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HEXAMETHONIUM AND INSULIN HYPOGLYCAEMIA

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In the course of experiments in which hexamethonium, a member of the polymethylene bistrimethylammonium series, and insulin were simultaneously administered to dogs, it was observed that the symptoms associated with insulin hypoglycaemia were considerably exaggerated. The following analysis revealed that this was due to potentiation of the insulin hypoglycaemia by hexamethonium.

METHODS

Experiments were carried out on six unanaesthetized dogs fasted for 18–24 hr. Blood samples were taken from the antebrachial cephalic vein at regular intervals for glucose determinations by the micro method of Hagedorn & Jensen (1923). All dogs received 2 mg./kg. hexamethonium alone, 0·4 unit/kg. insulin alone, and insulin plus hexamethonium in these doses. In addition, hexamethonium, in a dose of 5 mg./kg., was given in a number of experiments. All drugs were given intravenously, insulin being given 5 min. before hexamethonium if both were administered in the same experiment. The sequence of drug administration was randomized. Hexamethonium was given as the iodide.

RESULTS

Hexamethonium. Although there were no marked signs of discomfort, hexamethonium gave reproducible effects. These were: increased heart rate, ptosis, relaxation and injection of the nictitating membrane, dryness of the nose and shivering. Shivering almost always occurred following administration of hexamethonium, and if present before it was intensified. Room temperature varied between 18 and 20° C. on different days. In general, symptoms were wearing off after 1 hr. The increased heart rate was of shorter duration.

In twelve experiments on six dogs there was no significant consistent effect of hexamethonium on the fasting blood sugar level. In two experiments on two dogs there was a temporary reduction of 10–15 mg./100 ml. (Fig. 1). This could not be repeated, however, either with this dose, or when it was increased to 5 mg./kg. in four experiments on the same two animals.

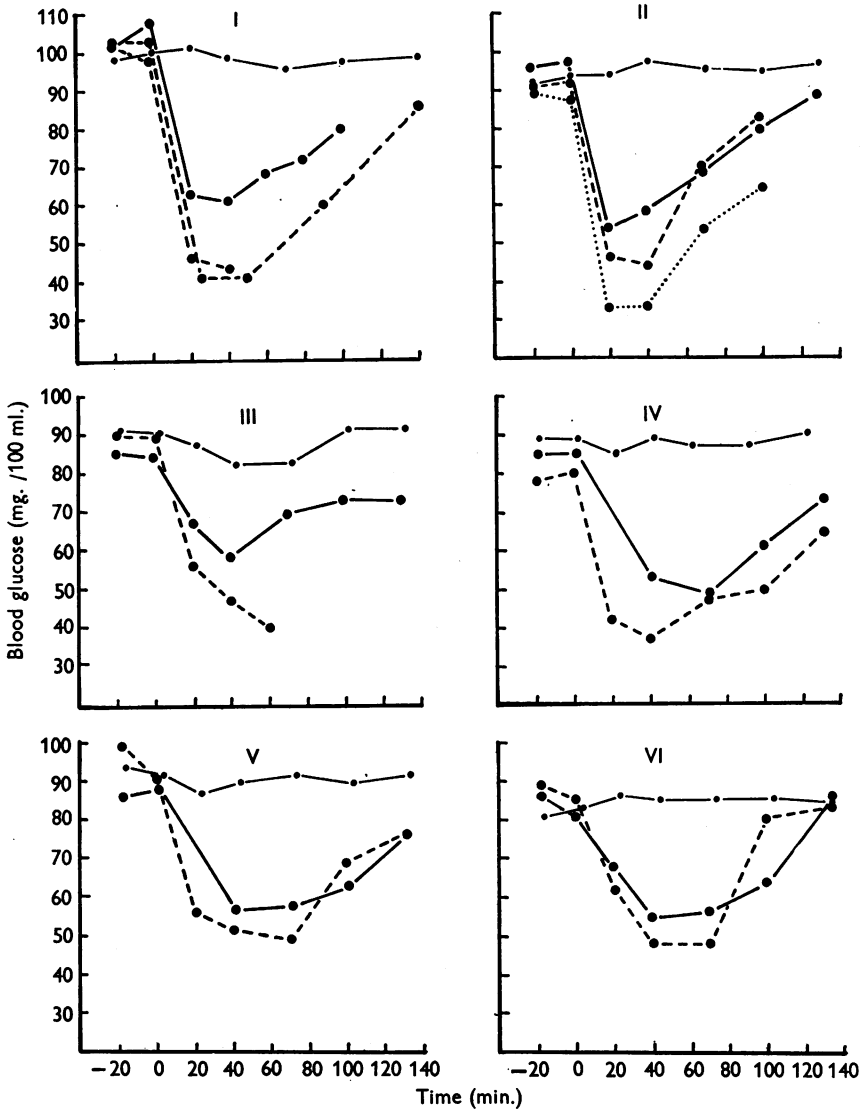

Fig. 1. Blood sugar curves of six dogs (I to VI) in response to insulin alone; hexamethonium alone, and the combination of both. Insulin or hexamethonium alone given at zero time; hexamethonium, 5 min. later when both were administered in the same experiment. ●——● Insulin (0·4 unit/kg.). For dogs I and II the curve is the average of three experiments in each case. ● - - - - - ● Insulin (0·4 unit/kg.) plus hexamethonium (2 mg./kg.). ● · · · · · · ● Insulin (0·4 unit/kg.) plus hexamethonium (5 mg./kg.). •——• Hexamethonium (2 mg./kg.). Average of two separate experiments in all dogs.

Insulin. Six dogs received insulin alone in ten experiments. There were no obvious symptoms except in one instance when the animal showed mild convulsive signs. The effect on the blood sugar in the six dogs is shown in Fig. 1. The mean of the lowest blood sugars in this group was 54·6 mg./100 ml.

Insulin plus hexamethonium. Six dogs received insulin plus hexamethonium in eight experiments. Varying degrees of convulsive activity were observed in six of the eight experiments, and in some instances there was severe collapse and agitation. When convulsions were very severe, as they were in two instances, they were terminated immediately by intravenous injection of a few ml. of 10% glucose. One dog which showed no convulsive signs received 5 mg./kg. of hexamethonium plus insulin on one occasion. This increased the hypoglycaemic response to insulin to a greater degree than did the smaller dose of hexamethonium and also produced convulsive activity (Fig. 1).

In every instance the simultaneous administration of hexamethonium reduced the blood sugar level to a greater degree than did insulin alone (Fig. 1). The mean of the lowest blood sugar levels was 43·1 mg./100 ml. Comparison of this mean value with that obtained with insulin alone shows a highly significant difference between the two ($P < 0.01$).

DISCUSSION

The effects of hexamethonium such as increased heart rate, ptosis, etc. are readily explained by its ganglion blocking action (Paton & Zaimis, 1951). The onset of shivering and the exaggeration of insulin hypoglycaemia caused by hexamethonium also indicate that it produces a temporary 'pharmacological sympathectomy' since it has been shown that shivering occurs more readily and that there is greater sensitivity to insulin in dogs following surgical sympathectomy (McDonough, 1939). The release of hormone from the adrenal medulla by a central nervous stimulating effect of hypoglycaemia was clearly demonstrated by Cannon, McIver & Bliss (1924). Further, Feldberg & Toh (personal communciation) have shown that hexamethonium prevents the rise of blood pressure following splanchnic nerve stimulation in the eviscerated cat. Hence the increased sensitivity to insulin caused by hexamethonium is readily explained by its action in preventing the nervous stimulation of the adrenal medulla in response to a fall in blood sugar.

The inability of hexamethonium to alter significantly the fasting blood sugar level with any regularity is in accord with the findings of McDonough (1939) following sympathectomy in dogs. The fact that there was a slight decrease in the blood sugar in two instances, however, suggests that the basal glycogenolytic level may be raised by nervous mechanisms under conditions of minor stress or activity. Cannon & Britton (1927), using the denervated heart as an index of adrenal activity in the cat, demonstrated that 'adrenine' was

liberated following even very mild exercise. It is conceivable that hyperglycaemia precipitated by emotional states might be prevented by hexamethonium and it would be of interest to find out whether in some instances diabetic hyperglycaemia could be reduced.

SUMMARY

1. Hexamethonium causes an increased sensitivity to insulin in unanaesthetized dogs. It is concluded that this is the result of the ganglion blocking action of hexamethonium preventing compensatory sympathetic activity in response to hypoglycaemia.

2. The effects of hexamethonium are consistent with the idea that this drug produces an effective 'pharmacological sympathectomy'.

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