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In Vitro Renal Transport Functions of the Progeny of Rats with Streptozotocin-Induced Diabetes[1] (41409)

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Abstract. The effect of streptozotocin-induced gestational diabetes in the rat on the development of renal tubular functions of progeny was determined using *in vitro* kidney slice techniques. Accumulation of *p*-aminohippuric acid (PAH) by renal cortical slices (PAH S/M ratios) from progeny of diabetic mothers (PDMs) was lowest at Day 1 of age and increased from 1 to 28 days of age. For PDMs, PAH S/M ratios were similar to those observed for progeny of control mothers (PCMs) except at 10 days of age when they were significantly lower. Accumulation of α-methylglucoside (MG) by renal cortical slices from PDMs (MG S/M ratios) was similar to that reported for PCMs, except at 10 days of age when accumulation was significantly depressed in PDMs. Accumulation of *N*-methylnicotinamide (NMN) by renal cortical slices (NMN S/M ratios) from PDMs was similar to that of PCMs. NMN S/M ratios were lowest at birth and increased with age. Accumulation of α-aminoisobutyric acid (AIB) by renal cortical slices (AIB S/M ratios) from PDMs was no different than that from PCMs. AIB S/M ratios were highest at birth and decreased with age. It was concluded that gestational diabetes differentially affected renal tubular transport functions in the progeny.

In rats several aspects of kidney function appear to have characteristic developmental patterns which are differentially affected by alterations in pre- and postnatal nutritional status (1–4). Pre- and postnatal overnutrition enhances (3) while pre- and postnatal malnutrition retards the development of some renal functions (1, 2, 4).

The human infant of the diabetic mother (IDM) is different than the infant of the nondiabetic mother and displays features of both over- and undernutrition. In a recent study 36% of IDMs were large for gestational age at birth and 4% were small for gestational age; 47% developed neonatal hypoglycemia (5).

To date, the direct effects of maternal diabetes on pre- and postnatal development of kidney function have not been determined. The present study was designed to evaluate the effects of gestational diabetes in rats on the development of specific renal tubular transport functions.

Methods and Materials. Female Sprague–Dawley rats were obtained from Spartan Research, Inc., Haslett, Michigan, or Harlan Industries Inc., Indianapolis, Indiana, on Day 1 of their first gestation. The same day rats were randomly separated into two groups. Rats from one group were injected ip with streptozotocin (50 mg/kg) (courtesy of Dr. W. E. Dulin, Upjohn Co.), dissolved in 0.1 *M* citric acid (pH adjusted to 3.8–4.2). Rats from the remaining group were injected with 0.1 *M* citric acid solution (pH adjusted to 3.8–4.2) and were considered controls. Two to four days after injection, animals were placed in metabolism cages and spot urine samples were collected and analyzed for glucose (Tes-tape, Eli Lilly Co.) Animals showing 0.1% glucose in the urine were considered diabetic. Diabetic animals were injected sc each afternoon between 4 and 8 PM with 2 units of

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NPH Iletin (isophane insulin suspension, Eli Lilly Co.). Controls received sc injections of saline. On the 18th day of gestation, 24 hr after the daily insulin or saline injection, approximately one ml of blood was collected from the orbital sinus into a small test tube pretreated with sodium fluoride and heparin. This was centrifuged, the plasma removed, frozen, and later deproteinized and analyzed for glucose by an enzymatic colorimetric assay (Glucostat, Worthington Biochemical Corp.).

Animals were housed in a temperature-controlled room with a 12/12-hr light/dark cycle. All animals received a standard rat chow (Wayne Lab Blox; 24% crude protein; 4.0% crude fat; 4.0% crude fiber; 68% carbohydrate by weight) and water *ad libitum*. Rats were allowed to deliver normally. At birth, live pups from diabetic mothers (PDMs) and live pups from control mothers (PCMs) were weighed and adjusted to 10 per litter. Stillborn were removed and counted. Preliminary studies revealed that several diabetic dams did not lactate. To eliminate this variable, PDMs and PCMs were cross-fostered to control dams. Since the composition of rat's milk changes as the litter matures, lactating controls which delivered litters at the same time as diabetic and control animals were used as foster mothers. Neonatal deaths are defined as those rats that were alive at birth but died within 24 hr.

At 1, 5, 10, or 28 days of age, progeny were killed by cervical dislocation, kidneys were removed, decapsulated, weighed, and placed in cold isotonic saline. Renal cortical slices 0.2–0.3 mm thick were prepared freehand. The accumulation of the prototype organic acid, *p*-aminohippuric acid (PAH) and the prototype organic base, *N*-methylnicotinamide (NMN) by the kidney slices was used as an index of intrinsic transport capacity. Approximately 50 mg of renal cortical slices was incubated in 2.7 ml of Cross and Taggart medium (6) containing 7.4×10^{-5} *M* PAH (Eastman Kodak) and 6.0×10^{-6} *M* (2.5×10^{2} μCi/ml) [^{14}C]NMN (New England Nuclear) and adjusted to pH 7.4. Incubations were carried out in a Dubnoff metabolic shaker at 25° under 100% oxygen for 90 min (6).

The accumulation of the nonmetabolizable sugar, α-methylglucoside (MG) by renal cortical slices was used to determine the intrinsic renal transport capacity for sugars. Approximately 50 mg of kidney cortex slices was incubated in 3 ml of Krebs–Ringer bicarbonate buffer (7) containing 2 m*M* MG (Sigma Chemical Co.) and 0.2 μCi/ml [^{14}C]MG (New England Nuclear). Incubations were carried out in stoppered reaction flasks filled with 95% oxygen, 5% carbon dioxide in a Dubnoff metabolic shaker at 37° for 90 min (8).

The accumulation of the nonmetabolizable amino acid, aminoisobutyric acid (AIB) by renal cortical slices was used to determine the capacity of kidney slices to accumulate amino acids. Approximately 50 mg of tissue was preincubated in 3 ml of Krebs–Ringer bicarbonate buffer (7). Preincubations were carried out in stoppered reaction flasks filled with 95% oxygen, 5% carbon dioxide in a Dubnoff metabolic shaker at 37° for 30 min. After preincubation, slices were transferred to the same medium plus 0.065 m*M* AIB (Sigma Chemical Co.) and 0.1 μCi/ml [^{14}C]AIB (New England Nuclear) and were incubated in stoppered reaction flasks filled with 95% oxygen, 5% carbon dioxide in a Dubnoff metabolic shaker at 37° for 60 min (9).

After incubation, slices were removed from the medium, blotted, weighed, and placed in tissue homogenizers with 3 ml of 10% trichloroacetic acid (TCA). Similarly, 2 ml of medium was mixed with 3 ml of TCA. Both medium and tissue homogenates were brought to a final volume of 10 ml with distilled water and centrifuged at 1400 rpm for 10 min. A 1.0-ml aliquot of supernatant was used to determine PAH spectrophotometrically as described by Smith *et al.* (10). Additionally, 1.0-ml aliquots were added to scintillation vials containing 10 ml of modified Bray's solution (6 g of 2,5-diphenyloxazole and 100 g of naphthalene per liter of dioxane). Radioactivity of [^{14}C]NMN, [^{14}C]MG, [^{14}C]AIB in the supernatants was determined using a

Beckman LS-250 liquid scintillation counter employing internal standards. Accumulation was expressed as the slice to medium (S/M) ratio. This was calculated as the concentration of PAH per gram of tissue (wet weight) divided by the concentration of PAH per milliliter of media. Similarly, in the case of [^{14}C]NMN, [^{14}C]AIB, or [^{14}C]-MG, disintegrations per minute (dpm) per gram of tissue (wet weight) were divided by dpm per milliliter of medium. Protein content of kidney cortex slices was determined by the Lowry procedure (11). Unless otherwise stated, all data are reported as mean ± SEM. Differences between the means were analyzed using the least significant difference (LSD) test after analysis of variance. The 0.05 level of probability was used as the criterion of significance (12).

Results. *Animals.* Plasma glucose concentration was significantly greater in diabetic than control rats (Table I). The average birth weight of live pups from diabetic mothers (PDMs) (6.23 ± 0.17) was not significantly different than that of pups from control mothers (PCMs) (6.50 ± 0.11) (Table I). The number of fetal and neonatal deaths is an indicator of the severity of maternal diabetes (13). Thirteen percent of the PDMs were born dead and 7.4% died within 24 hr after birth (Table I). These rates were significantly greater than those for controls (1.5 and 0%, respectively).

Body weight and kidney weight of PDMs were no different than those of PCMs at 1, 5, or 10 days of age (Fig. 1). However, by 28 days of age, PDMs weighed 29% less than PCMs (66 ± 6 versus 83 ± 2 g). Similarly, the kidneys from PDMs weighed 20% less than those from PCMs (0.63 ± 0.05 versus 0.78 ± 0.04). The kidney weight/body weight ratios from PDMs were no different than those for PCMs at any age studied.

The percentage of protein and water (Fig. 2) in renal cortical slices from PDMs was no different than that from PCMs at any age.

Accumulation of PAH, NMN, MG, and AIB. Accumulation of PAH by renal cortical slices (PAH S/M ratios) increased gradually from 1 to 28 days of age in PCMs. In PDMs, PAH S/M ratios increased from 1 to 5 days of age, decreased at 10 days of age, and increased to control values by 28 days of age (Fig. 3). PAH S/M ratios of PDMs were not different than those of PCMs at 1, 5, or 28 days of age. However, at 10 days of age, PAH S/M ratios of PDMs were 32% lower than those of PCMs (6.41 ± 0.8 versus 9.75 ± 1.4) (Fig. 3). This difference was statistically different.

Accumulation of NMN by renal cortical slices (NMN S/M ratios) from PDMs was not different than that from PCMs at any age (Fig. 3). In both groups, NMN S/M ratios gradually increased from 1 to 28 days of age (Fig. 3).

Accumulation of AIB by renal cortical

TABLE I. MATERNAL PLASMA GLUCOSE CONCENTRATION, PERINATAL MORTALITY, AND BIRTHWEIGHT OF THE PROGENY OF DIABETIC AND CONTROL SPRAGUE–DAWLEY RATS

	Control	Diabetic
Maternal plasma glucose (mg/dl)[a]	96.7 ± 4[e] (22)	321.9 ± 33* (22)
Birth weight (g)[b]	6.5 ± 0.1 (22)	6.23 ± 0.17 (22)
Stillborn rate (%)[c]	1.5	13**
Neonatal death rate (%)[d]	0	7.4

[a] Blood samples were collected on the 18th day of gestation from the orbital sinus 24 hr after the daily insulin or saline injection.

[b] Birthweight of live pups was determined by dividing litter weight by the number of pups.

[c] Does not include loss of entire litters.

[d] Neonatal deaths are defined as those rats that were alive at birth but died within 24 hr.

[e] Values represent the mean ± SEM (number of litters) unless otherwise indicated.

* Significantly different from control (Students' t; $P < 0.05$).

** Significantly different from control (χ^2 test; $P < 0.05$).

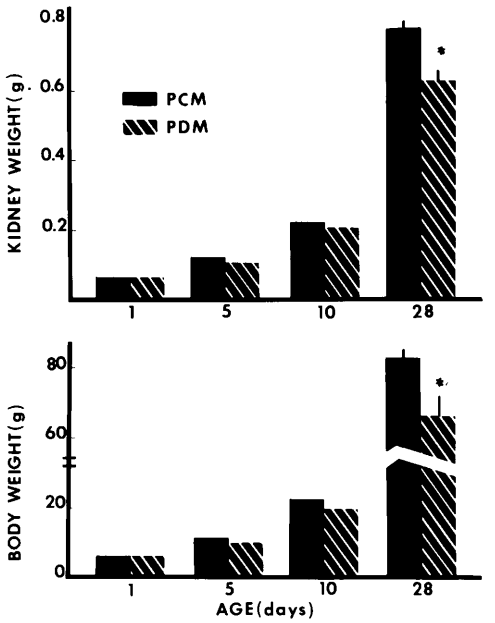

FIG. 1. Kidney weight (top) and body weight (bottom) of the progeny of rats born from diabetic (PDMs) and control mothers (PCMs). Each bar represents the mean ± SEM calculated from at least five observations. For the kidney weight, one observation consisted of kidneys pooled from one litter. For the body weight, one observation consisted of litter weight/litter number. Asterisks denote a statistical difference between PCMs and PDMs within an age group ($P < 0.05$).

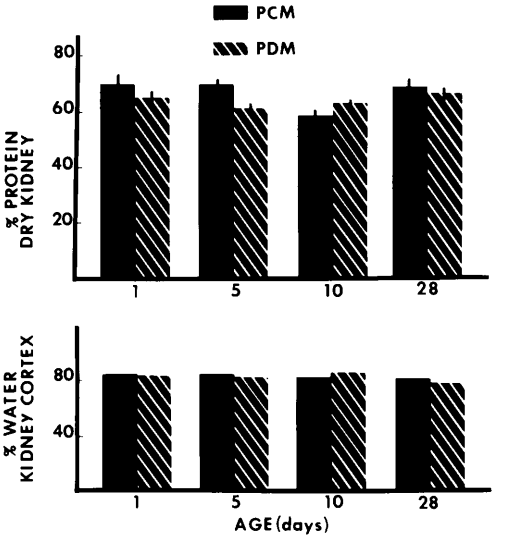

FIG. 2. Percentage of protein (top) and percentage of water (bottom) of cortical slices from kidneys of the progeny of diabetic (PDMs) and control (PCMs) mothers. Each bar represents the mean ± SEM calculated from at least five determinations (for percentage of water SEMs were too small to show on bar). One determination consisted of pooled slices from one litter.

slices (AIB S/M ratios) from PDMs was no different than that from PCMs at any age (Fig. 4). In both groups, AIB S/M ratios decreased with increasing age (Fig. 4).

Accumulation of MG by renal cortical slices (MG S/M ratios) from PDMs was no different from that from PCMs at 1, 5, or 28 days of age (Fig. 4). However at 10 days of age, MG S/M ratios from PDMs were 31% lower than those from PCMs (1.58 ± 0.1 versus 2.3 ± 0.3) (Fig. 4).

Discussion. Alterations in postnatal nutritional status may enhance (3) or retard (4) postnatal development of renal tubular transport functions in rats. Current evidence indicates that the nutritional state of the progeny of diabetic rats is differentially affected depending on the severity of the maternal diabetes (13–18).

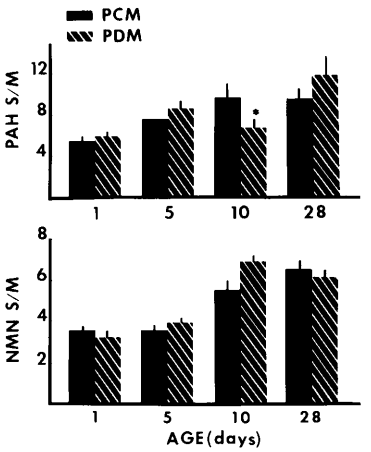

FIG. 3. PAH accumulation (PAH S/M ratios) and NMN accumulation (NMN S/M ratios) by cortical slices from kidneys of the progeny of diabetic (PDM) and control (PCM) mothers. Each bar represents the mean ± SEM of at least six determinations. Asterisks denote a statistical difference between PCM and PDM within an age group ($P < 0.05$).

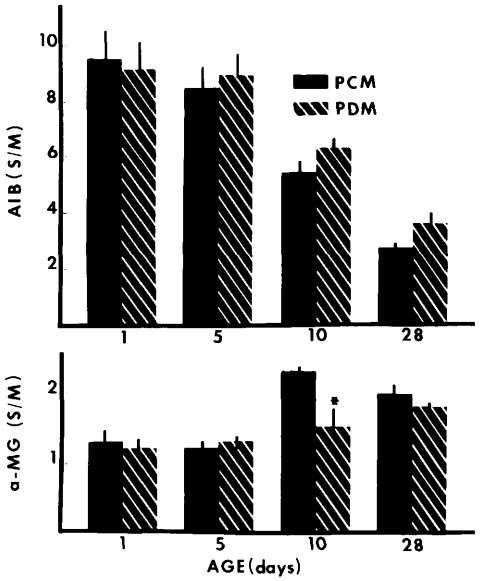

FIG. 4. AIB accumulation (AIB S/M ratios) and MG accumulation (MG S/M ratios) by cortical slices from kidneys of the progeny of diabetic (PDM) and control (PCM) mothers. Each bar represents the mean ± SEM of at least seven determinations (AIB) or the mean ± SEM of four determinations (MG). Asterisks denote a statistical difference between PCM and PDM within an age group ($P < 0.05$).

In this study, an attempt was made to control hyperglycemia in pregnant rats to produce a mildly diabetic model. Each rat received 2 units of NPH insulin per day and daily urine samples were tested for glucose and volume. There can be no doubt that the experimental rats were diabetic. In the absence of exogenous insulin, blood glucose concentrations were significantly greater in diabetic than in control rats (Table I). In addition, daily urine samples showed glucosuria and polyuria. That PDMs suffered greater perinatal losses than PCMs (Table I) may indicate that hyperglycemia was not well controlled and that PDMs in this study resemble those born from mothers characterized as having "severe" diabetes (13, 14).

Body weights and kidney weights of PDMs paralleled that of PCMs until 28 days (Table I, Fig. 1). At this age, the bodies and kidneys of PDMs weighed less than those of PCMs (Fig. 1). Since fetuses born of "severely" diabetic dams have been found to have degranulated beta cells in the pancreas (13), decreased pancreatic insulin stores (14), and decreased plasma insulin concentrations (14), it is probable that PDMs in this study produced inadequate insulin to support normal growth.

Accumulation of PAH by cortical slices from the kidneys (PAH/SM) reflects the ability of kidneys to transport organic acids. The accumulation of PAH is age related. As the rat increases in age to 28 days, so does the ability of kidney slices to accumulate PAH (4, 19). In this study, this developmental pattern can be seen in PCMs (Fig. 3). A similar pattern was observed for PDMs except at 10 days of age. At this age, renal cortical slices from PDMs accumulated significantly less PAH than those from PCMs (Fig. 3).

The depression in PAH S/M ratios may reflect abnormal renal metabolism. It is possible that PDMs were born mildly acidotic. Fetuses of diabetic animals can develop metabolic acidosis in two ways. The first is in conjunction with the mother during diabetic ketoacidosis (20, 21). The second occurs when maternal hyperglycemia produces fetal hyperglycemia. Robillard *et al.* (22) infused hypertonic glucose solutions into well-oxygenated fetal lambs. When fetal blood glucose concentration rose above 150 mg/dl there was a simultaneous increase in fetal plasma lactate levels and a decrease in plasma pH. In this study it was probable that the fetuses and newborn of diabetic rats developed lactate acidosis. In addition, other studies from this laboratory indicate that *in vitro* renal ammoniagenesis and gluconeogenesis are greater in slices from very young PDMs than in those from age-matched PCMs (in press). Metabolic precursors of gluconeogenesis as well as other metabolites can both stimulate and inhibit the accumulation of PAH by renal cortical slices. Amino acids such as alanine and glutamine can depress the uptake of PAH by kidney slices (6) while the gluconeogenic intermediate, α-ketoglutarate, can lower PAH S/M ratios by increasing the efflux of PAH from the slice (23). On the other hand, lactate stim-

ulates PAH accumulation by kidney slices (6). It is possible that 1- and 5-day-old PDMs were compensating a lactate acidosis that had developed *in utero*. There would have been greater amounts of lactate in kidney slices and this would have stimulated the uptake of PAH. Simultaneously, the presence of gluconeogenic intermediates may have depressed uptake or increased efflux of PAH. The cumulative effect was apparently normal PAH S/M ratios in 1- and 5-day-old PDMs. Ten-day-old PDMs may have had normal lactate levels but the kidney slices continued producing gluconeogenic intermediates in sufficient quantity to depress the PAH S/M ratios (Fig. 3). By 28 days, the metabolic abnormalities would have been corrected and metabolic substrates would have returned to normal levels. *In vitro* renal gluconeogenic and ammoniagenic capacity were normal in 28-day-old PDMs (in press). Therefore, the abnormal presence of metabolites may explain low PAH S/M rates formed by kidney slices from PDMs at 10 days of age.

The accumulation of organic base, NMN, by renal cortical slices from both PDMs and PCMs 1 to 28 days of age demonstrated the characteristic developmental pattern observed by others (4, 19), and paralleled organ growth (Fig. 3). However, there are reasons why the accumulation of NMN by renal cortical slices might not respond to metabolic substrates. First the presence of α-ketoglutarate in the medium had no effect on the ability of kidney slices from dogs to accumulate NMN (24). Second, this *in vitro* measure appears to be less sensitive than the uptake of PAH as an indicator of *in vivo* renal transport functions. Kim *et al.* (19) found that kidney slices required an ionic environment similar to the *in vivo* situation to accumulate PAH. This was not true for the accumulation of NMN. Kidney slices concentrated NMN regardless of the sodium or potassium concentration of the medium. Therefore, either the ability to transport organic base develops normally in the kidneys of PDMs or the *in vitro* accumulation of NMN is not sensitive enough to measure the difference.

The *in vitro* accumulation of MG by kidney slices reflects active transport of sugar at the luminal membrane and thus represents the active reabsorption of sugar by the kidneys *in vivo* (25). Evidence indicates that renal cortical slices from newborn rats were unable to maintain a concentration gradient while adult MG S/M ratios of 2.5 were attained by 14 days of age (8). In this study, renal cortical slices from 1 and 5-day-old controls had S/M ratios of approximately 1 (Fig. 4) which indicates diffusion. By 10 days of age, slices from control pups concentrated MG to develop S/M ratios greater than 2. MG S/M ratios from PDMs were similar to those of PCMs except at 10 days of age, when PDM S/M ratios were lower than those of PCMs (Fig. 4). Since amino acids as well as glucose can inhibit the influx of MG into kidney slices (26), it is possible that glucose, gluconeogenic intermediates, and/or amino acids have inhibited the uptake of MG by renal cortical slices from 10-day-old PDMs. This inhibition would not be seen at 1 and 5 days of age because these transport functions are not sufficiently developed to be inhibited. An S/M ratio above 1.0 indicates active transport of MG from medium to slice, however, an S/M ratio of 1 merely indicates passive diffusion. By 28 days of age, abnormal gluconeogenic activity as well as metabolic inhibitors would no longer be present.

The accumulation of AIB by renal cortical slices from both PCMs and PDMs was highest at birth and declined to adult values (Fig. 4). These data confirm observations by Webber and Cairns (27) and Segal *et al.* (28). That kidney slices from immature animals can form higher concentration gradients than those from adults is partly explained by a slower rate of efflux of AIB from immature kidney slices (29). That renal cortical slices from PDMs and PCMs concentrated AIB to the same degree at all ages probably indicates that the maturation of this transport function is the same for both populations. However, evidence indicates that accumulation of amino acids by renal cortical slices may reflect uptake at the peritubular cell membrane (30). Uptake at the luminal membrane would reflect tubular reabsorption whereas uptake at the

peritubular side probably has a nutritive role (31).

Conclusions. The development of transport functions in renal cortical slices from the progeny of diabetic dams was not significantly different than that of controls. At 10 days of age, however, kidney slices from PDMs accumulated significantly less sugar and organic acid than those from age-matched controls. It is possible that the presence of gluconeogenic intermediates as well as other metabolites affected the uptake or efflux of organic acids and sugars by kidney slices from progeny of diabetic dams.

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