Naturally Labeled ^{13}C-Glucose: A New Tool to Measure Oxidation Rates of Exogenous Glucose

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Stable isotopes are increasingly used for clinical investigations.[1,2] Lacking any radiation hazards, they offer major advantages against radioactive isotopes as far as tracer studies are concerned. Glucose, artificially enriched in ^{13}C, is available for metabolic studies, but is still relatively rare and expensive. With a group of physicists and clinicians of the University of Liège, Belgium, we have described the value of "naturally labeled ^{13}C-glucose" for metabolic studies in normal man,[3,4] in diabetes[5,6] or obesity,[5,6] in pharmacologic investigations,[7] or during prolonged exercise.[8,9] In this paper we will briefly summarize these data with special emphasis given to our exercise studies.

ENRICHMENT IN ^{13}C OF CERTAIN NATURAL SUGARS

The higher concentration of ^{13}C atoms in some natural sugars is related to a selective isotopic effect occurring during photosynthesis in certain types of plants.[10,11] The abundance of ^{13}C atoms in cane or maize sugar, from which the glucose used for oral glucose tolerance tests (OGTT) is often manufactured, is higher than that of sugar derived from most other plants. As previously reported,[3] the absolute ^{13}C abundance for most preparations of glucose available commercially is 1.100%, a value significantly higher than that found in human expired air in basal conditions (1.085%).

GLUCOSE TOLERANCE TESTS AT REST USING NATURALLY LABELED ^{13}C-GLUCOSE

The abundance of ^{13}C- and ^{12}C-atoms in expired air CO_2 can be determined, after physical isolation of CO_2, using mass spectrometry.[3] The relative abundance of ^{13}C- and ^{12}C-atoms in a sample is given by Craig:[12] $\delta\ ^{13}C$ (*per mil*) $= 10^3\ [(^{13}C/^{12}C\ \text{sample})/(^{13}C/^{12}C\ \text{standard}) - 1]$. One unit of $\delta\ ^{13}C$ corresponds to a change of about 1.10^{-5} in the ratio $^{13}C/^{12}C$.

In normal subjects at rest receiving 100 g naturally labeled ^{13}C-glucose orally, a marked rise in $\delta\ ^{13}C$ of expired air was observed, which reached its maximum 4 h after the glucose ingestion.[3] The simultaneous measurement of the amounts of CO_2 expired ($\dot{V}CO_2$) permitted us to calculate the amounts of exogenous glucose oxidized to CO_2 in normal resting subjects[4] (Figure 1). This value averaged 28.6 ± 1.44 g in 7 h. It indicates that about 30% of the glucose carbons of the load were recovered as CO_2 in the expired air in 7 h. This figure does not take into consideration factors such as equilibration between the glucose pools, changes in the bicarbonate–CO_2 pool, or the "crossing-over" of labels. As emphasized by Krebs et al.,[13] "the fate

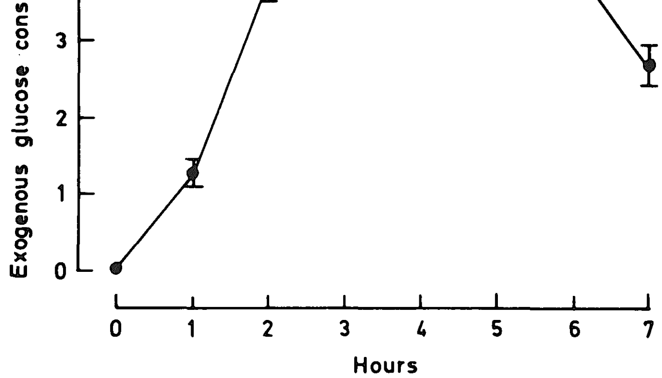

FIGURE 1. Time course of the oxidation of a 100-g exogenous glucose load. Results are given as means ± SEM (n = 8). Data from Mosora et al.[4]

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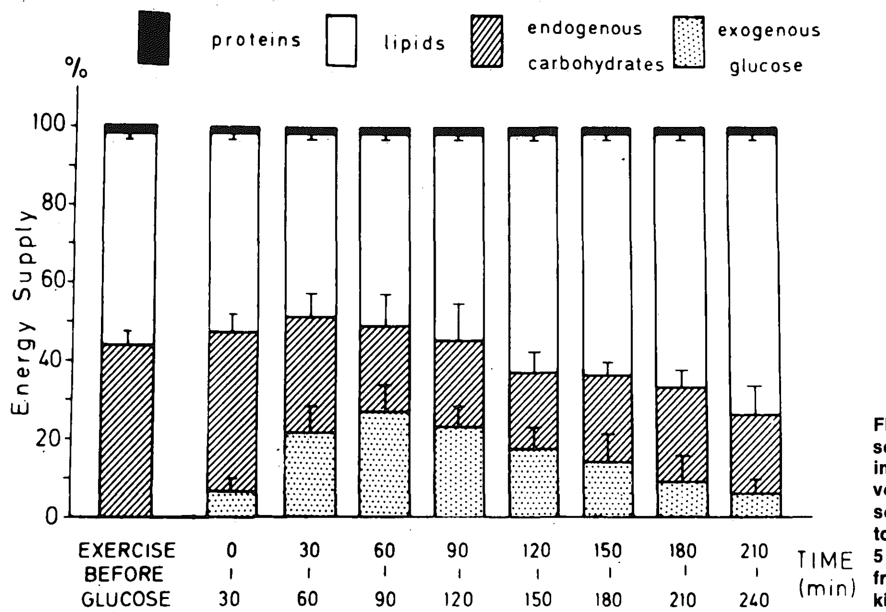

FIGURE 2. Respective contributions of the various sources of energy during muscular exercise after intake of 100 g glucose in normal healthy volunteers. Means and standard deviations of seven experiments are shown. The first column to the left represents data obtained during the last 5 min of the exercise-adaptation period. Data from Pirnay et al.[9] (Figure reproduced with the kind permission of the copyright holder.)

of a label does not allow prediction to be made about the *net* fate of the labelled metabolites." For these reasons, in our experimental conditions, the calculation of exogenous glucose oxidation would probably represent an *underestimate* of true *net* glucose oxidation.[4,7]

EXOGENOUS GLUCOSE OXIDATION DURING PROLONGED EXERCISE EVALUATED WITH NATURALLY LABELED ^{13}C-GLUCOSE

The distribution of substrates utilized during prolonged exercise and the evaluation of the contribution of exogenous glucose to the energy supply was determined using conventional respiratory quotient (RQ) measurements and the naturally labeled ^{13}C-glucose method previously described. The data have been reported in detail elsewhere.[8,9] Figure 2 demonstrates the respective contributions of the various sources of energy during prolonged muscular exercise (walk on a 10% uphill treadmill for 4 h; 40–50% of $\dot{V}O_2$ max) after 100 g glucose intake.

Cumulative exogenous glucose oxidation averaged 57 ± 13 (SD) g in 2 h and 95 ± 4 g in 4 h (eight subjects). This last figure indicates a *complete* oxidation to CO_2 of the amount of exogenous glucose given, since melting point determinations showed that the glucose used was partially hydrated: calculations indicated that the amount of pure glucose in the 100-g load given was in fact 95 ± 1 g (mean ± SD; four determinations).

Thus, in normal subjects submitted to a prolonged muscular exercise at 40–50% $\dot{V}O_2$ max, the rate of exogenous glucose oxidation was multiplied by a factor of four to five in comparison with the resting conditions: 28 g/7 h at rest versus 95 g/4 h during exercise. In these conditions, ingestion of 100 g glucose permitted an important sparing of endogenous glucose[9] (see Table 1). In addition, glucose ingestion markedly delayed the exercise-induced circulating glucagon rise and plasma FFA mobilization.[14] This last finding was consistent with the sparing effect that exogenous glucose ingestion also exerts on lipid utilization.[9]

Studies now in progress in our laboratories investigate to what extent insulin is necessary in insulinodependent patients for permitting oxidation of exogenous glucose during prolonged muscular exercise.

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TABLE 1
Carbohydrate oxidation during prolonged muscular exercise*

	Without glucose ingestion	With glucose ingestion (100 g)			
Time	1: Endogenous = total glucose	2: Total	3: Exogenous	4: Endogenous (2–3)	5: Spared (1–4)
After 1 h	63.1 ± 8.4	69.9 ± 10.8	20.8 ± 6.8	49.1 ± 7.4	14.0
After 2 h	118.6 ± 21.1	136.2 ± 22.9	56.9 ± 12.8	79.3 ± 16.2	39.3
After 3 h	157.3 ± 31.4	199.8 ± 36.6	84.3 ± 5.1	115.5 ± 24.6	41.8
After 4 h	185.2†	242.4 ± 46.6	94.8 ± 4.2	147.6 ± 33.6	37.6

Results are expressed as means ± 1 SD. The same three subjects were investigated under both experimental conditions.
* Data from Pirnay et al., 1977.[8]
† Only one subject has been able to exercise 4 h without glucose ingestion.

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