

## The Effects of Vagotomy on Hyperglycemia by Ruminant Administration of Butyric Acid in Sheep

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(Received, July 23, 1971)

### Summary

Intact and vagotomized sheep were infused with butyric acid continuously through the reticulo-rumen and the subsequent changes in blood glucose concentration were determined.

The infusion of butyric acid caused a remarkable increase in blood glucose level in intact sheep but the response was completely absent in the vagotomized sheep.

About 70 percent of the energy requirements of ruminants are supplied by volatile fatty acids (VFA) produced by fermentation of the feed in the reticulo-rumen. In addition, carbohydrate requirements of ruminants are met largely by gluconeogenesis in the liver. It can be predicted, through established metabolic reaction, that propionate is convertible into carbohydrate in the animal body.

The fact that the intravenous infusion of butyrate in sheep results in a marked increase in the plasma glucose level was first shown by Potter (1), and subsequently confirmed by Ash, Pennington and Reid (2). Phillips, Black and Moller (3) used adrenalectomized and insulin treated sheep. They also demonstrated butyric acid hyperglycemia. Recently, Phillips et al. (4) and Jones et al. (5) reported that pancreatectomy abolished the hyperglycemic response observed after butyrate injection in sheep.

During a series of investigations on the relationship between the rumen conditions and the parotid saliva secretion rate, the present authors unexpectedly found that the hyperglycemia which usually occurred after butyrate administration into the rumen was not developed in the vagotomized sheep. In this paper, the data and the possible reasons of this finding are presented.

### Experimental Procedure

The experimental animals used were two female sheep of the same body weight. Both animals had permanent ruminal fistulas, carotid arterial loops and

unilateral parotid fistulas. The body weight of each sheep was maintained at around 40 kg by daily feedings of 500 g of hay and 400 g of a commercial concentrate.

The trial was carried out in the following manner. The rumen contents were withdrawn as much as possible through the ruminal fistula and the wall of reticulo-rumen was washed by water warmed at 40°C. Then, the reticulo-omasal orifice was plugged by Watanabe's method (6), and 3 liters of artificial ruminal solution (7) (pH 7.2) were introduced into the reticulo-rumen. Thirty minutes later, the first arterial blood sample was taken through the carotid loop to know the control glucose and VFA concentrations. Then again thirty minutes later, the necessary amount of 0.5 M butyric acid to reduce the rumen pH from 7.2 to 5 was introduced into the reticulo-rumen. The rumen pH was maintained at 5 for two hours by the dripping of 0.5 M butyric acid appropriately into the reticulo-rumen where the pre-settled glass electrode pH meter recorded the rumen pH automatically. Immediately after the first administration of the butyric acid a second blood sample was taken. Blood samples were taken every 60 minutes thereafter for three hours. The reason for rumen pH reduction to 5 was that the authors first intended in this experiment to discover the relationship between the parotid secretion rate and the lower level of rumen pH. The data on the parotid saliva secretion will be published elsewhere. The above mentioned trial was carried out using an intact sheep as the control experiment. A vagotomy was performed on the same sheep three months after the control experiment. On the next day after the operation the same trial as above mentioned was performed on the vagotomized sheep.

**Surgical procedures of vagotomy:** Both dorsal and ventral abdominal vagus nerves were isolated from the surrounding connective tissues and were divided at the esophagus region between diaphragm and the cardia. In order to confirm the completeness of the vagotomy, the peripheral end of the ventral abdominal vagus was electrically stimulated to observe the motility of the reticulo-rumen. Section of both vagus was followed by cessation of rumen and reticulum motilities. The amount of feed consumed decreased and rumination was never observed in the vagotomized sheep. The vagotomized animals survived for 7-10 days after operation. In sheep A, two ulcers were found in the rumen by the post-mortem examination.

The blood glucose concentration was determined by the glucose oxidase method of Hugget and Nixon (8). The total VFA concentration in the blood was determined by Friedmann's method (9).

### **Results and Discussion**

The changes of blood glucose concentration accompanied with butyric acid administration into the reticulo-rumen of intact and vagotomized sheep are

shown in Figure 1. In the control experiment, the total amounts of butyric acid required to reduce the ruminal pH to 5 and to maintain it at that level for two hours were 0.60 and 0.63 moles in sheep A and sheep B, respectively. However, in the vagotomized animals, it was 0.49 and 0.50 moles in sheep A and sheep B, respectively. The VFA concentration of rumen content was maintained at 80 mM during the pH maintenance period in both animals. In the control experiment, the blood glucose concentration increased immediately after the addition of the butyric acid into the rumen. Even when the butyrate was infused continuously to the rumen, the blood glucose concentration decreased during the second hour of the experiment. The blood glucose increment could not be observed in the vagotomized sheep.

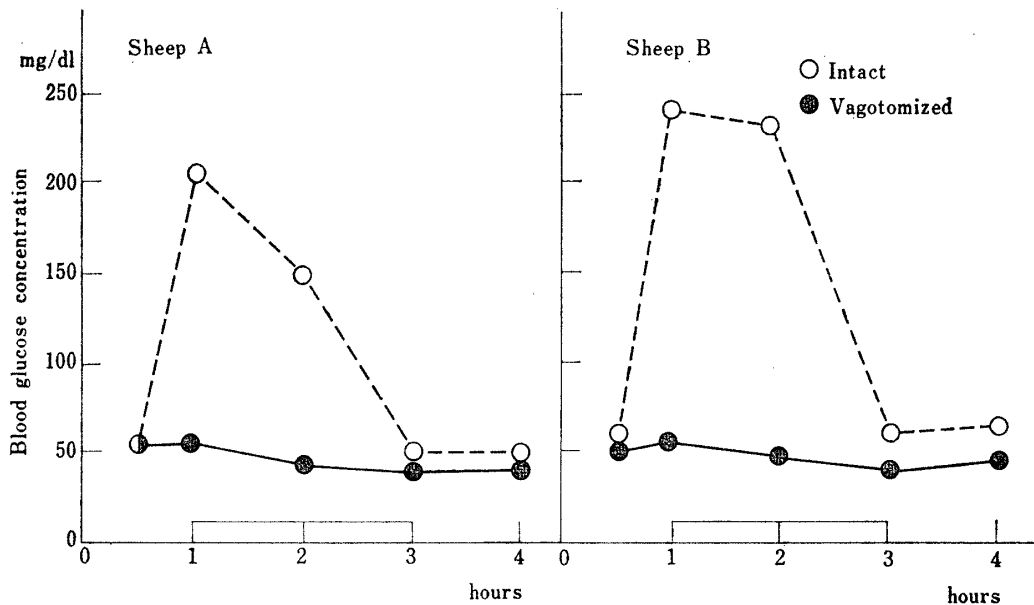


FIG. 1. Changes of the blood glucose concentration caused by butyric acid administration into the reticulo-rumen of intact and vagotomized sheep.

Rumen pH was maintained at 5 from 1 to 3 hour by continuous infusion of 0.5 M butyric acid.

Many investigators reported that the intravenous infusion of butyrate resulted in a marked increase of blood glucose level in sheep. However, Armstrong and Blaxter (10) reported that the infusion of butyric acid into the rumen does not cause hyperglycemia. Recently Stern *et al.* (11) observed that the intraruminal infusion of butyrate resulted in the increases of butyrate and glucose levels in peripheral blood. The present authors observed the remarkable increase of blood glucose level by the butyric acid introduction into the reticulo-rumen.

The changes of VFA concentration in arterial blood accompanied with butyric acid administration into the reticulo-rumen of intact and vagotomized sheep are shown in Figure 2. The VFA concentration in blood increased by the addition of

the butyric acid into the reticulo-rumen. The increment of VFA concentration in intact sheep was greater than that in vagotomized sheep, especially in sheep B. The mechanism of this is not known, however, the possible reasons are i) decrease of absorption rate through the rumen epithelium, ii) promoted metabolism of absorbed butyrate in the tissues. The two observations i.e. that the necessary amount to maintain rumen pH at 5 for two hours are larger and that the recovery of pH to normal level after the end of experiment are faster in intact sheep than in vagotomized sheep, may support the first assumption. On the other hand, the amount of parotid saliva decreased remarkably but its inorganic ion concentrations remained unchanged in vagotomized sheep.\*

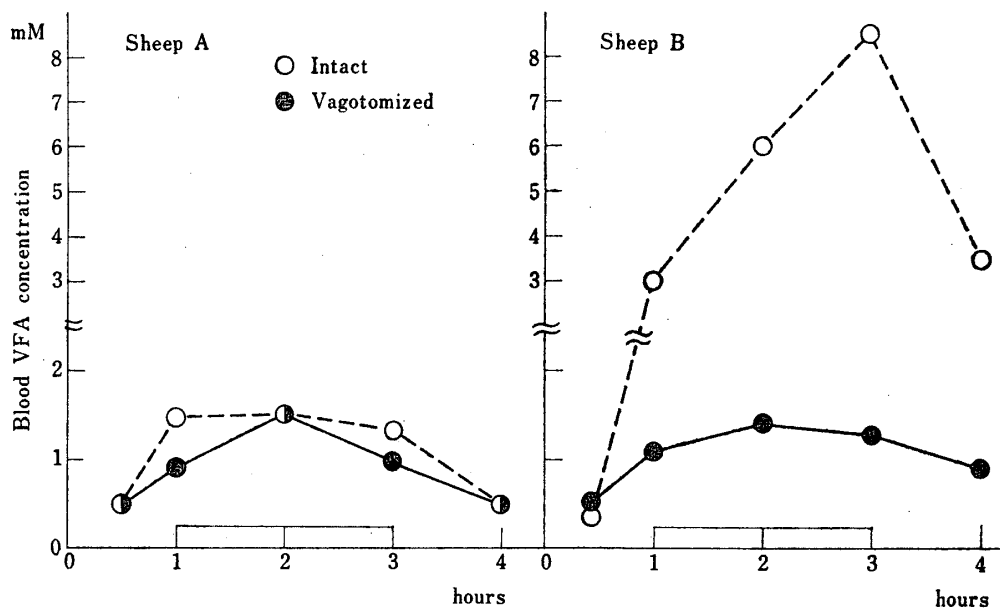


FIG. 2. Changes of the blood VFA concentration caused by butyric acid administration into the reticulo-rumen of intact and vagotomized sheep. Rumen pH was maintained at 5 from 1 to 3 hour by the continuous infusion of 0.5 M butyric acid.

On the mechanisms of butyric acid hyperglycemia, Ash et al (2) reported that the results of the study with  $^{14}\text{C}$ -butyrate with liver slices lead to the assumption that butyric acid induced hyperglycemia is not due to the accelerated gluconeogenesis nor a direct glycogenolytic effect of the butyrate in the liver. Phillips et al. (3) concluded that the butyric acid hyperglycemia was not due to the excess of adrenalin release. According to Phillips et al. (4) and Jones et al. (5), the mechanism of butyrate induced hyperglycemia may be mediated via the pancreas. They suggested that butyrate may stimulate the release of glucagon in the pancreas, which causes the increase of active phosphorylase level in the liver and the subsequent breakdown of glycogen. There was very little report on nervous

\* Obara, Y. et al, unpublished data.

control of glucagon secretion in pancreas. Yoshioka (12) demonstrated in the experiment using adrenalectomized and aloxan treated dog that the stimulation of vagus accelerated both insulin and glucagon secretion.

From the available data already published, it may be concluded that butyrate stimulates the glucagon release which causes a major part of the blood glucose level increase. In the present study, it was not examined whether or not vagotomy inhibited the glucagon secretion. However, it could be assumed that the vagus had a certain role on the development of butyrate hyperglycemia.

### Acknowledgement

The authors are grateful to Mr. Yasushi Ohtomo for management of the experimental animals.

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