Tumorigenic Action of Streptozotocin on the Pancreas and Kidney in Male Wistar Rats

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ABSTRACT

Pancreatic islet cell tumors were induced in 38 of 44 male Wistar rats (86%), which survived 9 to 14 months following the various treatment schedules. A single i.v. injection of streptozotocin alone, 30, 40, 50, or 65 mg/kg of body weight produced adenomas of pancreatic islet cells in 8 of 9 (89%), 6 of 7 (86%), 2 of 4 (50%), and 1 of 2 rats (50%), respectively. The neoplasms were seen in all of the 8 rats given a single i.p. injection of nicotinamide, 250 mg/kg of body weight, 15 min before a single i.v. injection of streptozotocin, 65 mg/kg of body weight. Among the 14 rats given a single i.p. injection of nicotinamide, 500 mg/kg of body weight, 15 min before a single i.v. injection of streptozotocin, 65 mg/kg of body weight, 13 rats (93%) developed pancreatic islet cell tumors.

Renal tumors were seen in only 3 rats treated with streptozotocin and nicotinamide. None of rats used in this study developed hepatic tumors.

This study demonstrates that streptozotocin, even in a dose of 30 mg/kg of body weight, has an exceedingly marked tumorigenic action on the rat pancreas, while it has little effect on the kidney and no effect on the liver.

INTRODUCTION

Streptozotocin, a broad-spectrum antibiotic isolated from Streptomyces achromogenes var. 128 (6), possesses antileukemic (5) and diabetogenic activities, the latter mediated through the specific destruction of the B-cells of the pancreatic islets of Langerhans (7, 15). Streptozotocin has an oncogenic activity on the kidney (2, 10, 11, 14) and pancreatic islet cells in 8 of 9 (89%), 6 of 7 (86%), 2 of 4 (50%), and 1 of 2 rats (50%), respectively. The neoplasms were seen in all of the 8 rats given a single i.p. injection of nicotinamide, 250 mg/kg of body weight, 15 min before a single i.v. injection of streptozotocin, 65 mg/kg of body weight. Among the 14 rats given a single i.p. injection of nicotinamide, 500 mg/kg of body weight, 15 min before a single i.v. injection of streptozotocin, 65 mg/kg of body weight, 13 rats (93%) developed pancreatic islet cell tumors.

In the field of pancreatic endocrine oncogenesis, only a few experimental models are available. We have demonstrated that pancreatic islet cell tumors can be induced not only by the combined administration of streptozotocin and nicotinamide but also by a single injection of streptozotocin alone, 65 mg/kg of body weight, or by a combined treatment of streptozotocin and nicotinamide and that these tumors are capable of secreting a large amount of insulin to p.o. glucose load (9). The present study demonstrates that the tumorigenic activity of streptozotocin, even in a dose of 30 mg/kg of body weight, is exceedingly marked on pancreatic islets and is less marked on kidneys in male Wistar rats.

MATERIALS AND METHODS

One hundred six male Wistar rats, 180 to 200 g, were used in this study. They were kept in metal cages and were given Oriental laboratory chow (Oriental Yeast Co., Tokyo, Japan) and water ad libitum, except for an overnight fast before they received the chemical agents. Animals were separated into 8 groups. Survivors were followed for 9 to 14 months.

A single i.v. injection of 30, 40, 50, or 65 mg of streptozotocin alone per kg of body weight was given in 11, 12, 10, and 17 rats, respectively. Twenty-two rats were given streptozotocin, 65 mg/kg of body weight, 15 min after a single i.p. injection of nicotinamide, 500 mg/kg of body weight. Identical treatment with nicotinamide, 250 mg/kg of body weight, instead of nicotinamide was given to 14 rats. Ten rats were kept as untreated controls.

Streptozotocin (Lot U9889, 11837 GGS-22B; The Upjohn Co., Kalamazoo, Mich.) was dissolved immediately before use in citric acid buffer adjusted to pH 4.5, and i.v. injections were given into caudal veins. Nicotinamide (Lot WTE 1323; Nakarai Chemicals, Kyoto, Japan) and picolinamide (Lot H 00423; Nakarai Chemicals) were dissolved in distilled water.

All of the rats that survived for 9 months or longer were autopsied. Their pancreata, portions of hepatic tissue, kidneys, and grossly abnormal tissues were fixed in Bouin's solution, and paraffin-embedded sections were cut at 5 to 6 μm and stained with hematoxylin and eosin. Serial sections were also cut in pancreata in which no grossly visible tumor was seen.

RESULTS

Tumorigenic Action of Streptozotocin on Pancreas. Rats given a single injection of streptozotocin, 30 mg/kg of body weight, showed mild glucose intolerance (19), while all rats given a larger dose of streptozotocin, 65 mg/kg of body weight, developed severe diabetic states (9). The diabetogenic activity of the agent was partially prevented by pretreatment with nicotinamide or picolinamide, the isomer of nicotinamide (4, 9). None of the rats given the combined treatment, however, demonstrated any signs of diabetes. Survival times of rats treated with streptozotocin alone appeared to be in inverse proportion to the dose. The number of rats surviving 9 months or longer and the incidences of pancreatic islet cell tumors are summarized in Table 1.

Of the 11 rats given 30 mg of streptozotocin per kg of body weight, 9 survived 9 months or longer after treatment; among these, 7 had grossly visible pancreatic islet cell tumors (Fig. 1). Light microscopic examination uncovered...
small islet cell tumors in 1 additional rat and in the rat with grossly visible tumors. Thus, pancreatic islet cell tumors occurred in 8 of 9 rats (89%). They were solitary in 5 and multiple in the remaining 3 animals.

Of the 7 rats given a single dose of streptozotocin, 40 mg/kg of body weight, and surviving 9 months or longer, 6 (86%) developed grossly visible islet cell tumors (Fig. 2). Two microadenomas of islets were uncovered by microscopic examination. Two rats had solitary and the other 4 had multiple tumors.

Only 4 and 2 rats survived 9 months or longer among those treated with streptozotocin alone, 50 and 65 mg/kg of body weight, respectively. Among these, 3 (50%) developed pancreatic islet cell tumors, multiple in a rat given streptozotocin, 50 mg/kg of body weight, and solitary in the remaining 2 rats.

Of the 22 rats given both streptozotocin and nicotinamide, 14 survived; among these, 11 had 24 grossly visible islet cell tumors of the pancreas, solitary in 4 and multiple in 7 rats. In 2 other rats subsequent light microscopic examination demonstrated 7 microadenomas, 1 adenoma in 1 rat and 6 adenomas in another. Thus, 93% of the survivors had pancreatic islet cell tumors.

Eight rats survived 9 months or longer of 14 pretreated with picolinamide. All of them developed grossly visible islet cell tumors; 5 had solitary and 3 had multiple neoplasms.

The control rats killed after 18 months had no abnormalities in the pancreas.

### DISCUSSION

Pancreatic islet cell tumors are extremely rare in Wistar rats (16), and we could find none among 10 untreated controls. Rakieten et al. (12) reported that male Holtzman rats given a single dose of streptozotocin had a 4% incidence of pancreatic islet cell tumors and that the incidence of these tumors increased to 64% when the rats were pretreated with nicotinamide. In contrast with these findings, the present study demonstrates that, although the number of rats was less, male Wistar rats given a single dose of streptozotocin, 50 or 65 mg/kg of body weight, had a 50% incidence of pancreatic islet cell tumors. Furthermore, a single i.v. injection of 30 or 40 mg/kg of body weight produced islet cell tumors with an 89 or 86% incidence, respectively. These results suggest that a dose of 30 mg of streptozotocin per kg of body weight is fully adequate to produce pancreatic islet cell tumors. The observation that, regardless of the combined treatment with nicotinamide or picolinamide, pancreatic islet cell tumors could be induced by a single dose of streptozotocin with a high incidence indicates not that nicotinamide acts as cocarcinogen but that nicotinamide prolongs the life span of rats treated with a diabetogenic dose of streptozotocin, 65 mg/kg of body weight, through the prevention of development of severe diabetic states. Relatively low incidences of pancreatic islet cell tumors in rats treated with streptozotocin, 50 and 65 mg/kg of body weight, may be attributed to the smaller number of survivors.

The discrepancy between the incidence of pancreatic islet cell tumors in this study and that reported by Rakieten et al. (12) remains unexplained. In part, this may have been due to the difference between rat strains. Streptozotocin composed of 2-deoxy-D-glucose and 1-[methyl-14C]strep- tozotocin was detected in pancreatic islets (1, 8, 17). Being a nitrosamide the 1-methyl-1-nitrosourea moiety of the streptozotocin molecule may alkylate the DNA of islet cells, and the oncogenic activity might be expressed with the development of functioning islet cell adenomas.

Streptozotocin concentrates in the kidney and the liver (1, 8, 17). In fact, renal tumors occurred not only in Holtzman rats treated with streptozotocin alone (2, 10, 11, 13, 14) but also in those treated with streptozotocin and nicotinamide, and the oncogenic activity of streptozotocin was decreased by nicotinamide (13). In contrast with these observations, renal tumors were seen only in rats

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**Table 1**

<table>
<thead>
<tr>
<th>Treatment (mg/kg x no. of doses)</th>
<th>Administration route</th>
<th>No. treated</th>
<th>No. surviving 9 mos. or more</th>
<th>Animals with tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptozotocin, 30 x 1</td>
<td>i.v.&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11</td>
<td>9</td>
<td>8</td>
</tr>
</tbody>
</table>

<sup>a</sup> Caudal vein used.
<sup>b</sup> Administered 15 min prior to streptozotocin.

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<sup>1</sup> Administered 15 min prior to Streptozotocin.
given streptozotocin and nicotinamide, while none of the other treatment schedules used in this study could produce such tumors in male Wistar rats. The reasons for these diametrically opposite results are unclear. They may be caused by the different strains of rat used in the 2 studies.

In conclusion, it is apparent from this study that streptozotocin, even in a dose of 30 mg/kg of body weight, has a strong oncogenic activity on the pancreas in male Wistar rats and that the tumorigenic action on the kidney is less than that on the pancreas. The drug does not have an oncogenic effect on the liver.

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**REFERENCES**


Fig. 1. An islet cell adenoma of the pancreas found in a rat killed 9 months after a single i.v. injection of streptozotocin, 30 mg/kg of body weight. H & E, × 126.

Fig. 2. Islet cell adenoma of the pancreas found in a rat killed 11 months after a single i.v. injection of streptozotocin, 40 mg/kg of body weight. H & E, × 20.
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