Characterization of a Mouse Model for Reduced GLUT1 Expression

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GLUT1 is a major glucose transporter of the developing embryo, however its function in development has not previously been determined. Diabetes suppresses the facilitative glucose transporter GLUT1 approximately 50% in the preimplantation embryo. Embryos of mothers with poorly controlled diabetes are reported to develop early intrauterine death, reduced body size, microphthalmia, micrognathia, anencephaly, caudal regression, and stillborn births. We have successfully suppressed GLUT1 in developing embryos and fetuses by a similar amount, with an antisense-GLUT1 transgene (i.e. GT1AS mice). Here we describe the developmental abnormalities resulting from GLUT1 suppression in the absence of diabetes, and the similarities of these abnormalities to those observed in diabetic embryopathy. GT1AS mouse homozygotes were nonviable. Mating of GT1AS heterozygotes produced small litters. Therefore, we interrupted gestation at days 11.5, 14.5 and 18.5 to determine the stages at which embryos were dying, their body weights, and malformations. Embryos, fetuses and placentas were assessed by H&E staining and Western analyses of GLUT1 protein. Transgenic embryos and fetuses were identified by Southern analyses. 25.6% of embryos and fetuses were markedly delayed in development (tiny, i.e. <50% normal body weight). They died early in gestation. These severely impaired embryos and fetuses were transgenic and presumed to be the homozygotes (100% lethal). 31.5% of all fetuses were small (i.e. <70% of nontransgenic littermate fetal weight). Transgenic fetuses exhibited stunted growth (32%), microphthalmia (2%), anencephaly & absence of the head (2%), micrognathia (1%); and impaired caudal development (caudal regression syndrome, 2%), and a greater than 400% increase in the stillborn rate, resembling the developmental abnormalities previously reported in fetuses from diabetic mothers. Kidneys were noted to be small or absent in severely affected embryos, consistent with caudal regression. None of the malformations were observed in fetuses from control nontransgenic matings. The overall frequency of embryonic and fetal malformations resulting matings of heterozygotes together was 38.6%. GLUT1 protein suppression in transgenic fetuses ranged from 0-58%, however the fetuses with severe growth impairment and malformations also had the lowest GLUT1 protein level, demonstrating a 56% reduction in this transporter. GLUT1 and GLUT3 expression were unchanged in placentas from fetuses of transgenic matings. Small heterozygotes survived to adulthood with up to 40% reduction of body size, while other heterozy-

gotes grew to near normal in size.

Conclusions : 1) Transgenic suppression of GLUT1 in mice in the absence of diabetes produced severe developmental delay and malformations, resembling embryos and fetuses from diabetic mothers. 2) Therefore, maternal diabetic suppression of embryonic GLUT1 may be an important contributor to the developmental abnormalities observed in this condition.