Brief Notes and Comments

Streptozotocin Resistance of the Genetically Diabetic KK Mouse

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SUMMARY

Intraperitoneally administered streptozotocin (100 mg. per kilogram) produced hyperglycemia (higher than 200 mg. per 100 ml.) in 100 per cent of C57BL, but in none of KK mice. Pretreatment with phentolamine (50 mg. per kilogram), an α-adrenergic blocking agent, decreased resistance of KK mice to the diabetogenic action of streptozotocin. On the other hand, pretreatment with propranolol (10 mg. per kilogram), a β-adrenergic blocking agent, induced resistance to streptozotocin in C57BL mice. This effect of propranolol was potentiated by administration of epinephrine (1 mg. per kilogram).

These findings suggest that the α-adrenergic system protects pancreatic β cells from cytotoxic action by streptozotocin, indicating a predominance of the α-adrenergic system in diabetic mice of the KK strain. DIABETES *23*:856-57, October, 1974.

Streptozotocin is a well known β cell cytotoxic antibiotic which has been used to produce experimental diabetes in various laboratory animals,[1,2] including the ob/ob and the spiny mouse,[3,4] in which diabetes develops spontaneously. In the course of studies comparing the response to streptozotocin of genetically diabetic animal models with that of normal animals as a possible index for identifying abnormalities of β-cell function, it was noted that the KK mouse was resistant to the antibiotic. Subsequent investigation revealed that the responsiveness of the KK and the C57BL mouse to the diabetogenic action of streptozotocin could be modified by variation in the activity of the α-adrenergic system.

MATERIALS AND METHODS

Female KK and C57BL/6-SLC mice, eight to ten weeks old, were used after twenty hours of fasting. Streptozotocin solution was administered at a dose of 100 mg. per kilogram intraperitoneally. To some groups of mice, phentolamine (50 mg. per kilogram), propranolol (10 mg. per kilogram) and/or epinephrine (1 mg. per kilogram) was given intraperitoneally fifteen minutes before streptozotocin administration. Blood was taken from orbitary veins three days after injection of the antibiotic, and blood glucose was determined by the glucose oxidase method.[5] Glucosuria was detected with test tape (Combistix, Ames) on the same day.

Phentolamine (Regitine) was purchased from Ciba and propranolol (Inderal) from Imperial Chemicals.

RESULTS

Results are summarized in figure 1. The control blood glucose levels were similar in KK and C57BL mice. Streptozotocin caused an elevation of the blood glucose level in all C57BL mice, and glucosuria was detected in five of the seven mice studied. In contrast, the same dose of streptozotocin had no effect on the blood glucose level in KK mice.

Of the fourteen KK mice pretreated with phentolamine, all were hyperglycemic and thirteen were glucosuric. On the other hand, of the eight C57BL mice pretreated with propranolol, four were hyperglycemic and glucosuric. Furthermore, pretreatment with propranolol and epinephrine completely blocked the diabetogenic action of streptozotocin in six C57BL mice.

DISCUSSION

Genetically diabetic mice (KK) in our laboratory were intolerant to oral glucose but were neither hyperglycemic nor glucosuric when kept on laboratory chow,[6,7] a condition which is similar to chemical

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Accepted for publication June 26, 1974.

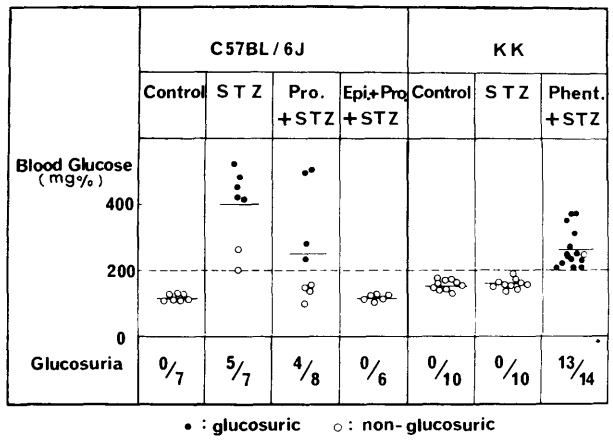

FIG. 1. Modification of diabetogenic action of streptozotocin by pretreatment with α- or β-adrenergic blocking agent. Blood and urine glucose were examined three days after streptozotocin (STZ) administration (100 mg. per kilogram). Propranolol (Pro.) (10 mg. per kilogram) or phentolamine (Phent.) (50 mg. per kilogram) with or without epinephrine (Epi.) (1 mg. per kilogram) was injected intraperitoneally fifteen minutes before STZ administration.

diabetes in man. In the present studies, KK mice showed a similar level of blood glucose to that of C57BL mice. The present studies clearly demonstrated resistance to streptozotocin in KK mice, suggesting an abnormality of β cells as a genetic trait of this strain.

The resistance could be completely depressed by pretreatment with phentolamine, an α-adrenergic blocking agent. Culbert et al.[8] demonstrated a protective effect of diazoxide against the diabetogenic action of streptozotocin. Diazoxide, a potent inhibitor of insulin secretion, mimics α-adrenergic action of catecholamine in the regulation of glucose-stimulated insulin secretion. From this evidence, it is postulated that the α-adrenergic system participates in the resistance of β cells to the cytotoxic action of streptozotocin.

In C57BL mice, a predominance of the α-adrenergic system was established by pretreatment with propranolol (a β-blocking agent), since propranolol induced resistance to streptozotocin. Propranolol-induced resistance was exaggerated by the administration of epinephrine. Dulin and Wyse[1] failed to show protection against the diabetogenic action of streptozotocin by administering epinephrine at the same dose as we used in the present studies. In their case, administered epinephrine might stimulate either α- or β-receptors on β cells as Robertson and Porte demonstrated.[9]

These findings support the hypothesis that the α-adrenergic system participates in the development of resistance to streptozotocin and suggest that a predominance of the α-adrenergic system exists in β cells of the genetically diabetic KK mouse.

ACKNOWLEDGMENT

We are indebted to Dr. W. E. Dulin of The Upjohn Company for the generous supply of streptozotocin.

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