Role of Hormonal Environment, Partial Hepatectomy, and Dose of Ethylnitrosourea in Renal Carcinogenesis


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SUMMARY

For evaluation of factors modifying renal carcinogenesis, several groups of 6-week-old C57BL × C3H F1 mice, of both sexes were exposed once to 60 or 120 μg of ethylnitrosourea per g of body weight. This treatment was preceded in some groups by partial hepatectomy and/or ovariectomy. Animals were killed at 90 weeks of age, and the incidence of renal tumors was evaluated.

Ethylnitrosourea induced papillary cystadenomas and solid granular and clear cell-type tumors. The incidence of tumors was dependent upon the dose. Sex difference was revealed in groups exposed to higher doses of ethylnitrosourea. Only the combination of partial hepatectomy and bilateral ovariectomy significantly augmented development of kidney tumors.

INTRODUCTION

Renal tumors rarely have been observed in a majority of mouse strains (2). Only BALB/c mice develop these lesions spontaneously late in life (1). Although various laboratory animals have been shown to be susceptible to induction of renal tumors by exogenous chemical carcinogens (9), mice appeared to be resistant to the induction of these neoplasms. However, a significant number of microscopic kidney tumors were observed in Swiss mice that were exposed to dimethylnitrosamine as adults (14). Total body or local X-irradiation led to renal carcinogenesis which was significantly enhanced by unilateral nephrectomy (11). In addition, lead acetate (16), 20-methylcholanthrene (12), methylnitrosourea (15), and, more recently, ENU (5) have been shown to be effective renal carcinogens in mice.

A number of studies in our laboratory are directed to assessing the role of the cell-replicating state and the hormonal environment in the outcome of carcinogenesis in liver (17) and other organs.

This paper deals with renal carcinogenesis, bringing forward the role of dose of ENU, hormonal environment, and partial hepatectomy in kidney tumor development.

MATERIALS AND METHODS

Mice. C57BL × C3H F1 mice of both sexes were utilized. Parent strains were purchased from The Jackson Laboratory, Bar Harbor, Maine, and bred in our animal facility. When they were 4 weeks of age, offspring were allocated to various experimental groups listed in Table 1. All animals were housed in plastic cages in sets of 10 and kept in a temperature-controlled laboratory. They were given Purina laboratory chow and water ad libitum.

Carcinogen. ENU has been used as carcinogen. The compound has been dissolved in trioctanoin and delivered once according to schedule (Table 1).

Treatment. When they were 6 weeks of age, animals of Groups 4M, 4F, and 5F were partially (two-thirds) hepatectomized according to the method of Higgins and Anderson (3). Other animals were either left intact (Groups 1M and 1F) or were subjected to sham operations (Groups 2M, 2F, 3M, and 3F). Groups 5, 6 and 7F were ovariectomized either at the time of hepatectomy (Groups 5 and 7F) or without that surgery (Group 6F). Forty-eight hr following surgery, mice of Groups 4M, 4F, 5F, and 6F were given 60 μg i.p. of ENU per g of body weight. At the same time, sham-operated groups (2M and F, and 3M and F) received 60 and 120 μg of ENU, respectively.

All survivors were sacrificed when 90 weeks old. Tissues were fixed in buffered formalin and stained with hematoxylin and eosin for histological study. The significance of the results (null hypothesis) was evaluated by the $\chi^2$ method of statistical analysis.

RESULTS

Treatment of animals with ENU induced papillary cystadenomas and solid granular and clear cell kidney tumors. Their detailed morphology and histogenesis are being presented as an integral part of studies evaluating the role of age in carcinogenesis (L. S. Lombard, J. M. Rice, and S. D. Vesselinovitch, unpublished data). Table 1 lists the incidence of renal tumors in various experimental groups. In the nontreated controls (Groups 1M and F), 0.5% developed kidney tumors. Animals treated with 60 μg of ENU per g of body weight (Groups 2M and F) developed renal tumors in 7.7% of male and 3.7% of female mice. The higher dose of ENU (120 μg/g body weight) increased the incidence of kidney tumors to 28.0% ($p < 0.025$) and 9.8% of males and females, respectively. The observed difference between males and females (Groups 3M and F) was statistically significant ($p < 0.05$).
demonstrated that several factors may influence the degree of hepatic metabolism of the carcinogens used which led to their carcinogenesis by diethyl- and dimethylnitrosamines was protein depletion (7). This increase was attributed to impaired kidney tumorigenesis. It has been reported that renal development of these tumors. been revealed in groups exposed to higher doses of ENU. dependent. Also, a statistically significant sex difference has increased in adult rats by partial hepatectomy (10) and renal carcinogenesis, but the combination of partial hepatectomy and bilateral ovariectomy which has been further enhanced by unilateral nephrectomy. These observations suggest that an increase in the macromolecular activity in the kidneys might augment carcinogenesis. Thus, in the present study, partial hepatectomy and concurrent unintentional infliction of trauma upon kidney at the time of ovariectomy might have enhanced carcinogenesis via such a mechanism.

The observed sex difference, which is reminiscent of a situation observed in the human population, needs further elucidation, since many reports on this topic are of "doubtful significance and sometimes even contradictory" (9).

No enhancement of renal tumors was observed when ENU treatment was preceded by partial hepatectomy (Groups 4M and F). However, 34.0% of the animals in Group 5F, which have been both ovariectomized and partially hepatectomized before administration of ENU, developed kidney tumors. This incidence was statistically significant from the incidence of kidney tumors observed in sham-operated (Group 2F; p < 0.005), partially hepatectomized (Group 4F; p < 0.005), ovariectomized (Groups 6F; p < 0.005), or ENU-nontreated, partially hepatectomized and ovariectomized (Group 7F; p < 0.005) groups of mice. Thus, only the combination of partial hepatectomy and bilateral ovariectomy enhanced ENU-induced renal carcinogenesis. Most of the tumors observed in the whole series were papillary cystadenomas.

DISCUSSION

Present studies demonstrated that even a single administration of ENU to young adult mice has been effective in inducing renal neoplasms and that the incidence was dose dependent. Also, a statistically significant sex difference has been revealed in groups exposed to higher doses of ENU. Neither partial hepatectomy nor ovariectomy per se influenced renal carcinogenesis, but the combination of partial hepatectomy and ovariectomy significantly augmented development of these tumors. The above observations and studies in the other laboratories demonstrated that several factors may influence the degree of kidney tumorigenesis. It has been reported that renal carcinogenesis by diethyl- and dimethylnitrosamines was increased in adult rats by partial hepatectomy (10) and protein depletion (7). This increase was attributed to impaired hepatic metabolism of the carcinogens used which led to their longer persistence in the body and, hence, longer exposure of the susceptible kidney cells (13). A similar explanation pertaining to present experiments, although possible, is not probable because ENU, unlike the nitrosamines, has a very short biological half-life with no specific enzymatic requirements for its metabolism and carcinogenic activation.

The incidence of kidney tumors induced by X-irradiation in mice (11) and dimethylnitrosamine in rats (4) has been increased by unilateral nephrectomy also. Malamud et al. (6) observed that such surgical procedure and touching of a normal kidney with forceps imperceptibly wet with isopropl alcohol-hexachlorophene led to a 2-fold increase in the specific activity of DNA in the kidney. Pashkis et al. (8) observed that kidneys undergo hypertrophy following partial hepatectomy which has been further enhanced by unilateral nephrectomy. These observations suggest that an increase in the macromolecular activity in the kidneys might augment carcinogenesis. Thus, in the present study, partial hepatectomy and concurrent unintentional infliction of trauma upon kidney at the time of ovariectomy might have enhanced carcinogenesis via such a mechanism.

REFERENCES

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Evaluation of Factors Modifying Renal Carcinogenesis


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