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Communication

A Single Oral Administration of Acetic Acid Increased Energy Expenditure in C57BL/6J Mice

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We have reported that acetic acid (AcOH) intake suppresses body fat mass and up-regulates the genes involved in fatty acid oxidation, but it is not clear whether the suppression of body fat mass by AcOH administration is due to an increase in energy expenditure (EE). In this study, we investigated to determine whether a single oral administration of AcOH would increase EE in C57BL/6J mice treated with 1.5% AcOH. The AcOH treatment group had significantly higher oxygen consumption (VO₂), EE, and fat oxidation (FAT) than the water treatment group. These results suggest that a single administration of AcOH increases EE, resulting in suppression of body fat mass.

Key words: acetic acid; energy expenditure; fat oxidation; oxygen consumption

Vinegar is made by acetic acid bacteria fermentation in cereals, fruits, etc. Acetic acid (AcOH) is the common and main component of all types of vinegars. We have found that AcOH affects hyperglycemia,¹⁾ hyperlipidemia²⁾ and hypertension.³⁾ In addition, recently we reported that steady vinegar intake for 12 weeks reduced body weight and visceral fat mass in obese subjects.⁴⁾ AcOH is metabolized in the liver to acetyl-CoA, with production of AMP,⁵⁾ which subsequently promotes the phosphorylation of 5'-AMP-activated protein kinase (AMPK).^{1,6,7)} AcOH-induced AMPK activation leads not only to downregulation of the genes involved in glucose metabolism and lipogenesis1,7) but also to upregulation of the expression of the peroxisome proliferator-activated receptor alpha (PPAR α) and fatty acid oxidation genes.8) AcOH-induced AMPK activation may be the underlying mechanism of the observed reduction in body weight and visceral fat mass, but there are no data to show that AcOH intake increases energy expenditure (EE). In this study, we investigated the effect of a single AcOH administration on EE in C57BL/6J mice.

The study was performed following the Guidelines for Animal Experimentation established at the 34th Annual Meeting of the Japanese Association for Laboratory Animal Science, held May 22, 1987. Nine-week-old male C57BL/6J mice were obtained from Charles River Laboratories Japan (Yokohama, Japan). The mice were housed individually in an environment where the temperature was controlled between 22–24 °C and the humidity maintained between 45 and 65%, under a 12-h light-dark cycle (7:00-19:00/19:00-7:00). The animals had free access to water and a purified diet (D12450B) purchased from Research Diets (New Brunswick, NJ) for 2 weeks prior to the investigation. On the first day of the experimental period, the animals were divided into two groups of similar mean body weight (AcOH group, 25.9 ± 0.3 g; water group, 25.8 ± 0.2 g) and food intake. Each mouse was placed into a metabolic chamber and limit-fed (D12450B, 80% of normal intake) during the dark period the day before respiratory gas measurement. This procedure unified the food intake and equalized the metabolic baseline. Food and water were withdrawn at 9:00 h, and the mice were treated at 12:00 h with 1.5% AcOH or water (0% AcOH) at 10 ml/kg of body weight via a stomach tube. CO₂ and O₂ analyzers (ARCO 2000, AlcoSystem, Chiba, Japan) and a metabolic chamber were used to assess the metabolic rate. The amounts of oxidized fat (FAT) and carbohydrate (CHO) were calculated as described by Ishihara et al.⁹⁾

All experimental data were analyzed using SPSS for Windows (version 11.5 J; SPSS, Chicago, IL). For intergroup comparisons, we performed analysis of covariance with a *post hoc* Bonferroni test using the value at 0 h as the covariate to control for the initial differences and reduce the error variance. For intragroup comparisons, we performed one-way repeated analysis of variance with a *post hoc* Dunnett test using the value at 0 h as the reference. Differences were considered significant at p < 0.05. Values are presented as mean \pm standard error (SE).

In the AcOH group, the VO₂, EE, CHO, and respiratory quotient (RQ) values were significantly higher at 1 h than at 0 h, whereas in the water group, the VO₂ and EE values were only marginally higher (p < 0.1) at this stage (Table 1). The higher VO₂ in the AcOH group was significant at 2 h and marginal (p < 0.1) at 3 h as compared with the water group. EE and FAT were significantly different in the AcOH group as compared with the water group at 3 h. Although CHO was higher in the AcOH group than in the water group, no significant difference was observed. These observations may explain why there was no change in the RQ value.

In this study, significantly higher VO₂, EE, and FAT were observed in the C57BL/6J mice. Although the calorific value of AcOH is 3.5 kcal/g^{10} and the AcOH

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Abbreviations: AcOH, acetic acid; AMPK, 5'-AMP-activated protein kinase; CHO, carbohydrate oxidation; EE, energy expenditure; FAT, fat oxidation; PPAR α , peroxisome proliferator-activated receptor alpha; RQ, respiratory quotient; VO₂, oxygen consumption

AcOH Administration Increased Energy Expenditure

Table 1.	Oxygen	Consumption,	Energy	Expenditure,	Fat Oxidation,	Carbohydrate	Oxidation,	and RQ	Values
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		0 h	1 h	2 h	3 h
VO ₂ (ml/h/g body wt)	Water AcOH	2.68 ± 0.06 2.62 ± 0.07	2.84 ± 0.05 $2.89 \pm 0.07^{\dagger}$	$\begin{array}{c} 2.60 \pm 0.06 \\ 2.76 \pm 0.06 \end{array}^{*}$	2.58 ± 0.05 2.66 ± 0.08
EE (cal/h/g body wt)	Water AcOH	$\begin{array}{c} 12.84 \pm 0.30 \\ 12.53 \pm 0.40 \end{array}$	13.57 ± 0.24 $13.96 \pm 0.27^{\dagger}$	$\begin{array}{c} 12.42 \pm 0.29 \\ 12.71 \pm 0.42 \end{array}$	$\frac{12.27 \pm 0.23}{13.10 \pm 0.22}^{*}$
FAT (mg/h/g body wt)	Water AcOH	$\begin{array}{c} 1.02 \pm 0.03 \\ 1.02 \pm 0.04 \end{array}$	1.06 ± 0.03 1.04 ± 0.04	1.01 ± 0.02 1.03 ± 0.04	$\begin{array}{c} 0.99 \pm 0.02 \\ 1.04 \pm 0.02 \end{array}^{*}$
CHO (mg/h/g body wt)	Water AcOH	$0.83 \pm 0.05 \\ 0.76 \pm 0.05$	$0.93 \pm 0.04 \\ 1.07 \pm 0.06^{\dagger}$	$0.74 \pm 0.04 \\ 0.77 \pm 0.04$	$0.76 \pm 0.05 \\ 0.84 \pm 0.05$
RQ	Water AcOH	$\begin{array}{c} 0.773 \pm 0.003 \\ 0.769 \pm 0.004 \end{array}$	$0.776 \pm 0.003 \\ 0.785 \pm 0.006^{\dagger}$	$\begin{array}{c} 0.767 \pm 0.002 \\ 0.768 \pm 0.003 \end{array}$	$\begin{array}{c} 0.769 \pm 0.004 \\ 0.771 \pm 0.003 \end{array}$

VO2, oxygen consumption; EE, energy expenditure; FAT, fat oxidation; CHO, carbohydrate oxidation

Average of 1 h before AcOH administration (0 h), and every hour for 3 h after AcOH administration (1, 2, 3 h)

*Significantly different between water and AcOH group

[†]Significantly different from the value at 0 h

energy administered was about 15.7 cal per individual, the differences in total EE for the 3 h after administration between the AcOH group and water group measured at 3 h was 63.0 cal per individual. Therefore, it is reasonable to suggest that AcOH suppresses body fat accumulation, as reported previously.⁸⁾

The values for VO_2 , EE, CHO, and RQ at 1 h after administration in the AcOH group were significantly higher than the values at 0 h. These values might have been affected by the action of administration, because increases were also observed in the water group. The increases were not significant, however, and there were no significant differences between the groups.

We focused mainly on the significant differences in VO₂, EE, and FAT because our previous study indicated that AcOH administration upregulated the expression of PPAR α and fatty oxidation-related genes in the liver 3 h after administration.⁸⁾ Although there was a time lag in the elevation of EE and FAT from AcOH administration in this study, it was found previously using HepG2 cells that genes encoding PPAR α and fatty oxidation-related enzymes need a few hours to up-regulate from the time of acetate treatment.⁸⁾ Therefore, the occurrence of this time lag after AcOH administration is not unexpected. Hereafter we intend to do further studies to investigate PPAR α and fatty oxidation-related gene expression due to a single oral administration of AcOH.

Ichikawa et al.¹¹⁾ reported that in OLETF rats continuously administrated powder of bitter melon malt vinegar, the rate of EE was higher than in the control group, although the effective components were not clearly identified. Yamashita et al.¹²⁾ found that AcOH administration increased the rates of VO₂. These results suggest that the AcOH in vinegar is the component that affects the metabolic rate. However, Yamashita et al. measured metabolic rates after 6 months of continuous AcOH administration, when significantly lower body weight was observed, and reported that the subjects with higher body mass index had lower VO₂.¹³⁾ Therefore, the higher VO₂ of the AcOH administration group in Yamashita's study can be considered not the reason AcOH reduces body weight gain, but a reflection of lower body weight. In this study, however, a single oral administration of AcOH was found to increase EE and VO_2 in C57BL/6J mice without any difference in body weight. This suggests that the lower body weight gain upon AcOH administration was caused by higher EE.

In conclusion, significantly higher VO₂, EE, and FAT were observed under single oral AcOH administration in C57BL/6J mice. This effect is perhaps caused by upregulation in the gene expression of PPAR α and fatty oxidation-related enzymes. We have reported that vinegar intake, AcOH being the main component, reduces body weight and body fat mass in obese subjects. Now we intend to do further clinical studies to investigate the effects of AcOH on EE.

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¹All values are mean \pm SE; n = 9