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ABSENCE OF FEEDING-INDUCED VARIATIONS IN PLASMA INSULIN IN HYPOGLYCAEMIC-KETONAEMIC COWS

By

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HOVE, K. and K. HALSE: *Absence of feeding-induced variations in plasma insulin in hypoglycaemic-ketonaemic cows.* Acta vet. scand. 1978, *19*, 215—228. — The effects of food intake on plasma insulin levels were studied in 38 cows with plasma sugar ranging from 41 to 86 mg/100 ml and acetoacetate (Acac) ranging from 0.2 to 18 mg/100 ml, measured before morning feeding. The animals were fed concentrates, silage and hay. Blood samples were taken immediately before feeding in the morning and at intervals of ½ to 1 hr. during the following 4 hrs.

In animals with low blood Acac, plasma insulin concentrations began to increase as early as ½ hr. after the start of feeding and reached maxima after 2 hrs. Simultaneously Acac increased and sugar decreased markedly. Animals with Acac levels > 1 mg/100 ml had low pre-feeding insulin concentrations, and the level of the hormone did not increase after feeding. They did not show systematic changes in Acac. But plasma sugar tended to decrease when food was given, even in the absence of insulin increments in peripheral blood.

Glucose was infused at a low rate (0.9 g/min.) for 18 hrs. into a hypoglycaemic, ketonaemic cow. As her glucose and ketone levels became normalized, she also responded to feeding with insulin increments. But throughout the experiment her plasma insulin remained considerably lower than in an identically treated control animal which had low Acac levels before the infusion. It appears that the endocrine adjustments during ketonaemia in cows include, beside low basal (pre-feeding) insulin levels, an inhibition of the normally occurring elevation of plasma insulin after feeding.

plasma insulin; ketonaemia; hypoglycaemia; effects of feeding; stage of lactation; dairy cows.

The concentration of circulating insulin plays a central role in metabolic regulation by coordinating the storage and mobilization of carbohydrates, amino acids and fats (*Cahill* 1971, *Basset* 1975). Low insulin appears to serve as a common signal for the

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mobilization of stored energy substrates in mammals. But the effects of insulin on lipolysis are poorly investigated in ruminants according to *Yang & Baldwin* (1973) and *Bauman & Davis* (1975). Under normal conditions of management, daily maxima in the plasma insulin concentration of cows are reached during the first few hours after a meal, while minima are usually observed in the hours just before morning feeding (*McAtee & Trenkle* 1971, *Hove & Blom* 1973, 1976, *Basset* 1974 a, b).

Positive correlations have been obtained between glucose entry rate and plasma insulin in sheep (*Basset et al.* 1971) and between plasma insulin and sugar levels in lactating cows (*Hove* 1974, *Schwalm & Schultz* 1976) and sheep nourished by infusions (*Tao et al.* 1974, *Tao & Asplund* 1975). These findings indicate that the activity of the endocrine pancreas is regulated by the availability of glucose in about the same way in ruminants as in other mammals. Other evidence points to the existence of non-glycaemic stimuli to the ruminant pancreas, however. Contrary to findings in monogastric animals, increments in plasma insulin after a meal in cows are frequently associated with a decrease in the blood sugar level (*Hove & Blom* 1973, 1976).

In bovine ketosis, metabolically characterized by hypoglycaemia, high levels of plasma free fatty acids and low insulin levels, the plasma insulin response to glucose loading appears to be abnormally small (*Hove* 1974, *Schwalm & Schultz, Hove,* to be published). A sluggish pancreatic β-cell function in such patients, seemingly compelled to spare glucose and to maintain a high rate of lipolysis, is consistent with findings in other species.

Further evidence of a low activity of the endocrine pancreas in hypoglycaemic-ketonaemic cows is presented in the following report concerning plasma insulin responses to feeding in cows with varying levels of ketones and glucose in blood plasma.

MATERIAL AND METHODS

Dairy cows of Norwegian Red breed, belonging to two different experimental herds, were used for the study.

Effects of feeding

Blood samples from 38 lactating cows were taken immediately before and at ½, 1, 2, 3 and 4 hrs. after start of morning feeding. The cows could be divided into four groups according to plasma concentrations of acetoacetate and stage of lactation (Table 1).

A control series of measurements was performed on five cows (C in Figs. 1, 2 and 3) in the low Acac range, from which food was withheld during 4 hrs. in the morning.

Effects of feeding during glucose infusion

Two cows were used for this experiment. Fagerlin: 10 years of age, 12 days post partum, milk yield 25 kg/day and Frida: 7 years old, 120 days post partum, milk yield 20 kg/day. The cows differed with regard to plasma Acac and sugar: Fagerlin was markedly ketonaemic and had a lower plasma sugar level than Frida. Her appetite seemed unimpaired, however. Both cows were fed and milked at ordinary intervals. The two cows were equally treated: Subsequent to an observation period of 30 hrs., during which 20 blood samples were taken, they received glucose intravenously by continuous infusion at a rate of 0.9 g/min. for 18 hrs. During the infusions 15 blood samples were taken. The animals were fed three times in the pre-infusion period, and once while glucose was administered.

Feeding

The rations consisted of grass silage, hay and concentrates. Silage and concentrates were provided at the beginning of the meal with an interval of about 20 min., and were consumed in the course of 1—1.5 hrs. Hay was given after 2 hrs. and consumed during the next 2 hrs.' period. The feed rations were allotted approximately according to protein and energy requirements, but the amounts of the different feeds consumed by individual cows were not accurately determined. Thus, the possibility of some degree of underfeeding as a cause of ketonaemia cannot be excluded.

Milking

Milking was performed at accustomed hours while the cows were eating the silage rations. The yields reported are based on routine measurements made at time intervals of three days to a fortnight from the day of blood sampling.

Blood sampling

For the determination of feeding effects, blood was drawn from the jugular vein with heparinized vacutainers. In the infusion experiment each animal was equipped with indwelling catheters in both jugular veins 2 hrs. before the first blood collection, one catheter for sampling (heparinized syringe) and one for the infusion. To avoid clotting the catheters were filled with heparinized saline when not in use. The blood samples were centrifuged immediately and plasma was stored at – 20 °C until analysed.

Analytical procedures

Plasma insulin was measured by radioimmunoassay using dextran-coated charcoal to separate bound and free insulin (*Poznanski & Poznanski* 1969). Crystalline bovine insulin and guinea-pig antibody against bovine insulin were used as reagents (*Hove* 1974).

Plasma sugar and Acac were determined by automated photometric methods. Sugar was estimated by the reduction of ferricyanide and Acac by the nitroprusside reaction in plasma dialysates (*Blom & Halse* 1975).

Statistical evaluation

Wilcoxon test for paired comparisons has been used unless otherwise stated. Correlation coefficients were calculated according to conventional parametric procedures. $P < 0.05$ was taken to represent statistical significance (two-tailed tests).

RESULTS

When the animals were grouped (Table 1 and Figs. 1—3), account was taken of the fact that bovine ketosis mainly occurs in early lactation. The Acac ranges used (Table 1) were chosen on the basis of extensive measurements of pre-feeding Acac and sugar levels in the blood plasma of indoor-fed cows (*Halse et al.*, to be published). From these studies it appeared that at stages of lactation where the susceptibility to ketosis is low (> 90 days post partum), the majority of animals had pre-feeding Acac values well below 1 mg/100 ml of plasma (Acac > 0.75: frequency about 1 %). Thus 1 mg/100 ml could be looked upon as the upper limit of a physiologically defined basal range for Acac in cows' plasma. In comparison, values above 1 mg/100 ml, frequently found in recently calved, high-yielding cows, can be

Table 1. Groups of cows representing different ranges of pre-feeding plasma acetoacetate (Acac) and different stages in the lactation cycle in Figs. 1—3. Early (< 90 days post partum) and late lactation (> 90 days post partum). Corresponding plasma sugar and milk yields. n = number of animals. Means and standard deviations.

Group	n	Acac, mg/100 ml	Stage of lactation	Plasma sugar, mg/100 ml	Milk yield, kg/day
1	15	low (< 1.0) 0.43 ± 0.19	early	79.9 ± 4.6	21 ± 4
2	4	moderately elevated (1.0—6.0) 3.4 ± 1.6	early	64.3 ± 5.2	19 ± 4
3	4	high (> 10.0) 14.5 ± 4.2	early	47.0 ± 4.5	23 ± 4
4	15	low (< 1.0) 0.38 ± 0.22	late	77.1 ± 6.4	16 ± 5
Control	5	low (< 1.0) 0.65 ± 0.20	late	72.2 ± 4.4	14 ± 4

thought of as representing statistically significant degrees of ketonaemia.

Most animals in the field with 1—6 mg of Acac/100 ml (moderate ketonaemia in Table 1) will appear to be healthy. Not even in the cows classified as markedly ketonaemic in Table 1 (Acac > 10 mg/100 ml) were symptoms of clinical ketosis observed. But the animals concerned had both Acac and sugar levels well within ranges obtained for typical cases of ketosis.

Plasma insulin, sugar and acetoacetate before feeding

For all three plasma parameters differences present before morning feeding between groups of cows (Table 1) persisted for the entire 4 hrs. period of sampling (Figs. 1, 2 and 3). The lowest insulin averages were consistently found for Group no. 3 with the lowest sugar- and the highest Acac-averages. Pre-feeding variations between individuals ($n = 38$) in insulin and sugar were positively correlated ($r = 0.59$, $P < 0.001$), while Acac was negatively correlated to both insulin ($r = -0.47$, $P < 0.01$) and sugar ($r = -0.85$, $P < 0.001$). The reproducibility of metabolite-related differences in insulin is also evidenced by the diurnal curves from the two individuals in Fig. 4.

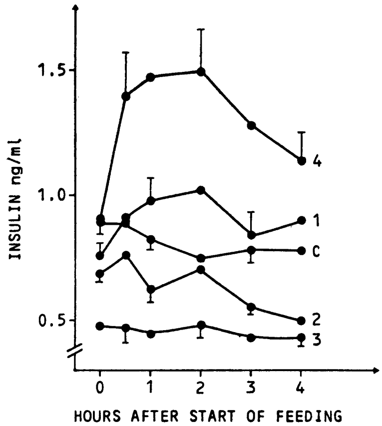
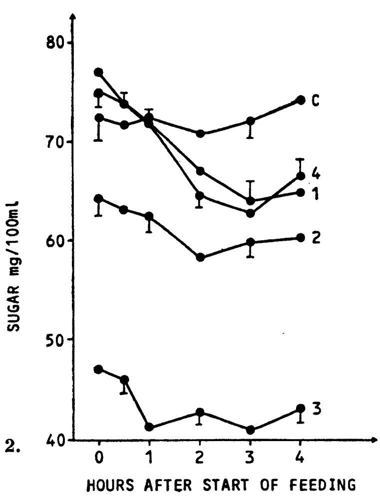


Figure 1. Variations in plasma insulin concentrations in the course of 4 hrs. in four groups of cows (Table 1) receiving morning food rations, and in a control group (C) from which food was withheld. Means and standards error. Group 1: Low acetoacetate (Acac), early lactation. 2: Moderately elevated Acac, early lactation. 3: High Acac, early lactation. 4: Low Acac, late lactation. C: Control cows, low Acac, late lactation.

Fig. 2.



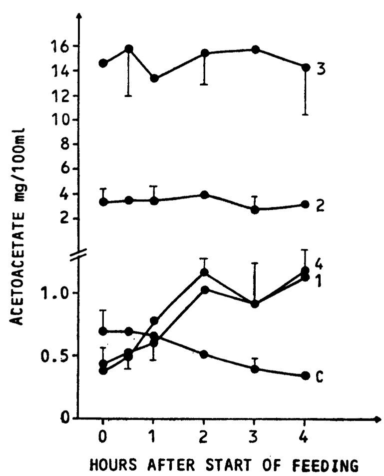


Fig. 3.

Figure 2. Plasma sugar curves corresponding to those for insulin in Fig. 1. Decreasing sugar levels after start of feeding. Significant changes not observed in the control group. Means and standard errors. Symbols as in Fig. 1

Figure 3. Plasma acetoacetate, means and standard errors, corresponding to the insulin and sugar measurements in Figs. 1 and 2. Increments after start of feeding in cows with low pre-feeding acetoacetate levels. Symbols as in Fig. 1.

Effects of feeding

Plasma insulin (Fig. 1). During the first 2 hrs. after start of feeding the insulin level rose considerably in animals with high initial levels of glucose (Groups 1 and 4), while no significant change was seen in the ketonaemic, low insulin groups. The feeding-induced increments in the first-mentioned groups were statistically significant as early as ½ hr. after start of feeding.

During the second 2 hrs.' period the hormone level dropped again in the two groups with the initial increase. Even in the moderately ketonaemic group a decrease was detected during this time interval (Group 2 in Fig. 1). No change was seen in the markedly ketonaemic cows. A slight downward shift in insulin was seen in the course of 4 hrs. in the control group without food (C in Fig. 1).

Plasma sugar (Fig. 2) decreased after feeding in all groups of cows. The decrease was greater in the two low-ketone groups than in the ketonaemic cows. (Average decrease 12—14 as against 7 mg/100 ml, change in insulin against change in sugar, $r = -0.41$, $P < 0.01$). The sugar level did not vary significantly

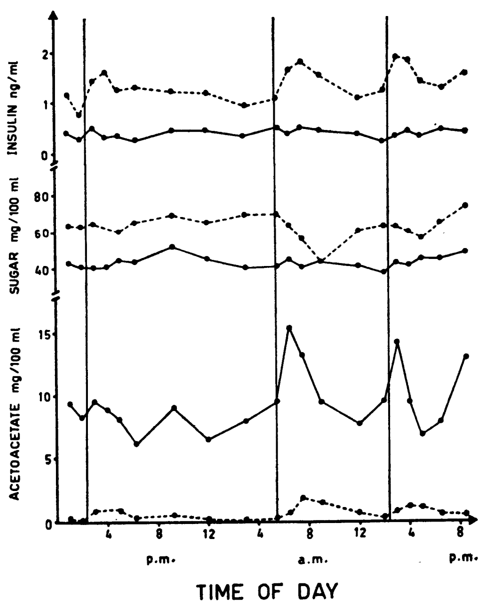


Figure 4. Diurnal variations in plasma insulin, sugar and acetoacetate in a hypoglycaemic, ketonaemic cow (● —— ●) and in a control animal with low ketone levels (● ----- ●). The beginning of meals indicated by vertical lines.

during 4 hrs. without food in the control group. Before glucose administration, effects of feeding on sugar concentrations could not be detected in the ketonaemic cow with pre-feeding values as low as about 40 mg/100 ml (Fig. 4).

Plasma acetoacetate (Fig. 3) increased after feeding in the low ketone groups to two to three times the initial value simultaneously with the decrease in sugar concentration. In the ketonaemic cows simultaneously observed, changes subsequent to feeding could not be detected.

Feeding during glucose infusion

In accordance with the findings mentioned above, the ketonaemic cow in Fig. 4 failed to show an insulin response at three successive feedings while the control animal responded very distinctly.

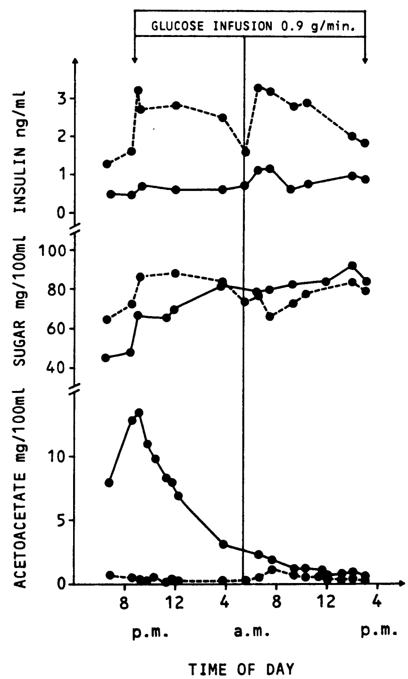


Figure 5. Effects of continuous glucose infusions for 18 hrs. in the same cows as in Fig. 4. Normalization of plasma glucose and acetoacetate in the ketonaemic cow. Insulin behaviour affected by the infusion. Persistence of difference in insulin between individuals. Ketonaemic cow (● —— ●), control animal (● ----- ●). The beginning of a meal indicated by vertical line.

A glucose infusion rate as low as about 0.9 g/min. (1.7 mg/kg min.) was sufficient to produce a sugar increase from about 45 to 80 mg/100 ml in a few hours in the ketonaemic individual. Concomitantly her Acac concentration was radically reduced. Insulin increased in response to the infusion in both cows. Averages were during the infusion 0.82 ± 0.21 (s) ng/ml in Fagerlin and 2.61 ± 0.62 in Frida as compared to 0.42 ± 0.08 and 1.33 ± 0.30 during the same hours of the day in the pre-infusion period. The increments were significant in both cows ($P < 0.001$). But in spite of the fact that the two animals reached approximately equal sugar plateau levels, Fagerlin's insulin level remained lower than Frida's throughout the period of infusion. However, when food was provided at the 10th hour of the infusion period, it was found that she had regained the ability to respond to feeding with an insulin increment (Fig. 5).

DISCUSSION

The present investigation has confirmed previous findings of decreased plasma insulin levels before morning feeding in hypoglycaemic cows (*Hove* 1974), the decrease being quantitatively related to the severity of the hypoglycaemia. The finding that the post-prandial behaviour of insulin was dependent on the sugar- and ketone levels, provides additional support for the view that insulin is of central importance in the regulation of metabolic processes in the cow, as in other mammals (*Basset* 1975).

In all cows with low ketone levels in the morning (Groups 1 and 4 in Figs. 1—3) feeding was followed by marked insulin increments and decreases in plasma sugar. In contrast, control cows with nearly identical morning levels (C in Figs. 1—3, insulin, glucose, Acac) left without food for 4 hrs. showed practically no change in insulin and glucose. The conclusion is drawn that insulin secretion was stimulated by feeding. Changes in the insulin level due to alterations in the turnover rate of the hormone appear unlikely. Reference is made to *Trenkle* (1971) who found that feeding did not affect the turnover rate of plasma insulin in sheep.

Conclusions concerning the exact nature of the secretory stimulus during feeding cannot be drawn from the present study. But the finding that the post-prandial insulin increment was absent in the hypoglycaemic-ketonaemic cows (Fig. 1), seems to imply that the sensitivity to a non-glycaemic stimulus (or stimuli) is dependent on the availability of carbohydrates. Direct evidence that pancreatic sensitivity to the feeding stimulus is permissively dependent on glucose levels was obtained in the glucose infusion experiment, in which the initially ketonaemic cow (Fig. 4) regained some ability to respond to feeding with an insulin increment when the hypoglycaemia was corrected (Fig. 5).

In both animals in the last mentioned experiment did glucose administration alone produce increments in insulin (pre-feeding). But throughout the period of infusion (18 hrs.) the insulin level of the initially ketonaemic cow remained far below that of the other animal (Fig. 5). This was true in spite of the fact that her plasma glucose concentration was nearly doubled, while the ketonaemia disappeared in the course of the experiment. The persistence of the difference between animals is consistent with previous findings of sluggish insulin responses to glucose loads in hypoglycaemic-ketonaemic cows (*Hove*, to be published).

Reduced glucose stimulation of pancreatic β-cells for protracted periods of time probably explains the observed sluggish behaviour of insulin. Increased pancreatic availability of glucose for some time in man will lead to increased insulin responses to secretory signals (*Porte & Pupo* 1969, *Goodner et al.* 1969). Low basal levels of insulin in blood plasma and reduced pancreatic insulin reserves are found in rats on high-fat, low-carbohydrate diets (*Farquhar et al.* 1966, *Blasquez & Lopez Quijada* 1968, 1969). It appears that the endocrine pancreas of a ketotic cow is functionally comparable to that of a high-fat adapted rat.

Findings very similar to those discussed above have been made previously by *Hart et al.* (1975) who studied cows of dairy and beef breeds on the same type of feed rations. In comparison to the beef cattle the dairy breed marked itself out by higher milk yields, higher blood ketones and lower glucose and insulin levels in blood plasma. To low initial insulin concentrations corresponded small insulin increments in response to feeding. In the present study all animals were of the same breed. But a difference related to milk yield and stage of lactation appears from a comparison of post-prandial insulin curves from Groups 1 and 4 in Fig. 1. Insulin averages for the two low-ketone groups differed only moderately in the morning, but the feeding-induced increments were far greater in the lowest yielders.

The difference in insulin behaviour mentioned above should be compared to *Hove*'s (1974) finding of systematic increases in basal plasma insulin levels with advancing stages of lactation. Neither in this investigation could the phenomenon observed be related to variations in blood metabolite levels (pre-feeding glucose or Acac). For the time being the reason why insulin secretion should be high in late lactation remains uncertain. Variations in the composition of food rations are known to affect the release of insulin to the blood during feeding (*Ross & Kitts* 1973, *Jenny & Polan* 1975, *Bhattacharaya & Alulu* 1975). But Groups 1 and 4 in the present investigation were fed the same type of rations.

Blood ketone increments during and after feeding, as seen in the low-ketone groups of cows (Fig. 3), may be a common phenomenon on a variety of diets (*Hove & Blom* 1973). Occurring at a time of day when it must be assumed that fat mobilization is counteracted by insulin, the ketonaemia of feeding seems to reflect increments in the supply of ketogenic substances (butyrate) from rumen fermentation.

Also decreases in blood sugar during a meal (Fig. 2) appear to occur commonly in cows (*Simkins et al.* 1965, *Radloff et al.* 1966, *Hove & Blom* 1973). In the low-ketone animals the hypoglycaemic shift could be interpreted simply as an insulin effect. But the glucose curve showed a downward trend after start of feeding even in the ketonaemic cow (Groups 2 and 3), which failed to show insulin increments. Possibly the metabolism of these animals was influenced by changes in the supply of insulin to the blood which were too small to be detected outside the portal circulation. Otherwise, it must be kept in mind that carbohydrate metabolism is influenced by several hormones. Growth hormone activity may be affected by feeding (cows: *Hove & Blom* 1973, sheep: *Basset* 1974 b, bulls: *Blom et al.* 1976). Plasma glucagon concentrations increase after feeding in sheep and calves (*Basset* 1972, *Bloom et al.* 1975). According to *Basset* (1975) simultaneous changes in insulin and glucagon can be of importance in determining blood sugar behaviour after feeding in ruminants. At present, however, it is not known to what extent variations in glucagon secretion in ketonaemic cows can account for the post-prandial decrease in plasma sugar in the absence of insulin increments in peripheral blood.

In conclusion, the generally low insulin levels and the low responsiveness of plasma insulin to common stimuli in ketonaemic cows appear to reflect endocrine adaptations to a metabolic condition which necessitates limitation of extramammary glucose utilization, a high rate of gluconeogenesis and an intensified mobilization of body fat.

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SAMMENDRAG

Fravær av fórings-framkalte variasjoner i plasma insulin hos kyr med hypoglykemi og ketonemi.

Virkningene av fóring på insulin i blodplasma ble studert hos 38 kyr med plasma sukker varierende fra 41 til 85 mg/100 ml og plasma acetoacetat (Acac) fra 0.2 til 18 mg/100 ml, ved måling før morgenfóring. Alle dyrene ble fóret med kraftfór, silofór og høy. Blodprøver ble tatt like før morgenfóring og med tidsintervall på ½ til 1 time i de følgende fire timer.

Hos individer med lave Acac-nivåer begynte plasma insulin å øke allerede ½ time etter fóring og nådde maksima etter omkring 2 timer. Samtidig økte Acac, og plasma sukker viste markert nedgang. Kyr med forhøyede Acac-verdier (> 1 mg/100 ml) og varierende grader av hypoglykemi hadde generelt lave insulinnivåer og hormonet viste ingen økning etter fóring. Heller ikke Acac forandret seg systematisk. Men en viss nedgang i plasma sukker etter fóring kunne påvises, selv i fravær av insulin inkrement i perifert blod.

Evnen til å reagere på fóring med insulin inkrement ble restituert i løpet av en periode med langsom, kontinuerlig, intravenøs infusjon av glukose hos en hypoglykemisk-ketonemisk ku, samtidig med at ketonemien forsvant. Men under hele forsøket hadde den betydelig lavere plasmainsulin enn en likt behandlet kontrollku med lave utgangsverdier for Acac.

Den endokrine tilpasning til ketonemi hos kyr ser ut til å innbefatte et lavt basalnivå (før fóring) av insulin og inhibisjon av den normalt forekommende økning i plasma insulin etter fóring.

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