The Renal Reabsorption of Glucose in the Developing Canine Kidney: A Study of Glomerulotubular Balance

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Extract

Twenty puppies, 18 hr-40 days of age, were used to investigate the relation between maximal tubular reabsorption of glucose (TmG) and glomerular filtration rate (GFR) during maturation. The renal threshold for glucose was examined in an attempt to obtain information concerning functional heterogeneity. There was a slow increase in dry kidney weight (DKW) over the first 2 weeks of life, relative to the more rapid rate noted thereafter. Examination of the clearance of inulin (C_{IN}) and TmG revealed a pattern of increase with age similar to that observed for the relation of DKW to age. The ratio of TmG to C_{IN} initially was high (4.22), fell markedly over the first few days, and thereafter continued to decrease exponentially until levels were achieved that were similar to values found in adult animals (2.75-3.31). These data suggest that the documented anatomical glomerular preponderance in the infant kidney may not have a consistent functional correlate. Analysis of the glucose threshold as a function of age revealed a statistically significant positive regression; however, the increase with age was small (range 190-254 mg/100 ml), and all values fell within the 95% confidence limits for adult thresholds. A comparison of splay between the youngest and oldest puppies demonstrates an increase in splay and thus in functional heterogeneity of the younger animals, a finding which may reflect a population of nephrons with relative glomerular preponderance, despite the presence of glomerulotubular balance for the kidney as a whole.

Speculation

Current evidence, including that of the present investigation, suggests that although functional tubular capacity at birth may be limited, glomerulotubular balance is maintained.

Introduction

A sustained balance between GFR and tubular reabsorption is one of the most consistently observed phenomena in renal physiology. When Tudvad [44] re-

ported in 1949 that the ratio of the TmG to the C_{IN} was lower in infants than in children and adults, it appeared that such balance did not exist in the immature kidney, but rather that the quantity of glomerular filtrate exceeded the tubular reabsorptive capacity,

accounting for inefficient conservation of filtered substances. In other studies in infants low ratios of the tubular maximum for *p*-aminohippurate (PAH) and the clearance of PAH to the C_{IN} [4, 34, 45, 46, 48], and low fractional reabsorption of phosphate [7, 12, 26, 31] were observed. Supported by morphologic studies of the immature kidney, which demonstrated relatively smaller tubules than glomeruli, these early data were synthesized into a formal concept of glomerulotubular imbalance with relative glomerular preponderance as a major characteristic of the immature kidney [14–16]. Recently, however, several studies have suggested that such a broad generalization may not be accurate and that balance similar to the mature state indeed may exist, at least for some of the substances handled by the immature kidney [6, 20, 42, 43].

Anatomical studies of the immature kidney have demonstrated greater heterogeneity in glomerulotubular relations than in the adult kidney [17, 29]. If this heterogeneity of structure has a functional counterpart, the existence of nephrons with large glomeruli and small tubules would be expected to result in a low threshold for glucose, a feature of the immature kidney that has not been investigated previously.

Inasmuch as it was the early work with glucose which provided the main support for the theory of glomerulotubular imbalance [44], the present studies were designed to reinvestigate the relation between TmG and GFR during maturation of the canine kidney. During the course of these studies, the renal threshold for glucose was examined in an attempt to obtain information concerning functional heterogeneity.

Materials and Methods

Twenty healthy mongrel puppies, 18 hr–40 days of age, obtained from unweaned litters whelped in our animal quarters, were used to investigate the glucose titration curve in the developing canine kidney.

Each puppy was separated from the litter 2 hours before the study. Atropine sulfate (0.5 mg/kg body wt) was injected subcutaneously 45 min before intravenous or intraperitoneal induction and intravenous maintenance of light anesthesia with Inactin [50]. The animal was placed in a supine position on a heated animal board. A tracheostomy tube was inserted and connected to a respirator [51]. Solutions were infused and blood sampled from cannulae in the right external jugular vein and the left femoral artery, respectively.

Urine was obtained through soft polyethylene tubing, inserted into each ureter through a small midline suprapubic incision and extended to the level of the renal pelvis. Urine samples were collected directly into glass tubes, which were weighed to determine volume. Careful attention was given to fluid balance so as to insure an adequate urine flow while minimizing extracellular volume expansion.

After a priming dose of 10% inulin (0.5 ml/kg body wt), an infusion of inulin in 0.85% NaCl was administered at the rate of 0.08 ml/min throughout the remainder of the experiment. A separate infusion of 0.45% NaCl was administered at a rate of 0.3 ml/min/kg body wt during a 30-min period of equilibration, after which this solution was replaced by successive infusions of 10 and 20% dextrose in water at 0.1 ml/min and 50% dextrose in water at 0.1 and 0.3 ml/min. An equilibration period of 15 min was allowed after changing either the concentration or rate of infusion, followed by two 10-min collection periods. Body weights determined at the beginning and end of each experiment on a balance accurate to 0.1 g changed no more than $\pm 5\%$. All animals were in positive fluid balance at the time TmG was reached. The animals were killed by an anesthetic overdose at the end of the procedure, at which time the kidneys were removed for determination of wet and dry weights.

Throughout the experiments, serial measurements were made of hemoglobin, hematocrit, body temperature, arterial blood pressure, arterial pH, and pCO_2 (which was maintained at 35–40 mm Hg by appropriate adjustment of the respirator). The cells from each 0.5–1.0-ml blood sample were returned to the animal in order to maintain the hematocrit at or near control levels.

Urine and plasma samples were analyzed in duplicate. Glucose was determined using a glucose oxidase method [5, 36, 52]. The diphenylamine method as modified by Walser *et al.* [47] was used for determination of inulin. Blood pH and pCO_2 were determined using an AME 1 Radiometer [53].

The renal threshold for glucose was taken as the plasma level at which glucose was first detected in the urine in increasing amounts. The first appearance of glucose could not be used to denote the threshold, inasmuch as concentrations in urine at the beginning of the experiments ranged as high as 40 mg/100 ml. The TmG was determined by averaging the values for glucose reabsorption from three or more periods during which the rate of reabsorption was stable despite

increasing filtered loads which exceeded reabsorption by a factor of ≥ 1.4 , with three exceptions. One puppy at 14 days of age and the 18-day-old puppy had ratios of filtered load to amount reabsorbed of 1.1 and 1.2, respectively. In subsequent experimental periods, the ratios increased to 1.4 and 1.7, while reabsorption remained constant. Because fractional sodium excretion increased to 4% and 3%, these periods were not included in the calculation of TmG. For several experimental periods before the termination of the study in the 40-day-old animal, reabsorption remained constant despite increasing filtered loads. In this puppy the highest ratio achieved was 1.2. The values from periods at the end of the studies in which sodium excretion was increasing were discarded if the rate of glucose reabsorption was constant or decreasing. TmG may not have been achieved in the youngest animals as, in some of these puppies, glucose reabsorption continued to rise with increased filtered loads even though fractional sodium excretion increased to levels as high as 25%. In these animals TmG was calculated by averaging the two or three highest reabsorptive rates at glucose values in plasma of less than 1,200 mg/100 ml, as, at higher values of glucose in plasma, there was a consistent fall in glomerular filtration rate. The C_{IN}

was accepted as the glomerular filtration rate, the control values having been determined before the infusion of any glucose-containing solution. The ratio of TmG to C_{IN} was calculated by dividing the average TmG by the average C_{IN} of corresponding periods. Conventional methods of statistical analysis were employed [41]. The computer program (POLFIT) used for the calculation of nonlinear regression is part of the library of the Albert Einstein College of Medicine.

Results

Pertinent data on all animals are shown in Table I. The relation of kidney weight to age is demonstrated in Fig. 1. There was a slow increase in DKW over the first 2 weeks of life, relative to the more rapid rate noted thereafter. This increase in weight presumably reflected the predominant growth of the proximal tubule [17, 30]. Kidney water increased linearly over the time period studied. The relation between dry and wet kidney weights (DKW/WKW) reflected the marked increase in water content during the first few days, as DKW changed relatively little. After 3 weeks of age, the rapid increase in DKW was reflected in a marked increase in the ratio of DKW/WKW.

Table I. Summary of experimental data for all animals

Age, days	Body wt, g	Kidney wt, ¹ g		C_{IN} , ² ml/min		Plasma glucose, ml/100 ml		TmG, mg/min	TmG/ C_{IN} , mg/ml	$(C_{NA} \times 100)/C_{IN}$ at TmG, %
		Wet	Dry	Control	At TmG	Threshold	TmG			
0.75	274	4.2	0.60	0.50	0.64	200	637	2.7	4.22	1.2
1.50	250	5.4	0.95	0.60	0.71	199	776	3.0	4.29	24.0
3.0	450	8.3	1.20	1.40	1.74	236	594	7.4	4.26	1.6
4.0	430	7.9	0.90	1.90	2.0	190	511	7.1	3.55	3.1
5.0	540	9.4	1.05	2.0	1.86	193	887	6.7	3.60	21.0
7.0	550	10.6	1.20	2.1	2.0	224	800	7.2	3.60	3.3
10	700	14.1	1.60	3.5	3.7	240	519	12.9	3.49	1.2
10	450	13.1	1.80	3.2	2.9	220	719	9.7	3.35	3.9
12	425	10.1	1.45	1.7	1.7	210	573	6.1	3.59	3.9
14	900	15.0	1.90	4.0	3.5	237	387	11.8	3.37	1.4
14	600	8.3	1.30	2.7	2.1	195	491	6.8	3.24	3.5
18	660	14.05	1.90	3.7	5.0	217	465	19.2	3.74	0.5
19	666	14.3	1.95	3.8	3.6	245	603	15.3	3.57	0.3
21	1350	22.8	2.95	6.0	6.9	250	604	22.2	3.22	0.8
22	1200	23.6	2.70	7.1	8.2	³	574	26.9	3.28	0.2
23	1350	24.6	4.40	9.3	9.7	200	452	30.0	3.09	3.4
34	1900	34.0	7.1	11.6	11.3	238	448	31.2	2.76	6.0
35	2000	37.2	6.3	10.8	9.8	240	408	26.9	2.75	1.2
39	1575	28.1	7.3	10.3	14.6	224	460	44.0	3.01	0.6
40	1375	27.0	7.2	11.2	12.9	254	395	42.7	3.31	0.7

¹ Both kidneys.

² C_{IN} : clearance of inulin; TmG: maximal tubular transport of glucose.

³ Threshold exceeded before definition.

Fig. 1. Change in kidney weight and water content with age. Each point represents the combined value of both kidneys. In addition to the 20 animals represented in our glucose data there are 9 puppies which, because of physiologic instability, were eliminated prospectively but are included in this analysis only. Regression with age for kidney water was $y = 0.54x + 4.46$, $r = 0.88$; for dry kidney wt/wet kidney wt (DKW/WKW), $y = 0.000166x^2 - 0.00381x + 0.15$, $r = 0.82$, deviation from linearity significant ($P = 0.10$); for DKW, $y = 0.00424x^2 + 2.73x + 0.89$, $r = 0.96$, deviation from linearity significant ($P < 0.01$).

Fig. 2. Glomerular filtration rate as a function of age. Absolute rate of filtration is shown in the upper panel ($y = -0.00044x^3 + 0.027x^2 - 0.14x + 1.4$, $r = 0.97$); filtration rate per gram of dry kidney in the lower, DKW: dry kidney weight.

Examination of the C_{IN} (Fig. 2) revealed a pattern of increase with age which appeared to be curvilinear with a slow rate of increase over the first 2 or 3 weeks relative to a somewhat more rapid rate thereafter. Indeed, the data best fit a third order regression equation, although the departure from linearity may have been accidental. Analysis of C_{IN} per gram of DKW as a function of age showed wide scatter of the experimental points with no demonstrable correlation.

Although both an increase [6] and a decrease [13, 24] in glomerular filtration rate have been observed at high filtered loads of glucose, no consistent changes in the C_{IN} were apparent in our data when initial values were compared with those values at high glucose loads, except for a consistent decrease in the C_{IN} when the level of glucose in plasma exceeded 1,200 mg/100 ml.

Analysis of the glucose threshold as a function of age (Fig. 3) revealed a statistically significant positive regression ($0.05 > P > 0.01$). However, the increase with age was small and all values fell within the 95% confidence limits for the glucose threshold of adult dogs examined in our laboratory as well as those reported in the literature [24, 37, 38, 40].

TmG as a function of age is shown in Fig. 4. A pattern similar to that observed for the relation of DKW and C_{IN} to age is apparent, with an accelerated rate of increase beginning at the 3rd week of life. The data accordingly are best described by a nonlinear

Fig. 3. Glucose threshold as a function of age. $y = 0.90x + 206.97$, $r = 0.46$, $0.05 > P > 0.01$.

Fig. 4. Maximal tubular reabsorption (T_m) of glucose as a function of age. Absolute rate shown in the upper panel ($y = 0.007x^2 + 0.68x + 2.6$, $r = 0.95$); T_m of glucose per gram of dry kidney (DKW) shown in the lower panel.

regression, although, again, the departure from linearity may have been accidental. When the T_mG , as an index of proximal tubular function, was factored by DKW, as an index of proximal tubular growth, no

clear pattern was apparent over the entire age range studied.

It has been noted previously that the apparent T_mG decreases as fractional sodium excretion increases [24]. A similar relation between sodium and glucose reabsorption was present in the adult dogs and in the puppies 21–40 days of age. In the puppies 10–14 days of age, however, as fractional sodium excretion increased to levels in excess of 20% (beyond the periods used for calculation of T_mG), no decrease in glucose reabsorption was seen. In the animals from birth to 7 days of age, glucose reabsorption continued to rise with increasing filtered loads even though fractional sodium excretion reached levels as high as 25%.

The ratio of T_mG to C_{IN} is related to age in Fig. 5. The ratio was high during the first 3 days of life, fell markedly by day 4, and thereafter continued to decrease at a slower rate until levels were achieved that were similar to values found in adult animals. An exponential rate of decline in the ratio is described. The deviation of this curve from a linear regression is significant ($P < 0.05$), making it quite unlikely that undue emphasis has been placed upon the early ages with high values. It should be noted that if the true maximal rate of reabsorption was not achieved in the youngest animals, the ratio of T_mG to C_{IN} is even higher during the first few days than reflected by our data.

A comparison of splay in the oldest and youngest puppies is shown in Fig. 6. Note that while all points follow a similar pattern, comparison between the two age groups reveals that at each L/T_m quantile values of T/T_m for the younger puppies are less than those for the older puppies. In addition, the point at which

Fig. 5. Ratio of maximal tubular reabsorption of glucose (T_mG) to inulin clearance (C_{in}) as a function of age. $y = 1.64e^{-0.0419x} + 2.5$, $r = 0.87$.

reabsorption becomes incomplete occurs at a lower filtered load in the younger animals.

Discussion

The maximal rate at which the proximal tubule is able to reabsorb glucose has been used as one of the classic markers of tubular function in adult animals, including man [40], and has served as a cornerstone of support for Smith's hypothesis [39] of functional glomerular preponderance in the immature kidney. Low ratios of T_{mPAH} and C_{PAH} to C_{IN} [4, 34, 45, 46, 48], decreased fractional tubular reabsorption of certain amino acids [7] and of phosphate [12, 26, 31], and the high anatomical ratio of glomerular surface area to proximal tubular volume [17] added further support to this interpretation.

More recently, however, a number of studies have suggested that such a broad generalization of the behavior of the infant kidney may not describe adequately the glomerulotubular relation for all substances. The low ratios of C_{PAH} to C_{IN} have been shown to be secondary to decreased extraction of PAH by the infant kidney [9] due to a relatively greater blood flow to juxtamedullary nephrons and thus to vasa recta [21, 27, 28]. There is no difference between infants and children in the ratio of tubular amino acid reabsorption to glomerular filtration rate [7], and no limitation in reabsorptive ability at 30–50 times normal blood levels for at least one amino acid [8]. Functional glomerulotubular balance has been shown for sodium and water in the young puppy [20], rat [10], and guinea pig [43]. These data suggest that the documented anatomical glomerular preponderance in the infant kidney may not have a consistent functional correlate, but rather that balance between filtration and reabsorption is present at all stages of postnatal development.

In comparison of data in the present study to values obtained in adult animals, the ratio of T_mG to C_{IN} for the youngest puppies was high, not low as found in premature infants [45], which suggests not glomerular but tubular preponderance during the first few days of life. To explain this difference, it is suggested either that the T_mG was not reached in the studies of Tudvad [44] and Tudvad and Vesterdal [45], or that saline loading produced depression of the T_mG [3, 22, 24, 32].

Brodehl *et al.* [6] found no difference in the ratios of T_mG to C_{IN} between infants 2.5–24 weeks of age and older children. However, their youngest infants had

Fig. 6. Splay of glucose titration data. T : glucose reabsorption; L : filtered load of glucose. Both terms are factored by maximal tubular reabsorption (T_m) to permit pooling of data from individual animals. Each point represents a mean T/T_m at L/T_m quantiles of 0.1.

high ratios of T_mG to C_{IN} , similar to the results in the youngest puppies in the present study (J. Brodehl, personal communication).

The presence of an apparently mature transport system for glucose relative to glomerular filtration does not, of course, necessarily imply a similar degree of tubular development for other substances. Smith [39] suggested that the tubular reabsorptive capacity for glucose in infants might be more highly developed than that for other substances. This has been shown to be true in the sheep fetus [1]. Since anaerobic glycolysis has been shown to proceed at a greater rate in newborn rats [49], rabbits [49], puppies [11], and premature infants [35], than in older animals and term infants, it is conceivable that the increased glucose utilization of this metabolic pathway might result in a generalized enhancement of glucose metabolism in neonates. Studies in rats [18] and infants [35] support this speculation.

Thus, although maximal glucose reabsorption, by virtue of its suggested unique level of maturation and its dependence on such variables as extracellular volume, glomerular filtration, and fractional sodium excretion, may not be representative of other proximal tubular mechanisms in the developing kidney, these data do suggest that glomerular preponderance is not present, even in very young animals.

The renal threshold for glucose has not been studied previously either in experimental animals or in infants. It is often stated, however, that small amounts of glycosuria are not infrequent in neonates [33], especially premature infants, in whom the degree of struc-

tural maturation is more comparable to the younger puppies. It is surprising, therefore, that such small differences with age were found in the glucose thresholds of the puppies. The slightly positive regression of glucose threshold with age that we observed nonetheless is real. It should be recognized that the glucose titration technique reflects overall glomerulotubular balance and not that of single nephrons. An analysis of splay, however, allows inferences to be made as to the glomerulotubular balance of populations of nephrons. If the lower threshold in the younger puppies is due to greater nephron heterogeneity, this should be manifest by an increased splay in their titration curves relative to older puppies and adult dogs. A comparison of splay in the youngest and the oldest puppies (Fig. 6) indeed does demonstrate an increase in splay and thus in functional heterogeneity in the younger animals. A minimal degree of splay was found in the older puppies, similar to adult dogs, in contrast to the marked splay in adult man [25, 40]. It has been noted previously that the extent of splay in the glucose titration curve in man is greater than that in the dog [39]; therefore, the infant, likewise, may show a much greater degree of splay than the puppy, the result of which would be a lower glucose threshold in infants.

The nonlinear increase in total kidney glomerular filtration rate observed in micropuncture studies in guinea pigs [43] supports the pattern of nonlinearity in our data and suggests that the slow rate of increase in the C_{IN} which we observed over the first 2 or 3 weeks of life reflected, as in the guinea pig, primarily changes in the rate of filtration in juxtamedullary nephrons and that the rapid increase thereafter was caused by changes in the filtration rate of the outer cortical nephrons. Parallel studies in which the distribution of renal blood flow was studied by the ^{133}Xe washout method in littermates of the puppies used in the present investigation demonstrated a similar developmental pattern [2].

The maturation of tubular reabsorption may be caused by an increase in the number of functional units, by a maturation of cellular reabsorptive mechanisms, or by both. Micropuncture studies in the developing guinea pig kidney [43] suggest an increase in the number of units as the primary factor. Analysis of TmG per gram of DKW over the first 3 weeks revealed a significant increase ($P = 0.025$), which suggests changes transcending a simple increase in tubular mass or number of functional units. *In vitro* studies of PAH uptake in dog kidney slices [19, 23] support this conclusion.

Summary

The renal handling of glucose was studied in puppies from birth to 40 days of age in order to investigate glomerulotubular balance of the developing kidney and to determine whether the previously demonstrated morphologic heterogeneity and glomerular preponderance of the nephrons of the immature kidney have functional counterparts.

The glucose threshold increased slightly with age although all values fell within the range observed in adult dogs. The ratio of TmG to C_{IN} was high at birth, decreased markedly by day 4, and reached adult values after 3 weeks of age. This pattern of change reflected the more rapid increase in C_{IN} than TmG. These findings fail to support the concept of glomerular preponderance as a characteristic of the immature kidney.

The slightly lower threshold for glucose in the youngest puppies appeared to reflect increased nephron heterogeneity, as demonstrated by greater splay of the titration curve in the youngest animals. This finding may reflect a population of nephrons with relative glomerular preponderance, despite the presence of glomerulotubular balance for the kidney as a whole.

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