A Paradoxical Effect of Chlorpropamide on the Plasma Glucose and Immunoreactive Insulin Response to Intravenous Glucose in Normal Dogs

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SUMMARY

The effect of various doses of chlorpropamide on plasma glucose and immunoreactive insulin responses to an acute intravenous glucose challenge has been studied in normal dogs. The effects of chlorpropamide were compared to those of placebo in each dog. The administration of 375 mg. of chlorpropamide for four days decreased the ability of the dogs to dispose of a glucose load, and the deterioration in glucose tolerance was accompanied by a marked suppression of the plasma insulin response. Administration of 125 mg. of chlorpropamide for four days led to changes that were qualitatively similar but quantitatively less striking. These results indicate that excessive amounts of chlorpropamide can lead to deterioration in glucose tolerance; this effect seems analogous to induction of glucose intolerance in normal subjects by administration of insulin, as first described by Somogyi. When the chlorpropamide was decreased to a daily dose of 50 mg., dogs were able to dispose of the intravenous glucose load more efficiently than normal. However, this improvement in glucose tolerance was not associated with a significant rise in plasma insulin response. Thus, although it seems reasonable to attribute deterioration in glucose tolerance after excessive doses of chlorpropamide at least partly to inhibition of insulin release, the improvement that occurs after smaller doses does not appear to be due to an absolute increment in the plasma insulin response to glucose. DIABETES 22:367-71, May, 1973.

Since the *acute* administration of sulfonylurea compounds decreases plasma glucose levels[1] and increases plasma insulin levels,[2] it seemed reasonable to attribute their hypoglycemic action to an increase in pancreatic insulin secretion. However, plasma insulin levels in diabetic patients have not been shown to be increased when plasma glucose levels have been lowered by *chronic* treatment with sulfonylurea compounds.[3-5] Thus, the reason plasma glucose falls in these patients is not self-evident, nor is it clear why these compounds appear to affect glucose and insulin metabolism differently when given acutely or chronically. In order to gather data on this latter question, we administered chlorpropamide to normal dogs and measured their plasma glucose and insulin responses to a standard intravenous glucose challenge. It soon became clear that the problem was more complex than initially conceived and that the amount of sulfonylurea compound administered was also an extremely important variable. In fact, the efficiency with which normal dogs disposed of an intravenous glucose load improved or deteriorated as the amount of sulfonylurea varied. The plasma insulin response to the intravenous glucose challenge was also markedly dependent upon the administered dose. In this paper we describe plasma glucose and insulin response to an acute intravenous glucose load observed in normal dogs that had received 50, 125, or 375 mg. of chlorpropamide for four consecutive days.

METHODS

Normal female dogs were used for all studies. The experiments were paired in that the effect of chlorpropamide on the plasma glucose and insulin response of each dog was compared to that observed after administration of a placebo. In each instance, they were given a pill by mouth for four consecutive mornings with a morning meal. On the fifth morning they received neither food nor pill, and their plasma glucose response to an acute intravenous challenge was determined. Dogs received 50, 125, or 375 mg. of chlorpropamide, and in each dog the order of receiving chlorpropamide or pla-

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cebo was randomized. The duration between the paired studies was never less than one week, and it was at least two weeks when chlorpropamide was given initially.

Dogs were anesthetized with sodium pentobarbital (30 mg. per kilogram body weight) and 0.5 gm. of glucose per kilogram body weight was administered by rapid intravenous injection. Venous blood was drawn for measurement of plasma glucose and immunoreactive insulin immediately before glucose was given and five, fifteen, thirty, sixty, and ninety minutes after glucose administration. Blood for glucose was placed in tubes containing sodium fluoride and potassium oxalate, and blood for measurement of insulin was collected in tubes containing EDTA. In both instances, plasma was separated immediately by centrifugation and stored frozen.

Plasma glucose concentration was measured with an AutoAnalyzer[6] and plasma immunoreactive insulin by the method of Hales and Randle.[7] In both instances samples obtained after chlorpropamide and placebo administration were analyzed at the same time. The fractional disappearance of glucose from plasma (K value) was determined from the plasma glucose values at five, fifteen, thirty, and sixty minutes, and expressed as a per cent. Statistical comparisons were made by use of the paired t test.

RESULTS

The effect of four daily doses of 375 mg. of chlorpropamide on the plasma glucose and insulin responses of six normal dogs is illustrated in figure 1. It is clear that this dose resulted in a significant fall in the mean fasting plasma glucose concentration from 80 mg./100 ml. to 54 mg./100 ml. ($p < .01$). The mean plasma glucose concentration was also lower in the treated animals five minutes after an intravenous injection of 0.5 gm. of glucose per kilogram body weight. However, this difference had narrowed by fifteen minutes; by thirty minutes the mean plasma glucose level was actually *higher* in the treated animals, and the glucose concentration in the animals who received chlorpropamide was significantly higher ($p < .05$) sixty minutes after glucose had been in-

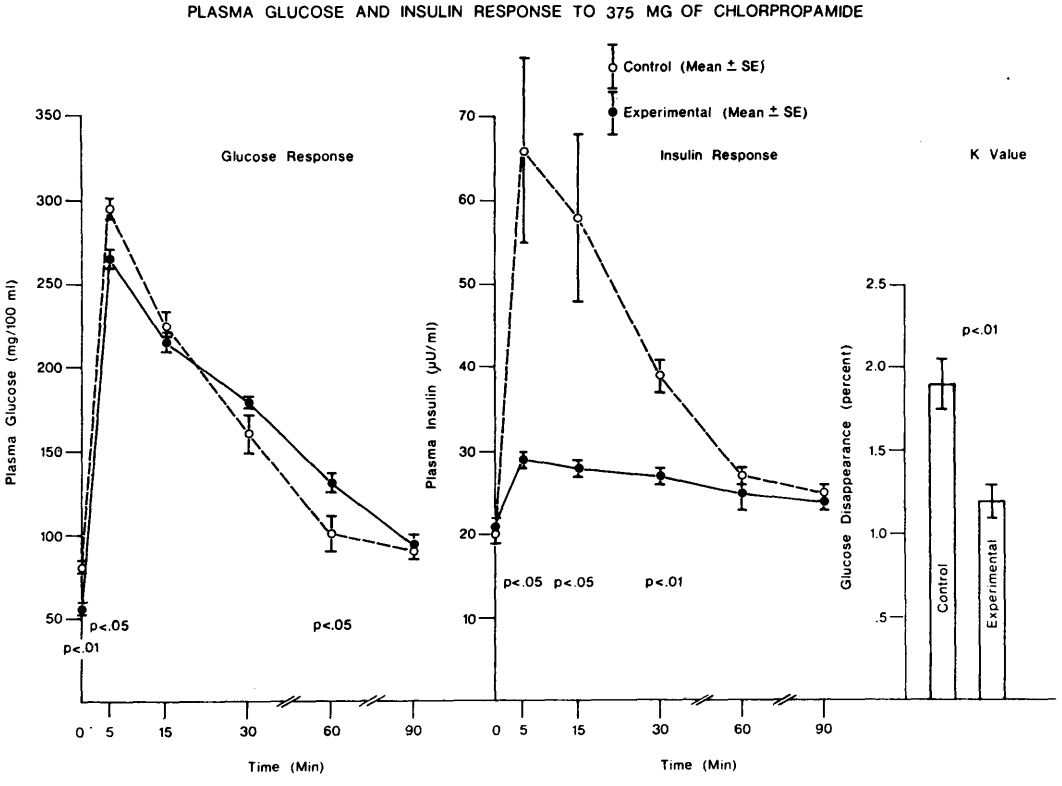

FIG. 1. Changes in plasma glucose concentration, plasma immunoreactive insulin concentration, and fractional disappearance rate (K) of glucose from plasma in response to an acute intravenous glucose challenge (0.5 gm. per kilogram body weight) after four days of chlorpropamide treatment (375 mg. per day).

jected. Obviously, treatment of normal dogs with 375 mg. of chlorpropamide for four days led to a deterioration in their glucose tolerance, and this was accompanied by a marked suppression of their insulin response to the acute glucose challenge. These results, depicted in figure 1, indicate that the mean plasma insulin concentration of dogs treated with chlorpropamide was significantly lower five, fifteen, and thirty minutes after the acute glucose challenge. It is of interest to note that the production of fasting hypoglycemia by chlorpropamide was not associated with an increase in fasting plasma insulin concentration. The change in glucose tolerance associated with this apparent suppression of insulin response can be expressed as a change in fractional disappearance of glucose from plasma (K value). Figure 1 indicates that treatment of normal dogs with this amount of chlorpropamide led to a statistically significant fall in the K value ($p < .01$).

A similar analysis of the response to 125 mg. of chlorpropamide is seen in figure 2. This dose of chlorpropamide led to a less marked, but still statistically significant, fall in fasting plasma glucose concentration. As before, the fall in fasting plasma glucose was not accompanied by an increase in fasting insulin concentration. Although the effect of 125 mg. of chlorpropamide on the plasma glucose response was qualitatively similar to that of 375 mg., it was quantitatively less striking. The mean plasma glucose levels of the chlorpropamide treated dogs were never significantly higher than the control values, and the mean K value, although lower after chlorpropamide treatment, was not statistically different from the control values. The effect of 125 mg. of chlorpropamide on the plasma insulin response to the acute glucose challenge was also qualitatively similar to that seen in dogs receiving the higher dose, but the decrease in insulin response was statistically significant only at the five minute time interval.

The effects of 50 mg. of chlorpropamide are depicted in figure 3, and are quite different from those of the larger doses. Mean fasting plasma glucose levels were not lower following four days of treatment. However, mean plasma glucose levels were significantly *lower* fifteen, thirty, and sixty minutes after the glucose challenge. Although the mean plasma insulin levels were slightly higher in the treated animals, these differences were minimal and did not begin to approach

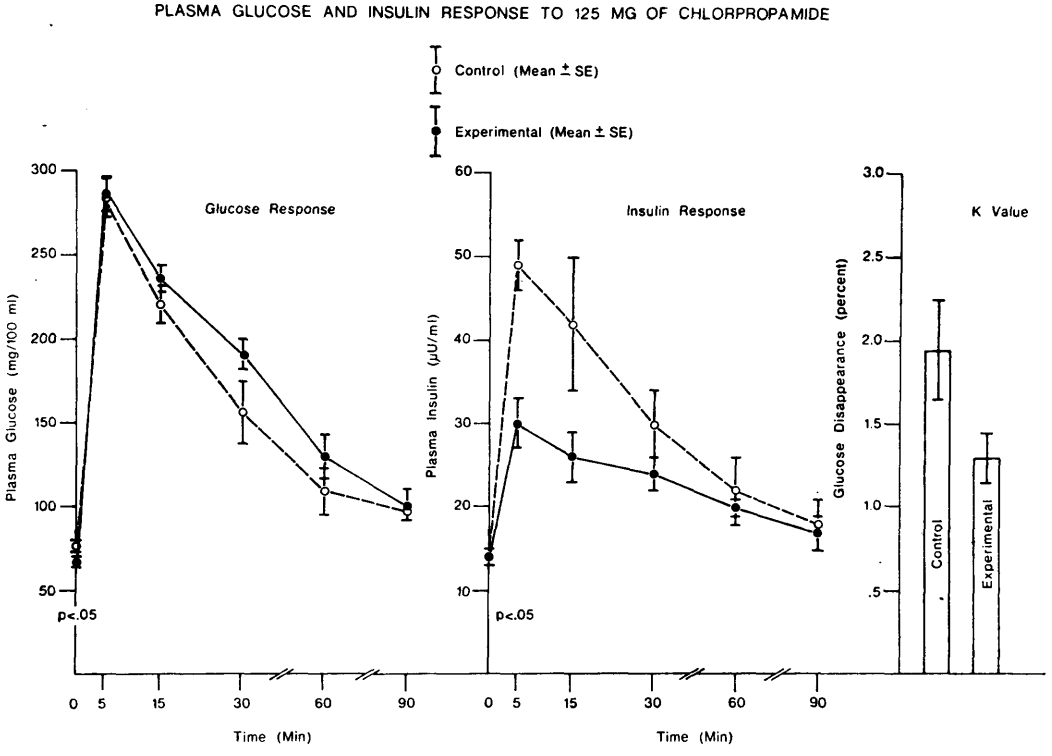

FIG. 2. Changes in plasma glucose concentration, plasma immunoreactive insulin concentration, and fractional disappearance rate (K) of glucose from plasma in response to an acute intravenous glucose challenge (0.5 gm. per kilogram body weight) after four days of chlorpropamide treatment (125 mg. per day).

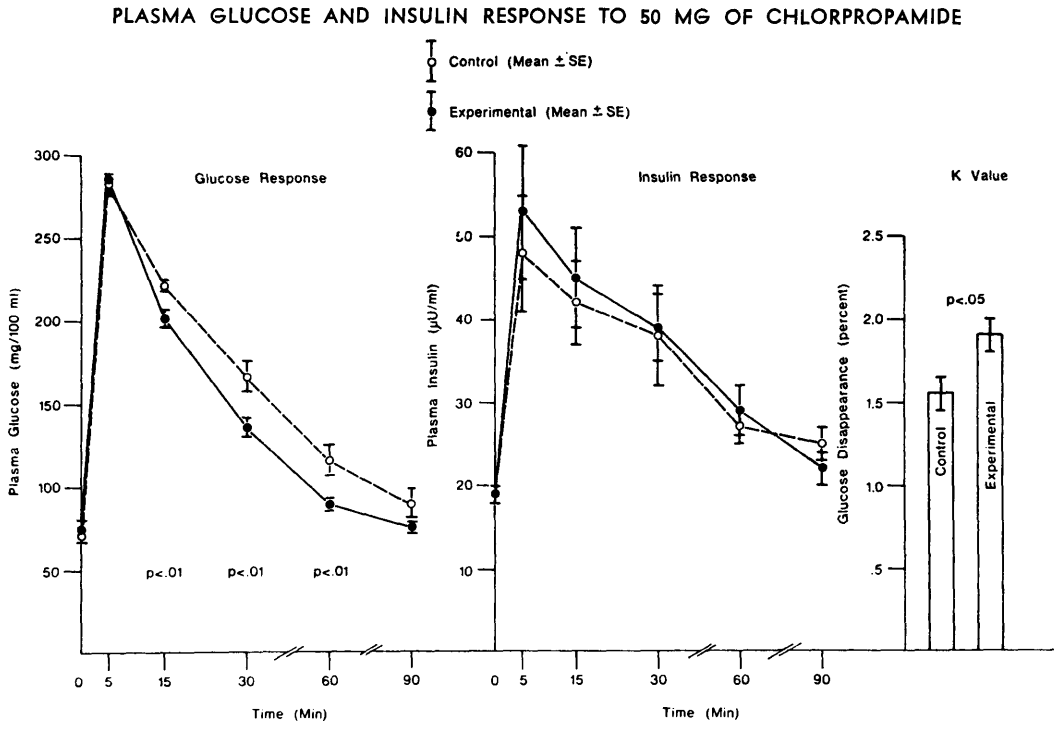

FIG. 3. Changes in plasma glucose concentration, plasma immunoreactive insulin concentration, and fractional disappearance rate (K) of glucose from plasma in response to an acute intravenous glucose challenge (0.5 gm. per kilogram body weight) after four days of chlorpropamide treatment (50 mg. per day).

statistical significance. Thus, the significant increase in mean K value that resulted from four daily doses of 50 mg. of chlorpropamide was not associated with evidence of significantly increased insulin secretion.

DISCUSSION

These results indicate that administration of chlorpropamide to normal dogs can lead to an inhibition of their insulin response and a deterioration of their glucose tolerance. The inhibition of the insulin response to glucose of the chlorpropamide-treated dogs seems analogous to the impaired insulin response of isolated hamster islets which Sodoyez and associates[8] observed after prolonged sulfonylurea administration. However, the effect on glucose tolerance seems to be different from the paradoxical effect described by Dulin and associates[9] in which large doses of tolbutamide failed to produce hypoglycemia in normal rats. In that instance, the inability of large doses of tolbutamide to decrease blood glucose concentration was shown to result from the acute discharge of adrenal hormones. In this instance, the animal is slightly hypoglycemic before the administration of the acute intravenous glucose challenge, the deterioration of glucose tolerance is seen only in response to an acute glucose challenge, and the entire sequence of events seems to closely resemble the induction of glucose intolerance by excessive insulin administration described by Somogyi. In a series of elegant studies Somogyi was able to show that excessive insulin administration could lead to deterioration of glucose tolerance in both healthy subjects and patients with diabetes mellitus[10] and that decreasing the amount of insulin could lead to lower blood glucose levels in diabetic patients receiving excessive amounts of insulin.[11] This general phenomenon, in which "hypoglycemia begets hyperglycemia,"[12] seems to provide the best explanation for the deterioration of glucose tolerance produced by chlorpropamide in these experiments. Why glucose intolerance develops is not clear. Somogyi suggested that the adrenal response to hypoglycemia might be responsible for the deterioration of glucose tolerance,[13] while more recently growth hormone has been proposed as being the responsible agent.[14] In the current instance, although these factors may also have been operative, hyperglycemia was associated with suppressed insulin response. Thus, it appears that hypoglycemia can inhibit the pancreatic response to hyperglycemia in subjects that normally have the ability to release insu-

lin and that this decreased insulin response may account for the deterioration of glucose tolerance in such individuals.

Although these experiments were carried out in normal dogs, they appear to have some relevance to the use of these drugs in patients with diabetes. In the first place, they indicate that the administration of a sulfonylurea compound can lead to a worsening of the response to a glucose load. The effect was unequivocal with the 375 mg. dose, but the mean insulin response was also suppressed and the mean glucose somewhat worse following the 125 mg. dose. Since these dogs averaged 20 kg. in weight, this would be equivalent to a 375 mg. dose in a 60 kg. subject. Thus, it at least seems reasonable to suggest that the "Somogyi phenomenon" might well occur in patients treated with sulfonylurea compounds, particularly in patients who do not have significant fasting hyperglycemia.

Finally, these experiments once again indicate that plasma glucose concentration can be lowered by sulfonylurea compounds without a rise in plasma insulin concentration. This was true of the effect of 375 mg. and 125 mg. of chlorpropamide on fasting plasma glucose levels, in which significant fasting hypoglycemia could be produced without an increase in fasting insulin levels, and it was also true of the ability of 50 mg. of chlorpropamide to improve glucose disposal rate in the absence of any significant change in insulin response. On the other hand, in the case of the 375 and 125 mg. doses, it could be argued that the production of fasting hypoglycemia should have resulted in an inhibition of pancreatic insulin secretion and that the existence of fasting insulin levels in these dogs which were as high as those in normal dogs is actually evidence that chlorpropamide was stimulating insulin secretion. However, this explanation has no bearing on the changes that were observed with the 50 mg. dose, and these results serve as another indication that the blood glucose lowering effect of the sulfonylurea compounds need not be related to a concomitant rise in pancreatic insulin secretion.

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