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Metabolic phenotype in an AL amyloidosis transgenic mouse model

J. E. Ward^{1,2}, P. SooHoo^{1,3}, G. Toraldo², R. Jasuja², L. H. Connors^{1,4}, C. O'Hara^{1,3}, and D. C. Seldin^{1,2}

¹Department of Pathology, Boston University, Gerry Amyloid Research Laboratory, Boston University School of Medicine, Boston, MA, USA

²Department of Medicine, Boston University School of Medicine, Boston, MA, USA

³Department of Pathology, Boston University School of Medicine, Boston, MA, USA

⁴Department of Biochemistry, Boston University School of Medicine, Boston, MA, USA

Abstract

In an attempt to elucidate the *in vivo* process of protein aggregation and mechanisms of amyloid organ disease, we have engineered a genetically defined mouse model of AL amyloidosis. These transgenic mice broadly expressing a human amyloidogenic lambda 6 immunoglobulin light chain (LC) using a cytomegalovirus (CMV) promoter have circulating LC and develop typical Congo red-positive amyloid deposits in the stomach, previously described at the XIth International Symposium on Amyloidosis in Woods Hole [1]. The CMV-lambda 6 transgenic mice display neurologic and metabolic phenotypes. The transgenic mice are larger and have metabolic dysregulation, accompanied by a decreased respiratory exchange ratio, indicating preferential lipid oxidation. With age, the mice develop hyperglycemia upon glucose challenge. We hypothesize that this may be due to a non-fibril-dependent effect of overexpression of LC in tissues, perhaps pancreas.

Introduction

We have engineered a transgenic mouse model of AL amyloidosis, expressing a human amyloidogenic lambda 6 light chain (LC) cloned from a patient with aggressive, multi-organ amyloidosis. The LC transgene is expressed using a CMV promoter, and human LC protein is detected mainly in epithelial cells of several organs, such as the kidney, pancreas, lungs, stomach, intestines, and subsets of cells in the brain, spinal cord, and heart. Human LC is detected in the blood, urine, and CSF. CMV-lambda 6 transgenic mice have a variety of phenotypes and here we report upon their body composition and metabolic dysregulation.

Methods

Body composition was quantitated by magnetic resonance to directly measure total body fat mass and total body lean mass on unanesthetized mice of various ages (EchoMRI-900, Echo

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Medical Systems). Three independent transgenic lines were generated, with different random integration of the transgene in the genome. All lines had alterations in the body composition. A single line (line 55) was chosen for additional study. In order to examine if the changes in body composition were associated with the metabolic alterations, indirect calorimetry was utilized to examine substrate utilization. Age-matched, old, and young male transgenic mice were observed for 48 hours, first fed (24 hours) and then fasted (24 hours), in the Oxymax open circuit calorimeter (Columbus Instruments). The amount of heat produced per liter of O₂ consumed depends on whether the body is utilizing protein, carbohydrate, or fat as the primary source. The respiratory exchange ratio (RER) calculated from the ratio of the measured volume of gas produced (VCO₂) to the measured volume of gas consumed (VO₂). Exercise capacity of transgenic and age-matched wild-type friend virus B-type (FVB) mice (Jackson Labs) was assessed by running on a variable speed, multilane treadmill at a 10° angle (Exer-6M, Columbus Instruments). Food consumption was measured using a feeding jar. Glucose challenge was performed by injecting 1 g/kg of 10% glucose intraperitoneally (IP) into fasted mice and measuring blood sugars by glucometer at 30, 60, and 120 minutes.

Results and discussion

The CMV-lambda 6 transgenic mice displayed significantly different body composition compared with wild-type littermates. Transgenic mice ($n = 13$) were heavier than their wild-type counterparts ($n = 12$) (Figure 1), but did not consume more food than their non-transgenic counterparts (data not shown), nor did they have any apparent abnormality of digestion or stool consistency. The transgenic mice had an increase in both fat (average 6.1 g vs. 4.3 g, $p = 0.043$) and lean (muscle) (average 21.6 g vs. 20.1 g, $p = 0.0037$) mass. Furthermore, their exercise capacity was significantly diminished. RER was decreased in both young (3 months) and old (9 months) transgenic males while fed, indicating preferential usage of fat rather than glucose for energy in the transgenics (Figure 2). The transgenic mice developed hyperglycemia in response to IP challenge with glucose, with blood sugars 30% higher than littermate controls in older mice (13 months).

In summary, the presence of the human lambda 6 transgene leads to a dysregulation of normal metabolism and body composition that would not appear to be explained by the amyloid deposition in the stomach. Further elucidation of the mechanism of metabolic dysregulation may provide insight into toxic effects of non-amyloid LC oligomers in other tissues where the LC is highly expressed, e.g. the pancreas.

References

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Figure 1. Three-month-old transgenic CMV-lambda 6 mice (*triangles*) have increased body mass compared to non-transgenic controls (*circles*), ($p = 0.0085$, t -test with unequal variances). The bar marks the average mass.

Figure 2. RER is decreased in 9-month-old transgenic mice (*grey line*) when compared to wild-type controls (*black lines*) during the fed state, indicating a preferential use of fat for energy, rather than glucose.