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Effect of Glipizide on Insulin Secretion From Cultured Human Fetal Pancreatic Islets

The use of oral hypoglycemic sulfonylurea agents during gestation has been discouraged.[1] Nevertheless, a number of type II diabetic women become pregnant while on sulfonylurea therapy. Furthermore, gestational diabetes appears to be increasing in prevalence, and the use of an oral agent to normalize maternal blood glucose values while avoiding fetal toxicity from hyperglycemia and hyperinsulinemia is attractive. These considerations are important, especially in developing societies where establishing programs of multiple injections of insulin and self-monitoring of blood glucose may be difficult.[2] The stimulus-secretion coupling of the human fetal pancreas for insulin has been shown to be different than that of the adult and also different from that of murine fetal models.[3] Therefore, we undertook an investigation of the insulin-secretory response to varying concentrations of glipizide by human fetal pancreatic islets.

Fetal pancreata were obtained from the National Diabetes Research Interchange (Philadelphia, PA). The tissues utilized were obtained aseptically after dilation and extraction between 14 and 24 wk gestation and stored immediately in ice-cold (0–2°C) sterile RPMI-1640 culture medium (Gibco, Grand Island, NY) containing 10 mM Hepes and 2 mM glutamine, pH 7.4, for 60–116 h. Informed consent and approval of the appropriate institutional review boards was obtained for all studies. Pooled islets from two to six fetal pancreata were used for assay of stimulated insulin release as previously described.[4] Briefly, islets that excluded trypan blue were batch incubated for two successive 1-h periods in 2 ml of Krebs-Ringer buffer in glass tubes at 37°C under 95% O_2/5% CO_2. From the 1st to the 2nd h, molarity increased from 2 mM glucose to 25 mM glucose, and/or 10 mM L-leucine and 10 mM L-arginine, with or without potentiator, i.e., 1 mM 3-isobutyl-1-methylxanthine (IBMX) or varying concentrations of glipizide (Pfizer, Groton, CT). At the end of each hour the buffer was removed for radioimmunoassay of insulin release, with human insulin as a standard. Nonsecreted insulin was extracted with acidic ethanol and also assayed. Fractional secretion for hours 1 (F1) and 2 (F2) are defined as the amount of insulin released during that time, expressed as a percent of total insulin available.[4] The fractional stimulatory ratio (FSR) is defined as F2/F1.

Figure 1 summarizes the results of the experiments. Incubation in high glucose with amino acids led to a slight increase in secretion over the 1st h with an FSR of 1.65 ± 0.32 (SEM, $N = 2$). Maximal secretion was achieved only with the addition of IBMX to glucose and amino acids, leading to an FSR of 7.80 ± 3.10 ($N = 2$). Glucose and IBMX led to an FSR of 1.9 ± 0.40 ($N = 2$). Addition of glipizide in concentrations of 500, 1000, or 1500 ng/ml was not accompanied by an increase in FSR above that seen with high glucose and amino acids alone [1.60 ($N = 2$), 1.73 ± 0.34 ($N = 3$), and 1.90 ± 0.35 ($N = 2$), respectively].

Our studies document that glipizide in concentrations at or greater than those achieved in vivo does not lead to an increase in fetal β-cell insulin secretion. In view of the evidence linking infant morbidity and mortality to fetal hyperinsulinemia in pregnancy complicated by diabetes, these observations may be important to the offspring of diabetic women who may be exposed to the compound during gestation. Previous reports of the use of oral hypoglycemic agents for the

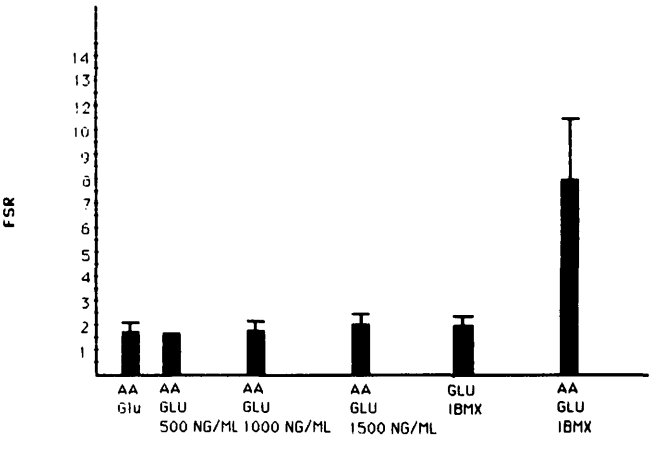

FIG. 1. Fractional stimulatory ratio of 2–6 pooled human fetal islet preparations in response to amino acids (AA), glucose (GLU), 3-isobutyl-methylxanthine (IBMX), and varying concentrations of glipizide (500, 1000, and 1500 ng/ml). *Error bars* indicate SEM. Degress of freedom are indicated in text.

treatment of gestational diabetes have been encouraging in small series but have documented neonatal hypoglycemia ascribed to delayed clearance of the oral hypoglycemic agent and the effect on fetal peripheral glucose utilization.[2] The sulfonylurea agent used in our study has a much shorter plasma half-life[5] than agents used in previous studies. In view of the economics and logistics of tablet therapy as opposed to multiple insulin injections, the use of oral agents in gestational diabetes may warrant further study when dietary strategies do not eliminate maternal hyperglycemia.

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Reliability of Self-Reported Data

The article "Self-Reported Data: Reliability and Role in Determining Program Effectiveness" (DIABETES CARE 1985; 8:486–90) concluded that the Maine self-reported data were reliable and useful. The authors recommended that other programs that use self-reported data conduct similar reliability studies. Although I agree with this recommendation, this type of study is expensive and often difficult to design (especially when more than one data source is involved). The Colorado Diabetes Control Program (DCP) was faced with such a problem. We had self-reported data asked in the same fashion as the Maine data question [i.e., In the past 12 months how many times have you been hospitalized for your diabetes? *1*) one time, 2) two times, etc.]. Initial validation of our data identified 30% overreporting of hospitalizations and no underreporting.

Based on these results the Colorado DCP staff developed recommendations for self-reporting of hospitalization data: *1*) solicit place and dates, both month and year, for hospital admissions; 2) obtain "number of days" for each hospitalization reported; 3) solicit "reason for each hospitalization"; and 4) obtain Release of Medical Information, which covers the hospital usually providing care and any other hospital identified as having provided care.

These recommendations were incorporated into the last page of a new data collection tool. Authorization for Release of Medical Information was included at the bottom of the page. Validation of this tool on 53% of the records showed 100% agreement between hospitalizations reported by participants and those identified from actual hospital records. Number of days of hospitalization also showed essentially no difference.

After identifying this improvement in self-reported data, the Colorado DCP feels comfortable in reporting hospitalization data with this new assessment tool. Our patient education program demonstrated a 54.5% reduction in diabetes-related hospitalizations during the 12-mo period posteducation. Length of stay was reduced 34.5%, and estimated cost savings were $321 per participant. The benefit/cost ratio was 4.4:1.

It is our recommendation that self-reported data continue to be used as an evaluation tool and that validation of a random sample of the data is appropriate. The method presented here may make it easier to validate data and improve the quality of data collected. Inclusion of the medical release form with the initial questionnaire allows for immediate validation of the self-reported responses, either on all or a sample of the data collected. Requesting the specific month and year helps identify incorrect time periods and provides better information to medical records departments when hospital records are requested.

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Reliability of Self-Reported Data: A Reply

Suzanne Pecoraro, RD, MPH, of the Colorado Diabetes Control Program (DCP) is absolutely correct in suggesting that the Maine reliability study was relatively expensive and somewhat difficult to design. The authors suggested that other programs that use self-reported data should conduct a reliability study, but not necessarily the same reliability study.

The recommendations made by the Colorado DCP staff to request greater details regarding a self-reported hospitalization, as well as the Authorization for Release of Medical