Hypoglycemic Effect of L-leucine During Periods of Endogenous Hyperinsulinism

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The phenomenon of L-leucine-induced hypoglycemia has been described in certain patients with idiopathic infantile hypoglycemia and in others with insulin secreting tumors of the pancreas.[1,2] More recently, we have demonstrated that leucine-induced hypoglycemia can be experimentally produced in normal dogs pretreated with insulin.[3] On the basis of those experiments, it was suggested that L-leucine lowered blood glucose concentration by inhibiting hepatic glucose output during periods of exogenous hyperinsulinism, and that insulin fulfilled a permissive role. Since the amount of insulin administered was relatively great, the current experiments were undertaken in an effort to demonstrate an effect of L-leucine on glucose homeostasis under more physiological conditions. The results of the experiments to be described indicate that L-leucine can also lower blood glucose concentration during periods of endogenous hyperinsulinism following the administration of intravenous glucose.

METHODS

Normal mongrel dogs of both sexes were used in these experiments. Hyperglycemia was produced in two different ways. In one series of experiments, acute hyperglycemia was produced by a rapid intravenous infusion of glucose (0.5 gm./kg.). In other experiments, sustained hyperglycemia was produced by a rapid intravenous infusion of glucose (0.3 gm./kg.) followed by a continuous infusion of glucose (0.017 gm./kg./min.) for the succeeding ninety minutes (Harvard Apparatus infusion pump). In both instances experiments were performed in the morning after an overnight fast. Blood was drawn for determination of glucose concentration before the infusion of glucose, and at regular intervals thereafter until the end of the experiment. Leucine was prepared by dissolving 30 mM of L-leucine in 200 ml. distilled water. An equal volume of 0.45 per cent NaCl was used as a control solution. The solutions were administered by rapid intravenous infusion. Each dog was studied four times during acute hyperglycemia. On two occasions glucose plus L-leucine was administered, while on the other two occasions each dog received glucose plus saline. Each dog was studied twice during sustained hyperglycemia, once with L-leucine, and once with saline. The order in which L-leucine or saline was given was randomized, and no dog was used for an experiment more than once a week. All dogs were anesthetized with pentobarbital. Blood glucose was determined by Nelson's modification of Somogyi's method.[4]

RESULTS

Average blood glucose concentrations of nine normal dogs at various time intervals after receiving an acute infusion of glucose and L-leucine or saline are illustrated in figure 1. It is apparent that L-leucine had no effect during the period of hyperglycemia. On the other hand, it is clear that the blood glucose concentration of dogs receiving L-leucine was significantly lower sixty and ninety minutes after the glucose infusion. Results of the experiments in which hyperglycemia was maintained by glucose infusion are seen in figure 2. In this instance, L-leucine had no significant effect on blood glucose concentration, although the duration and intensity of the period of endogenous hyperinsulinism was undoubtedly greater than that following a single injection of glucose. The lack of response to L-leucine during periods of sustained hyperglycemia cannot be attributed to the severity of the hyperglycemia per se, as the intravenous injection of insulin on several occasions during similar periods produced a sharp and prompt fall in blood glucose concentration.

DISCUSSION

The results of these experiments indicate that L-leucine can significantly modify blood glucose concentration of normal dogs as they recover from hyperglycemia produced by acute infusion of glucose. Although plasma insulin levels were not measured, the demonstration that this degree of hyperglycemia would act

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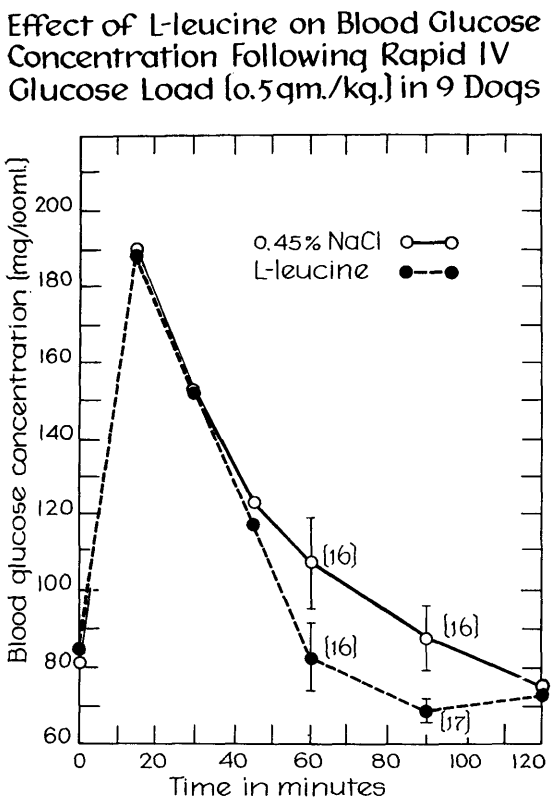

FIG. 1. Effect of L-leucine on blood glucose concentration following rapid intravenous glucose load (0.5 gm./kg.) in nine dogs
I = ± 2 S.E. ($P < 0.01$ at sixty and ninety minutes)
( ) = Number of observations (in parentheses)

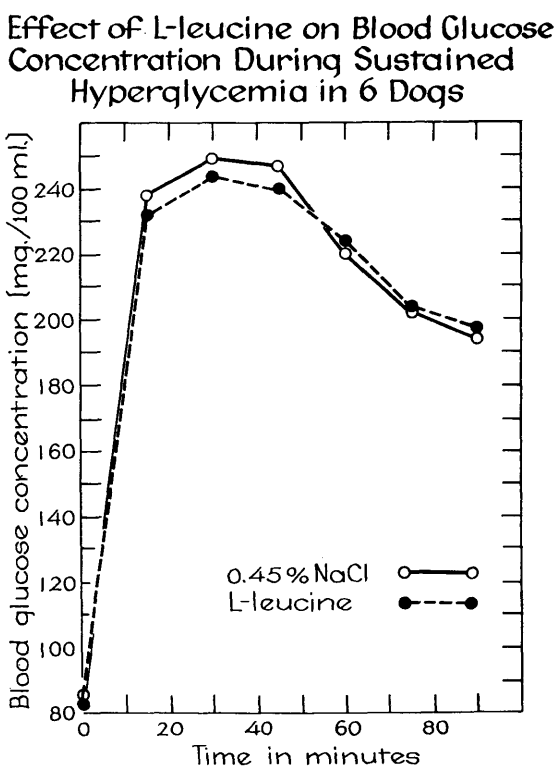

FIG. 2. Effect of L-leucine on blood glucose concentration during sustained hyperglycemia in six dogs. None of the above differences is statistically significant.

as a potent stimulus to insulin secretion has been well-documented.[5-8] Since L-leucine has little effect on blood glucose concentration of normal subjects, it is assumed that the experimental observations are related in some manner to the endogenous hyperinsulinism resulting from the experimentally induced hyperglycemia. Although some degree of hyperinsulinism may be necessary for the production of L-leucine induced hypoglycemia, an excess of insulin alone is not sufficient. In the first place, it is evident that L-leucine had no effect on glucose concentration as long as hyperglycemia persisted. Secondly, it is almost certain that the degree of hyperinsulinism was more profound during periods of sustained hyperglycemia, and yet L-leucine had no discernible effect under those conditions. Consequently, it is suggested that endogenous hyperinsulinism is fulfilling the same permissive role that was previously ascribed to an excess of exogenous insulin.[3]

However, in addition to stimulating insulin secretion, hyperglycemia also decreases hepatic glucose output. Soskin and co-workers[9] initially demonstrated that an immediate response to the acute infusion of glucose was cessation of net hepatic glucose output and retention of a portion of the administered glucose load. This was followed by a period in which the liver neither retained nor released glucose, with resumption of hepatic glucose output as blood glucose concentration fell further. Consequently, the homeostatic response to hyperglycemia consists of an inhibition of hepatic glucose output as well as increased insulin secretion. In light of these observations, it is then apparent that the added glucose load is disposed of by a combination of hepatic and peripheral glucose uptake. As blood glucose concentration begins to fall, the liver would no longer take up glucose, and the stimulus to insulin secretion would decline. Although insulin secretion would diminish as the hyperglycemia disappeared, there would be a period of time in which plasma insulin levels would remain elevated in the face of a falling blood glucose concentration. It is obviously incumbent upon the liver to increase hepatic glucose output at this time in order to prevent significant hypoglycemia. Since it is precisely at this time that L-leucine exerts its hypoglycemic effect, it is suggested that L-leucine acts to inhibit

hepatic glucose output during periods of endogenous hyperinsulinism. Since there is no net hepatic glucose output during periods of hyperglycemia, the observation that L-leucine had no effect at these times is to be expected. Finally, inability to demonstrate an effect of L-leucine on blood glucose concentration 120 minutes after the administration of a glucose load would be attributed to the fact that the blood glucose concentration had been normal for the preceding sixty minutes. Since dependence on hepatic glucose output would be much less at this time, any minor effect of L-leucine would be very difficult to document. Although these experiments do not rule out other possible explanations for the effect of L-leucine, it is suggested that they are most consistent with the thesis that L-leucine lowers blood glucose concentration by inhibition of hepatic glucose output at times when this homeostatic mechanism is most essential for maintenance of euglycemia.

SUMMARY

Lowering of blood glucose concentration by L-leucine has been demonstrated during periods of endogenous hyperinsulinism produced by intravenous infusion of glucose in normal dogs. This effect of L-leucine was only observed following an acute glucose infusion, and was limited to periods of rapidly falling blood glucose concentration.

L-leucine had no discernible effect on blood glucose concentration during periods of sustained hyperglycemia.

These experiments are consistent with the thesis that L-leucine inhibits hepatic glucose output, and that the resultant fall in blood glucose concentration is greatest when this homeostatic mechanism is most essential for maintenance of euglycemia.

SUMMARIO IN INTERLINGUA

Effecto Hypoglycemic de L-Leucina Durante Periodos de Endogene Hyperinsulinismo

Le reduction del concentration de glucosa sanguinee per L-leucina esseva demonstrate durante periodos de endogene hyperinsulinismo le qual habeva essite producite in canes normal per le infusion intravenose de glucosa. Le effecto de L-leucina esseva observate solmente post infusion acute de glucosa e esseva restringite a periodos de rapidemente declinante concentrationes de glucosa sanguinee.

L-leucina habeva nulle discernible effecto super le concentration sanguinee de glucosa durante periodos de continue hyperglycemia.

Iste experimentos es compatibile con le these que L-leucina inhibi le rendimento hepatic de glucosa e que le resultante declino del concentration sanguinee de glucosa es le plus grande quando iste mechanismo homeostatic es le plus urgentemente requirite pro mantener un stato de euglycemia.

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