The Effect of Intravenous Infusion of Acetate on Glucose-Induced Insulin Secretion in Sheep

Hitoshi Mineo, Miki Nishimura, Seiyu Kato and Jun-ichi Ushijima

Department of Veterinary Medicine, The College of Dairying, Ebetsu-shi 069

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Abstract The effect of intravenous infusion of acetate on glucose-induced insulin secretion in sheep was examined. Intravenous infusion of acetate at the dose of \(10^{-6}, 10^{-5}\) and \(10^{-4}\) mol/kg/min for 130 min did not affect both concentrations of plasma glucose and insulin. Glucose injection (0.5 mmol/kg) increased plasma glucose concentration similar in any infusion of acetate and physiological saline. The concentration of plasma insulin after glucose injection under the acetate infusion was higher than under the saline infusion. The degree of the enhancement effect of acetate on glucose-induced insulin secretion was similar in any infusion rate of \(10^{-6}, 10^{-5}\) and \(10^{-4}\) mol/kg/min. Though acetate in blood may not stimulate insulin secretion strongly, it may be able to activate the response of pancreatic B cell to glucose in sheep.

Key word: acetate, insulin, sheep

It has been reported that the short chain fatty acids, produced by rumen fermentation, stimulate insulin secretion in ruminants. This effect is known to be stronger in propionate and/or butyrate than in acetate, both in vivo\(^{1-9}\) and in vitro\(^{10,11}\) experiment. Since little propionate and butyrate could be reached the pancreas due to prior metabolism by the rumen epithelium and the liver following absorption in physiological state\(^{12}\), STERN et al.\(^{13}\) concluded that propionate and butyrate are probably not major physiological regulators of insulin secretion in goats. In contrast with propionate and butyrate, acetate is largely produced in the rumen, presented in blood and utilized for principal energy source in ruminants. However, there are very few reports whether acetate has any physiological significance on insulin secretion in ruminants. Therefore we examined the significance of acetate presented in blood on insulin secretion induced by glucose in sheep.

Materials and methods

Three crossbred wethers, weighing 36.0-37.0 kg, were used. They were housed in metabolic cages and fed orchard grass hay (100 g) and alfalfa pellets (2% of body weight) once daily at 19:00. Water was available freely. The left common carotid artery had been exteriorized in a loop of skin at least two months before experiments.
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began. In addition, polyethylene catheters were inserted into both jugular vein at least a week before experimentation. The catheters were flushed and filled with sterilized solution of 3.8% trisodium citrate.

Expt. 1: To test the effect of intravenous infusion of acetate on insulin secretion, solutions of sodium acetate were given through a polyethylene catheter at constant rates \((10^{-6}, 10^{-5} \text{ and } 10^{-4} \text{ mol/kg/min})\) for 130 min by a peristaltic pump. Physiological saline was infused as a control. Blood was collected through indwelling catheter placed in the carotid artery before the start of sampling. Sampling of arterial blood was undertaken from 20 min before and during the infusion period.

Expt. 2: The effect of intravenous infusion of acetate on insulin secretion induced by glucose was examined. Physiological saline or acetate were infused to one jugular vein from 30 min before the glucose injection until the end of experiment. Solution of glucose (1 M) was injected through the other jugular venous catheter at a dose of 0.5 mmol/kg body weight in about one minute. Infusion rates of acetate were the same to Expt. 1, though the infusion period was 150 min. Sampling of arterial blood was undertaken from 45 min before the injection of glucose. All experiments were begun at 10:00. The pH of sodium acetate solution was adjusted to 7.4 with NaOH and the rate of infusion was 1 ml/min. Blood sample was taken in heparinized syringe and immediately transferred into polyethylene test tube cooled in water with ice. Plasma was separated by centrifugation at 4°C and stored at −20°C for analysis. Glucose was determined by glucose oxidase method\(^{14} \). Insulin assay was due to the method of radioimmunoassay by Sasaki and Takahashi\(^{15} \).

The values are expressed as mean±standard error of mean. The results were analyzed statistically by the Student’s \(t\)-test.

**Results**

Expt. 1: Intravenous infusion of physiological saline for 130 min did not change both plasma glucose and insulin levels in sheep. Acetate infusion also did not affect the glucose and insulin concentration in all infusion rates (Fig. 1).

Expt. 2: The results are shown in Fig. 2. Increase of plasma glucose and insulin immediately after glucose injection was statistically significant as compared with the preinjection value in all infusion rates \((P<0.05)\). In the saline control, glucose injection increased plasma glucose concentration from preinjection value of 64.9±1.2 mg/100 ml to a maximum of 107.3±3.3 mg/100 ml five min after the injection. Similar increases of plasma glucose concentration were observed by glucose injection during the acetate infusion at rates of \(10^{-6}, 10^{-5} \text{ and } 10^{-4} \text{ mol/kg/min} \). The significant difference of plasma glucose concentration was not observed between in the saline and the acetate infusions. Plasma insulin concentration was increased by glucose injection from a preinjection value of 6.6±0.2 \(\mu U/ml\) to a peak of 31.5±5.4 \(\mu U/ml\) in the saline control. This response had a tendency to be enhanced by the acetate infusion at rates of \(10^{-6}, 10^{-5} \text{ and } 10^{-4} \text{ mol/kg/min} \) and the peak values of plasma insulin were 69.4±32.9, 74.2±32.9 and 72.3±9.7 \(\mu U/ml\), respectively. The significant increase of
Fig. 1. Effect of acetate infusion on insulin and glucose concentration in plasma of sheep. Three sheep received intravenous infusion of physiological saline and sodium acetate at three doses ($10^{-6}$, $10^{-5}$ and $10^{-4}$ mol/kg/min) for 130 min as indicated by horizontal bar. Vertical bars show standard error of mean.

Fig. 2. Effect of glucose injection on insulin and glucose concentration in plasma of sheep during saline and acetate infusion. Physiological saline and sodium acetate were infused intravenously at three doses ($10^{-6}$, $10^{-5}$ and $10^{-4}$ mol/kg/min) for 150 min as indicated by horizontal bar. Vertical bars show standard error of mean. Glucose (0.5 mmol/kg) was injected at zero time. (□) indicates a significant difference from the value immediately before glucose injection ($p<0.05$). * indicates a significant difference between the saline and the acetate infusions at each sampling time ($p<0.05$).
plasma insulin was observed in the acetate infusion at a rate of $10^{-4}$ mol/kg/min as compared with that in the saline infusion ($P < 0.05$).

**Discussion**

In Expt. 1, plasma insulin and glucose concentrations were not changed by the infusion of acetate at three doses. These results do not suggest that the insulin secretion is not stimulated by acetate in sheep. A larger dose and/or rapid injection of acetate was reported to stimulate insulin secretion in sheep\(^7\). The response of insulin secretion may not become clear, because acetate was infused slowly at low dose in this experiment. In Expt. 2, glucose injection caused a rapid increase in plasma glucose and insulin concentrations during both saline and acetate infusions. Peak values of plasma glucose after glucose injection during acetate infusion at each rate were approximately similar to saline control. However, the concentration of plasma insulin after glucose injection had a tendency to be higher in the acetate infusion than in the saline control. The significant increment of insulin was observed by glucose injection during the acetate infusion at a rate of $10^{-4}$ mol/kg/min. These results seem to suggest that acetate in blood can enhance insulin secretion induced by glucose injection in sheep. It has been reported that acetate, used as a metabolite of ethanol, potentiated glucose-induced insulin secretion in the rat both *in vivo*\(^6\) and *in vitro*\(^7\) experiments. The mechanism of this effect of acetate on insulin secretion induced by glucose is not clear. SASAKI *et al.*\(^18\) reported that the insulin response to glucose in sheep was increased during the feeding on roughage diet. Our results may explain their finding. In monogastrics of which energy source is glucose, glucose has known to be a most important stimulating factor for insulin secretion in physiological state and, at the same time, to enhance the insulin release from islets of Langerhans by other stimulating agents\(^19\). Ruminants utilize short chain fatty acids, produced by microbial fermentation in the rumen, for energy source. Acetate is largely produced and utilized as compared with other short chain fatty acids in ruminants. It has been reported that acetate utilization is strongly dependent on the level of insulin, as indicated by the high levels of acetate occurring in the blood during alloxan diabetes in sheep\(^20\). So, it seems to suggest that acetate in blood can activate response of pancreatic B cell to glucose, though acetate itself may not stimulate strongly insulin secretion in sheep. In this experiment, dose-response manner was not observed between the infusion rate of acetate and peak value of insulin response to glucose. Further study is necessary to investigate the physiological significance and mechanism of insulin secretion from endocrine cell of pancreas in sheep.

**References**

めん羊のグルコース誘起性インスリン分泌に対する
酢酸塩の静脈内注人への効果

峰尾 仁・西村美樹・加藤清雄・牛島純一

酪農学園大学獣医学科、江別市 069

めん羊のグルコース誘起性インスリン分泌に対する、
酢酸塩の静脈内注人への効果について検討した。酢酸塩を
10^{-6}, 10^{-5} および 10^{-4} mol/kg/min の用量で、130 分
間にわたり静脈内に連続注入したが、血漿グルコースおよ
びインスリン濃度に影響を及ぼさなかった。グルコース
注人は (0.5 m mol/kg) では、酢酸塩および生理的食塩
水連続注入時において、血漿グルコース濃度を同程度に
上昇させた。グルコース注入後の血漿インスリン濃度は、
食塩水連続注入時よりも、酢酸塩連続注入時の方が高かっ
た。グルコース誘起性インスリン分泌に対する酢酸塩の
増強効果の大きさは、10^{-6}, 10^{-5} および 10^{-4} mol/
kg/min の連続注入割合においても同じであった。めん羊
においては、血液中の酢酸塩はインスリン分泌を
強く刺激することはないが、グルコースに対する肝臓
B 細胞の反応を活性化する可能性がある。

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