to the oestrogen- and progesterone-receptor status of the tumours. A direct causal relationship between the increased expression of *HER*-2 and cell transformation has been shown by Hudziak et al. (1987), who transfected 3T3 cells with *HER*-2, which led to amplification of the unaltered gene in these cells, overexpression of the respective protein, cellular transformation and subsequent tumour formation upon grafting of the transformed cells to athymic mice. Muller et al. (1988) demonstrated in transgenic mice that the activated c-*neu* gene linked to a mouse mammary tumours virus (MMTV) promotor resulted in the appearance of mammary adenocarcinomas, leading the authors to the conclusion that the expression solely of the c-*neu* oncogene is sufficient to induce malignant transformation. Similar experiments were performed by Bouchard et al. (1989), who concluded that the expression of the c-*neu* oncogene was necessary, but not sufficient, to induce malignant transformation. Bouchard et al. (1989) used constructs having the MMTV long terminal repeat immediately adjacent to the *neu* cDNA, whereas in the constructs of Muller et al. (1988) the MMTV long terminal repeat and the *neu* cDNA sequences were separated by a 600-base-pair sequence, representing the rat 30S sequences derived from the Harvey murine sarcoma virus genome. This could account for the observed differences between the results of the two groups. These differences notwithstanding, the presence of long terminal repeat sequences containing several HREs in the constructs used, and the expression of c-*neu* in the mamma epithelium, a primary target tissue for hormonal steroids, strongly suggests the importance of steroid hormones, in this specific case of sex steroids, in oncogene expression and oncogenesis (see below).

Hormonal control of protooncogene expression

A wealth of information has been recently amassed on the direct effects of steroid hormones on protooncogene expression. Interesting in this respect are the effects of oestrogens on the expression of c-*fos* (Loose-Mitchell et al. 1988; Weisz and Bresciani 1988) and c-*myc* (Weisz and Bresciani 1988) in rat uterus. Administration of oestradiol to immature rats causes within 30 min an increase of c-*fos* mRNA, reaching a maximum at 3 h (Loose-Mitchell et al. 1988). This effect is abolished by actinomycin D. Other steroid hormones, such as dexamethasone, dihydrotestosterone and progesterone, had no such effect. Weisz and Bresciani (1988) followed the effects of oestrogens on the expression of 20 protooncogenes. c-*fos* and c-*myc* responded very rapidly, within 30 min and 90 min, respectively, to the hormone, whereas the other oncogenes did not respond to the hormonal stimulation. Loose-Mitchell et al. (1988) demonstrated the presence of a 12-base-pair sequence having a sequence 5′-GGTCTAGGAGACC-3′ at position −219–207 with respect to the start site of transcription, similar to the palindromic oestrogen-responsive element in the *Xenopus* vitellogenin gene. Another similar sequence 5′-GGTCTGCCTAGGC-3′ is present at position 2102–2114 of the gene. It is thus suggested that the effects of oestrogens on c-*fos*, and probably also on c-*myc*, expression are mediated by direct interaction of the hormone-receptor complex with these sequences, which could represent oestrogen-responsive elements instrumental for c-*fos* activation.

A search for the presence of various HREs in protooncogenes, whose expression is increased in various tumours, has indeed revealed such sequences and has initiated studies on the hormonal inducibility of the respective genes. It is important to note that many retroviruses involved in tumour induction in animals – a classic example being the MMTV – but also human retrovirus and HIV-1, have HREs in their genome (Miksicek et al. 1986). The effects of various steroid hormones on MMTV are well documented. The experiments of Muller et al. (1988) and Bouchard et al. (1989) have already been mentioned above. Markham et al. (1986) have shown that the ability of HIV-1 to infect human peripheral blood monocytes productively was improved by hydrocortisone. That this effect is mediated by the glucocorticoid-responsive element present in the virus genome is suggested in transfection assays (Spandidos et al. 1990). The human papillomavirus type 16 in combination with an activated H-*ras* gene transforms primary cells only in the presence of the glucocorticoid hormone dexamethasone. It has been found that the HPV-16 genome carries a glucocorticoid-responsive element sequence (Pater et al. 1988). In this respect the paper by Stavenhagen and Robins (1988) should be mentioned showing that the mouse sex-limited protein gene has been rendered androgen-dependent through endogenous virus insertion, having an HRE in its 5′ long terminal repeat 2 kb upstream of the gene.

Possible mechanisms of steroid hormone involvement in cell transformation

Steroid hormones represent one of the most important categories of regulatory molecules, controlling cellular growth, proliferation, and differentiation, as well as metabolic processes. Most of these effects are mediated by regulation of key genes, such as the protooncogenes, in a precisely defined temporal and tissue-specific pattern. Expression of mutated or of normal genes at an inappropriate time period or location could have grave consequenes for various cellular functions. If the affected genes belong to the protooncogene family, the link to cellular transformation is obvious. As mentioned above, some protooncogenes seem to be under the direct control of steroid hormones. Mutations in these genes as a consequence of action of a carcinogen would lead to a hormone-dependent synthesis of mutated proteins, and their involvement in the cell transformation process.

A similar effect on cell transformation would result if the carcinogen were to induce an alignment of a protooncogene, normally not subjected to hormonal control, to hormone-responsive elements, rendering it steroid-hormone-dependent.

Gene rearrangement and chromosomal translocation are such possibilities. Chorazy (1985) has discussed the role of movable genetic elements in this context. In a study on chromosomal rearrangement in leukemias and various solid tumours, de Braekeller (1988) demonstrated preferential breakage and deletions in bands known to contain protooncogenes, growth factor receptor and differentiation genes.

Insertional mutagenesis, i.e. integration of viral sequences, containing HREs in their regulatory regions, near protooncogenes is one potential basic mechanism of conferring hormone responsiveness to protooncogenes. The role of MMTV in breast tumour formation (Peters et al. 1983) and the effects of sex steroids on this process is one such classic example. Conforming with this notion are results, already referred to, of androgen dependence of the mouse sex-limited protein gene caused by endogenous virus insertion, possessing an HRE in its long terminal repeat (Stavenhagen and Robins 1988). As already mentioned, in many of the tumours showing increased expression of protooncogenes, a parallel amplification of the expressed gene is also observed. It is possible that some of the amplified genes could be positioned near HREs, rendering the genes responive to the hormonal stimulus. It should be mentioned that steroid hormones not only stimulate but also repress gene activity; therefore, the possibility should also be considered that, with mechanisms similar in principle to those described above, oncosuppressor genes could be repressed, and therefore also the synthesis of tumour – inhibitory substances, which are thought to be the products of these genes.

Conclusions

On the basis of the above considerations and taking into account the three-stage model of carcinogenesis, the role of steroid hormones in tumour formation can be regarded as that of a conditional carcinogen or a promotor (Butenandt 1950), acting on cells already initiated by the action of the solitary carcinogen, i.e. on cells on which the carcinogen has damaged hormone-responsive protooncogenes or has provoked alignment of protooncogenes to hormone-responsive elements. In the specific case of hormonal steroids the promoting role of the hormone is visualized as a direct action of the hormone in the form of its complex with the receptor, on genes involved in cell proliferation and differentiation. Other tumour promoters act by other mechanisms. In the case of the tumour promotor 12-*O*-tetradecanoylphorbol 13-acetate, well studied both at the level of experimental pathology and of biochemistry (Hecker 1978, 1987), the action on cell proliferation is exerted at the level of the membrane, by way of activation of the inositol phospholipid diacylphosphate/phosphokinase C pathway. Other promotors could exert their cell-proliferative effects by activating other key sites in the chain of events leading to DNA replication. The possibility that hormone inducibility of a gene could be influenced by effects on regulatory elements other than the HREs or on changes in the structure and function of the steroid-receptor molecule itself has not been discussed, but certainly represents a field of future research endeavours.

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