Animal Model

The eSS Rat

A Model of Non–insulin-dependent Human Diabetes

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Biologic Features

Spontaneous diabetes mellitus was discovered and characterized in an inbred rat line called eSS (e Stilmann Salgado) maintained in the School of Medicine, Rosario University, Rosario, Argentina. The eSS rat develops a mild diabetic syndrome not related to obesity, showing early impaired glucose tolerance. Males are more affected than females. Diabetes symptoms such as hyperglycemia and glycosuria worsen as age advances. In spite of evident weight loss and physical deterioration in eSS males older than 1 year, these animals survive until 18 to 24 months without exogenous insulin. ESS males have an excess of circulating insulin compared with age-matched animals of a control line, although the former were unable to normalize the blood-glucose level (Table 1). As the insulin release of eSS rats decreases with age, glucose intolerance is further impaired. Increased levels of plasma triglycerides and total cholesterol were observed in 12-months-old eSS rats compared with controls. An improvement in the metabolic disturbances was registered in calorie-restricted animals for 12 months since weaning (i.e., lower levels in blood triglycerides, total cholesterol, blood fasting glucose, and blood glucose after oral load). Conversely, a diet with 15 g/dl of protein instead of the usual 25 dl, was effective in inducing later-onset severe glucose intolerance. This would be attributed to the fact that 25 g/dl of protein, capable of provoking the maximal growth in the rat, worsens the relative insufficiency of insulin in the eSS line.

Light microscopic studies performed in the pancreas of eSS males demonstrated notable changes compared with controls. The islets of 6-months-old eSS animals showed a disrupted structure, with cells forming groups or cords separated by mild fibrosis. There were neither lymphocytic infiltrates nor necrosis. Occasionally, in some young animals nesidioblastosis was seen. In eSS males older than 12 months, the islets were dramatically scarcer and smaller than in eSS males of 6 months, where they were almost reduced to small clusters of cells (Figure 1). The volume density of both endocrine tissue and B cells was lower in eSS than in control males. At the ultrastructural level, pancreatic B cells from the diabetic line exhibited dilatations of the endoplasmic reticulum containing fine granular material and more numerous immature secretory granules than in control rats. The renal lesions of older eSS males were similar to those found in human diabetes of long duration. This diabetic nephropathy was characterized by a diffuse glomerulosclerosis with thickening of the basement membrane and of Bowman's capsule (Figure 2). Tubular nephrosis was prominent, with dilatation of renal tubules by hyaline casts (Figure 3). eSS male rats develop bilateral cataracts with aging. This fact is related to the intensity of hyperglycemia and the age of onset of the diabetic syndrome (Figure 4).

Comparison with Human Disease

Similarities between the non–insulin-dependent diabetes and the eSS rat syndrome are many: 1) progressive glu-
Table 1. Plasma Glucose and Plasma Insulin Levels in Fasting State and 120 Minutes After Glucose Load in eSS Males and in a Control Line

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Line</th>
<th>Plasma glucose (mg/dl)</th>
<th>Plasma insulin (μU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>eSS (n = 8)</td>
<td>162 ± 16</td>
<td>221 ± 40</td>
</tr>
<tr>
<td></td>
<td>control (n = 14)</td>
<td>120 ± 9</td>
<td>164 ± 20</td>
</tr>
<tr>
<td>15–18</td>
<td>eSS (n = 16)</td>
<td>174 ± 42</td>
<td>378 ± 1</td>
</tr>
<tr>
<td></td>
<td>control (n = 4)</td>
<td>110 ± 30</td>
<td>191 ± 50</td>
</tr>
</tbody>
</table>

** P < 0.01
*** P < 0.001.
Mean ± SD
n.s.: not significant.

Figure 1. Small pancreatic islet of a male eSS rat more than 1 year old compared with adjacent acini (H&E, X400).

Figure 2. Renal glomerulus of a male eSS rat with focal thickening of the basement membrane (H&E, X200).

Figure 3. Tubules greatly distended with acidophilic hyaline ("thyroid-like") material in kidney of a male eSS rat (H&E, X100).

Figure 4. Massive cataractous degeneration of the subcapsular lens (H&E, X100).
cose intolerance with advancing age, influenced by changes in the diet; 2) relative insulin insensitivity; and 3) the occurrence of secondary manifestations such as glomerulosclerosis and cataracts. Conversely, the slow evolution of this murine non–insulin-diabetes, which is diagnosed at an early age, supports the hypothesis that it could be a model for maturity-onset diabetes of young subjects. Therefore, the eSS rat would be of potential usefulness in improving the understanding of varied unanswered aspects of human diabetes mellitus.

**Availability**

The originators and primary sources of eSS rats are Dr. Maria Cristina Tarrés and Dr. Stella Maris Martinez (Cátedra de Biología, Facultad de Ciencias Médicas, UNR, Santa Fe 3100, 2000 Rosario, Argentina).

**References**


