



Distinct Effects of Metformin on Pdx-1 Before and After Birth

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Dear Editor,

In a recent article (*Int J Endocrinol Metab* 8:211-214, 2010), Hashemitabar *et al.* (1) have shown that intraperitoneal injection of metformin in pregnant mice induces an increase in the levels of Pdx-1 and insulin mRNA in neonatal mice but not in 19.5 embryonic fetuses. On the basis of these results, the authors concluded that metformin affects the regulatory region of the insulin gene only after birth. The transcriptional factor Pdx-1 is expressed in both endocrine and exocrine tissues and is essential for pancreatic development in the embryonic stage (2). Mice with knocked out Pdx-1 gene do not develop a pancreas; therefore, this deletion is lethal (3). However, after pancreatic development, Pdx-1 is expressed only in insulin-producing β cells and somatostatin-producing δ cells (4). Pdx-1 transactivates the insulin gene in β cells obtained from mature animals (5). However, the expression of the insulin gene is not regulated by Pdx-1 in the embryonic stage. Insulin-expressing cells are observed even in Pdx-1 homozygous

mutant mice (6). Metformin has 2 distinct effects on the levels of Pdx-1 protein. First, although metformin does not regulate Pdx-1 gene expression, it increases Pdx-1 protein levels after 24 h in isolated rat islets (7), suggesting that metformin has a post-transcriptional effect on Pdx-1 production. Second, metformin induces the translocation of Pdx-1 from the cytoplasm to the nucleus of MIN6 pancreatic cells and increases binding of Pdx-1 to the reporter gene construct that includes the promoter for the human proinsulin gene (7). Therefore, the ability of metformin to increase the expression levels of the insulin gene in mature pancreatic β cells could be partly explained by the synergistic effect of the 2 above-mentioned mechanisms involved in the metformin-mediated regulation of Pdx-1 protein levels. This hypothesis is consistent with the findings of Hashemitabar *et al.*, who have clearly shown that the main effect of metformin on Pdx-1 takes place after birth and that metformin does not interfere with the embryonic development of the pancreas.

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