Effects of infused sodium acetate, sodium lactate, and sodium β-hydroxybutyrate on energy expenditure and substrate oxidation rates in lean humans[1–3]

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ABSTRACT Infusion of sodium acetate in lean humans results in a decrease in respiratory exchange ratio, which may be advantageous in patients with respiratory failure. However, this potential decrease in respiratory work was observed to be offset by significant thermogenesis. The metabolic effects of sodium acetate, sodium lactate, and sodium β-hydroxybutyrate, infused at a rate of 20 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ for 3 h, was monitored in six healthy human volunteers. Respiratory exchange ratio decreased from 0.85 ± 0.02 at baseline to 0.75 ± 0.02, 0.75 ± 0.02, and 0.80 ± 0.02, after acetate, lactate, or β-hydroxybutyrate, respectively ($P < 0.05$ for each). Acetate produced a larger thermic effect (22.7% of energy infused) than did lactate (16.3%) or β-hydroxybutyrate (13.6%). Thus, sodium salts of organic acids may potentially decrease the respiratory requirements by decreasing the respiratory exchange ratio. However, this effect is partially offset by the thermic effect of these substrates. The maximal doses and safety of these anions during larger infusion periods remain to be determined. *Am J Clin Nutr* 1993;58:608–13.

KEY WORDS Acetate, lactate, β-hydroxybutyrate, energy expenditure, glucose oxidation, respiratory gas exchanges

Introduction

Nutritional support is fundamental in the management of patients in intensive-care medicine. Nutritional status influences the outcome of many critical illnesses, in both surgical and medical patients (1). These patients frequently present with respiratory failure and may require mechanical ventilatory support. The choice of the type of nutriments may thus be important because the amount of carbon dioxide per kilojoule produced varies according to the substrates oxidized (2). Because total ventilation has to match metabolic carbon dioxide production for blood PCO_2 (partial pressure of carbon dioxide) and pH to be maintained, it is evident that a diet providing the maximum amount of energy per liter carbon dioxide (ie, providing an appropriate amount of energy during oxidation while producing little carbon dioxide) may be highly advantageous.

In this regard, sodium salts of organic anions may be of interest. When these compounds are metabolized, 1 mol sodium bicarbonate/mol substrate is formed (3, 4). As a result, respiratory exchange ratio decreases as urinary bicarbonate excretion increases (4–6). A detailed description of this process was recently published (7). Infusion of sodium acetate decreased respiratory exchange ratio as it increased urinary bicarbonate excretion. The decrease in respiratory exchange ratio led to a relative decrease in ventilation, ie, a decrease in ventilation relative to pulmonary gas exchanges, as reflected by a decrease in the ratio of total ventilation to oxygen consumption. However, acetate was shown to induce a large thermogenic effect, and the 10% decrease in respiratory exchange ratio was offset by an equivalent increase in oxygen consumption, therefore resulting in no change in net respiratory carbon dioxide elimination ($\dot{V}CO_2$) (7).

It was therefore the aim of this study to compare in healthy subjects the relative thermic effect of three sodium salts of organic acids that may be used in total parenteral nutrition: sodium acetate, sodium lactate, and sodium D,L-β-hydroxybutyrate.

Subjects and methods

Subjects

Six healthy human subjects (two males, four females) with a mean age of 22.7 y (range 21–30 y), mean height of 171.7 cm (158–185 cm), mean weight of 67.2 kg (47.5–76 kg), and mean %fat of 22.0 (16.0–27.8%) [determined from skinfold-thickness measurements (8)] participated in four different protocols. All subjects were in good health, were not taking any medication, and had provided informed written consent. The experimental protocol was approved by the ethical committee of Lausanne University School of Medicine.

Experimental protocol

All studies were performed in the morning after an overnight fast. Subjects had been on a weight-maintaining diet containing

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≈ 50% of total energy as carbohydrate during the 3 d before the experiment began. The experiments were performed while the subject was in a supine position. An indwelling venous cannula was inserted into an antecubital vein of one arm for the infusion of test substances. A venous cannula was inserted into an antecubital vein of the contralateral arm for subsequent withdrawal of blood samples. Oxygen consumption and carbon dioxide production were continuously measured with an open-circuit indirect calorimeter, as previously described (9). Briefly, a transparent ventilated hood was placed over the subject's head. The air at the outlet of the hood was continuously analyzed for oxygen (Magnos 3 G delta; Hartmann & Braun, Frankfurt, Germany) and carbon dioxide (Uras 3 G delta; Hartmann & Braun) concentrations, and the total air flow through the hood was measured with a digital pneumotachograph (Godart-Stathan BV, Bilthoven, Holland).

Subjects were studied in four different protocols, separated by 7–10 d. After a 1-h baseline measurement period, one of the three test substances—sodium acetate, sodium lactate, or sodium β-hydroxybutyrate—was infused at the rate of 20 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ for 3 h. In the fourth protocol, an infusion of glucose at a rate of 11.1 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ (ie, isoenergetic with the infusion of β-hydroxybutyrate, which provided the highest rate of energy infusion of the three test substances) was administered for 3 h; this protocol was used as a control. Sodium acetate, sodium D,L-β-hydroxybutyrate (purchased from Fluka, Buchs, Switzerland), and sodium lactate (purchased from Bichsel AG, Interlaken, Switzerland) were prepared as sterile solutions (0.5 mol/L).

Respiratory gas exchanges were monitored throughout the experiments. Blood samples were collected at 30-min intervals for determining plasma hormone and substrate concentrations. A urine collection was made during the 3-h infusion test for determining urinary excretion of urea, nitrogen, acetate, lactate, β-hydroxybutyrate, and bicarbonate. In the basal state, urinary nitrogen excretion was assumed to be 0.1 $mg \cdot kg^{-1} \cdot min^{-1}$ (9).

Calculations

Energy and substrate oxidation rates were calculated in the basal state (baseline) and during the last hour of infusion of test substances (time 180–240 min). Because plasma acetate, lactate, or β-hydroxybutyrate concentrations had reached a near steady state by this time, it was assumed that the total amount of each substance infused (minus the amount of substance excreted in the urine) had been completely oxidized. This assumption is possible because none of the three substrates can be stored as such in the body. Because the urinary excretion of each of these substrates was negligible (< 1% of the infused substrate appeared in urine during the 3-h collection period), the net oxidation rate (or net rate of disappearance) of these substrates corresponds to their rate of infusion. Each substrate metabolized can be either converted to carbon dioxide and water, or to fatty acids, or, in the case of lactate, to glucose. The net substrate oxidation rate obtained represents the sum of direct oxidation of the substrate and of conversion of the substrate into fat or glucose with oxidation of neoformed fat or glucose to carbon dioxide and water. The overall stoichiometric pathway for these indirect oxidation processes is identical to that of direct oxidation of these substrates (7, 10).

Oxygen consumption, carbon dioxide production, and energy expenditure were calculated for each individual substrate according to the following equations:

$$1 \text{ mmol acetate} + 44.8 \text{ mL } O_2 \rightarrow 22.4 \text{ mL } CO_2 + 1 \text{ mmol } NaHCO_3 + 0.879 \text{ kJ} \quad (7)$$

$$1 \text{ mmol lactate} + 67.2 \text{ mL } O_2 \rightarrow 44.8 \text{ mL } CO_2 + 1 \text{ mmol } NaHCO_3 + 1.364 \text{ kJ} \quad (11)$$

$$1 \text{ mmol } \beta\text{-hydroxybutyrate} + 100.8 \text{ mL } O_2 \rightarrow 67.2 \text{ mL } CO_2 + 1 \text{ mmol } NaHCO_3 + 1.561 \text{ kJ} \quad (10)$$

The $NaHCO_3$ produced is either excreted in the urine or increases the bicarbonate pool size. These two phenomena lead to extrapulmonary carbon dioxide loss.

Because urinary excretion of acetate or lactate was negligible (< 1% of the infusion rate), net oxidation of acetate or lactate was assumed to be similar to their rate of infusion. Net oxidation of β-hydroxybutyrate was calculated as net β-hydroxybutyrate oxidation = (β-hydroxybutyrate infusion rate) − (β-hydroxybutyrate urinary excretion).

Nonacetate, nonlactate, or non-β-hydroxybutyrate $\dot{V}O_2$ were calculated by subtracting from total $\dot{V}O_2$ the oxygen consumption due to the complete oxidation of the substrate administered, as described previously for acetate (7). Similar calculations were carried out for nonacetate, nonlactate, and non-β-hydroxybutyrate $\dot{V}CO_2$. Glucose and fat oxidations were then determined from these corrected values of $\dot{V}O_2$ and $\dot{V}CO_2$ as previously described (7, 12). The thermic effects of acetate, lactate, and β-hydroxybutyrate were calculated in percent of energy infused, as

$$\text{Thermic effect (\%)} = \frac{EE_{(120-180)} - EE_0}{\text{substrate energy infused}} \times 100$$

where EE is energy expenditure in kJ/min, 120–180 and 0 refer to the time (min) of infusion, and substrate energy infused is in kJ/min.

Analytical procedures

Plasma glucose concentration was measured on a glucose analyzer (Beckman, Brea, CA). Plasma insulin concentration was determined by radioimmunoassay (13). Plasma free fatty acid concentration was measured by a colorimetric method by using a kit from WAKO, Freiburg, Germany. Plasma and urine β-hydroxybutyrate, acetoacetate, lactate, and acetate concentrations were measured enzymatically by using kits from Boehringer Mannheim, Mannheim, Germany. Because the β-hydroxybutyrate solution infused was racemic (ie, 50% L form), and enzymatic determinations of ketone bodies do not detect the L forms, the measured urinary concentrations of these substrates were multiplied by 2. Venous blood and urine gas analyses were performed by using a gasometric device (ABL 3; Radiometer, Copenhagen, Denmark). Urinary bicarbonate concentration was calculated from urinary pH (Titrator TTT 2; Radiometer) and urinary PCO_2 (ABL 3; Radiometer) by using the Henderson-Hasselbalch equation (14).

Statistical analysis

The time course of plasma hormone, substrate, and gas exchanges was analyzed by analysis of variance for repeated measurements, and comparisons between test substances and control by analysis of variance and paired *t* tests. The Scheffé test was used to detect differences between the various substrates. All results are expressed as $\bar{x} \pm$ SEM.

Results

Baseline plasma acetate, lactate, and β-hydroxybutyrate concentrations were 0.02 ± 0.01, 1.87 ± 0.50, and 0.02 ± 0.01 mmol/L, respectively. Substrate infusion at a rate of 20 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ increased plasma acetate, lactate, and β-hydroxybutyrate to 0.42 ± 0.15, 3.74 ± 0.20, and 0.94 ± 0.07 mmol/L after 3 h, respectively. A near steady state of plasma concentration was obtained during the third hour of infusion for each individual substrate (**Fig 1**).

Plasma glucose, insulin, and free fatty acid concentrations during infusion of these substrates are shown in **Figure 2.** Infusion of glucose slightly increased glycemia from 4.6 ± 0.2 to 5.7 ± 0.2 mmol/L and plasma insulin from 63 ± 3 to 100 ± 9 pmol/L and decreased free fatty acid concentrations from 0.43 ± 0.07 to 0.21 ± 0.06 mmol/L ($P < 0.05$ for each). Plasma glucose decreased continuously to reach a mean value of 4.5 ± 0.1 mmol/L after 3 h of infusion of acetate, lactate, or β-hydroxybutyrate ($P < 0.05$ vs basal). Plasma insulin concentration did not change during infusion of any of these substrates; by contrast, free fatty acid concentration was transiently suppressed at 30 min after acetate infusion ($P < 0.05$) and throughout both β-hydroxybutyrate and glucose infusions ($P < 0.01$ vs baseline at 60 min until the end of the infusion).

Venous plasma bicarbonate concentration and pH increased from 24.9 ± 0.41 and 7.38 ± 0.01 mmol/L at baseline to 31.1 ± 0.7 and 7.45 ± 0.01 mmol/L after acetate ($P < 0.001$), 32.3 ± 1.5 and 7.47 ± 0.02 mmol/L after lactate ($P < 0.001$), and 30.1 ± 0.49 and 7.46 ± 0.01 mmol/L after β-hydroxybutyrate ($P < 0.001$). Venous plasma bicarbonate (24.8 ± 0.38 mmol/L) and pH (7.39 ± 0.01) were unaltered after glucose. Urinary bicarbonate excretion amounted to 43 ± 2, 40 ± 2, 32 ± 4, and 2 ± 3 mmol over 3 h after acetate, lactate, β-hydroxybutyrate, and glucose, respectively. Excretion of urinary ketone bodies was 0.05 ± 0.01 mmol/min.

Oxygen consumption and carbon dioxide elimination are shown in **Figure 3.** Oxygen consumption increased significantly by 6.0%, 6.6%, and 5.5% after acetate, lactate, and β-hydroxybutyrate infusions, respectively, but it remained constant during the infusion of glucose. $\dot{V}CO_2$ decreased by 4.9% and 5.3% after acetate and lactate infusions, respectively ($P < 0.05$), but it remained unchanged after β-hydroxybutyrate, and increased by 2.5% after glucose infusion (NS).

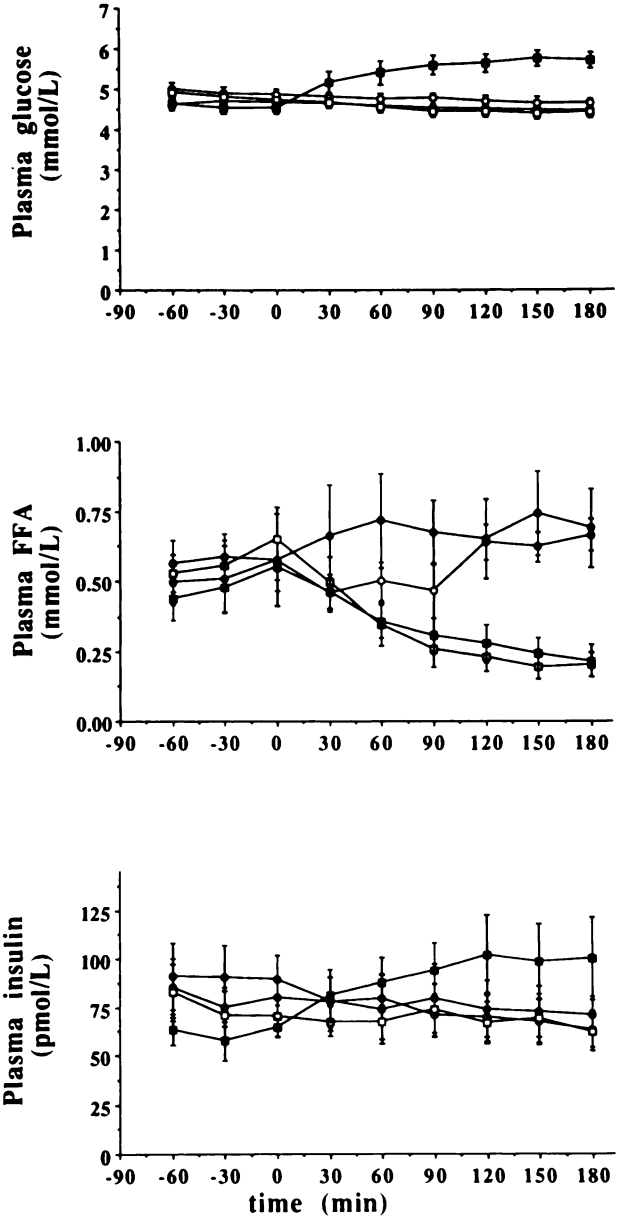

FIG 2. Plasma glucose, free fatty acids (FFA), and insulin concentrations during infusion of sodium acetate (○), lactate (●), β-hydroxybutyrate (□), or glucose (■). $n = 6$.

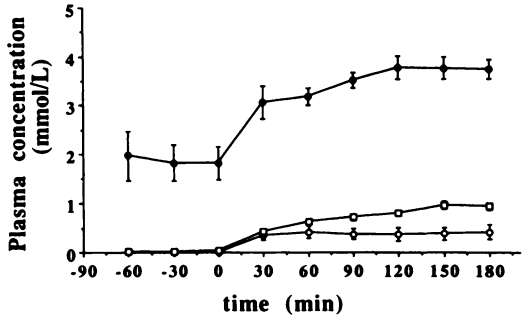

FIG 1. Plasma concentration of acetate (○), lactate (●), and β-hydroxybutyrate (□) during infusions of the corresponding substrate. $P \leq 0.01$ vs 0 min for all times between 30 and 180 min. $n = 6$.

Energy expenditure and net substrate oxidation rates calculated from respiratory exchanges are shown in **Table 1.** Net carbohydrate oxidation was inhibited by 22% after acetate, by 55% after lactate, and by 25% after β-hydroxybutyrate infusions. Lipid oxidation rate decreased by 81%, 13%, and 77% after acetate, lactate, and β-hydroxybutyrate infusions, respectively. Total energy expenditure increased significantly in all conditions, except during infusion of glucose, resulting in a thermogenic effect of 22.7% for acetate, 16.3% for lactate, and 13.6% for β-hydroxybutyrate infusions. Energy produced per liter respiratory oxygen, and carbon dioxide exchanged are shown in **Table 2.** Acetate, lactate, and β-hydroxybutyrate all increased substantially the energy expended per liter carbon dioxide excreted.

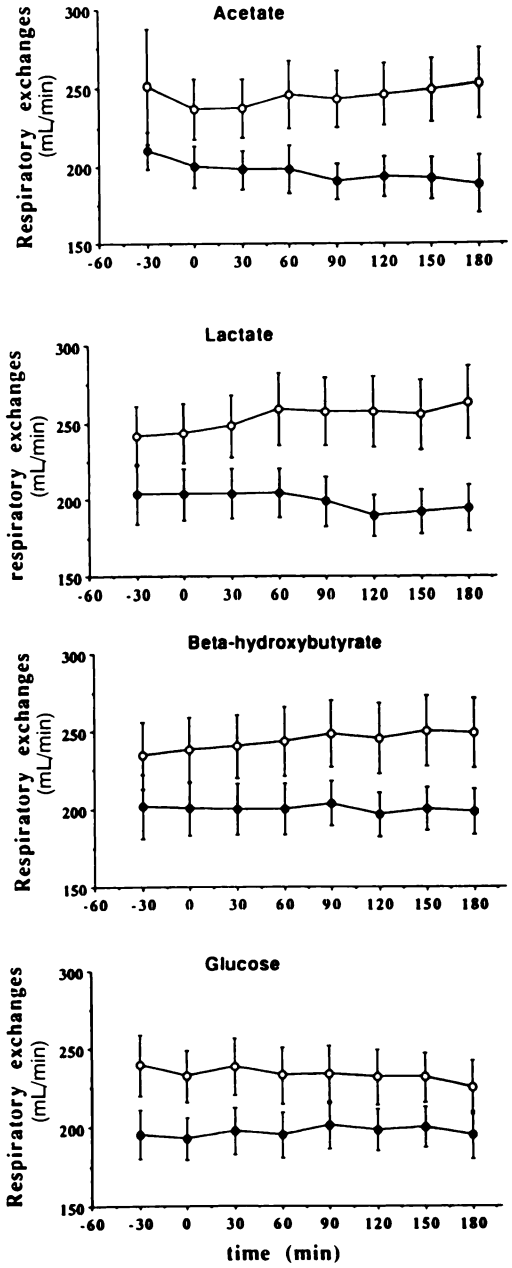

FIG 3. Respiratory exchanges of oxygen (○) and carbon dioxide (●) during infusion of sodium acetate, sodium lactate, sodium β-hydroxybutyrate, and glucose. $n = 6$.

Discussion

Infusion of sodium salts of lactic acid, acetic acid, and β-hydroxybutyric acid increased their relative plasma concentration markedly, and a near steady state was attained during the last hour of infusion. Because neither acetate nor lactate were excreted to any significant extent in the urine (< 1% of the rate of substrate infused), it can be deduced that the rate of net metabolism of these two substrates during this period was equal to the rate of infusion. Urinary β-hydroxybutyrate in contrast represented ≈5% of the infusion rate, and therefore net metabolism of an equimolar infusion of this substrate was lower than that of acetate or lactate. Each mole of these substrates when metabolized leads to the generation of 1 mol sodium bicarbonate, which will be excreted in the urine or will increase the bicarbonate pool size (10). Sodium bicarbonate is formed during oxidation of these substrates to carbon dioxide and water, but also when the substrate is converted into fat or glucose. The urinary bicarbonate excretion and the increase in plasma bicarbonate concentration were comparable after acetate and lactate infusions, but lower after β-hydroxybutyrate because of its lower net metabolism. This corroborates that the total bicarbonate generation rate was stoichiometric with the rate of substrate infused.

It has been demonstrated by other investigators when administering various substrates and by us that total and alveolar minute ventilation vary according to the amount of carbon dioxide to be eliminated through the lung (2, 5, 7, 15). This phenomenon is complex because it depends on two factors: *1*) the relative amount of carbon dioxide produced and oxygen consumed during substrate oxidation and *2*) the total energy expenditure, which influences total carbon dioxide production. In this regard, sodium acetate, sodium lactate, and sodium β-hydroxybutyrate all led to a relative decrease in ventilation because the amount of energy produced per minute increased without an increase in pulmonary carbon dioxide elimination, or even with a slight decrease in pulmonary carbon dioxide elimination. This relative sparing of ventilation is attested by the marked increase in the energy yield per liter carbon dioxide eliminated through the lung. On the other hand, each of these substrates substantially increased resting energy expenditure. The thermic effect of these substrates and their relative differences can be accounted for by the metabolic pathways used for metabolism of these substrates. The thermic effect of a substrate is dependent on the number of moles of adenosine triphosphate (ATP) used per mole substrate metabolized. ATP is hydrolyzed during the initial activation of substrates to phosphorylated substrate (eg, glucose to glucose 6-phosphate) or to substrate-CoA (eg, acetate to acetyl CoA) or in the processes of gluconeogenesis and lipogenesis. On the assumption that 84 kJ is an average expenditure for the synthesis of 1 mol ATP under usual conditions (16), an estimate of the theoretical thermogenesis can be obtained as follows:

$$\text{Substrate thermogenesis} = \frac{\text{ATP used for substrate processing} \times 84}{\text{energy released by substrate oxidation}} \times 100$$

Acetate has to be converted first to acetyl CoA with the consumption of 2 mol ATP/mol acetate metabolized. The complete oxidation of 1 mol acetate in the tricarboxylic acid cycle releases 878 kJ. This initial consumption of 2 mol ATP accounts for an estimated thermic effect of $(2 \times 84)/878$, or ≈ 19% of the energy content of acetate during oxidation to carbon dioxide and water. The value of 22.7% measured in this experiment slightly exceeds this theoretical value. We previously reported that the thermic effect of acetate infused at higher rates (2.5 mmol/min) was even higher (≈28%). This suggests that lipogenesis, which is a process in which ≈38% of the energy content of acetate is expended (7), becomes an important pathway of acetate metabolism when it is infused at high rates.

Metabolism of lactate involves conversion to pyruvate, which has subsequently two major metabolic fates: pyruvate can be converted to acetyl CoA through dehydrogenation and decarboxylation by the pyruvate dehydrogenase complex, and enter the tricarboxylic acid cycle; this pathway does not involve consump-

TABLE 1
Substrate oxidation rate and energy expenditure at baseline (0 min) and during the third hour of infusion of sodium acetate, lactate, β-hydroxybutyrate, or glucose*

	Sodium acetate		Sodium lactate		Sodium β-hydroxybutyrate		Glucose	
	0 min	120–180 min	0 min	120–180 min	0 min	120–180 min	0 min	120–180 min
Carbohydrate oxidation (kJ/min)	2.41 ± 0.19	1.88 ± 0.20†	2.33 ± 0.49	1.05 ± 0.38‡	2.37 ± 0.27	1.77 ± 0.36‡	2.11 ± 0.25	2.65 ± 0.17
Lipid oxidation (kJ/min)	2.13 ± 0.38	0.41 ± 0.34‡	2.39 ± 0.46	2.09 ± 0.52	2.17 ± 0.25	0.50 ± 0.46§	2.31 ± 0.30	1.76 ± 0.15†
Acetate oxidation (kJ/min)	0	1.19 ± 0.08§	—	—	—	—	—	—
Lactate oxidation (kJ/min)	—	—	0	1.84 ± 0.12§	—	—	—	—
β-Hydroxybutyrate oxidation (kJ/min)	—	—	—	—	0	2.04 ± 0.11§	—	—
Energy expenditure (kJ/min)	4.78 ± 0.36	5.05 ± 0.38†	4.85 ± 0.52	5.15 ± 0.44†	4.83 ± 0.44	5.09 ± 0.44†	4.68 ± 0.32	4.66 ± 0.31
$\dot{V}O_2$ (L/min)	0.236 ± 0.018	0.250 ± 0.021†	0.242 ± 0.018	0.258 ± 0.022†	0.236 ± 0.020	0.249 ± 0.022†	0.235 ± 0.017	0.228 ± 0.018
$\dot{V}CO_2$ (L/min)	0.199 ± 0.014	0.189 ± 0.013†	0.203 ± 0.017	0.192 ± 0.014†	0.201 ± 0.017	0.199 ± 0.014	0.194 ± 0.015	0.199 ± 0.014

$\bar{x}$ ± SEM.
†‡§ Significantly different from baseline: †$P < 0.05$, ‡$P < 0.01$, §$P < 0.005$.

tion of ATP, and therefore is not accompanied by thermogenesis. Alternatively, pyruvate can enter the gluconeogenic pathway to be converted into glucose; in this process, 2 mol ATP/mol lactate will be consumed (17). Glucose, when metabolized to glucose-6-phosphate and to triose-phosphates in peripheral tissues, requires hydrolysis of 2 mol ATP/mol glucose, which corresponds to 1 mol ATP/mol lactate. On the other hand, complete oxidation of 1 mol lactate will release 1363 kJ. This degradation of lactate through gluconeogenesis with subsequent oxidation of glucose will therefore result in a theoretical thermogenesis amounting to (3 × 84)/1363, or ≈18% of the energy content of lactate. This value is not significantly different from the values of ≈16% measured in this study. This indicates that gluconeogenesis in the present experiment was the major pathway of lactate metabolism.

Metabolism of β-hydroxybutyrate involves conversion into acetoacetate and either of two pathways: *1*) acetoacetate can be activated with ATP into acetoacetyl CoA + AMP under the action of the enzyme acetoacetyl CoA, and 2 mol ATP/mol acetoacetate metabolized will then be used to regenerate AMP; or *2*) acetoacetate can react with succinyl CoA to form acetoacetyl CoA under the action of enzyme succinyl CoA-acetoacetate CoA transferase, and 1 mol ATP/mol acetoacetate is hydrolized in this reaction. On the assumption that these two pathways of acetoacetate activation are active in equal proportions, an average of 1.5 mol ATP is expended/mol β-hydroxybutyrate metabolized. Because complete oxidation of 1 mol β-hydroxybutyrate releases 1561 kJ, the theoretical cost of β-hydroxybutyrate utilization can be calculated as (1.5 × 84)/1561, or 8%. The observed thermic effect of β-hydroxybutyrate (13%) was substantially higher than this theoretical value, suggesting, as for acetate, that part of the β-hydroxybutyrate metabolized underwent lipogenesis.

Calculation of substrate oxidation rate by indirect calorimetry yields net substrate oxidation rate, or rate of net substrate disappearance (10, 12, 18). The assumption in the present experiment that the infused substrates (minus their urinary excretion) were completely oxidized also provides net rates of utilization, or disappearance, of these substrates. However, the metabolic pathways followed by these substrates remain undefined. As mentioned above, it is likely that gluconeogenesis represents the major pathway of lactate utilization. Therefore, lactate oxidation rate represents direct lactate oxidation in the tricarboxylic acid cycle plus lactate conversion into glucose and oxidation of the neoformed glucose. This means that the net carbohydrate oxidation rate measured during lactate infusion underestimates the true carbohydrate oxidation rate by the amount of glucose formed from lactate. On the assumption that all lactate was already converted into glucose, yielding ≈ 10 μmol glucose·kg^{-1}·min^{-1}, true carbohydrate oxidation rate can be estimated to be equal to net carbohydrate oxidation rate plus 10 μmol·kg^{-1}·min^{-1}. It can thus be estimated that, in these experiments, lactate may have slightly increased carbohydrate oxidation (2.3 kJ/min basal vs 2.9 kJ/min; carbohydrate oxidation + lactate gluconeogenesis during infusion, NS).

Net lipid oxidation was markedly inhibited by infusions of acetate or β-hydroxybutyrate. Inhibition of lipid oxidation has already been reported during administration of acetate (7) or ethanol (19). The mechanisms responsible for the inhibition of lipid oxidation remain unelucidated. The observation of a thermic effect larger than theoretically expected during infusion of acetate or β-hydroxybutyrate suggests that de novo lipogenesis occurred. As a result, net lipid oxidation as obtained from indirect calorimetry is likely to underestimate somewhat actual rates of lipid oxidation.

Beta-hydroxybutyrate and acetate slightly decreased net carbohydrate oxidation rate. This indicates a reduction of the rate of hepatic and/or muscular glycogen hydrolyzed and oxidized. Beta-hydroxybutyrate is known to be oxidized as an energetic substrate in the brain during starvation (20, 21). Acutely administered, β-hydroxybutyrate may also be transported and oxidized in brain cells after an overnight fast (22). Beta-hydroxybutyrate may thus inhibit brain glucose oxidation, which may account for the suppression of hepatic glucose production observed after administration of ketone bodies in humans (23, 24).

In conclusion, sodium acetate, sodium lactate, and sodium β-hydroxybutyrate when infused for 3 h in normal human subjects decreased the respiratory exchange ratio and increased bicarbonate generation and extrapulmonary carbon dioxide loss. This extrapulmonary carbon dioxide elimination may have led to a marked decrease in alveolar ventilation. On the other hand, all three substrates also had a substantial thermic effect, which was more important with acetate and lactate than with β-hydroxybutyrate. This thermic effect led to an increase in total $\dot{V}O_2$ and $\dot{V}CO_2$. Therefore, the net decrease in respiratory carbon dioxide elimination was of small magnitude. The thermic effect of lactate

TABLE 2
Energy yield of respiratory oxygen and carbon dioxide exchanges at baseline (0 min) and during infusion of sodium acetate, lactate, and β-hydroxybutyrate*

	Sodium acetate		Sodium lactate		Sodium β-hydroxybutyrate	
	0 min	120–180 min	0 min	120–180 min	0 min	120–180 min
Energy						
(kJ/L O_2)	20.2 ± 0.2	20.0 ± 0.2	19.9 ± 0.3	19.8 ± 0.2	20.2 ± 0.2	20.4 ± 0.1
(kJ/L CO_2)	23.9 ± 0.4	27.1 ± 0.4†	23.9 ± 0.4	26.7 ± 0.6†	23.8 ± 0.2	25.6 ± 0.5‡

* $\bar{x}$ ± SEM.
†‡ Significantly different from baseline: †$P < 0.01$, ‡$P < 0.05$.

significantly exceeded the theoretical energy cost of oxidizing lactate, indicating that gluconeogenesis is likely to be the major metabolic pathway of lactate under the present conditions. Similarly, lipogenesis from acetate is likely to be a significant pathway of acetate metabolism. However, these experiments were performed under conditions of low infusion of energy. For this reason, only preliminary information can be obtained at this stage. It may be expected that lactate administered during concomitant infusion of carbohydrate, which would increase plasma glucose and insulin, may be directly oxidized rather than follow the gluconeogenesis pathway because of the suppression of gluconeogenesis by insulin. This may lead to a marked reduction of its thermic effect. Further studies will help to better define the thermic effect of these substrates under various metabolic conditions. Other issues will have to be addressed before utilization of these substrates in a clinical setting; administration of these substrates during extended periods of time may lead to excessive generation of bicarbonate and alkalosis and to an increase in the sodium pool size. Further studies are required to determine the maximal doses, the tolerance, and the safety of these substrates.

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