

Sodium Acetate Induces a Metabolic Alkalosis but Not the Increase in Fatty Acid Oxidation Observed Following Bicarbonate Ingestion in Humans\textsuperscript{1,2}

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Abstract

We conducted this study to quantify the oxidation of exogenous acetate and to determine the effect of increased acetate availability upon fat and carbohydrate utilization in humans at rest. Eight healthy volunteers (6 males and 2 females) completed 2 separate trials, 7 d apart in a single-blind, randomized, crossover design. On each occasion, respiratory gas and arterialized venous blood samples were taken before and during 180 min following consumption of a drink containing either sodium acetate (NaAc) or NaHCO\textsubscript{3} at a dose of 2 mmol/kg body mass. Labeled \([1,2\textsuperscript{13}C]\) NaAc was added to the NaAc drink to quantify acetate oxidation. Both sodium salts induced a mild metabolic alkalosis and increased energy expenditure \((P < 0.05)\) to a similar magnitude. NaHCO\textsubscript{3} ingestion increased fat utilization from 587 \pm 83 kJ/180 min to 693 \pm 101 kJ/180 min \((P = 0.01)\) with no change in carbohydrate utilization. Following ingestion of NaAc, the amount of fat and carbohydrate utilized did not differ from the preingestion values. However, oxidation of the exogenous acetate almost entirely \((90\%)\) replaced the additional fat that had been oxidized during the bicarbonate trial. We determined that 80.1 \pm 2.3\% of an exogenous source of acetate is oxidized in humans at rest. Whereas NaHCO\textsubscript{3} ingestion increased fat oxidation, a similar response did not occur following NaAc ingestion despite the fact both sodium salts induced a similar increase in energy expenditure and shift in acid-base balance. J. Nutr. 137: 1750–1756, 2007.

Introduction

Acetate is quickly converted to acetyl-CoA by the enzyme acetyl-CoA synthetase, with the oxidation of acetate reported to account for between 5 and 13\% of total energy expenditure at rest and in the fasted state \((1–3)\). There are, however, many situations where acetate availability is increased, such as following ethanol ingestion \((4,5)\), following an increased consumption of dietary fiber \((6,7)\) and during renal dialysis using acetate \((8,9)\). Such increased acetate availability has resulted in acetate oxidation contributing up to at least 40\% of resting energy expenditure \((9,10)\). The metabolic consequence of such an elevation in acetate availability has, however, remained largely ignored. This is despite 1 study reporting a significant decline in respiratory exchange ratio following an infusion of acetate; the results suggested either increased fat oxidation or substantial oxidation of the infused acetate \((11)\). If increasing exogenous acetate affects substrate oxidation, there may be adverse effects on lipid metabolism in humans; for example, in the case of excessive chronic alcohol intake. However, the effect of acetate administration on substrate utilization has received little attention and the limited evidence is equivocal concerning the effects of acetate on metabolism \((10,12,13)\).

Chiolero et al. \((13)\) showed that intravenous sodium acetate (NaAc)\textsubscript{6} administration had a large suppressive effect \((P < 0.05)\) upon both fat and carbohydrate utilization \((decreases of 81 and 22\%, \text{respectively}, \text{when compared with preinfusion values})\). In contrast, Akanji et al. \((10)\) and Burnier et al. \((12)\) both reported that infusion of NaAc did not affect carbohydrate utilization but did result in a small but significant \((P < 0.05)\) decrease in long-chain fatty acid oxidation. One weakness of these studies is the failure to report substrate utilization data from a placebo trial. Another limitation with these investigations was that the amount of acetate oxidized was assumed rather than calculated from experimental data. This could have a profound effect on any subsequent calculation of fat and carbohydrate utilization. Indeed, in these previous studies the amount of acetate oxidized was estimated to be between 90 and 100\% of the infused rate \((10,12,13)\).

Although several studies have utilized isotope methods to examine acetate oxidation in the fasted state \((2,14,15)\) when the plasma acetate concentration is low, to the authors’ knowledge, we are not aware of any studies that have adequately characterized acetate oxidation in the fed state.

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\textsuperscript{6} Abbreviations used: NaAc, sodium acetate; NaNCO\textsubscript{3}, sodium bicarbonate; PCO\textsubscript{2}, partial pressure of carbon dioxide; PDB, Pee Dee Belemnitella.

1,2 Supported by a University of Aberdeen research studentship \((to \ G.I.S.)\).
only 1 study (9) has measured acetate oxidation when the plasma acetate concentration substantially increased.

Using 14C labeled NaAc, Skutch et al. (9) calculated that from 869 mmol of acetate infused over a 4-h period only 54% was oxidized during this time. The results from this study are, however, confounded by the fact that glucose was simultaneously infused with the acetate. Furthermore, some of the tracer may have been lost during the dialysis, leading to an underestimation of the amount of acetate oxidized (16).

We conducted this study to quantify the amount of acetate oxidized when acetate availability was increased using stable isotope techniques and also to determine the effect of acetate metabolism upon fat and carbohydrate utilization.

Methods

Subjects. Eight healthy subjects [6 males and 2 females (mean ± SEM) age 29 ± 3 y, height 1.76 ± 0.03 m, and body mass 71.62 ± 5.29 kg] volunteered to participate in this study. All the participants gave their written informed consent after the purpose, procedures, and possible health risks were explained to them. The Grampian Research Ethics Committee approved all the experimental procedures used within this study.

Experimental design. Each subject reported to the laboratory at 0800 on 2 separate occasions, with at least 1 wk between visits. On each occasion, after resting for a period of at least 60 min, subjects ingested 500 mL low-energy cordial drink (42 kJ/500 mL; 2.5 g of carbohydrate/500 mL). The drinks contained either NaAc (trihydrate) or NaHCO3 at a dose of 2 mmol/kg body mass and the sequence of drink administration was subjected to a randomized, crossover, single-blind experimental design.

Diet and activity before testing. Subjects were instructed to perform a prolonged, intense bout of exercise ~60 min in duration 5 d before each visit to the laboratory in an attempt to minimize 13C glycogen stores. We instructed subjects to record their dietary intake over the 5d period before the initial visit and then replicate this intake before the following visit. During the experimental period, subjects avoided ingesting foodstuffs derived from carbohydrates from C4 plants (e.g. sugar cane, maize) to maintain a low background 13C enrichment in expired CO2. Subjects fasted overnight and consumed 500 mL of tap water 1 h prior to reporting to the laboratory.

13C labeling. To quantify exogenous acetate oxidation, a dose of 2 mg [1,2,13C] NaAc/kg body mass (Cambridge Isotope Laboratories) was added to the NaAc drink, giving enrichments of 707.6 8δ13C vs. Pee Dee Belemnite (PDB) determined by elemental analyzer-isotope ratio mass spectrometry (Europa Scientific Geo 20–20). To prime the bicarbonate pool, NaH13CO3 (Cambridge Isotope Laboratories) at a dose of 0.064 mg/kg body mass was infused immediately before ingestion of the acetate drink. Preliminary studies demonstrated that this amount of NaH13CO3 was sufficient to markedly increase breath 13CO2/12CO2 from ~25 8δ13C vs. PDB to approximately ~19 8δ13C vs. PDB over the first 5 to 10 min before returning close to basal levels after 60 min (~24 8δ13C vs. PDB).

Procedures. Upon entering the laboratory, each subject was asked to void completely before body mass was recorded. During the preingestion period, 2 consecutive 4-min respiratory gas collections were taken using the Douglas bag method after the expired air passed through a mixing chamber (MLA245 Gas Mixing Chamber, ADInstruments). This arrangement allowed the simultaneous collection of a small volume of expired gas in 10-mL Exetainer tubes (Labco) in duplicate directly from the mixing chamber while also collecting whole breaths in the Douglas bag. Preliminary studies revealed that, the fraction of expired O2 and CO2 at rest sampled directly from the mixing chamber took 2.5 min to stabilize. As such, the mouthpiece was inserted at least 3 min before any respiratory collections were taken.

The breath samples stored in the Exetainer tubes were later analyzed for 13C content by continuous flow isotope ratio MS (Europa Scientific). The gas collected in the Douglas bags was immediately analyzed for percentage oxygen and CO2 using a gas analyzer (Servomex 1440, Servomex Group) with the volume measured using a dry gas meter (Harvard dry gas meter, Harvard Apparatus, Edenbridge). The volume of gas collected in the Exetainer tubes was then added to the expired volume collected in the Douglas bag before we performed any respiratory gas calculations. Gas temperature was also recorded during the measurement of gas volume using a thermocouple situated within the dry gas meter (RS components NTA912, Corby). The gas analyzer was calibrated before, during, and immediately after each test using gases of known composition.

Upon completion of the second resting gas sample, a 21-g butterfly needle was introduced into a superficial vein on the dorsal surface of a warmed hand and a 6.5-ML arterialized venous blood sample obtained. The patency of the cannula was maintained by regular flushing with 0.9% sterile saline, the volume of which totaled ~5 mL for each trial.

Subjects were then instructed to consume the prepared drink within 5 min and additional blood and respiratory gas samples were taken every 30 min for the next 180-min period. Two urine samples were also collected during each trial, 1 prior to drink ingestion and another at the end of the 180-min period. We instructed subjects to empty their bladders as completely possible; the entire volume of urine was collected from each subject.

Blood analyses. One portion of each blood sample (~1.5 mL) was collected, without contacting air, in a heparinized syringe, capped, placed on ice, and later analyzed for blood pH, base excess, O2 percent saturation of hemoglobin, and the partial pressure of CO2 (PCO2).

Sample analysis was performed using a blood gas analyzer (ELG 500, Radiometer Copenhagen). We calculated blood bicarbonate concentration using the Henderson-Hasselbalch equation.

The remaining portion of blood (5 mL) was dispensed into a tube containing K3 EDTA (1.3 g/L). Duplicate aliquots of whole blood (100 μL) were rapidly deproteinized in 1 mL of ice-cold 2.5% perchloric acid. After centrifugation at 17,500 × g; 4 min, the supernatant was frozen at −20°C and subsequently used to determine lactate concentration (17). Approximately 3 mL of blood was also centrifuged (17,500 × g) with the plasma separated and frozen at −20°C and later used to determine glyceral (18), FFA (Wako NEFA C test kit, Wako Chemicals), and acetate (19) concentration.

The remaining blood in the EDTA tube was used to determine hemoglobin concentration using the cyanmethemoglobin method and whole blood volume by microcentrifugation. The values obtained were used to calculate changes in plasma volume using the equations described by Dill and Costill (20).

Urine analyses. The volume of each urine sample was recorded after an aliquot of urine (~2 mL) was drawn into a syringe, immediately capped, and placed on ice for later determination of POCO2 (ELG 500, Radiometer Copenhagen). An aliquot (20 mL) was also taken and subsequently analyzed for pH using a pH electrode (BDH Gelpas, VWR International) attached to a pH meter (Accumett AB15, Fisher Scientific UK). From the urinary pH and POCO2, the urinary bicarbonate concentration was calculated using the Henderson-Hasselbalch equation. A final 5-ML aliquot was frozen at −20°C and used to determine acetate concentration by GC-MS as described above for plasma acetate (19).

Calculations. The isotopic enrichment in the breath samples was expressed as δ per mil difference between the 13C:12C ratio of the sample and a known laboratory reference standard according to the formula of Craig (21):

\[ \delta^{13}C = \left( \frac{^{13}C^{\text{sample}}}{^{12}C^{\text{sample}}} \right) - 1 \times 10^3 \text{ per mil} \]

The δ 13C was then related to an international standard (PDB).

Acetate oxidation was calculated according to the following formula:

\[ \text{Acetate oxidation} = \frac{V_{\text{CO2}} \left( \delta \text{Exp} - \delta \text{Ex}_{\text{basal}} \right)}{\left( \delta \text{Ing} - \delta \text{Exp}_{\text{basal}} \right)} \times (1/k) \]

where δ Exp is the 13C enrichment of expired air following ingestion of sodium acetate, δ Ing is the 13C enrichment of the ingested solution,
\[ \delta \text{Exp}_{\text{bic}} \] is the $^{13}$C enrichment of expired air at the matched time point during the bicarbonate trial, and \( k \) is the volume of CO$_2$ (in liters) produced by the oxidation of 1 g acetate (2 mol/L mol = 44.8 L of CO$_2$/136.08 g = 0.329 L of CO$_2$/g). The appearance of $^{13}$C is low at rest following administration of carbon-labeled tracers. A correction factor of 54% was therefore used in the acetate trial to account for loss of label within the bicarbonate pool and via nonoxidative pathways (22,23).

Total carbohydrate and fat utilization were calculated according to Frayn (24). During the NaAc trial, postingestion fat and carbohydrate oxidation was calculated after the VO$_2$ and VCO$_2$ values were corrected to account for oxidation of the ingested acetate. The metabolic calculations were performed according to those detailed by Akanji et al. (10). Briefly, the oxidation of 1 mol NaAc consumes 2 mol O$_2$ (44.8 L) and liberates 1 mol CO$_2$ (22.4 L) (10,16,25). These values were then subtracted from the total VO$_2$ and VCO$_2$ during the 180-min postingestion period to give the nonacetate VO$_2$ and VCO$_2$ from which postingestion fat and carbohydrate utilization was based. Energy expenditure was also calculated according to Elia et al. (26). A comparison of the substrate oxidation pre- to postingestion was made based upon the assumption that because the subjects were in a fasted state, the preingestion substrate oxidation rates would have remained constant had the sodium salts not been ingested. The preingestion substrate utilization rates were thus converted into an absolute amount that would be oxidized over a similar 180-min period.

**Statistical analysis.** After testing for normality of distribution using the Kolmogorov-Smirnov test, the blood gas variables and blood metabolites were analyzed using a 2-way ANOVA (SPSS version 12) with repeated measures (trial x time). Where a significant interaction was found, we performed a Tukey’s post-hoc test. Where a significant main effect for time was observed, further 1-way ANOVA was performed with the Tukey’s test used to identify the significant mean differences. All other data were analyzed using paired t-tests. Results are presented as mean ± SEM. Differences were considered significant at \( P < 0.05 \).

### Results

**Substrate utilization and energy expenditure.** Breath $^{13}$C enrichment (Fig. 1) was similar prior to ingestion of both sodium salts. NaHCO$_3$ ingestion had little effect on breath enrichment, remaining at \( \sim -26.50 \) δ‰ vs. PDB over the 180-min period postingestion (\( P > 0.05 \)). In contrast, ingestion of the 2 mmol/kg body mass NaAc drink markedly increased breath enrichment after 30 min before peaking at 46.07 ± 1.83 δ‰ vs. PDB 90 min postingestion (\( P < 0.01 \)). Breath enrichment then slowly returned toward the baseline value but was still significantly higher than the preingestion value over the last 90 min. After accounting for retention of $^{13}$C in bicarbonate and other nonoxidative pools, we calculated that 80.1 ± 2.3% of the ingested acetate was oxidized during the 180-min postingestion period.

Energy expenditure increased to a similar extent following ingestion of the 2 sodium salts (Table 1). In both cases, the increase in energy expenditure was not due to an increase in carbohydrate oxidation (Fig. 2). Following NaHCO$_3$ ingestion, the amount of fat oxidized increased by 18% compared with preingestion (\( P = 0.01 \)) and this was also higher than the corresponding value during the NaAc trial (\( P = 0.02 \)). In contrast, fat oxidation did not change following NaAc ingestion. Oxidation of the exogenous acetate almost entirely (\( \sim 90\% \)) replaced the additional fat that was oxidized during the bicarbonate trial.

**Blood and urine metabolites.** The plasma acetate concentration was similar prior to the ingestion of both drinks (Fig. 3). Ingestion of NaHCO$_3$ did not affect plasma acetate concentration, but a significant increase occurred 30 min postingestion of the NaAc drink to 1235 ± 256 μmol/L with the concentration remaining elevated until 60 min postingestion (1343 ± 194 μmol/L, \( P < 0.01 \)). Plasma acetate then decreased over the next 30 min and did not differ between trials from 90 min postingestion onwards (Fig. 3).

Urine acetate concentration increased from 62 ± 19 μmol/L preingestion to 3557 ± 803 μmol/L postingestion during the NaAc trial (\( P = 0.002 \)), with 827 ± 123 μmol or 0.60 ± 0.09% of the ingested acetate excreted in the urine. Ingestion of NaHCO$_3$ did not affect urinary acetate concentration (72 ± 17 and 67 ± 17 μmol/L pre- and postingestion, respectively; \( P = 0.86 \)).

Following ingestion of NaHCO$_3$, plasma glycerol and FFA increased over the initial 60 min postingestion and remained higher than the preingestion concentration over the next 120 min (Fig. 3). In contrast, during the NaAc trial, neither plasma glycerol nor FFA concentration changed over the first 60 min postingestion, with the values remaining at \( \sim 53 \) μmol/L and \( \sim 190 \) μmol/L, respectively. Plasma FFA was also significantly lower during the NaAc trial compared with the NaHCO$_3$ trial over this period. Between 60 and 90 min after ingestion of NaAc, plasma glycerol and FFA increased by 14 μmol/L and 110 μmol/L, respectively, and did not differ between trials over the last 90 min (Fig. 3). There was also no difference between trials in the blood lactate response (\( P = 0.51 \)), with the plasma concentration decreasing over time in both trials (Table 2).

The ingestion of the 2 sodium salts similarly increased plasma volume (\( P = 0.29 \)) (Table 2). NaHCO$_3$ ingestion resulted in a rapid increase in plasma volume over the first 30 min postingestion (\( P < 0.05 \)) compared with a smaller and nonsignificant increase (\( P = 0.06 \)) over the same time period following NaAc ingestion. Additional increases occurred over the next 30 min in both trials (\( P < 0.05 \)), with plasma volume remaining relatively

### Table 1: Energy expenditure in men and women pre- and postingestion of NaAc and NaHCO$_3$

<table>
<thead>
<tr>
<th>Time</th>
<th>Energy expenditure</th>
<th>Difference</th>
<th>Energy expenditure</th>
<th>Difference</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>kJ/180 min</td>
<td>%</td>
<td>kJ/180 min</td>
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<tr>
<td>Preingestion</td>
<td>803 ± 43</td>
<td>833 ± 58</td>
<td>803 ± 43</td>
<td>833 ± 58</td>
</tr>
<tr>
<td>Postingestion</td>
<td>896 ± 56$^a$</td>
<td>66 8</td>
<td>916 ± 75$^a$</td>
<td>84 10</td>
</tr>
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$^a$ Values are means ± SEM, \( n = 8 \). *Different from preingestion (\( P < 0.05 \)).

**Figure 1.** Changes in breath enrichment following ingestion of 2 mmol NaAc/kg body mass enriched with [1,2-$^{13}$C] NaAc or NaHCO$_3$. Data are means ± SEM, \( n = 8 \). Letters indicate significant differences, \( P < 0.01 \): a, vs. preingestion; b, between trials at matched times.
stable for the last 90–120 min of the study at ~10.5% during the NaHCO₃ trial and ~11.5% following NaAc ingestion.

Blood gases and acid-base balance. The mean percentage of blood oxygen saturation was similar during the trials (95.1 ± 0.6 vs. 95.3 ± 0.5% during the NaAc and NaHCO₃ trials, respectively). Baseline blood pH, bicarbonate, base excess, and PCO₂ also did not differ between the trials (Fig. 4; Table 3).

Ingestion of the sodium salts induced a mild metabolic alkalosis. Following ingestion of NaHCO₃, blood pH increased after 30 min before peaking at 7.456 ± 0.011 after 60 min. Blood pH then remained significantly higher than at preingestion for the next 120 min. In contrast, following NaAc ingestion, blood pH took considerably longer to increase and was lower compared with the NaHCO₃ trial 30 min postingestion (7.422 ± 0.014 vs. 7.449 ± 0.010, respectively; *P*, 0.01). Blood pH did, however, increase over the next 30 min during the NaAc trial and did not differ between trials over the last 120 min of the study (Fig. 4).

Blood bicarbonate and base excess responded similarly to blood pH during both trials (Table 3). In contrast, blood PCO₂ remained unchanged following ingestion of either sodium salt (Table 3).

Urine pH and bicarbonate excretion. Following ingestion of the sodium salts, urine pH increased from 6.32 ± 0.26 to 7.93 ± 0.06 (*P* < 0.001) during the NaAc trial and from 6.15 ± 0.27 to 7.73 ± 0.29 (*P* = 0.001) during the NaHCO₃ trial. This response was mirrored by an increased amount of bicarbonate excreted in the urine from 2.36 ± 1.15 to 40.30 ± 6.02 mmol (*P* < 0.001) during the NaAc trial and from 1.59 ± 0.53 to 37.49 ± 7.37 mmol (*P* = 0.002) during the NaHCO₃ trial over 180-min periods pre- and postingestion.

Discussion

In this study, the ingestion of 2 mmol/kg body mass NaAc and NaHCO₃ both induced a mild metabolic alkalosis and resulted in similar increases in resting energy expenditure. Despite the absence of a change in carbohydrate oxidation following ingestion of either sodium salt, fat oxidation was significantly higher following NaHCO₃ ingestion compared with the ingestion of NaAc. Furthermore, the increased fat oxidation in the NaHCO₃ trial was almost entirely replaced by the oxidation of exogenous acetate during the NaAc trial. These results demonstrate for the first time, to our knowledge, that increased acetate availability suppresses the increased fat utilization normally stimulated by inducing a mild metabolic alkalosis.

The 8% increase in energy expenditure observed in this study following NaAc ingestion is comparable to the increase (6–12%) observed in previous studies following NaAc infusion (12,13). Ingestion of NaHCO₃ also increased resting energy expenditure in this study despite the low energy content of the administered drink. However, in both cases, this increased energy expenditure...
represents a small (<0.5%) increase in daily energy expenditure. The observed metabolic response during the NaHCO3 trial does, however, support previous work in humans (27) and in canines (28–30), where NaHCO3 administration increased oxygen consumption and/or energy expenditure. The increased energy expenditure during the NaHCO3 trial in our study was entirely consummated in the increase in fat oxidation. This was mirrored by the increase in lipolysis. Indeed, if a recovery factor of 81% was used, which is known to temporarily lost in the bicarbonate and other nonoxidative pools.

The differences in fat oxidation between trials may be due to the differing lipemic responses following ingestion of the sodium salts. Plasma FFA and glycerol were both lower following bicarbonate ingestion compared with acetate ingestion. However, acetate oxidation (Figs. 3 and 4) as a result of an alkalosis-induced increase in lipolysis. In contrast to the response observed during the NaHCO3 trial, acetate ingestion did not affect fat oxidation when compared with the preingestion value. The findings from this study also contrast with previous studies (10,12,13), where NaAC administration suppressed fat utilization compared with preadministration values. The difference in findings may be due to the extent to which acetate contributed to energy expenditure.

Indeed, in our study, acetate oxidation only contributed 10.9 ± 0.2% of total energy expenditure compared with 36 and 40% as reported by Akanji et al. (10) and Burnier et al. (12), respectively. The present findings did, however, demonstrate for the first time, to our knowledge, that by increasing exogenous acetate availability, the increase in fat oxidation observed following NaHCO3 ingestion is suppressed despite the induction of a comparable metabolic alkalosis.

Importantly, our findings were independent of the correction factor used in the acetate trial to account for label (13C) temporarily lost in the bicarbonate and other nonoxidative pools. Indeed, if a recovery factor of 81% was used, which is known to account for loss of 13C in the bicarbonate pool (33) and will therefore almost certainly lead to an underestimate of the true rate of acetate oxidation, there still would have been no change in carbohydrate or fat oxidation pre- and postingestion in the acetate trial. Furthermore, fat oxidation would still tend to be lower following acetate when compared with bicarbonate ingestion using the bicarbonate-only recovery factor (570 ± 68 vs. 694 ± 101 kJ, respectively; P = 0.06).

The differences in fat oxidation between trials may be due to the differing lipemic responses following ingestion of the sodium salts. Plasma FFA and glycerol were both lower in the NaAc trial over the first 60 min compared with NaHCO3 ingestion. It is well accepted that pH influences the rate of lipolysis with a 0.2% of total energy expenditure compared with 36 and 40% as reported by Akanji et al. (10) and Burnier et al. (12), respectively. The present findings did, however, demonstrate for the first time, to our knowledge, that by increasing exogenous acetate availability, the increase in fat oxidation observed following NaHCO3 ingestion is suppressed despite the induction of a comparable metabolic alkalosis.


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It is interesting to note that the glycerol and FFA concentration increased markedly at a time when acetate was returning toward baseline levels, suggesting that the 2 events may be associated. Despite the glycerol and FFA concentrations being lower during the NaAc trial compared with the NaHCO₃ trial over the first 60 min postingestion, they did not differ from the preingestion value. As such, there was no evidence to suggest that acetate inhibited lipolysis per se. We propose, therefore, that acetate may suppress the stimulatory effect that increased blood pH has on lipolysis rather than influencing the basal rate of lipolysis.

The differences in fat utilization between experimental trials may have also been due to a greater change in acetyl group availability in the NaAc trial. Following an infusion of acetate, increases in acetyl-CoA and acetyl carnitine have previously been observed in human skeletal muscle (38–40). Furthermore, such changes in acetyl group availability have been postulated to modulate fat oxidation either through a decrease in free carnitine (due to acetylation of the carnitine pool) and/or increased malonyl-CoA content (through carboxylation of acetyl-CoA by the enzyme acetyl-CoA carboxylase producing malonyl-CoA). Either of these mechanisms would limit fatty acyl-CoA translocation across the mitochondrial membranes. To confirm this hypothesis, further studies incorporating muscle sampling techniques are required to examine changes in malonyl-CoA and free carnitine content when acetate availability is increased.

The effects of acetate administration on lipid metabolism observed in this study may help explain the dyslipidemia observed following long-term hemodialysis, where acetate was employed as the primary buffer in uremic subjects (41,42) and observed following chronic alcohol ingestion (43–45). In both circumstances, significant elevations in plasma acetate concentration were noted. Over the entire 180-min period following acetate ingestion, there appeared to be a mismatch between fat availability and oxidation, with an increase in plasma FFA concentration but no change in fat utilization. This may have resulted in increased lipid storage in and/or VLDL-triglyceride secretion from the liver. This hypothesis is strengthened by the fact that repeated administration of NaAc has been shown to result in hyperlipidemia and hepatic lipid accumulation in rats (46).

In contrast to its effect upon lipid metabolism, administration of NaAc did not affect carboxyhydrate utilization, supporting the findings of Akanji et al. (10) and Burnier et al. (12) but in contrast to the results of Chiolero et al. (13), who reported significantly decreased carboxyhydrate oxidation. The possibility that a higher dose of NaAc than given in our study might suppress carboxyhydrate utilization cannot, however, be discounted, because the dose of acetate administered by Chiolero et al. (13) was 69% higher than we used.

In conclusion, over a 3-h period following the ingestion of a bolus of NaAc (2 mmol/kg body mass), 80% of the administered dose was oxidized, which was quantified using stable isotope techniques. Ingestion of NaAc or NaHCO₃ at this dose resulted in a similar increase in energy expenditure but did not affect the amount of carboxyhydrate utilized. In the NaHCO₃ trial, the increase in resting energy expenditure was attributable to a significant increase in fat oxidation. In contrast, there was no change in fat catabolism following acetate ingestion, with the oxidation of the exogenous acetate almost entirely accounting for the increase in fat oxidation observed during the bicarbonate trial.

The site(s) where NaAc metabolism inhibits fat utilization remains to be elucidated.

Literature Cited


