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**METABOLISM OF EXOGENOUS
 $1-^{14}\text{C}$ -L-FUCOSE IN THE SHAM AND GAMMA
IRRADIATED RAT**

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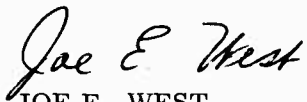
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ABSTRACT

This study was performed to obtain information on the degradative pathway of exogenously administered 1-¹⁴C-L-fucose in the rat. Previous studies suggest that the catabolism of L-fucose in the mammal proceeds by the following pathway:

L-fucose → L-fucono-1, 5-lactone → L-fuconate → 2-keto-3-deoxy-L-fuconate (KDF).

The fate of KDF, however, has not been elucidated. Evidence obtained in this study suggests that KDF is oxidized to α-ketoglutarate with subsequent production of CO₂. Under experimentally induced gluconeogenic and glycogenic states, ¹⁴CO₂ from 1-¹⁴C-L-fucose is utilized for the formation of blood glucose and hepatic glycogen to a limited extent. Although the hepatic activity of L-fucose dehydrogenase influences the amount of ¹⁴CO₂ incorporated into glucosyl residues of hepatic glycogen it does not appear to be a significant factor involved in the shunting of L-fucose through this pathway. Examination of the available data indicates that the primary pathway for L-fucose metabolism in the rat proceeds via phosphorylation and formation of GDP-fucose with subsequent incorporation into glycoproteins. It is suggested that the enzymic phosphorylation of L-fucose is the primary determinative influencing metabolism of exogenous L-fucose in the rat.

I. INTRODUCTION

The methylpentose L-fucose (6-deoxy-L-galactose) is one of several sugar constituents of various glycoproteins and mucopolysaccharides.⁶ Serum levels of protein-bound L-fucose have been reported to increase in human diabetes¹² and cancer¹⁶ but remain relatively unchanged in animals exposed to lethal doses of ionizing radiation when compared to increases in levels of other protein-bound carbohydrates.⁴ The pathophysiologic significance of these findings is not clear at the present time. Knowledge concerning the metabolism of this methylpentose in normal and disease states, however, assumes a new importance in obtaining an explanation of disease-induced alterations in serum fucose levels.

Although the catabolism of L-fucose has been extensively studied in bacteria^{5,7} only a small amount of information is available pertaining to its catabolism in mammals. It appears that ¹⁴C-labelled exogenous L-fucose in the rodent is either incorporated into macromolecules or excreted in the urine, with less than 2 percent oxidized to ¹⁴CO₂ in 6 hours.¹ This latter finding markedly contrasts with the 39 percent oxidation reported for man in the same time interval.¹⁹

In mammals the degradation of L-fucose, as far as is known, proceeds as follows:²⁴
L-fucose → L-fucono-1, 5-lactone → L-fuconate → 2-keto-3-deoxy-L-fuconate (KDF).
Enzymes involved in the degradation of L-fucose to KDF have been identified in the mammalian liver,²⁴ however, the fate of KDF is unknown.

The purpose of this report is to present evidence for the existence of a pathway in the rat through which L-fucose is metabolized to α-ketoglutarate. Further oxidation of α-ketoglutarate yields CO₂ which, under certain experimental conditions, is utilized

for the production of blood glucose and hepatic glycogen. This study indicates that the activity of hepatic L-fucose dehydrogenase (L-fucose: NADP oxidoreductase), the enzyme catalyzing the initial step in the degradation of L-fucose to L-fucono-1, 5-lactone,¹⁸ is not a significant rate-limiting factor for the operation of this pathway.

A previous study² failed to detect any incorporation of labelled carbon atoms of 1-¹⁴C-L-fucose into glucosyl residues of rat hepatic glycogen. To demonstrate that incorporation occurs, we employed ionizing radiation and starvation to enhance hepatic gluconeogenesis and glycogenesis²¹ together with a schedule of 1-¹⁴C-L-fucose administration designed to "trap" ¹⁴C-labelled glucosyl residues within the core of the glycogen molecules. Sham irradiation was used to assess the effect of a lethal exposure to ionizing radiation on L-fucose metabolism during the early postirradiation period.

II. MATERIALS AND METHODS

Twenty-four male Sprague-Dawley rats with a mean weight of 271 ± 13 g (S.D.) were used in this study. Animals were housed individually and maintained on a diet of standard laboratory chow for a period of 2 weeks prior to use.

Twelve animals were selected at random for exposure to ⁶⁰Co gamma radiation (single whole-body exposure to a midline tissue dose of 850 rads at 20 rads/minute). Twelve control animals were sham irradiated. Food but not water was withheld during the 24-hour period before and after irradiation procedures.

Each animal received an initial 0.3 ml-intraperitoneal injection of a normal saline solution containing 12.6 μ Ci/ml 1-¹⁴C-L-fucose (New England Nuclear Corporation, Boston, Massachusetts, specific activity of 4.7 mCi/mmole) immediately after

irradiation. A second similar injection was administered 6 hours after irradiation.

Purity of the ^{14}C -labelled fucose was checked by borate ion-exchange chromatography.⁸

Animals were sacrificed by decapitation 24 hours after irradiation. Blood was collected from the neck vessels, and the liver was immediately extirpated, freed of adhering nonhepatic tissue, weighed, and minced into hot 30 percent KOH for the isolation and purification of glycogen by a method previously described.²¹ Blood serum was obtained by centrifugation of clotted blood and treated as described below.

Serum trichloroacetic acid (TCA)-soluble and TCA-insoluble fractions were prepared according to the method of Bekesi and Winzler.¹ Radioactivity of the TCA-soluble fraction was determined by assaying 1.0-ml aliquots dissolved in 10.0 ml of scintillation medium described by Davila et al.³ The TCA-insoluble fraction was dissolved by the addition of 1.0 ml 1 N NaOH. Radioactivity determinations of these fractions were performed by assaying 0.3-ml aliquots of the solubilized material in 10.0 ml of scintillation medium³ to which 1.0 ml of methanolic 1 M Hyamine hydroxide (New England Nuclear Corporation, Boston, Massachusetts) was added.

Radioactivity of sugars present in the serum of gamma and sham irradiated animals was determined on pooled sera of four animals in each group. An ethanolic extract¹⁵ was prepared for each serum pool and subjected to borate ion-exchange column chromatography.⁸ One-ml aliquots of the column eluate were assayed for radioactivity as described above for the TCA-soluble fractions. Identification of sugars was performed by comparing column elution positions with those of authentic sugar standards. Glucose in the column eluate and serum was assayed by a method employing glucose oxidase.²²

Purified hepatic glycogen obtained by the method described above was hydrolyzed with 2.0 ml of 2 N H_2SO_4 for 3 hours at 100°C . The acid hydrolysate was subsequently neutralized with 0.3 N $\text{Ba}(\text{OH})_2$. Glucose, the product of glycogen hydrolysis, was assayed according to the method described above. Specific activity of the glucose of glycogen was determined by two methods as follows: isolation as glucose pentaacetate¹⁰ and isolation by borate ion-exchange chromatography.⁸

Activity of hepatic L-fucose dehydrogenase was determined by the method described by Mobley et al.¹⁴ Protein content of each liver homogenate was measured by the biuret method.⁹

All radioactivity measurements were performed by liquid scintillation spectrometry with a Mark II system, Model 6844 (Nuclear-Chicago Corporation, Chicago, Illinois). Sample to channels ratio method was used to correct for quenching.

Glucose of glycogen specific activity values were reduced to a "standard" body weight of 100 g and a "standard" injected dose of ^{14}C of 3 μCi by a method similar to that previously described.²¹

The t-test for unpaired observations was used to determine statistical significance. Differences for which the probability of coincidental occurrence was less than 5 percent were considered significant.

III. RESULTS

The data presented in Table I indicate that, under the experimental conditions employed in this study, exogenously administered L-fucose is primarily incorporated into the TCA-insoluble fraction of serum. Approximately 2 percent of the total serum radioactivity is present in the TCA-soluble fraction. No significant differences were

observed in either TCA-soluble or TCA-insoluble fractions when gamma irradiated and sham irradiated animals were compared. The activity associated with the TCA-insoluble fraction is presumably associated with proteins.

Table I. Trichloroacetic Acid-Soluble and Trichloroacetic Acid-Insoluble Radioactivity in Serum after Administration of 1- ^{14}C -L-fucose

Treatment*	Serum radioactivity	
	Soluble†	Insoluble†
Sham irradiation (6)	1222 $\pm$ 144	48,417 $\pm$ 12,351
850 rads (6)	1352 $\pm$ 193	60,220 $\pm$ 17,051

* Number of animals is shown in parentheses

† Results expressed as dpm/ml, mean $\pm$ S.D.

To determine the nature of the radioactivity associated with the serum TCA-soluble fraction, an alcoholic extract of serum was prepared and subjected to borate ion-exchange chromatography. Only two radioactive components were resolved. One component was eluted from the chromatographic column in the same fraction as an authentic standard of L-fucose, the other component appeared in the D-glucose fraction. The latter fraction was isolated, assayed for glucose content with glucose oxidase, and finally assayed for radioactivity. Serum glucose concentration and specific activity are shown in Table II. Approximately 20 percent of the TCA-soluble radioactivity can be accounted for as ^{14}C -glucose in sham and gamma irradiated animals. The remaining 80 percent is presumably due to ^{14}C -fucose. Table II also contains data on the concentration and radioactivity of hepatic glucose of glycogen. No significant difference exists between sham and gamma irradiated animals when specific activity or total radioactivity

of the glucose of glycogen is compared. There is, however, a significant difference in the concentrations of hepatic glycogen and serum glucose when these animals are compared. Postirradiation hyperglycemia and hepatic glycogen accumulation are well documented.²¹ Since the increase in hepatic glycogen observed in animals exposed to ionizing radiation occurs in terms of concentration and total amount,²¹ we have arbitrarily expressed the amount of ^{14}C incorporated into hepatic glycogen as total radioactivity/liver as shown in Table II. There is an increase, although not significant because of the rather large standard deviation, in the total amount of ^{14}C incorporated into hepatic glycogen of gamma irradiated animals when the mean value is compared to that obtained for sham irradiated controls.

Results obtained from experiments performed to measure the activity of hepatic L-fucose dehydrogenase are shown in Table III. A significant difference exists between enzymic activities, expressed on a mg protein basis, when values for sham and gamma irradiated rats are compared. There is, however, no significant difference when values obtained for total enzymic activity/liver are compared. We have included in Table III values found for hepatic protein content and liver wet weight to illustrate that a significant enhancement of enzymic activity, on a mg protein basis, in livers of gamma irradiated rats may be attributed to a significant decrease in protein content of the supernatant used for assaying FDH activity.¹⁴ The significant increase in liver wet weight induced by exposure of the animals to ionizing radiation²¹ affects the observation that there is no significant difference in total enzymic activity/liver when values obtained for these animals are compared.

Table II. Serum Glucose and Hepatic Glucose of Glycogen Concentrations and Radioactivities of Glucose Residues

Treatment*	Serum glucose		Hepatic glycogen		
	Concentration [†]	Specific activity [‡]	Concentration [§]	Specific activity ^{**}	Total activity ^{††}
Sham irradiation (6)	93.5 ± 7.5	257	11.8 ± 2.7	63 ± 33	5,820 ± 1117
850 rads (6)	127.7 ± 11.9 ^{‡‡}	204	17.8 ± 4.1 ^{‡‡}	67 ± 50	10,715 ± 7245

* Number of animals is shown in parentheses

[†] Concentration expressed as mg/dl, mean ± S.D.

[‡] Specific activity expressed as dpm/mg, mean of pooled serum of four animals

[§] Concentration expressed as mg glucose/g liver wet weight, mean ± S.D.

^{**} Specific activity expressed as dpm/mg, mean ± S.D.

^{††} Total radioactivity expressed as dpm/liver, mean ± S.D.

^{‡‡} Significant, P < 0.05, one-tailed test

Table III. Liver Weight, L-Fucose Dehydrogenase (FDH) Activity and Protein Content in Gamma and Sham Irradiated Rats

Treatment*	Liver wet weight [†]		FDH activity ^{‡‡}		Protein content [§]
	g	Percent of body weight	Units/mg protein	Total units/liver	
Sham irradiation (6)	5.43 ± 0.50	3.70 ± 0.10	0.013 ± 0.001	7.46 ± 1.64	105.0 ± 16.7
850 rads (6)	6.58 ± 0.12 ^{**}	4.35 ± 0.10 ^{**}	0.017 ± 0.003 ^{**}	8.36 ± 2.27	75.6 ± 10.8 ^{**}

* Number of animals is shown in parentheses

[†] All values are expressed as the mean ± S.D.

[‡] Units employed are μ moles NADPH formed/minute

[§] Protein content refers to protein present in the supernatant of liver homogenates prepared according to method of Mobley et al.¹⁴ and is expressed as mg/g liver wet weight, mean ± S.D.

^{**} Significant, P < 0.05, one-tailed test

IV. DISCUSSION

Data presented in this study clearly demonstrate that the metabolic machinery exists in the liver of a mammal to synthesize ¹⁴C-D-glucose from 1-¹⁴C-L-fucose with subsequent incorporation of ¹⁴C-labelled glucosyl residues into hepatic glycogen and blood glucose under certain experimental conditions. These experimental

conditions, starvation and starvation plus irradiation, are known to enhance hepatic gluconeogenesis and de novo glycogenesis.²¹

Since it is known that the glucosyl residues in the outer tiers and peripheral branches of the hepatic glycogen molecule are more metabolically active than glucosyl residues of the inner core of this polysaccharide,²³ we selected a schedule of multiple administration of 1-¹⁴C-L-fucose which would provide ¹⁴C-glucosyl residues for incorporation throughout the glycogen molecule during postirradiation glycogenesis and thereby effectively "trap" these residues within the core of the molecule. This approach is important because postmortem glycogenolysis could reduce the number of ¹⁴C-labelled residues in the peripheral chains if time between administration of ¹⁴C-fucose and isolation of glycogen was not sufficient to allow labelling of core residues.

We believe that several considerations contributed to the failure of Coffey et al.² to isolate ¹⁴C-labelled glycogen from livers of fasted rats after administration of 1-¹⁴C-L-fucose. One of which is that only a 3-hour interval elapsed between the time of ¹⁴C-fucose administration and glycogen isolation. More important, however, is their administration of unlabelled L-fucose (200 mg) together with labelled material (1 μ Ci), a procedure which would considerably dilute L-fucose specific activity and therefore glycogen specific activity to below detection levels since results obtained in this study indicate that only 0.04 percent of the administered activity was incorporated into hepatic glycogen in sham irradiated animals.

The observation that ¹⁴C-labelled L-fucose is incorporated into serum glycoproteins to the same extent in sham and gamma irradiated rats during the early

postirradiation period is consistent with the results reported by Evans et al.⁴ for protein-bound fucose levels in serum.

It is evident from results obtained for the incorporation of ^{14}C from 1- ^{14}C -L-fucose into serum glycoproteins and hepatic glycogen that much more ^{14}C activity appears in the former. It appears that this pathway for glycoprotein incorporation is the predominant route for the metabolism of exogenous L-fucose in the rat. Bekesi and Winzler¹ suggest that exogenous fucose utilization for protein incorporation proceeds in the following manner: L-fucose $\rightarrow$ L-fucose-1-phosphate $\rightarrow$ GDP-L-fucose.

An additional pathway for exogenous L-fucose utilization has recently been proposed by Yuen and Schachter²⁴ for the mammal as follows: L-fucose $\rightarrow$ L-fucono-1,5-lactone $\rightarrow$ L-fuconate $\rightarrow$ 2-keto-3-deoxy-L-fuconate (KDF). The fate of KDF, however, is unknown. The enzyme initiating this series of reactions has been identified as L-fucose dehydrogenase and is present in pig¹⁸ and rat^{14,21} liver. Other enzymes involved in this pathway although present in pig liver²⁴ have not been investigated in rat liver.

Assuming KDF is an intermediate in fucose degradation in the rat, our results support the hypothesis that KDF is a precursor of α -ketoglutarate for the following reasons. Yuen and Schachter²⁴ postulated that KDF can be either cleaved by an aldolase with the production of pyruvate or oxidized to α -ketoglutarate. In our experiments, 1- ^{14}C -L-fucose could be expected to yield 1- ^{14}C -pyruvate or 1- ^{14}C - α -ketoglutarate. Both compounds upon oxidation would yield $^{14}\text{CO}_2$ available for incorporation into glucose and hepatic glycogen. In addition, 1- ^{14}C -pyruvate could be directly converted to glucose. However, Rust et al.¹⁷ reported that the ^{14}C -pyruvate from 2- ^{14}C -alanine

is readily incorporated into hepatic glycogen in the x irradiated rat whereas the incorporation of $^{14}\text{CO}_2$ from $\text{NaH}^{14}\text{CO}_2$ into glycogen proceeds to a limited extent, i.e., less than 1 percent of the tracer dose. Since the amount of ^{14}C -labelling of glycogen found in our experiments is of a similar order of magnitude as that observed by Rust et al.¹⁷ for $^{14}\text{CO}_2$, it is not unreasonable to suggest that α -ketoglutarate is an intermediate degradation product of exogenous L-fucose in the rat and that the source of ^{14}C in blood glucose and hepatic glycogen is $^{14}\text{CO}_2$, the product of ^{14}C - α -ketoglutarate oxidation rather than ^{14}C -pyruvate oxidation.

Shull and Miller²⁰ have demonstrated that L-fucose is not glycogenic in fasted mice; however, potential products of L-fucose degradation are glycogenic in fasted mice and rats.¹³ These results suggest that the enzyme initiating L-fucose degradation may be a rate-limiting step for the conversion of carbon atoms of L-fucose to those of D-glucose. Mobley et al.¹⁴ have recently reported that FDH activity is increased in the liver of the fasted and diabetic rat. Although we did not measure enzyme activity in livers of fed rats, our results for fasted rats confirm the results of Mobley et al.¹⁴ if we compare our fasted enzyme activities with those obtained by Metzger and Wick¹³ for the fed animal. There is, however, no significant difference in total enzyme activity per liver. In fact, the amount of total activity as measured in vitro is of such a magnitude that the role of FDH activity as a rate-limiting step is untenable. It is realized that we cannot assume, as pointed out by Kim and Miller,¹¹ that in vitro enzymic activity values correspond to the in vivo system. Nevertheless, we did observe an enhanced ^{14}C -incorporation into hepatic glycogen in livers of gamma irradiated animals which had increased activities of FDH.

It appears more logical to suggest that the utilization of exogenous L-fucose in the rat is determined by the phosphorylating enzyme catalyzing the formation of L-fucose-1-phosphate. It remains to be experimentally demonstrated that the relative affinity (K_M) and/or activity of the phosphorylating enzyme for the substrate L-fucose is greater than that of FDH.

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13. ABSTRACT

This study was performed to obtain information on the degradative pathway of exogenously administered 1-¹⁴C-L-fucose in the rat. Previous studies suggest that the catabolism of L-fucose in the mammal proceeds by the following pathway: L-fucose → L-fucono-1, 5-lactone → L-fuconate → 2-keto-3-deoxy-L-fuconate (KDF). The fate of KDF, however, has not been elucidated. Evidence obtained in this study suggests that KDF is oxidized to α-ketoglutarate with subsequent production of CO₂. Under experimentally induced gluconeogenic and glycogenic states, ¹⁴CO₂ from 1-¹⁴C-L-fucose is utilized for the formation of blood glucose and hepatic glycogen to a limited extent. Although the hepatic activity of L-fucose dehydrogenase influences the amount of ¹⁴CO₂ incorporated into glucosyl residues of hepatic glycogen it does not appear to be a significant factor involved in the shunting of L-fucose through this pathway. Examination of the available data indicates that the primary pathway for L-fucose metabolism in the rat proceeds via phosphorylation and formation of GDP-fucose with subsequent incorporation into glycoproteins. It is suggested that the enzymic phosphorylation of L-fucose is the primary determinative influencing metabolism of exogenous L-fucose in the rat.