# Splanchnic Galactose Extraction Is Regulated by Coingestion of Glucose in Humans

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**When compared with galactose alone, coingestion of glucose with galactose decreases plasma galactose. The objective of this study was to determine if this was due to increased peripheral clearance or increased first pass clearance of galactose. Five adult volunteers were studied on 2 occasions during infusion of [6,6-$^2H_2$]glucose and [1-$^{13}$C]galactose and ingestion of galactose alone at 11, 22, and 33 $\mu$mol · kg$^{-1}$ · min$^{-1}$ or galactose plus glucose at 11, 22, and 33 $\mu$mol · kg$^{-1}$ · min$^{-1}$ of each sugar. At 33 $\mu$mol · kg$^{-1}$ · min$^{-1}$ of galactose alone (1) plasma galactose increased to 2.3 ± 0.3 mmol/L and galactose rates of appearance (Ra) to 18.3 ± 1.6 $\mu$mol · kg$^{-1}$ · min$^{-1}$; (2) plasma glucose and glucose Ra were unaffected; (3) splanchnic extraction of galactose plateaued at approximately 15 $\mu$mol · kg$^{-1}$ · min$^{-1}$; and (4) galactose became the primary source of glucose Ra (75% ± 9%). Coingestion of glucose and galactose at 33 $\mu$mol · kg$^{-1}$ · min$^{-1}$ each resulted in (1) decreased plasma galactose (0.3 ± 0.1 mmol/L) and galactose Ra (6.4 ± 1.8 $\mu$mol · kg$^{-1}$ · min$^{-1}$); (2) increased plasma glucose and insulin; (3) doubling of splanchnic extraction of galactose; and (4) decreased contribution of galactose to glucose Ra (11% ± 4%). We conclude that coingestion of glucose with galactose increases the splanchnic extraction, but decreases the conversion of galactose to glucose.**



GALACTOSE IS A unique dietary sugar, which is found primarily as a constituent of the milk-derived disaccharide, lactose. However, small amounts of galactose are found in a variety of foods.[1] In infants, lactose provides approximately 40% of their total caloric intake, of which galactose alone represents half. Lactose is hydrolyzed in the brush border of the small intestine by lactase and the resultant monosaccharides, glucose and galactose, are transported into the portal circulation utilizing the Na-dependent glucose transporters.[2] It has long been assumed that galactose consumption is associated with first pass hepatic clearance, since systemic plasma galactose concentrations in the fed newborn and in adults following lactose consumption do not exceed 200 to 500 $\mu$mol/L, ie, less than 10% of glucose concentration (4 to 6 mmol/L).[3,4] In addition, intravenously administered labeled galactose has been used as a test of hepatic function in the past.[5-7]

Following oral galactose alone, plasma glucose concentrations increased modestly ($\approx$ 1.0 mmol/L), while the plasma galactose concentrations increased nearly 2 mmol/L.[8] When oral galactose was administered with oral or intravenous (IV) glucose, the glucose and insulin responses were significantly greater, but the increase in plasma galactose did not exceed 0.2 mmol/L, a 10-fold reduction.[8] The mechanism by which coingestion of glucose and galactose affects the plasma concentration of galactose remain to be determined. To our knowledge, nothing is known about the contribution of galactose to glucose production during ingestion of galactose or during coingestion of glucose with galactose. Therefore, the present studies were undertaken to determine (1) whether the splanchnic uptake of galactose is saturable; (2) if the coingestion of glucose with galactose increases the splanchnic uptake of galactose; and (3) whether the contribution of galactose to glucose production is dependent on the coingestion of glucose.

## MATERIALS AND METHODS

### *Tracers*

[1-$^{13}$C]galactose (99 atom% $^{13}$C) and [6,6-$^2H_2$]glucose (99 atom% $^2$H) were purchased from Cambridge Isotope Laboratory, Andover, MA.

### *Subjects*

Five healthy adult female volunteers between the ages of 18 and 35 years were recruited. All were free of any identified diseases as assessed by a medical history, physical examination, and normal screening laboratory studies, including a normal blood hemoglobin, plasma chemistries, and negative pregnancy test in all women with child bearing potential. The subjects were 26.8 ± 0.9 years of age, 166.4 ± 1.9 cm tall, 62.8 ± 4.5 kg in weight, and had a body mass index (BMI) of 22.6 ± 1.2 kg/m$^2$ (mean ± SE).

### *Study Design*

The protocol was approved by the Institutional Review Board for Human research at Baylor College of Medicine, Houston TX. Informed consent was obtained from each subject.

All subjects were instructed to consume a normal diet providing approximately 30 kcal/kg/d with a caloric distribution of approximately 50% carbohydrate, 15% protein, and 35% fat. The day prior to study, the subjects consumed a prescribed 8:00 PM snack at home and subsequently fasted (except for ad libitum water) until completion of the studies.

On the morning of the study, the subjects were admitted to the Metabolic Research Unit of the Children's Nutrition Research Center at 6:30 AM. Two IV catheters were placed in each antecubital fossa under Emla cream (Astra Pharmaceuticals, Wayne, PA) analgesia, 1 for isotope infusion and the other for blood sampling. Baseline blood (10 mL) was obtained (zero time) following which the subjects received a primed constant infusion of [6,6-$^2H_2$]glucose and [1-$^{13}$C] galactose (20 $\mu$mol/kg and 0.33 $\mu$mol · kg$^{-1}$ · min$^1$ of each tracer). Beginning at zero time, the subjects consumed a drink every 15 minutes composed of

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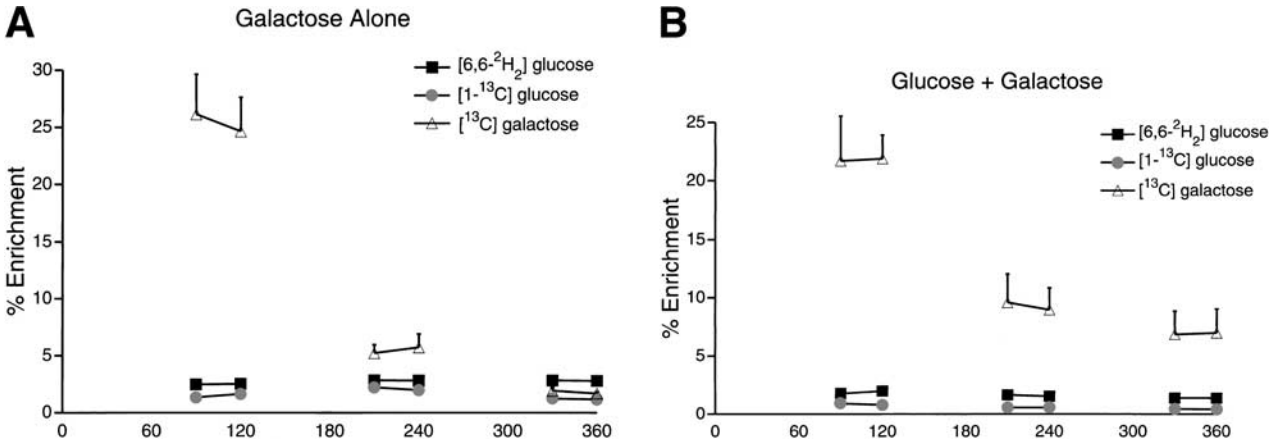


**Fig 1. Isotopic enrichments during the final 30 minutes of each 2-hour ingestion rate period, ie, 11, 22, and 33 $\mu$mol · kg$^{-1}$ · min$^{-1}$ of each sugar, respectively, during (A) ingestion of galactose alone and (B) coingestion of glucose with the galactose. Standard error bars that are not visible are imbedded in the figure.**

unlabeled galactose on 1 study day and on another, galactose plus glucose. No independent enteral galactose tracer was utilized since the endogenous production of galactose is essentially zero when compared with the ingested amount.[9] Therefore, we assume that any galactose appearing in the systemic circulation was derived from ingested galactose. On 1 study day, the subjects ingested both glucose and galactose at the rate of 11 $\mu$mol · kg · $^{-1}$min$^{-1}$ for each monosaccharide from 0 to 120 minutes, 22 $\mu$mol · kg$^{-1}$ · min$^{-1}$ from 120 to 240 minutes, and 33 $\mu$mol · kg$^{-1}$ · min$^{-1}$ from 240 to 360 minutes. This is equivalent to the consumption of approximately 1, 2, and 3 glasses (8 oz) of milk over each 2-hour period, respectively. On the other study day, the subjects were studied in an identical fashion except they received galactose alone at 11, 22, and 33 $\mu$mol · kg$^{-1}$ · min$^{-1}$. The order of the studies was randomized, and the studies were separated by at least 2 weeks. Blood samples (10 to 15 mL) were obtained at 0, 90, 120, 210, 240, 330, and 360 minutes. Blood samples were transferred to EDTA tubes, which were placed on ice and centrifuged at 4°C. The plasma was separated and stored at –70°C until assayed.

### *Analytical Methods*

Plasma was analyzed for glucose, galactose, and lactate using a YSI Analyzer (Yellow Springs Instruments, Yellow Springs, OH). In addition, plasma galactose was measured using an internal standard ([U-$^{13}$C]galactose) and a reverse isotope dilution methodology. Plasma insulin concentrations were determined using a commercially available radioimmunoassay kit (Linco, St Charles, MO). The enrichment of [6,6-$^{2}$H$_2$]glucose and [1-$^{13}$C]galactose were measured using the di-O-isopropylidene derivative and gas chromatography –mass spectrometry (GC/MS) using the EI mode and selected monitoring of the ions m/z 287, 288, 289, and 293.[10] Using this derivative, the glucose and galactose peaks are very well separated.[10] The $^{13}$C enrichment of glucose was determined by GC-combustion-isotope ratio mass spectrometry (IRMS) using the same derivative.

### *Calculations*

The rates of appearance (Ra) of glucose and galactose into the systemic circulation were calculated using near steady state enrichments of the [6,6-$^{2}$H$_2$]glucose and [$^{13}$C]galactose obtained during the final 30 minutes of each 2-hour period at the 3 ingestion rates (Fig 1A and B) and established isotope dilution equations:

$$\text{Ra} = [(E_i/E_p) - 1] \cdot I \ (\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1})$$

in which Ra is the rate of appearance, $E_i$ and $E_p$ are the enrichments of the isotope in the infusate and the plasma, respectively, and $I$ is the rate of infusion of [6,6-$^{2}$H$_2$]glucose and [1-$^{13}$C]galactose, respectively.[11]

The absolute splanchnic extraction ($\mu$mol · kg$^{-1}$ · min$^{-1}$) was calculated by subtracting galactose Ra from ingested galactose, and the fractional splanchnic extraction was calculated by dividing absolute splanchnic extraction by ingested galactose.

The fraction of total glucose Ra derived from galactose was calculated as follows:

$E_{[13C]glucose}/E_{[13C]galactose}$, in which $E_{[13C]glucose}$ is the plasma enrichment of $^{13}$C glucose derived from $^{13}$C galactose, and $E_{[13C]galactose}$ is the plasma $^{13}$C enrichment of galactose.

The flux of galactose to glucose ($\mu$mol · kg$^{-1}$ · min$^{-1}$) ($Ra_{Gal \rightarrow Gluc}$) was calculated using the equation:

$$Ra_{Gal \rightarrow Gluc} = (E_{[13C]glucose}/E_{[13C]galactose}) \times \text{Glucose Ra.}$$

Finally, the fraction of glucose production (GPR) derived from galactose was calculated as $Ra_{Gal \rightarrow Gluc}$/GPR. The fraction of GPR derived from galactose could only be calculated in the galactose alone experiment, because the ingested glucose was unlabeled precluding partitioning the systemic glucose Ra into that derived from the diet and that from GPR.

### *Statistics*

All data are expressed as mean ± SE. Comparisons between the studies were performed using a paired Student's *t* test with the level of significance being at the $P < .05$ level.

## RESULTS

### *Substrate and Hormone Concentrations*

*Plasma galactose concentration.* Ingestion of galactose alone at 11 $\mu$mol · kg$^{-1}$ · min$^{-1}$ did not result in any increase of the galactose concentration when compared with baseline values (0.03 ± 0.01 mmol/L), but when the ingestion rate of galactose alone was increased from 11 to 22 and then to 33 $\mu$mol · kg$^{-1}$ · min$^{-1}$, the plasma galactose concentration increased from 0.05 ± 0.02 to 0.45 ± 0.16 and then to 2.28 ± 0.28 mmol/L ($P < .01$). During the ingestion of glucose plus galactose at the corresponding rates for each sugar, the concentration of galactose increased only from 0.03 ± 0.01 to

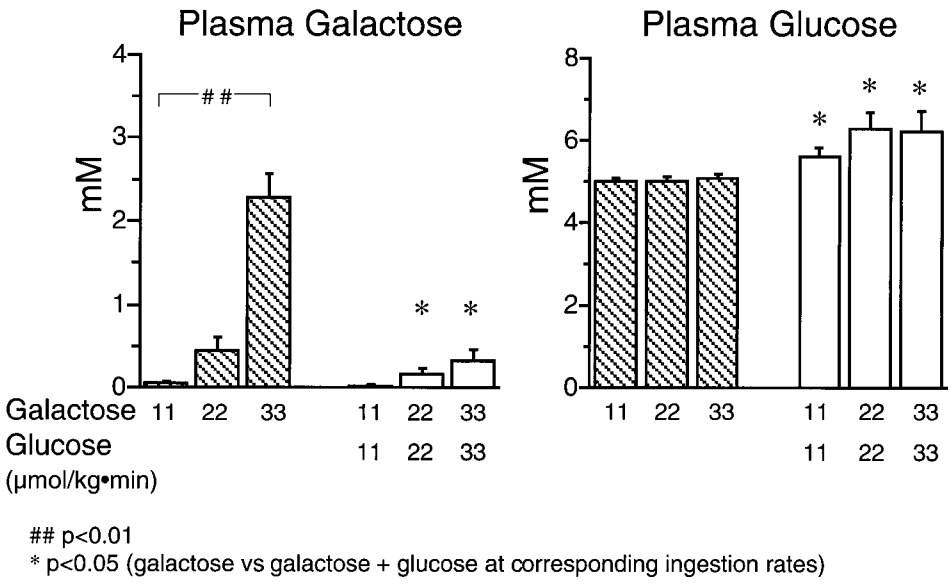


**Fig 2. The plasma glucose and galactose concentrations during ingestion of galactose alone and galactose plus glucose at rates of 11, 22, and 33 $\mu$mol · kg$^{-1}$ · min$^{-1}$ of each sugar over a 2-hour period at each rate. Data depicted as mean ± SE. Standard error bars that are not visible are imbedded in the figure.**

0.17 ± 0.07 and finally to 0.33 ± 0.13 mmol/L (not significant [NS]); values not different from that obtained at baseline (0.04 ± 0.01 mmol/L). Thus, when compared with ingestion of galactose alone, coingestion of glucose with galactose resulted in significantly lower plasma galactose concentrations ($P < .05$ at the 22 and $P < .01$ at 33 $\mu$mol · kg$^{-1}$ · min$^{-1}$) (Fig 2).

*Plasma glucose concentration.* When galactose was ingested alone at 11, 22, and 33 $\mu$mol · kg$^{-1}$ · min$^{-1}$, plasma glucose concentrations did not increase and were not changed from baseline (4.7 ± 0.1 (at baseline); 5.0 ± 0.1 (at 11 $\mu$mol · kg$^{-1}$ · min$^{-1}$ ), 5.0 ± 0.1 (at 22 $\mu$mol · kg$^{-1}$ · min$^{-1}$) and 5.1 ± 0.1 mmol/L (at 33 $\mu$mol · kg$^{-1}$ · min$^{-1}$) (NS). When compared with the concentrations obtained during ingestion of only galactose, coingestion of glucose with galactose resulted in higher plasma glucose concentrations at each ingestion rate, 5.0 ± 0.1 (galactose alone at 11 $\mu$mol · kg$^{-1}$ · min$^{-1}$) versus 5.6 ± 0.2 ($P < .05$) (at 11 $\mu$mol · kg$^{-1}$ · min$^{-1}$ of each of the sugars); 5.0 ± 0.1 versus 6.3 ± 0.4 mmol/L ($P < .05$) (at 22 $\mu$mol · kg$^{-1}$ · min$^{-1}$) and 5.1 ± 0.1 mmol/L versus 6.2 ± 0.5 mmol/L (at 33 $\mu$mol · kg$^{-1}$ · min$^{-1}$) ($P < .05$). No dose response was observed, ie, the plasma glucose concentration did not increase with the progressively greater ingestion rates of galactose + glucose (Fig 2).

*Plasma lactate concentrations.* When galactose was ingested alone, the lactate concentrations increased stepwise. Thus, during ingestion of galactose alone at 11 $\mu$mol · kg$^{-1}$ · min$^{-1}$, lactate concentration increased from 1.13 ± 0.07 mmol/L (baseline) to 1.35 ± 0.12 mmol/L ($P = .055$) to 1.67 ± 0.14 mmol/L at 22 $\mu$mol · kg$^{-1}$ · min$^{-1}$ ($P < .05$) and to 2.04 ± 0.09 mmol/L at 33 $\mu$mol · kg$^{-1}$ · min$^{-1}$ ($P < .05$). When galactose was coingested with glucose at 11 $\mu$mol · kg$^{-1}$ · min$^{-1}$ of each sugar, the lactate concentration increased ($P < .01$) from 0.93 ± 0.11 (baseline) to 1.64 ± 0.15 mmol/L, but there was no further increase at the higher ingestion rates of the 2 sugars (1.50 ± 0.10 and 1.48 ± 0.05 mmol/L, respectively). The lactate concentrations obtained during ingestion of galactose alone were higher than those obtained during coingestion of galactose with glucose only at the highest ingestion rate ($P < .01$).

*Plasma insulin concentrations.* During ingestion of galactose alone, insulin concentrations remained constant (6.9 ± 1.0, 7.4 ± 0.7, and 6.3 ± 0.9 $\mu$U/mL) (Fig 3). These values were slightly higher than the baseline concentration (3.7 ± 0.4 $\mu$U/mL) ($P = .07$; $P < .05$ and $P = .07$ at the 3 ingestion rates, respectively). During ingestion of both glucose and galactose at 11 $\mu$mol · kg$^{-1}$ · min$^{-1}$, the plasma insulin concentration was 14.3 ± 2.0 $\mu$U/mL, ie, higher ($P < .01$) than the baseline value (5.0 ± 0.6 $\mu$U/mL) and also higher ($P < .01$) when compared with galactose alone at all rates of infusion. The plasma insulin concentration increased ($P < .05$) to 20 ± 3 $\mu$U/mL during the ingestion of both glucose and galactose at 22 $\mu$mol · kg$^{-1}$ · min$^{-1}$ with no further increase (18.3 ± 1.3 $\mu$U/mL) at the

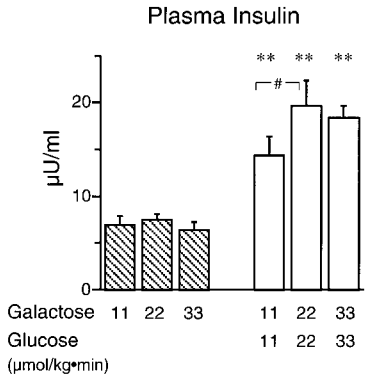


**Fig 3. The plasma insulin concentrations during ingestion of galactose alone and galactose plus glucose at rates of 11, 22, and 33 $\mu$mol · kg$^{-1}$ · min$^{-1}$ of each sugar over a 2-hour period at each rate. Data depicted as mean ± SE.**

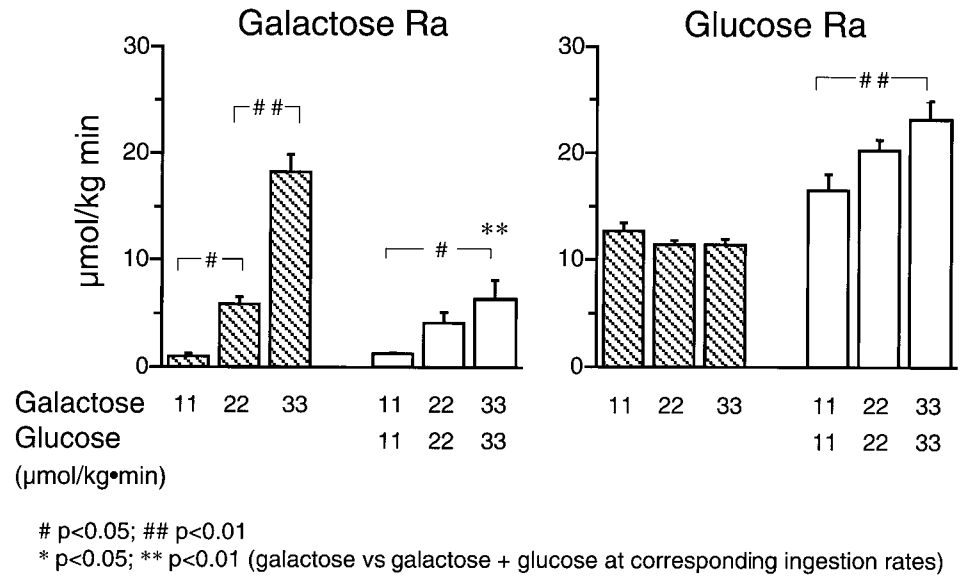


**Fig 4. The Ra of galactose and glucose into the systemic circulation during ingestion of galactose alone and galactose plus glucose at rates of 11, 22, and 33 $\mu$mol · kg$^{-1}$ · min$^{-1}$ of each sugar over a 2-hour period at each rate. Data depicted as mean ± SE.**

ingestion rate of 33 $\mu$mol · kg$^{-1}$ · min$^{-1}$ of each monosaccharide (Fig 3).

*Plasma Appearance Rates of Galactose and Glucose*

The Ra of galactose into the systemic circulation increased ($P < .01$) from 1.0 ± 0.2 to 18.3 ± 1.6 $\mu$mol · kg$^{-1}$ · min$^{-1}$ in response to the increase in the ingestion rate of galactose alone from 11 to 33 $\mu$mol · kg$^{-1}$ · min$^{-1}$) (Fig 4). In contrast, during coingestion of glucose with the galactose, the corresponding increase in Ra of galactose into the systemic circulation was only from 1.3 ± 0.1 to 6.4 ± 1.8 $\mu$mol · kg$^{-1}$ · min$^{-1}$ ($P < .05$). The latter value was lower ($P < .01$) than that measured during the highest rate of ingestion of galactose alone (Fig 4).

The Ra of glucose remained constant during ingestion of galactose alone (≈ 12 $\mu$mol · kg$^{-1}$ · min$^{-1}$) (Fig 4). During the combined ingestion of glucose and galactose at 11 $\mu$mol · kg$^{-1}$ · min$^{-1}$, glucose Ra increased ($P < .05$) to 16.5 ± 1.5 $\mu$mol · kg$^{-1}$ · min$^{-1}$. Glucose Ra increased further ($P < .01$) to 20.2 ± 1.1 and 23.4 ± 1.5 $\mu$mol · kg$^{-1}$ · min$^{-1}$ during the higher rates of ingestion of both sugars (Fig 4). Thus, at all 3 ingestion rates, glucose Ra was significantly higher during coingestion of glucose with the galactose when compared with ingestion of galactose alone (Fig 4).

*Splanchnic Extraction of Galactose*

During ingestion of galactose alone, the splanchnic extraction of galactose increased ($P < .05$) from 10.0 ± 0.2 to 14.8 ± 1.6 $\mu$mol · kg$^{-1}$ · min$^{-1}$ and the fractional extraction decreased from 91% ± 2% to 45% ± 5% ($P < .01$) over the 3 doses used (Fig 5). In contrast, the rate of splanchnic extraction of galactose during ingestion of galactose plus glucose increased ($P < .01$) from 9.8 ± 0.1 to 26.6 ± 1.8 $\mu$mol · kg$^{-1}$ · min$^{-1}$, and the fractional extraction decreased only slightly from 89% ± 1% to 81% ± 6% (NS), the latter rate and percentage being greater ($P < .01$) than those observed with galactose alone (Fig 5).

*Contribution From Galactose to Glucose Ra*

The contribution from galactose to glucose was calculated from the enrichments of [$^{13}$C]glucose (derived from [$^{13}$C]galactose) obtained during the final 30 minutes of each ingestion rate period (Fig 1A and B). The estimated rate of glucose derived from galactose increased ($P < .01$) from 0.8 ± 0.1 to 8.3 ± 0.9 $\mu$mol · kg$^{-1}$ · min$^{-1}$ between the 11 and 33 $\mu$mol · kg$^{-1}$ · min$^{-1}$ rates of ingestion of galactose alone, which corresponds to an increase in the contribution of galactose to glucose Ra from 6% ± 1% to 75% ± 9% ($P < .01$) (Fig 6). The rate of glucose derived from galactose during combined sugar ingestion increased from 0.7 ± 0.2 to only 2.5 ± 0.8 $\mu$mol · kg$^{-1}$ · min$^{-1}$ or from 4% ± 1% to 11% ± 4% of glucose Ra ($P < .01$ cf galactose alone) (Fig 6). Since no tracer of glucose was included within the orally ingested glucose, we are unable to partition the fraction of circulating glucose derived from the meal versus endogenous glucose production.

## DISCUSSION

The present studies demonstrate that the splanchnic uptake of galactose when ingested as a monosaccharide is saturable at about 15 $\mu$mol · kg$^{-1}$ · min$^{-1}$, and glucose production is derived almost exclusively from the conversion of galactose to glucose under these conditions. This presumably occurs as a result of the direct uptake of galactose by the liver on a first pass basis and the conversion of galactose to glucose via galactose-1-phosphate, uridine-5′-diphosphogalactose (UDP galactose), uridine-5′-diphosphoglucose (UDP glucose), glucose-1-phosphate, and glucose-6-phosphate.[12]

Although Williams et al[8] demonstrated that coingestion of glucose with galactose (in the form of lactose) resulted in lower plasma concentrations of galactose, they could not determine whether the lower concentration was the result of increased galactose clearance from the systemic circulation or a decreased entry of galactose into the systemic circulation. Our

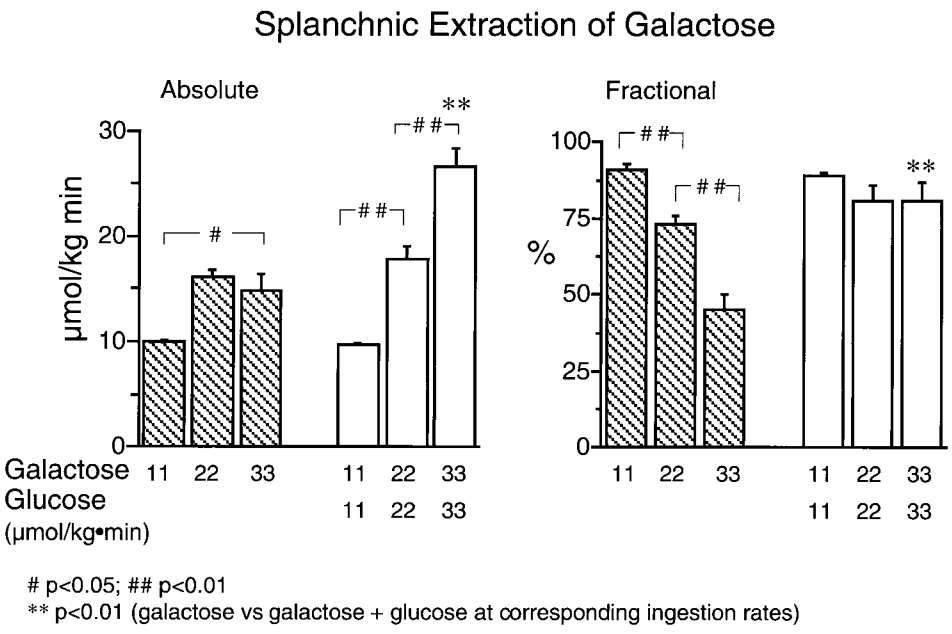


**Fig 5. The absolute rate of splanchnic extraction and the fractional extraction of galactose during ingestion of galactose alone and galactose plus glucose at rates of 11, 22, and 33 $\mu$mol · kg$^{-1}$ · min$^{-1}$ of each sugar over a 2-hour period at each rate. Data depicted as mean ± SE.**

study demonstrates that coingestion of glucose more than doubled the first pass splanchnic clearance of the ingested galactose in humans. However, the present study was not designed to determine whether the increased extraction of galactose was the result of the glucose alone or the effect of increased portal insulin on the uptake of glucose and/or galactose or a result of intrahepatic metabolic events, increasing the transport of these sugars. We would favor the latter explanation, since the plasma insulin concentrations plateaued at approximately 19 $\mu$U/mL during both the 22 and 33 $\mu$mol · kg$^{-1}$ · min$^{-1}$ rates of combined ingestion of glucose and galactose and, yet the rate of extraction of galactose continued to increase. Further experimental studies will be required to obtain definitive evidence.

During combined ingestion of galactose and glucose, the rate of conversion of galactose to glucose was dramatically reduced when compared with that obtained during the ingestion of galactose alone. This, in part, could be due to portal hyperinsulinemia, which occurred only during the coingestion with glucose, reducing hepatic glucose production and, thus, the fraction of galactose converted to glucose. The calculated conversion of galactose to glucose was based on the peripheral galactose enrichment, not that at the porta hepatis. Since only part of the ingested galactose ap-

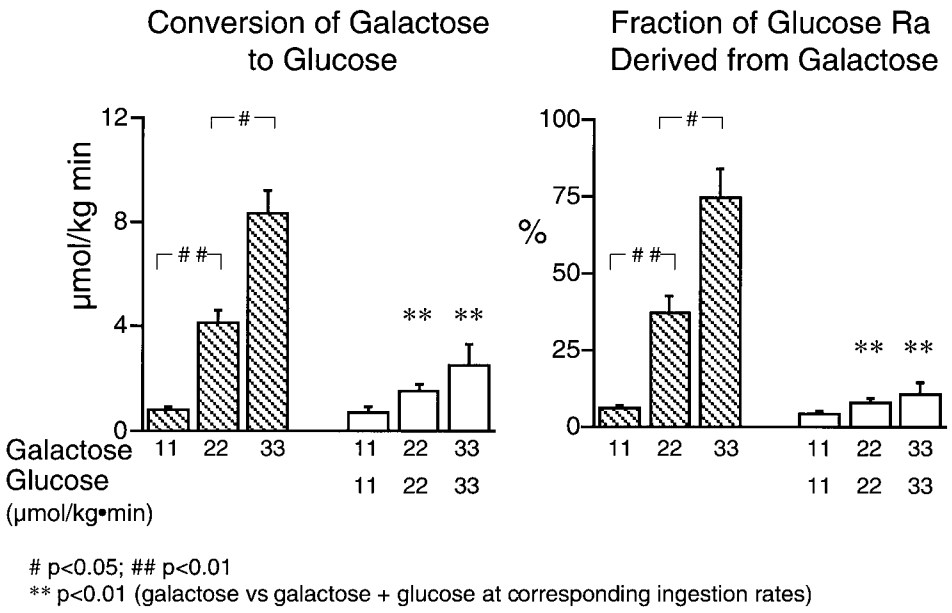


**Fig 6. The rate of conversion of galactose to glucose and the percent of glucose Ra derived from galactose during ingestion of galactose alone and galactose plus glucose at rates of 11, 22, and 33 $\mu$mol · kg$^{-1}$ · min$^{-1}$ of each sugar over a 2-hour period at each rate. Data depicted as mean ± SE.**

peared in the systemic circulation, the enrichment of the tracer, which was infused systemically, must have been lower in the portal circulation than in the peripheral vein as a result of dilution of the celiac arterial enrichment by unlabeled substrate entering the portal vein. Thus, our measurements represent minimal estimates for conversion of galactose to glucose.

In summary, our results demonstrate that during ingestion of galactose alone, splanchnic extraction of galactose is saturable at about 15 $\mu$mol · kg$^{-1}$ · min$^{-1}$, and that galactose becomes the major source of glucose production. In contrast, during coingestion of equal amounts of glucose and galactose, splanchnic extraction of galactose increases resulting in lower plasma concentration and appearance rate of galactose and reduced contribution from galactose to glucose despite the higher rate of splanchnic extraction of galactose.

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