Minireview

Cancer Epidemiology, Biomarkers & Prevention

Do Steroid Hormones Play a Role in the Etiology of Glioma?

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Abstract

Gliomas are the most common type of primary malignant brain tumor and have a very poor prognosis. Little is known, however, about the etiology of these tumors. Evidence from a number of sources suggests that endogenous steroid hormones may play a role in the development of gliomas. First, the descriptive epidemiology of glioma suggests a relative protection of females compared with males, particularly during the premenopausal years. Second, some gliomas and glioblastomas express estrogen receptors (ER), especially ERβ, as well as aromatase, the enzyme responsible for the conversion of testosterone to estradiol, and possibly other steroid hormone receptors. Third, experimental studies indicate that glioblastomas transplanted into animals grow at a slower rate in females compared with males. Finally, experimental studies show that estradiol, 2-methoxyestradiol, and a number of selective estrogen receptor modulators inhibit proliferation of gliomas and induce cell death. These hormonal agonists and antagonists may act either through classical steroid hormone receptors or independently of such receptors. In view of these findings, further clinical, experimental, and epidemiologic studies are needed to elucidate the role of steroid hormone agonists and antagonists in the development and proliferation of glioma. If hormonal pathways are involved in gliomagenesis, this could eventually lead to the design of preventive strategies. *Cancer Epidemiol Biomarkers Prev; 19(10); 2421–7. ©2010 AACR.*

Little is known about the etiology of brain neoplasms, which in general are highly fatal (1). Gliomas, which include astrocytomas, oligodendrogliomas, and ependymomas, are the most common type of primary malignant brain tumor, accounting for approximately 80% of cases (2). Gliomas originate from glial cells (astrocytes or oligodendrocytes). Gliobastoma multiforme, the highest grade of glioma, is the most common and most aggressive type of malignant glioma. Most cases of glioblastoma multiforme (~90%), referred to as "primary glioblastoma multiforme," develop rapidly without detectable evidence of a less malignant precursor tumor, whereas about 10% of glioblastomas, referred to as "secondary glioblastoma multiforme," develop slowly from low-grade astrocytomas (3). The only established risk factors for gliomas are high-dose ionizing radiation and certain rare genetic conditions, which together account for only a small proportion of cases (1, 4, 5). However, evidence from a number of sources suggests a possible role of endogenous ovarian steroid hormones in the development of glioma. Given that this topic has received little attention in major reviews on brain tumor epidemiology to date (1, 4-6), we review here findings from descriptive and analytic epidemiology, clinical studies, and experimental animal and cell culture studies pertinent to the potential role of steroid hormones in the development of glioma.

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Descriptive Epidemiology

The incidence rate of glioma in adulthood is 50% greater in men than in women (5, 7). For example, the age-adjusted annual incidence rate of glioma in the United States is 7.6 in 100,000 in males and 5.4 in 100,000 in females (2), and the male-to-female excess has been stable over time and is evident internationally (7-9). Using New York State tumor registry data for the period from 1976 to 1995, McKinley et al. (7) calculated crude, and age- and sex-specific incidence rates for three types of glial tumors: glioblastoma multiforme, astrocytoma not otherwise specified, and anaplastic astrocytoma. In addition, the authors calculated the rate ratio for glioblastoma multiforme in females relative to males by 5-year age intervals. This analysis indicated that, overall, males were 1.5 to 2.0 times more likely to develop glioblastoma multiforme compared with females. Furthermore, the rate ratio for glioblastoma multiforme in women compared with men decreased from 1.0 in the age interval 5-9 years to 0.8 in the age interval 10-14 years and continued to decrease throughout the premenopausal years, reaching a low of 0.51 in the age interval 50-54 years. Thereafter, the rate ratio increased somewhat and remained at a constant level of about 0.65. The authors proposed that the timing of the decline in the incidence rate in females

relative to males was suggestive of a protective role of estrogens during the premenopausal years.

Analytic Epidemiology

A number of epidemiologic studies (10-24), most of which have used a case-control design (10-12, 14-17, 19, 21, 22), have examined menstrual and reproductive factors and the use of exogenous hormones in relation to risk of glioma in women (10-24). Overall, these studies have yielded weak and inconsistent results. The most consistent finding to date has been a positive association between a relatively late age at menarche and increased risk of glioma observed in two cohort studies (18, 24) and four case-control studies (11, 16, 17, 22). Findings concerning other reproductive factors, including age at first birth, parity, and menopausal status, have not been consistent. Three studies (17, 22, 24) found that women who had ever used oral contraceptives were at decreased risk, but there were no clear trends with duration of use, and the remaining studies provided no evidence of an association (16, 18-20). Several studies (16, 17, 22) reported that ever users of menopausal hormone therapy had reduced risk of glioma, but there was no trend with duration of use, and other studies (18, 19, 23, 24) showed no association of ever use of hormone therapy or duration of use with glioma risk. In a recent report, we found no association with ever use of hormone therapy, duration of use, or with ever use or duration of use of estrogen or progestin (24). The large Million Women Study (23) showed no significant association of current or past use of hormone therapy with glioma. In that study, among current users, the use of estrogen only, but not estrogen plus progestin, was associated with a small but significant increase in risk (relative risk 1.34, 95% confidence interval, 1.05-1.72; ref. 23).

Many of the epidemiologic studies on glioma have had limitations. Most have been case-control studies, which are susceptible to information bias. In addition, because glioma has a very poor prognosis, case-control studies are subject to possible biases from the use of proxies for cases who are too sick to be interviewed, as well as from effects of the illness on recall of past events. Furthermore, some of the cohort studies have had small numbers of cases (18, 24). Finally, menstrual and reproductive variables may not adequately reflect steroid hormone concentrations at key time periods relevant to the induction of glioma. These methodologic limitations may account in part for the failure to detect consistent associations.

Steroid Hormones and the Brain

Steroid hormones play a key role in brain development and differentiation (25, 26). Furthermore, there is evidence that endogenous estrogens and other estrogenic compounds are neuroprotective in a variety of neurologic disorders, including Alzheimer's disease, Parkinson's disease, schizophrenia, and ischemic injury caused by stroke (27-32). These neuroprotective effects include improved myelination, decreased edema, inhibition of apoptosis, and decreased inflammation (32). Steroid hormones may also play a role in the development of brain tumors and/or control their growth, because steroid hormone receptors are members of a superfamily of ligand-activated transcription factors that are potentially oncogenic (25, 33).

Clinical and Experimental Studies

Research into possible hormonal modulation of the growth of gliomas *in vivo* and *in vitro* has had as its primary goal the development of new and more effective treatments. However, findings from these studies have also shed light on pathways involved in the development and progression of glioma in humans. This research has drawn upon knowledge of the role of endogenous and exogenous sex steroids in the etiology and pathogenesis of breast cancer and endometrial cancer and from an understanding of the tissue-specific nature of steroid hormone action (34-36). For example, selective estrogen receptor modulators (SERMs) may function as either estrogen antagonists or agonists, depending on the target tissue and on the estrogen receptor (ER) subtype mediating a specific response (34). Thus, individual SERMs can act as pure agonists, pure antagonists, or as mixed agonist/antagonists.

Steroid receptors in normal glial cells and glioma cells

Steroid hormone receptors are ligand-activated transcription factors that may be located in the plasma membrane, the cytosol, and/or the nucleus of target cells. Binding of endogenous or exogenous steroids to these classical receptors results in receptor dimerization and interactions with enhancer or repressor elements in target genes, leading to changes (increases or decreases) in gene transcription over a period of hours to days (37). Increasing evidence suggests that many cells also express G protein-coupled receptors that bind estrogens with high affinity (e.g., GPR30), and that these receptors may also play important roles in signal transduction (38). Hormone receptors are thought to play a role in the control of cell growth (25, 39), and estrogens have mitogenic activity in several cell types (40).

Two classical ERs have been distinguished: ERα, identified and cloned in 1986, and ERβ, identified in 1996 (36). Our understanding of estrogen action in different tissues and the role of these two ER subtypes has advanced greatly in the past two decades (30, 34). Because the expression of the putative G protein-coupled receptor (GPR30) has not been explored in glioma, we will focus here on the nuclear hormone receptors ERα and ERβ. Each of these receptors can bind to estradiol and other estrogenic compounds, forming homodimers and/or heterodimers. These dimers can, in turn, bind to estrogen response elements (ERE) in DNA and recruit other components of the transcriptional machinery, altering gene

expression (30, 34, 41). Numerous coactivators and corepressors can modulate receptor function (41). In addition, estradiol and other steroid hormones as well as SERMs can operate through nonclassical pathways (i.e., not directly involving ER binding to EREs; refs. 30, 41).

Since the 1980s, several investigators have attempted to identify steroid hormone receptors in normal human brain cells and in human glioma and glioblastoma cells, as well as in rat glial and glioma cell lines (42-51). Classical ERs and/or progestin, glucocorticoid, and androgen receptors are expressed in normal rat glial cells (26, 42). Santagati et al. (26) found low levels of ERα mRNA in cultures of rat astrocytes and oligodendrocytes and suggested that glial cells grown in culture may express this ER. Findings concerning the presence of ERs and other steroid hormone receptors in human and rat glioma and glioblastoma cell lines are varied and inconsistent. Several studies reported finding either no detectable ERs or progestin receptors or very low levels in human gliomas/glioblastoma (43-47), whereas glucocorticoid and/or androgen receptors were detected in a higher proportion of gliomas (43, 46, 47). However, several more recent studies have documented ER expression in a substantial proportion of gliomas, glioblastomas, and astrocytomas (25, 35, 36, 49, 52, 53).

Although ERα has been detected in about one third of lower-grade tumors (52), it seems that most gliomas are ERα negative (36). Because many astrocytes express ERα *in vivo* (32, 53), and there is also evidence that oligodendrocytes may express ERα (54, 55), it is possible that ERα expression is reduced or lost during tumor development. However, it is also possible that very low levels of ERα in gliomas have gone undetected due to technical limitations, especially of immunohistochemistry. There can be enormous variability in ER immunostaining even in breast cancer samples, depending on the antibody used and the specifics of the protocol, especially with respect to antigen retrieval (56, 57).

In contrast to ERα, ERβ is expressed in glial neoplasms (35) as well as in nonneoplastic astrocytes (36). Batistatou et al. (36) reported that ERβ was highly expressed in nonneoplastic astrocytes and low-grade astrocytic neoplasms, and its expression declined in high-grade neoplasms, paralleling their loss of differentiation. In other neoplasms, including breast, prostate, and ovarian cancer, loss or reduction of ERβ expression is associated with the malignant phenotype, indicating a potential tumor suppressing function for ERβ (58-61).

Actions of steroid hormone receptor agonists and antagonists on gliomas

An early experiment in which a human glioblastoma cell line was transplanted into athymic mice (62) indicated that tumor growth was markedly greater in males compared with females, suggesting that sex-steroid hormones influence the growth of glioblastomas. In a second experiment (63), nude rats were transplanted with glioblastoma multiforme cells. Female rats survived longer than male rats, and estrogen-treated animals (both male and female) survived longer than ovariectomized, untreated male rats and progesterone-treated rats. Studies by the same group confirmed that estradiol increased survival in the nude rat model of glioblastoma multiforme and that the actions of estradiol occurred early in tumor progression (64).

The effects of a number of other hormone agonists and antagonists on glioma cells have been investigated, as described below. Treatment with micromolar concentrations of 2-methoxyestradiol has been shown to induce cell death in both human glioma cell lines and in one rat glioma cell line (65-67). Additionally, *in vivo*, i.p. administration of high doses of 2-methoxyestradiol, injected as a monotherapy, resulted in a dose-dependent inhibition of tumor growth in a rat orthotopic model of glioma (68). Moreover, the nonselective steroid receptor agonist tibolone was reported to have a strong dose-dependent inhibitory effect on human primary glioblastoma cells *in vitro* but not on rat C6 glioma cells (69). (Tibolone is referred to as "non-selective" because it binds to all major steroid receptors.) A recent report indicated that pharmacologic doses of melatonin inhibited the local production of estrogens but also seemed to inhibit the growth of C6 rat glioma cells, potentially suggesting that endogenous estrogens might promote tumor growth (70). However, it is also possible that inhibition of glioma cell proliferation by melatonin was unrelated to its effects on estrogen synthesis.

A variety of other estrogenic agents have also been studied. Genistein, an isoflavone that binds preferentially to ERβ and that also inhibits protein tyrosine kinases and topoisomerase II, rapidly inhibited DNA synthesis in human glioma cells in a concentration-dependent manner (71). The SERM tamoxifen, which can have both estrogenic and antiestrogenic effects, also inhibits glioma cell proliferation and induces apoptosis *in vitro* (51, 72-74). Interestingly, both tamoxifen and a benzopyranone with SERM activity, CC-8490, have been reported to induce apoptosis *in vitro* and *in vivo* in ER-negative glioma cells (75). Tamoxifen also markedly inhibited tyrosine phosphorylation of the neu/c-erbB receptor as well as DNA synthesis and cell proliferation in the malignant glioma cell lines U251-MG and T98G (76).

The actions of tamoxifen in glioma cells may depend on its interaction with specific ER isoforms, the stage of tumor development, and the dose. Tamoxifen seems to be a pure antagonist for ERβ acting on EREs in the promoters of target genes but can have agonist activity on ERβ when the response is mediated by non-ERE mechanisms (77). Another possibility is that ER-related proteins may be expressed in gliomas and may mediate the response to tamoxifen (51). Finally, especially at high doses, tamoxifen might act independently of any steroid receptor by influencing calmodulin (78), various kinases (70), or intracellular calcium (79), or through other mechanisms (80). A number of studies indicate that inhibition of cell proliferation in gliomas by tamoxifen seems to operate

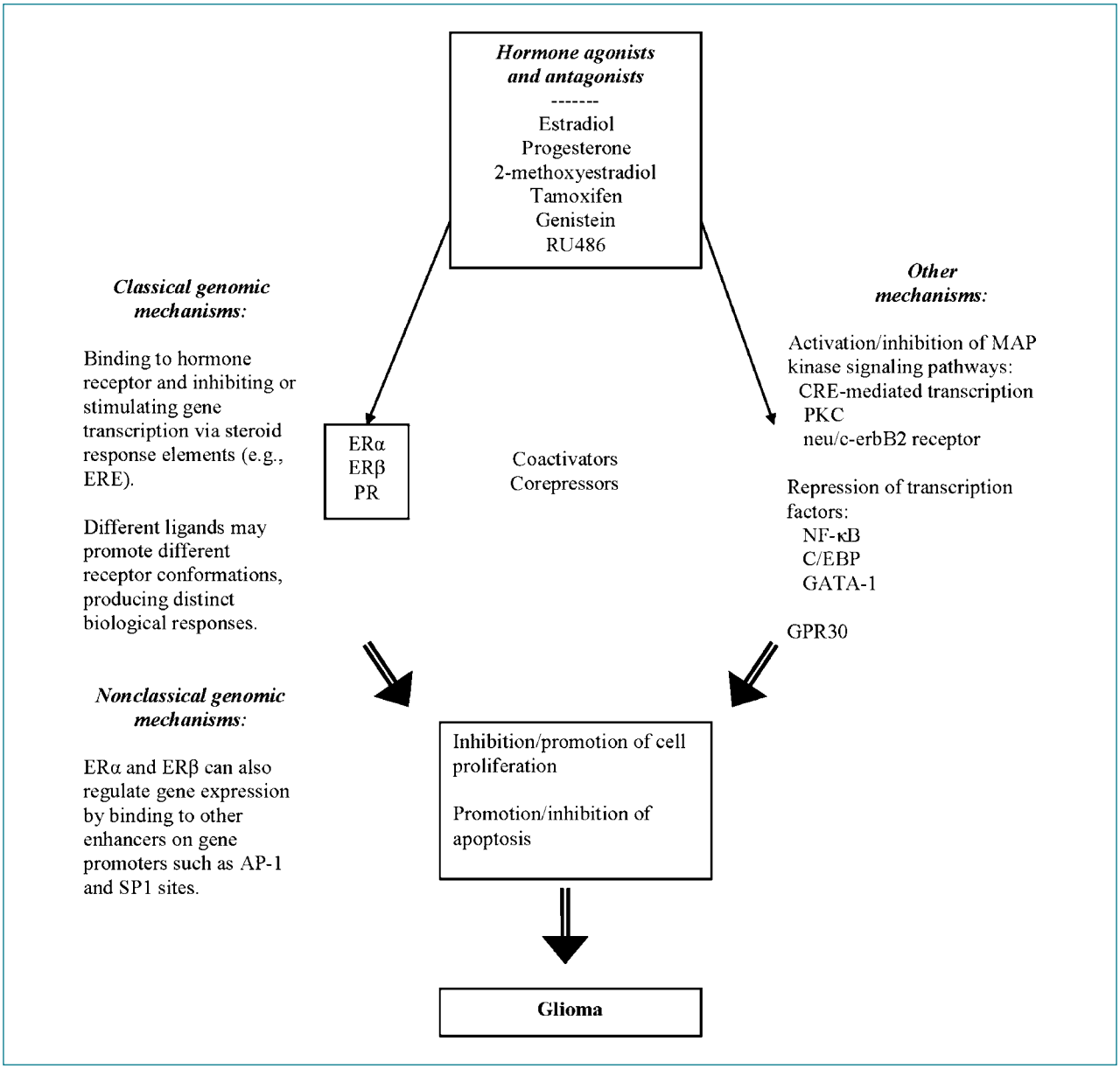

Figure 1. Schema indicating possible pathways by which steroid hormone agonists and antagonists might play a role in the development of glioma. MAP, mitogen-activated protein; CRE, cAMP response element; PKC, protein kinase C.

through a protein kinase C signal transduction pathway (72, 79).

In addition to estrogenic agents, the progestin and glucocorticoid receptor antagonist RU486 (mifepristone) suppressed tumor volume and weight in nude mice bearing xenografts of the human malignant glioma U87MG cell line (81). Furthermore, RU486 abolished the stimulatory effect of the glucocorticoid dexamethasone on the proliferation of U87MG cells *in vitro*. This suggests that the antiproliferative effect of RU486 is due to the inhibition of glucocorticoid binding to its receptor proteins (81).

Figure 1 provides a general schema illustrating pathways, both dependent on binding to the classical ERs and independent of ER action at EREs, by which steroid hormones may influence the development of glioma.

Conclusions

There is suggestive evidence that ovarian steroid hormones, and especially estrogens, may play a role in the development of gliomas. Specifically, the incidence rate of glioma is higher in men compared with women, with the lowest rates in women during their reproductive

years, suggesting that estrogens might exert a protective effect. This hypothesis is supported by experimental evidence that estradiol and SERMs can inhibit the proliferation of gliomas. However, further work is necessary to identify the specific compounds, receptors, and pathways involved.

Experimentally, studies of tumor growth in nude mice, in which it is possible to independently manipulate the hormonal status and chromosomal sex of tumor cells, would help determine whether the observed sex differences are due to hormonal status, chromosomal sex, or a combination of both factors. There is also a need for clinical and experimental studies to elucidate target genes regulated by estradiol and SERMs in both normal glial cells and glioma/glioblastoma cells and to determine specific pathways implicated in the rapid transition to a transformed phenoptype in primary glioblastoma multiforme. A high priority should be given to clarifying the roles of ERα, ERβ, and novel estrogen binding sites such as GRP30 in the normal proliferation, differentiation, and function of glia as well as glial transformation. Likewise, there is currently little information on which promoters drive classical ER transcription in glia, or which ERβ splice variants are expressed in glia and glial tumors. Identification of genes that are specifically regulated by ERβ, whose expression seems to decline in high-grade neoplasms (34), could be especially valuable. Another question that merits attention is whether loss of ERα expression may be an early step in malignant transformation, because ERα is highly expressed in most glia but seems to be greatly reduced in gliomas. Epidemiologically, it would be potentially informative to use large cohorts with stored blood samples to examine circulating sex steroid levels in relation to risk of subsequent glioma, because steroid hormones can penetrate the blood-brain barrier (82, 83). Owing to the low incidence of glioma, such a strategy would require the pooling of data from a number of large studies and would require careful attention to methodologic problems of measuring steroid hormones.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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