



Pdx-1 and Insulin Gene Expression in Embryonic and Neonatal Pancreas of Mice: Effects of Metformin Treatment

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Dear Editor,

Pancreatic and duodenal homeobox-1 (Pdx-1) plays an important role in mediating the effects of glucose-regulating hormones such as insulin and glucagon-like peptide-1 (GLP-1) (1, 2). The research paper entitled "The effects of metformin on Pdx-1 and insulin gene expression in mouse embryonic and neonatal pancreas" published by Hashemitabar *et al.* in 2010 (3) reports the effects of metformin on Pdx-1 and insulin gene expression in the pancreas of mouse embryos and neonates. The data showed that doubling the dose of metformin from 75 mg/kg to 150 mg/kg and even increasing the dose to 250 mg/kg did not affect Pdx-1 and insulin gene expression in both embryonic and neonatal pancreas. Interestingly, the authors found that compared to metformin-treated embryos, metformin-treated neonates showed

up-regulation of Pdx-1 and insulin gene expression. This finding is interesting and suggests a possible maternal role in preventing the effects of metformin on Pdx-1 and insulin gene expression in mouse embryonic pancreas. The study design was novel; however, some vital data that could have further strengthened the findings of this study were missing. Firstly, the authors divided the pregnant C57BL/6 mice into 2 groups (control: saline-treated and experimental: metformin-treated). I think that an additional group of mice, which neither received saline nor metformin, should have been included in the study. This group of pregnant mice should have been killed at the time that coincided with the commencement of treatment. Comparing Pdx-1 and insulin gene expression in the embryonic pancreas obtained from these mice with the expression in the embryonic pancreas obtained from mice belonging to the other 2 groups would have provided data on the effect of growth on Pdx-1 and insulin gene expression. Furthermore, measurements on these mice would have provided baseline data for the other 2 groups, especially the metformin-treated embryos. Secondly, since the authors did not report the effects of various doses of metformin on the concentra-

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tions of glucose, insulin, and other glucose-regulating hormones such as GLP-1, the study lacks data on the antidiabetic effect of metformin. I believe that the authors did not measure these parameters. If that is the case, I think the authors should have collected blood samples (from pregnant mice and if possible, from neonates) at the time of sacrifice. These samples could have been used for measuring fasting plasma levels of insulin, GLP-1, and glucose. The authors could have then investigated the relation between the obtained values and the lack of change in Pdx-1 and insulin gene expression, and these data could have provided some new insights. Thirdly, I assume that this was a preliminary study. If that is the case, I would like to recommend that the doses of metformin be increased to detect the toxic or teratogenic effect of metformin (4). With the results, the authors would be able to compare or correlate the data with those of the Pdx-1 and insulin gene expression as well as some of the suggested parameters. Moreover, the neonates could be allowed to grow for some more weeks before sacrifice. This will help to clarify if the increase in Pdx-1 and insulin gene expression observed after birth was due to metformin or growth. Furthermore, the authors may want to perform a similar study in neonates as well. This will help to determine whether "the insensitivity of embryonic pancreases to metformin is probably due to their lack of functional maturity," as con-

cluded by the authors (3). This may also provide information on the possible maternal influence in preventing or delaying the effect of metformin on Pdx-1 and insulin gene expression. I would like to state that the above-mentioned are my personal opinions and suggestions and are not intended to criticize the authors' work. Instead, they are posited in view of the significance of this study. The results of this study add to the already existing information and have the potential to extend the frontiers of this field.

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None Declared.

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