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Transgenerational Impact of Intrauterine Hyperglycaemia to F2 Offspring without Pre-Diabetic Exposure on F1 Male Offspring

Authors : Jun Ren, Zhen-Hua Ming, He-Feng Huang, Jian-Zhong Sheng

Abstract : Adverse intrauterine stimulus during critical or sensitive periods in early life, may lead to health risk not only in later life span, but also further generations. Intrauterine hyperglycaemia, as a major feature of gestational diabetes mellitus (GDM), is a typical adverse environment for both F1 fetus and F1 gamete cells development. However, there is scare information of phenotypic difference of metabolic memory between somatic cells and germ cells exposed by intrauterine hyperglycaemia. The direct transmission effect of intrauterine hyperglycaemia per se has not been assessed either. In this study, we built a GDM mice model and selected male GDM offspring without pre-diabetic phenotype as our founders, to exclude postnatal diabetic influence on gametes, thereby investigate the direct transmission effect of intrauterine hyperglycaemia exposure on F2 offspring, and we further compared the metabolic difference of affected F1-GDM male offspring and F2 offspring. A GDM mouse model of intrauterine hyperglycemia was established by intraperitoneal injection of streptozotocin after pregnancy. Pups of GDM mother were fostered by normal control mothers. All the mice were fed with standard food. Male GDM offspring without metabolic dysfunction phenotype were crossed with normal female mice to obtain F2 offspring. Body weight, glucose tolerance test, insulin tolerance test and homeostasis model of insulin resistance (HOMA-IR) index were measured in both generations at 8 week of age. Some of F1-GDM male mice showed impaired glucose tolerance ($p < 0.001$), none of F1-GDM male mice showed impaired insulin sensitivity. Body weight of F1-GDM mice showed no significance with control mice. Some of F2-GDM offspring exhibited impaired glucose tolerance ($p < 0.001$), all the F2-GDM offspring exhibited higher HOMA-IR index ($p < 0.01$ of normal glucose tolerance individuals vs. control, $p < 0.05$ of glucose intolerance individuals vs. control). All the F2-GDM offspring exhibited higher ITT curve than control ($p < 0.001$ of normal glucose tolerance individuals, $p < 0.05$ of glucose intolerance individuals, vs. control). F2-GDM offspring had higher body weight than control mice ($p < 0.001$ of normal glucose tolerance individuals, $p < 0.001$ of glucose intolerance individuals, vs. control). While glucose intolerance is the only phenotype that F1-GDM male mice may exhibit, F2 male generation of healthy F1-GDM father showed insulin resistance, increased body weight and/or impaired glucose tolerance. These findings imply that intrauterine hyperglycaemia exposure affects germ cells and somatic cells differently, thus F1 and F2 offspring demonstrated distinct metabolic dysfunction phenotypes. And intrauterine hyperglycaemia exposure per se has a strong influence on F2 generation, independent of postnatal metabolic dysfunction exposure.

Keywords : inheritance, insulin resistance, intrauterine hyperglycaemia, offspring
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