Diabetogenic Potential of Coxsackie B Viruses in Nature

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With 2 Figures

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Summary

Thirty-seven clinical isolates of coxsackievirus (CV) serotypes B-1, B-3, B-4, and B-5 were inoculated into male SJL mice. Twelve strains resulted in minor abnormalities of glucose metabolism in one or more of six infected mice (Tables 1 and 2). Sequential infection of male SJL mice with CVB-3, CVB-4, and CVB-5 resulted in abnormal glucose metabolism in 25 percent of the mice (Fig. 1). The glucose index of the abnormal animals was similar to that produced by sequential infection with reovirus and cytomegalovirus but less than that seen with more severe beta cell tropic agents such as streptozotocin or encephalomyocarditis virus.

Infection of autoimmune New Zealand (NZB × NZW) F₁ male mice with CBV-3, CVB-4, and CVB-5 resulted in transient elevation of the blood glucose concentration associated with acute acinar pancreatitis (Fig. 2). In spite of recent evidence that infection with the coxsackie B viruses can result in human diabetes mellitus, the diabetogenic potential of CVB field strains appears to be limited. Diabetes mellitus may occur as a rare event, limited to genetically susceptible hosts. Autoimmune mechanisms or repeated infection with other CVB serotypes may convert minimal beta-cell destruction into clinically overt disease.

Introduction

In humans, infection with viruses of the Coxsackie B group can produce a variety of distinct clinical syndromes. These include respiratory illness, pleuritis, aseptic meningitis, paralysis, myocarditis, pericarditis, hepatitis,
and encephalitis (8). Most infections with the coxsackie B viruses are asymptomatic, but a wide range of severity, including fatality, can occur. The factors that determine the pathogenicity of these viruses are incompletely understood. Recently, coxsackie B viruses (CVB) have been isolated from patients at the onset of insulin dependent diabetes mellitus and serologic studies have indicated recent Coxsackie B virus infection in patients with newly diagnosed insulin dependent diabetes mellitus (3, 4, 7, 12, 16). After repeated growth in pancreatic beta cells all six prototype strains of the Coxsackie B virus group have been shown to cause diabetes in susceptible strains of mice (14). We have examined mice infected with 37 field strains of the Coxsackie B viruses for hyperglycemia and glucose intolerance in order to determine the diabetogenic potential of Coxsackie B viruses in nature.

Materials and Methods

Cell Cultures and Viruses

Cells were grown in Eagle's minimal essential medium supplemented with 10 percent calf serum (2 percent after monolayers were formed) 100 μ of penicillin and 100 μg of streptomycin per ml. Coxsackie virus isolates were obtained from the Viral and Rickettsial Disease Laboratory of the State of California, Department of Health Services. Virus stocks were prepared in the BGM line of grivet monkey kidney (BGMK) cells. The diabetogenic D variant of the M strain of EMC virus was obtained from Ji-Won Yoon (17).

Mice

SJL male mice 4—6 weeks of age were purchased from the Jackson Laboratories, Bar Harbor, Maine. New Zealand NZW × NZB F1 hybrid mice were obtained from the Division of Research Services, National Institutes of Health, Bethesda, Maryland or from Eric Gershwin, Department of Medicine, University of California, Davis. Mice were inoculated with 10⁵ plaque forming units (PFU) of virus by the intraperitoneal (i.p.) route.

Glucose Assay

Glucose concentrations were measured in blood from the retroorbital venous plexus by a glucose oxidase assay using dianisidine dihydrochloride as the indicator dye. For glucose tolerance tests, blood glucose was measured one hour after the intraperitoneal injection of 2 mg of glucose per gram weight. For each mouse, nonfasting glucose (NFG) levels were performed on day 7 and 14 and glucose tolerance tests (GTT) were performed on day 10 and 17 following infection. These four values were combined to give a weighted glucose index designed to give more importance to the persistence of nonfasting hyperglycemia (11). Mice with a glucose index exceeding the mean of controls by 3 standard deviations (S.D.) were considered abnormal. A F-test of variances was used to compare experimental and control groups. A paired t-test was used to compare repeated blood glucose concentrations in the New Zealand mice.

Pathology

The mouse pancreas was fixed in formalin, sectioned, and stained with hematoxylin and eosin.