The glucose-galactose paradox in neonatal murine hepatic glycogen synthesis

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KUNST, C., R. KLIEGMAN, AND C. TRINDADE. *The glucose-galactose paradox in neonatal murine hepatic glycogen synthesis.* Am. J. Physiol. 257 (Endocrinol. Metab. 20): E697–E703, 1989.—In adults glucose incorporation to glycogen is indirect after recycling from lactate. In neonates galactose entry to glycogen exceeds that for glucose, but the pathway is unknown. The pathway of hexose incorporation to glycogen was studied in 5–7-day-old rats and 6-h-old rats injected intraperitoneally (IP) with either double-labeled [6-^{3}H]glucose (nonrecycling), [U-^{14}C]glucose (recycling), or [6-^{3}H]glucose and [U-^{14}C]galactose in saline. In another group of pups, 1 g/kg of glucose or galactose was administered in addition to tracers to determine glycemia and net glycogen synthesis between 15 and 180 min after injection. Blood glucose increased from 3.4 ± 0.4 to 8.5 ± 1.5 mM in 5–7-day-old pups in response to IP glucose; there was no glycemic response to galactose, although galactose levels increased from 0.5 to 6.3 mM at 15 min. Hepatic glycogen increased after IP glucose from 14 ± 2 at 15 min to 30 ± 3 at 120 min ($P < 0.01$), whereas after IP galactose glycogen was 44 ± 6 μmol/g at 120 min ($P < 0.05$). After IP glucose, ^{3}H and ^{14}C disintegration per minute in glycogen increased slowly with ^{14}C exceeding ^{3}H at 120 and 180 min. In contrast IP [^{14}C]galactose resulted in a much greater peak of ^{14}C incorporation into glycogen. The ratio of ^{3}H to ^{14}C in glycogen relative to the injectate after IP glucose decreased from 0.69 ± 0.12 to 0.36 ± 0.03 ($P < 0.01$) between 15 to 180 min, whereas the ratio after galactose was 0.20 ± 0.007 to 0.15 ± 0.02 at these times. The 6-h-old pups also demonstrated augmented incorporation of [^{14}C]galactose in glycogen relative to [^{3}H-^{14}C]glucose. In contrast to 5–7-day-old pups there was no evidence of glucose recycling in 6-h-old pups. In conclusion galactose entry into glycogen exceeds that for glucose and is not dependent on recycling. Direct incorporation of galactose exceeds that for direct incorporation from [^{3}H]glucose, suggesting a preferential utilization of galactose for neonatal glycogen synthesis.

newborn; metabolism

LACTOSE, THE SUGAR in mammalian milk, is composed equally of glucose and galactose (14). Glucose may serve as a precursor for tissue glycogen and as a carbohydrate fuel for oxidative metabolism, whereas galactose, the C4 epimer of glucose, has many potential roles (1, 14). Galactose may be oxidized or function as a precursor for glycogen synthesis as glucose does but also serves as a structural component in complex lipids, mucopolysaccharides, and glycoproteins. Nonetheless, there is no specific requirement for galactose in mammalian diets because the activity of the UDP-glucose epimerase produces sufficient quantities of galactose for macromolecule synthesis. Therefore the reason for such a large quantity of galactose in the normal newborn diet remains an enigma.

Kliegman et al. (11, 13) and Sparks et al. (19) have studied galactose as a potential regulator of hepatic glycogen synthesis. Kliegman et al. (11–13) demonstrated that compared with glucose, net hepatic carbohydrate uptake was enhanced after galactose administration to neonatal dogs. However, rather than simply enhancing the rate of glycogen synthesis, galactose may have served as a preferential precursor for hepatic glycogen synthesis when compared with glucose. Glucose is incorporated into hepatic glycogen predominantly by the indirect pathway after recycling of lactate during gluconeogenesis (8, 9, 16, 17). This unexpected phenomenon has been described in both adult and newborn mammals (8, 9, 16, 17). Presently there is a paucity of information related to the partitioning of galactose between direct or indirect (recycling) incorporation pathways for glycogen synthesis in the newborn mammal. The goals of the current experiments are to determine in the newborn rat, whether galactose is preferentially incorporated into hepatic glycogen compared with glucose and whether glycogen synthesis from galactose is by a direct or indirect mechanism.

METHODS AND MATERIALS

Materials

D-[6-^{3}H]glucose, D-[U-^{14}C]glucose, and D-[U-^{14}C]galactose were purchased from New England Nuclear (Boston, MA). According to New England Nuclear specifics on this lot, the galactose was contaminated with <0.1% glucose. All enzymes were purchased from Sigma Chemical (St. Louis, MO). Scinti-verse II was purchased from Fisher (Fair Lawn, NJ). Galactose (Sigma Chemical) and glucose (Mallinckrodt, St. Louis, MO) contained no detectable contamination, as determined by our assays, with glucose or galactose, respectively. All chemicals and standards were analytical and reagent grade.

Animals

Pregnant Sprague-Dawley rats, purchased from Zivic Miller, were housed in cages with free access to rat chow and water. During their fasting periods and throughout

the experiment, pups were housed in an Armstrong Incubator at 37°C and 70% humidity. Pups for the 5–7-day-old group were housed with their mother until 20 h before the experiment. At this time the pups were removed from their mother and placed in the incubator.

Pups for the newborn group were delivered at term gestation (21 days). Before cesarean section the mother was anesthetized with ether. The umbilical cords of the pups were clamped; the pups were dried and immediately placed in the incubator. Average weight of the newborn rats was 5.5 ± 0.5 g. The average weight of the 5–7-day-old pups was 11 ± 2 g. There were no differences of pup weights between groups studied at the two age periods.

Experimental Design

The 5–7-day-old pups were fasted for 20 h before the experiment to deplete hepatic glycogen stores. The less mature series of newborn pups were fasted after birth for 6 h before investigation. The 5–7-day-old pups typically are gluconeogenic and capable of recycling, whereas the less mature 6-h-old pups do not demonstrate active gluconeogenesis and should be incapable of recycling and glycogen synthesis from the indirect pathway. All pups from each age period were randomly assigned to one of five groups. These groups were planned to determine the influence of *1*) fasting on glucose or galactose tracer incorporation into glycogen and *2*) substrate-induced changes in glycogen synthesis. Incorporation of tracer quantities of either glucose or galactose into hepatic glycogen should not be affected by mass action kinetics, rate-limiting enzyme activities, or dilution by exogenous substrate administration. When the data of tracer incorporation revealed similar results between fasted pups and those given substrate amounts of glucose or galactose, the data were pooled. This provides a more consistent picture of substrate incorporation into glycogen by increasing the sample size of the individual groups. In addition pups that received only tracer quantities of glucose or galactose (e.g., fasted) were pooled to present the data on fasting levels of glucose, glycogen, etc. The five initial groups follow.

Fasting control. Pups in this group were injected intraperitoneally (IP) with tracer amounts of D-[6-^{3}H]glucose and D-[U-^{14}C]glucose in normal saline solution. Each tracer was given as a dose of 6,250,000 disintegrations per minute (dpm)/kg.

Glucose alimented. These pups were injected IP with a glucose solution (1 g glucose/kg) containing tracer amounts of D-[6-^{3}H]glucose and D-[U-^{14}C]glucose as above. IP injection of substrate creates a "fed" as opposed to the fast state. Because substrate quantities of glucose did not influence either appearance of label in blood or glycogen, the data for radioactivity from *groups 1* and *2* were pooled.

Fasting control. These pups were injected IP with tracer quantities of D-[6-^{3}H]glucose and D-[U-^{14}C]galactose in a normal saline solution.

Glucose alimented. These pups were injected IP with a glucose solution (1 g glucose/kg) containing tracer quantities of D-[6-^{3}H]glucose and D-[U-^{14}C]galactose.

Galactose alimented. These pups were injected IP with a galactose solution (1 g galactose/kg) containing tracer quantities of D-[6-^{3}H]glucose and D-[U-^{14}C]galactose. Because substrate quantities of galactose did not produce different levels of radioactivity in blood or glycogen the results of radiolabeled tracers from *groups 3–5* were pooled.

The ratio of ^{3}H-^{14}C was normalized to a standardized injectate ratio of 1:1. All pups were killed by decapitation at serial intervals during a 3-h period after IP injection. Blood samples taken from the neck vessels by heparinized capillary tubes were immediately placed on ice. Five seconds after death the liver was freeze-clamped between aluminum blocks cooled to the temperature of liquid nitrogen. The liver was then stored at −80°C.

Analyses

Circulating substrates. Blood was precipitated with 10% perchloric acid (PCA) and then neutralized with K_2CO_3. Glucose was assayed as reported previously (11). Galactose was fluorometrically determined using galactose dehydrogenase (11). All analyses were done in duplicate and adapted to micro methods.

Hepatic determinations. ^{3}H and ^{14}C label incorporation into hepatic glycogen was determined for all groups after liver homogenization and subsequent alcohol precipitation at 0°C. Hepatic glycogen was further purified with a methanol-chloroform (1:2) wash. Glycogen was redissolved in double-distilled water and an aliquot was counted on a β-scintillation counter to determine [^{3}H]- and [^{14}C]glucose content of glycogen. Homogenized liver was enzymatically assayed for glycogen according to Vannucci and Duffy (20).

Glucose radioactivity. Neutralized samples of PCA-treated blood were evaporated to dryness to remove ^3H_2O and were then reconstituted with unlabeled water. Galactose was completely converted to galactonate with galactose dehydrogenase before placement of the neutralized sample on a Dowex AG 1-X8 column (11). Glucose was eluted first in the water wash (pH 8). Galactonate was eluted next in the 0.02 N HCl wash. Lactate and additional three-carbon substrates were eluted in the 0.05 N HCl wash. This method completely separated glucose from the galactonate and three-carbon substrates.

Radioactivity in ^{3}H and ^{14}C was counted by liquid scintillation for 10 min by means of internal and external standards. All counts were corrected for background, blanks, quenching as well as ^{14}C in the ^{3}H channel and were expressed in dpm.

Statistical analyses. Figure notations are recorded as the means ± SE. Statistical analyses were used according to standard computer programs for the Student's *t* test.

RESULTS

6-h-Old Rats

Blood glucose and radioactivity. Blood glucose levels in pups during the immediate newborn period were not in a steady state as noted by rising blood glucose concentrations with time in the fasted pups injected with only tracers in normal saline (Fig. 1). This pattern of rising blood glucose in fasting newborn rats is not unusual at

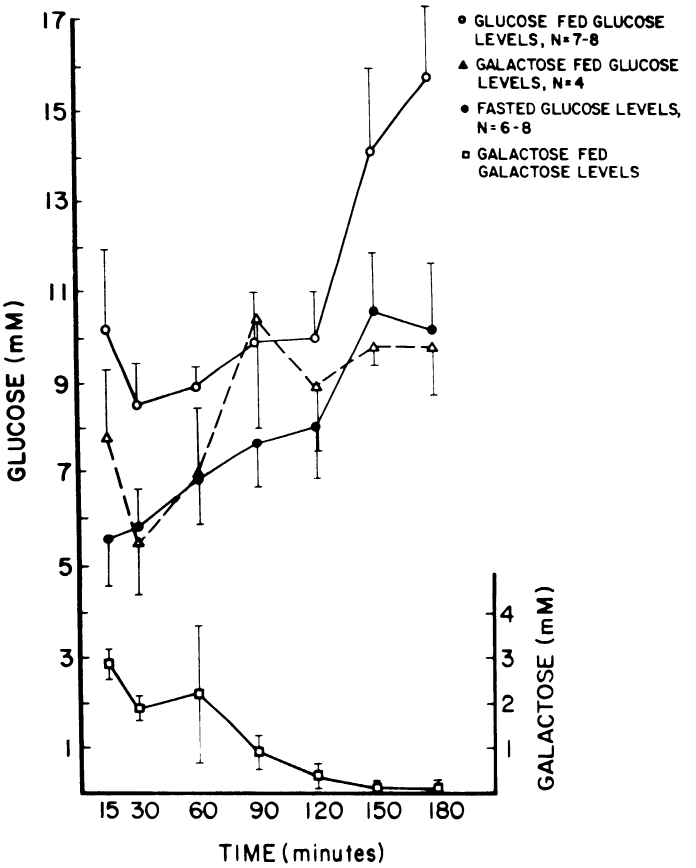

FIG. 1. Blood glucose and galactose levels in 6-h-old rat pups; ○, blood glucose after intraperitoneal (IP) glucose administration (*groups 2* and *4*); △, blood glucose after IP galactose administration (*group 5*); □, blood galactose after IP galactose administration (*group 5*); ●, fasting blood glucose levels (*groups 1* and *3*). Groups that were pooled demonstrated no individual differences before combining data.

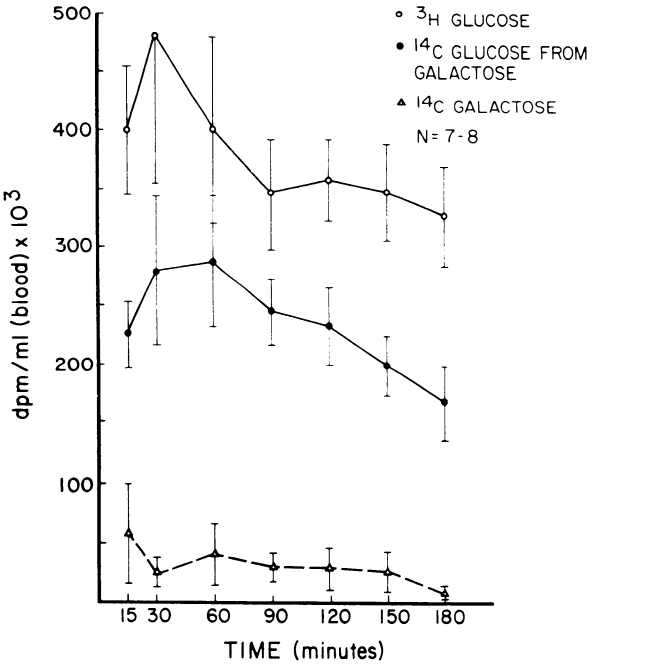

FIG. 2. Disintegration per minute (dpm) appearing in circulation in 6-h-old pups; ○, [^{3}H]glucose after intraperitoneal (IP) [^{3}H]glucose administration (*groups 1–5*); ●, ^{14}C appearing in glucose after IP [^{14}C]-galactose administration (*groups 3–5*); △, [^{14}C]galactose after [^{14}C]-galactose administration (*groups 3–5*). Individual data were pooled into above groups after determining that there were no differences within groups receiving same tracers.

this time of life and is typical for the species and age. After IP glucose administration (with tracers) blood glucose levels increased compared with fasted control pups and were elevated at 15 ($P < 0.01$), 30 ($P < 0.05$), 150 ($P < 0.05$), and 180 ($P < 0.02$) min (Fig. 1).

After galactose and tracer injection blood galactose levels were increased (fasted pups had no detectable galactose) within 15 min and declined to very low levels at 150 and 180 min (Fig. 1). Blood glucose concentrations after galactose injection were not different from that among fasted pups injected with only tracer quantities of hexoses (Fig. 1).

Because there were no differences in radioactivity appearing in blood between tracer and substrate plus tracer-injected pups the blood radioactivity data were pooled for these respective groups. Radioactivity in blood [^{3}H]glucose was evident at 15 min after IP injection. [^{3}H]glucose radioactivity was highest at 30 min and declined slowly thereafter (Fig. 2).

Radioactivity in [^{14}C]galactose was evident within 15 min of injection but at an amount that was 10% of that after [^{3}H]glucose throughout the entire study period ($P < 0.001$, Fig. 2). ^{14}C from galactose appeared rapidly into circulating glucose and was present in greater amounts than that of the parent compound's radioactivity (Fig. 2). At each time interval the amount of [^{14}C]glucose (derived from galactose) was four- to fivefold greater than that present in the [^{14}C]galactose ($P < 0.001$) (Fig. 2).

Hepatic glycogen metabolism. Hepatic glycogen content in fasted newborn pups at 6 h of age receiving only tracer quantities of hexoses was constant for 120 min and then declined. Glycogen content in fasted pups were lower at 180 min than at the start of the study ($P < 0.01$). Glycogen content in glucose- and galactose-injected pups were similar to that of control fasted pups (150–225 μmol/g) at each time interval, except at 150 min when glycogen was transiently higher in glucose (229 ± 35) ($P < 0.01$) but not galactose (160 ± 15) injected pups compared with fasted (125 ± 15 μmol/g) pups.

Radioactivity incorporated into glycogen was determined in pups injected with [^{14}C]galactose and [^{3}H]-glucose or [^{14}C]glucose and [^{3}H]glucose (Fig. 3). Although net glycogen synthesis was not demonstrated in these immature pups, incorporation of label into hepatic glycogen was evident as early as 15 min after IP injection. Considering that equal quantities of tracers were administered this was most marked for ^{14}C incorporation into glycogen after galactose alimentation. The incorporation of ^{14}C and ^{3}H from injected glucose was reduced at each time point compared with galactose (Fig. 3). When these results were expressed as the ratio of [^{3}H]glucose-[^{14}C]-glucose and [^{3}H]glucose-[^{14}C]galactose it became apparent that more [^{14}C]galactose was incorporated than [^{14}C]glucose, because this ratio was reduced in galactose-injected pups (Fig. 4).

5–7-Day-Old Mature Rat Pups

Blood glucose and radioactivity. In contrast to the 6-h-old newborn pups, the more mature 5–7-day-old pups

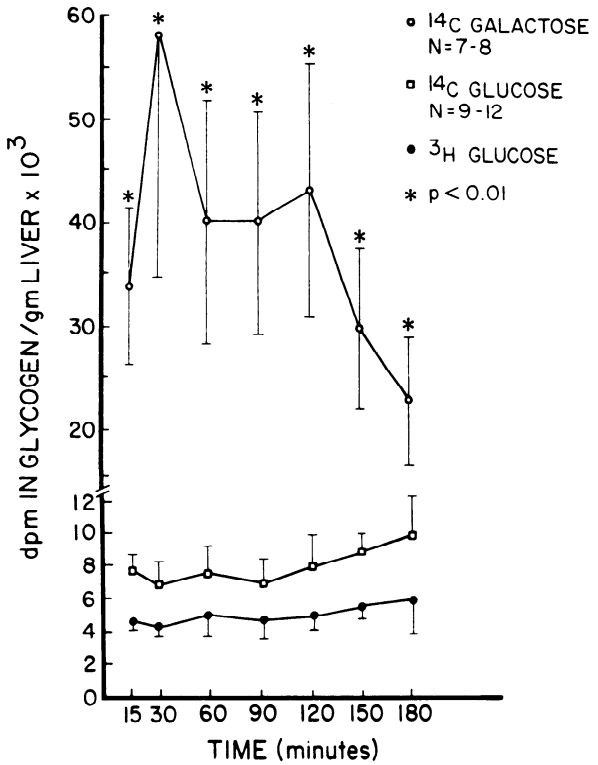

FIG. 3. Appearance of ^{3}H and ^{14}C in hepatic glycogen in 6-h-old pups. ○, ^{14}C from [^{14}C]galactose administration (*groups 3–5*); □, ^{14}C from [^{14}C]glucose administration (*groups 1* and *2*); ●, ^{3}H from [^{3}H]-glucose administration (*groups 1–5*); dpm, disintegrations per minute.

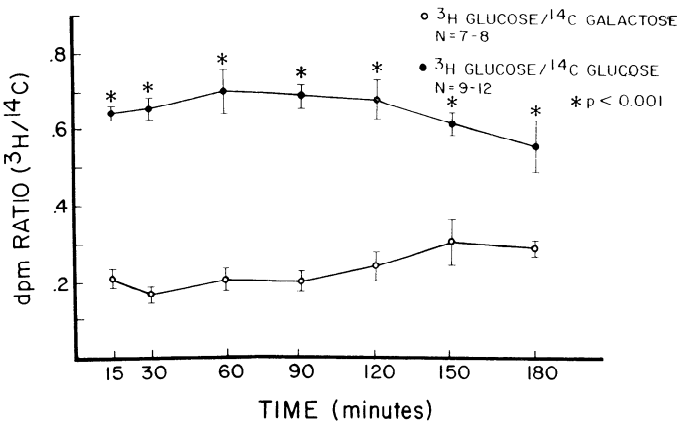

FIG. 4. Ratio of ^{3}H-^{14}H in hepatic glycogen in 6-h-old pups. ●, ratio of ^{3}H-^{14}C after [^{3}H]glucose and [^{14}C]glucose (*groups 1* and *2*); ○, ratio of ^{3}H-^{14}C after [^{3}H]glucose and [^{14}C]galactose (*groups 3–5*); dpm, disintegrations per minute.

demonstrated stable fasting blood glucose concentrations during the study period (Fig. 5). After glucose injection, blood glucose levels increased markedly at 15 min and then declined during the remaining period of study (Fig. 5) ($P < 0.001$ to $P < 0.01$).

Blood galactose was not detected in the fasted 5–7-day-old rats before galactose injection. Galactose blood levels were highest 15 min after injection and declined throughout the study period (Fig. 5). Blood glucose was unaffected after IP galactose injection.

Radioactivity in [^{3}H]glucose in blood was significantly greater than that in either [^{14}C]galactose or [^{14}C]glucose derived from galactose. The pattern of blood radiolabeled tracers was similar to that noted among the 6-h-old pups

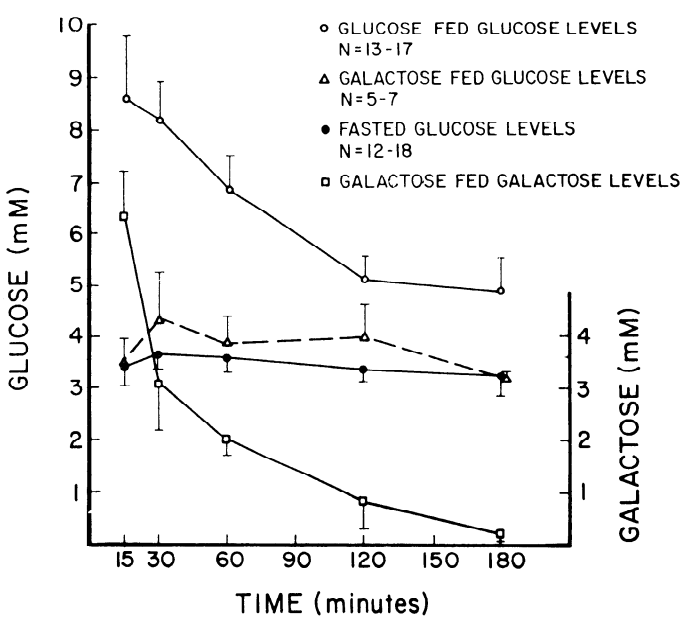

FIG. 5. Blood glucose and galactose in 5–7-day-old rat pups; ○, blood glucose after intraperitoneal (IP) glucose administration (*groups 2* and *4*); Δ, blood glucose after IP galactose administration (*group 5*); ○, fasting blood glucose levels (*group 1* and *3*); □, blood galactose after IP galactose administration (*group 5*).

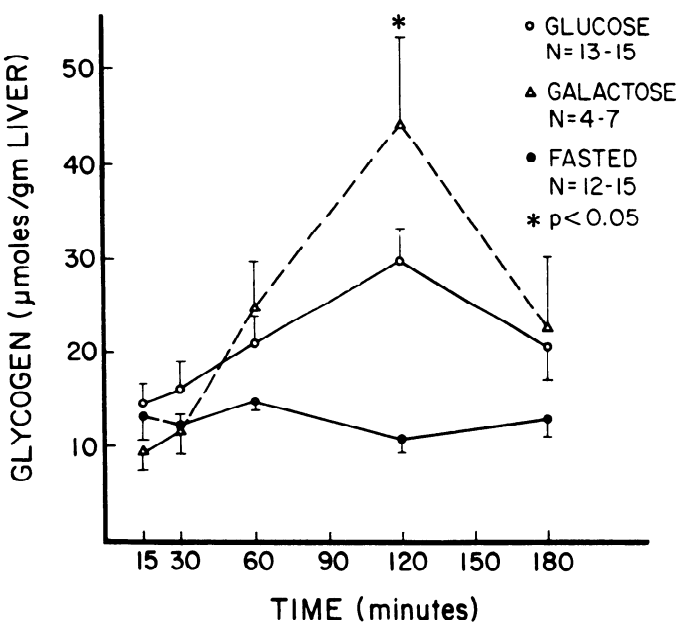

FIG. 6. Hepatic glycogen in 5–7-day-old pups; ○, glycogen after glucose administration (*groups 2* and *4*); ●, glycogen after galactose administration (*group 5*); Δ, fasted controls (*group 1* and *3*).

(Fig. 2 for 6-h-old pups). In more mature pups the amount of radioactivity in galactose was consistently <25% of that in [^{3}H]glucose. Furthermore, ^{14}C from galactose appeared rapidly in the circulating glucose pool, suggesting conversion of galactose to glucose within 15 min after [^{14}C]galactose injection. This observation was also noted in the 6-h-old pups.

Hepatic glycogen metabolism. Glycogen levels among the fasted more mature 5–7-day-old rats were in a steady state at basal levels (Fig. 6). Fasting hepatic glycogen content in these mature pups was very low compared with the glycogen level among immature pups in the first

6 h of life (10–15 vs. 160–220 μmol/g, $P < 0.001$). Glycogen content increased in glucose-injected pups after 60 min of IP injection and achieved maximum concentrations at 120 min, declining thereafter at 180 min to levels that were still greater than that in fasted controls (Fig. 6). In contrast, galactose-injected rats had a higher peak of hepatic glycogen content that was significantly greater than that after glucose administration at 120 min (Fig. 6).

The appearance of ^{14}C from galactose in hepatic glycogen in 5–7-day-old rats was significantly greater than that observed in the less mature 6-h-old pups ($P < 0.01$ to $P < 0.001$) (Figs. 3 and 7). There was a 10-fold difference between the two age groups. As noted in the younger pups the incorporation of ^{14}C from galactose into glycogen among older pups, was markedly increased compared with incorporation of ^{14}C and ^{3}H after injection with [^{14}C]glucose or [^{3}H]glucose in older pups (Fig. 7). At maximum points of incorporation among the older pups, there was a 30-fold difference between galactose- and glucose-injected pups. This also becomes remarkedly evident when the ratios of [^{3}H]glucose-[^{14}C]galactose and [^{3}H]glucose-[^{14}C]glucose are compared (Fig. 8). These ratios demonstrate that galactose incorporation into glycogen is the greatest of all tracers. Because these tracers were injected at a ratio of 1.0, the decreased ratio of the galactose-injected pups becomes even more striking.

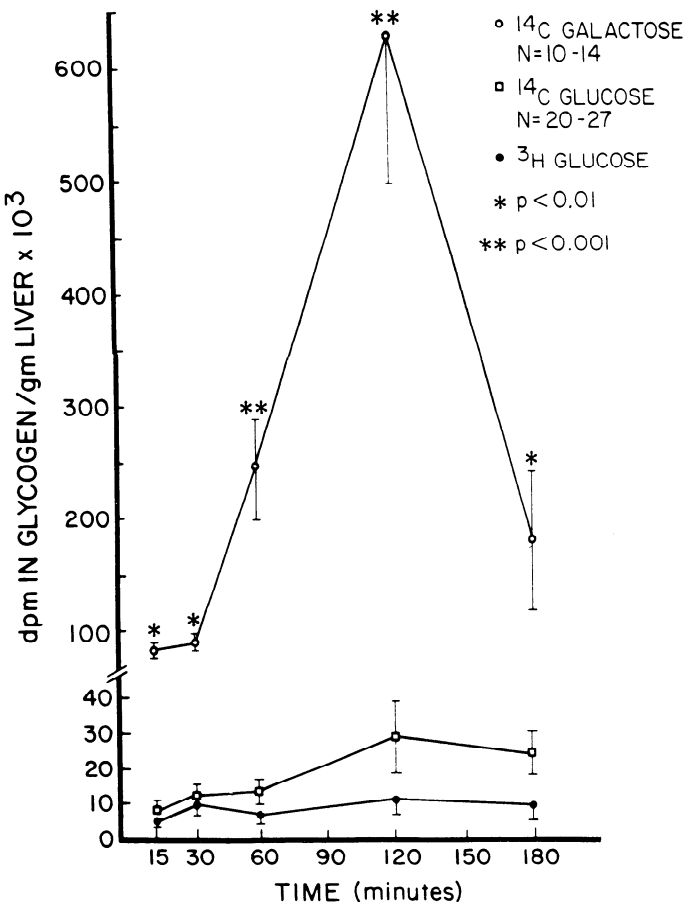

FIG. 7. Appearance of ^{3}H and ^{14}C in hepatic glycogen in 5–7-day-old rats; ●, ^{14}C after [^{14}C]galactose administration (*groups 3–5*); □, ^{14}C after [^{14}C]glucose administration (*groups 1* and *2*); ●, ^{3}H after [^{3}H]-glucose administration (*groups 1–5*); dpm, disintegrations per minute.

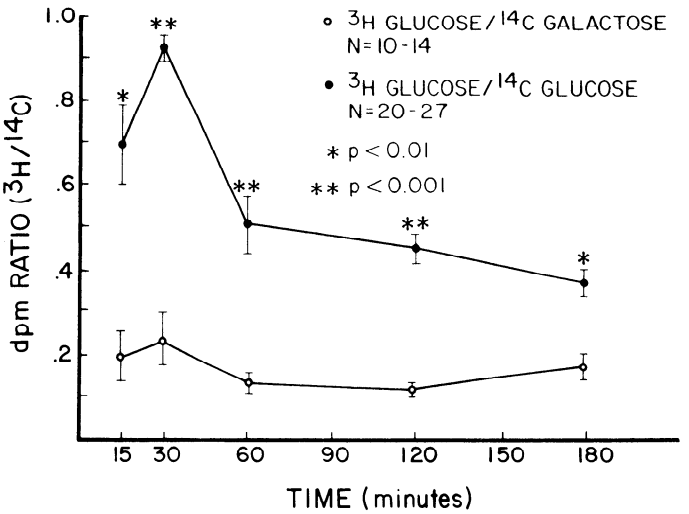

FIG. 8. Ratio of ^{3}H-^{14}C in hepatic glycogen of 5–7-day-old pups; ○, [^{3}H]glucose-[^{14}C]galactose (*groups 3–5*); ●, [^{3}H]glucose-[^{14}C]glucose (*groups 1* and *2*); dpm, disintegrations per minute.

DISCUSSION

Quantitatively galactose represents a significant proportion of nutrient intake for the newborn mammal (14). As a hexose its quantitative significance is equaled by glucose, yet there is a paucity of data about the role of galactose in newborn carbohydrate metabolism. Previous studies in the newborn human have demonstrated rapid clearance of injected galactose (5, 6). Indeed, galactose tolerance appeared superior to glucose tolerance in the immediate neonatal period of the human infant (6). Therefore it would appear that galactose alimentation may be especially beneficial as a source of carbohydrate for the neonate.

The utilization of glucose in the neonatal period appears to be attenuated as evident by a slow disappearance rate after glucose administration compared with that among older subjects (14). In addition newborn mammals often demonstrate hyperglycemia and reduced suppression of endogenous glucose production during a glucose infusion (2, 11, 18, 21). Furthermore, when directly compared, galactose as opposed to glucose has been more readily incorporated into hepatic glycogen in neonates (11, 13). In this latter study galactose resulted in a lower systemic glucose appearance rate than that after glucose administration. These data suggest that hepatic carbohydrate uptake was enhanced after galactose as opposed to glucose alimentation and that hepatic glycogen synthesis was one potential pathway for galactose utilization.

In both the adult and newborn mammal glucose may be a poor direct precursor of hepatic glycogen synthesis (8, 9, 11, 15–17). Indeed, many studies have suggested that glucose carbons enter the glycogen synthetic pathway only after being converted to lactate and pyruvate (8, 9, 16, 17). Subsequent recycling of these glucose-derived three-carbon precursors in the gluconeogenic pathway, provides the substrate for hepatic glycogen synthesis. This mechanism may be of use when plasma glucose concentrations exceed the liver's capacity to increase hepatic glucose uptake (16, 17). This problem is particularly of concern in the neonatal mammal, because

low hepatic glucokinase activity may limit hepatic glucose uptake (22).

In contrast to that for hepatic glucose uptake, neonatal tissue appears to be capable of significant galactose uptake. The activity of galactokinase exceeds that of hexokinase (or glucokinase) in most newborn mammalian liver tissue (3, 13). This would suggest that hepatic galactose uptake is not as limiting as hepatic glucose uptake in the newborn period. Furthermore, it has been speculated that hepatic tissue takes up a significant proportion of circulating galactose in a "first-pass" phenomenon (4, 7, 14). This may be very relevant to the observations of the current investigation.

The present investigation demonstrated that ^{14}C incorporation (derived from galactose) into glycogen greatly exceeded ^{14}C or ^{3}H incorporation from glucose. This pattern was associated with net glycogen synthesis in the older pups but was associated only with label appearing in glycogen in the less mature newborn pups. This latter event represents a dynamic state of glycogen synthesis and glycogenolysis during the immediate postnatal period that favors net glycogenolysis.

Incorporation of ^{3}H derived from glucose is only possible by the direct pathway via glucose → glucose 6-phosphate → UDP glucose → glycogen (14). ^{14}C from glucose may be incorporated directly into hepatic glycogen and also indirectly after conversion of [^{14}C]glucose to [^{14}C]lactate and subsequent recycling through hepatic gluconeogenesis. The ^{3}H on the six carbon of glucose is lost before gluconeogenesis and hence cannot be recycled to glycogen (10). Both pathways of glucose incorporation to glycogen are evident in the newborn period. Nonetheless, galactose incorporation exceeded that for both the glucose labels by a large order of magnitude. This large difference between [^{14}C]galactose and [^{14}C]glucose incorporation into glycogen cannot be explained by differences between an indirect or a direct pathway. ^{14}C from glucose and galactose should be handled the same way by the traditional direct pathway after glucose conversion to glucose 6-phosphate and galactose conversion to galactose 1-phosphate. Mixing of label between these two phosphorylated compounds is possible and is the usual response. It is clear that galactose carbon has entered the hepatic glucose 6-phosphate pool because blood glucose had been rapidly labeled with ^{14}C after [^{14}C]galactose administration.

The mechanism for enhanced galactose incorporation into glycogen remains to be determined. Galactose or its metabolites may activate the enzymes of glycogen synthesis, inhibit glycogenolysis, or inhibit galactose entry into the glycolytic pathway (e.g., by inhibition of phosphoglucomutase) (13, 19). These potential mechanisms have been demonstrated in vivo and in vitro in various investigations by means of substrate quantities of galactose (11, 13, 19). In the current study we employed subgroups of pups that received only tracer quantities of galactose or tracers combined with substrate quantities of galactose. The observations among tracer-injected pups suggest that the mechanism of enhanced ^{14}C incorporation into glycogen after galactose administration is not because of enzyme activation or enzyme inhibition as tracer quantities of galactose are incapable of altering enzyme activities.

Because of the observations with tracers alone, and the very rapid increase of label from galactose appearing in circulating glucose, with the markedly increased ^{14}C incorporated into glycogen from galactose we speculate that the first pass phenomenon is responsible for the preferential incorporation of galactose into hepatic glycogen (4, 7). This first pass phenomenon may relate to the increased activity of hepatic galactokinase compared with that for glucokinase or hexokinase (13). If a greater proportion of the injected hexose is taken up by the liver (galactose) then more will become available for hepatic glycogen synthesis. Glucose in contrast may be distributed throughout the systemic circulation to be utilized by muscle, brain, adipose tissue, and other glucose-requiring cells. After glycolysis in these varied tissues a certain proportion of glucose will be converted to lactate that then may return to the liver as a precursor for hepatic glycogen synthesis. The direct access of galactose (in larger quantities than glucose) to hepatic metabolic pathways during a first pass may explain its preferential position for neonatal hepatic glycogen synthesis. The observation that the circulating radioactivity in galactose was 10–20% of that for [^{3}H]glucose suggest that less galactose had entered the circulation and that more had been taken up by the liver (11).

In both age pups there was a reciprocal relationship between [^{14}C]galactose in blood and ^{14}C appearing in hepatic glycogen, relative to the results for [^{3}H]glucose. This would suggest a more rapid hepatic uptake of [^{14}C]-galactose, with more rapid disappearance of [^{14}C]galactose from the circulation. The immediate appearance of ^{14}C label from galactose in circulating glucose also suggests that hepatic galactose uptake is rapid and causes an accelerated clearance of galactose from the systemic circulation. The net effect of these results would be enhanced galactose incorporation into glycogen either as a futile cycle during periods of glycogenolysis (6-h-old pups) or during periods of net glycogen synthesis (fasted 5–7-day-old pup). In both states galactose contributes to both hepatic glycogen synthesis and to hepatic glucose production, without producing hyperglycemia.

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