Induction of Malignant Kidney Tumors in Rats with Streptozotocin

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SUMMARY

Diabetes was induced in rats with Streptozotocin and alloxan and the tumorogenic effects of these two compounds were compared. One hundred thirty Lewis and Sprague-Dawley rats survived the induction of diabetes with streptozotocin. Fifty-six of these animals were sacrificed within 8 months of streptozotocin administration and three were found to have renal tumors. Twenty-four of 74 (30.8%) streptozotocin rats sacrificed more than 8 months after the induction of diabetes had grossly visible renal tumors. The lesions were epithelial in type and, although rarely invasive, had malignant cytological characteristics. Two of these animals had gross tumor spread to the liver and lungs. Forty % of the renal tumors were bilateral. No tumors were found in 72 rats surviving diabetic induction with alloxan and 260 littermate controls. Streptozotocin (an /N-nitrosomethylamide) is chemically related to dimethylnitrosamine (an N-nitrosodimethylamine), a known carcinogenic agent in rats. It is concluded that streptozotocin can induced renal cancer in rats.

INTRODUCTION

Streptozotocin [an N-nitrosomethylamide (C₄H₁₂N₃O₇)] (8) is derived from Streptomyces achromogenes and has diabetogenic (9), antimicrobial (14), and antitumoral (5) activity. It has been used most extensively as an experimental inducer of permanent diabetes in animals by taking advantage of its direct toxicity to pancreatic β cells. Along this line it has recently been demonstrated that streptozotocin can favorably influence the course of insulin-secreting islet cell tumors in man (2-4, 11). In the course of our studies on the pathogenesis of the glomerular lesions in rats with chemically induced diabetes we discovered a high incidence of kidney tumors in animals given streptozotocin and it is this experience which we are reporting herein.

RESULTS

Approximately one-fifth of the animals died within 2 months of receiving streptozotocin or alloxan (Table 1). Kidney tumors were not found in any of the 260 control or in the 72 surviving alloxan diabetic rats despite following many of these animals for as long as 16 months. Three of 36 Lewis rats sacrificed within 3 months of streptozotocin administration had kidney tumors. Seventy-four Sprague-Dawley and Lewis rats were sacrificed more than 8 months after streptozotocin infusion and 24 (30.8%) of these animals had gross kidney tumors. The majority of these tumors were found in animals studied at approximately 1 year.

The tumors were of the epithelial type. They were single or multiple and varied from small nodules barely visible to the naked eye to huge tumor masses weighing up to 200 g, filling much of the abdominal cavity and adhering to adjacent organs such as the pancreas, spleen, and stomach. The large masses frequently had totally necrotic liquefied centers with thin rims of viable tumor tissue. In approximately 40% of the cases the tumors were present...
bilateral. The tumors occurred in the renal cortex, often raised the renal capsule, and frequently extended into the medulla. They were well demarcated from the renal tissue by a pseudocapsule created by compression of the surrounding parenchyma.

Structurally, the tumors were tubular, papillary, solid, or any mixture of these characteristics. Two of the 3 lesions in the Lewis rats studied in the 1st 8 months after streptozotocin were small papillary tumors benign in appearance. All other tumors had histological features suggestive of cancer. The cells were usually tightly packed and had pleomorphic round or oval nuclei containing scanty peripheral chromatin and large central basophilic nucleoli. The cytoplasm varied from relatively dark, granular, and eosinophilic to pale and foamy resembling the classical clear cells of human adenocarcinoma of the kidney. Mitoses, bizarre cells, and areas of necrosis were frequent. With massive tumor growth, the renal parenchyma was invaded the normal kidney tissue. In 2 animals, tumor involved the lungs and liver.

**DISCUSSION**

The data presented here demonstrate that streptozotocin frequently induces renal tumors in rats. The failure of alloxan to do so suggests that streptozotocin has a direct tumorogenic action unrelated to its diabetogenic effects. Although only 2 animals had gross evidence of spread of tumor, the cytological characteristics of the large majority of the renal lesions allow them to be classified as histologically malignant. Previous experiences of renal tumors in Holtzman (1, 12) and Sherman (12) rats treated with streptozotocin have been reported but the lesions in these animals, although similar to those reported here, were thought to be benign.

Streptozotocin (an N-nitrosomethylamide) is chemically closely related to dimethylnitrosamine (an N-nitrosodiethylamine) a compound known to induce kidney tumors in rats (6, 7, 10, 13). Under conditions of complete dietary protein restriction 100% of animals surviving dimethylnitrosamine administration develop renal tumors (6). Most dimethylnitrosamine tumors are sarcomatous in type, but as these are often not grossly visible we may have missed some of these lesions in our rats. However, it is more likely that the failure to find sarcomatous lesions in our rats reflects differences in the chemical compounds used. Approximately 40% of dimethylnitrosamine lesions are of the epithelial type and are virtually identical to the tumors found in our rats. The dimethylnitrosamine studies emphasized the close resemblance between the rat tumors and those of human renal adenocarcinoma. The low metastasis rate was thought to be due to the lack of renal vein involvement with tumor in these rats (10). However, this low rate may reflect a high incidence of adenomatous lesions.

Although streptozotocin can continue to be a valuable tool in the experimental induction of diabetes, its tumorogenic capacities in the rat demands caution in its use in humans.

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