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EFFECT OF HEXAMETHONIUM ON THE RESPONSE TO INSULIN IN ANIMALS AND MAN

BY

D. R. LAURENCE AND R. S. STACEY

From the Department of Therapeutics, St. Thomas's Hospital Medical School, London

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The work described below was planned to investigate two aspects of the action of hexamethonium in relation to insulin hypoglycaemia.

Cannon, McIver, and Bliss (1924) first clearly demonstrated that hypoglycaemia increased sympathetic activity and adrenaline secretion, and that, by the mobilization of glucose from the liver, this forms a protective mechanism against an extreme fall in blood sugar. Hexamethonium, by blocking sympathetic impulses to the liver and adrenal medulla, might be expected to modify the course of hypoglycaemia and by impairing the protective mechanism to lead to a greater fall in blood sugar.

Secondly, we have shown in a previous paper (Laurence and Stacey, 1952) that hexamethonium raises the convulsant dose of nicotine in rats and mice but does not affect that of certain other convulsants. It was thought that the effect of hexamethonium on hypoglycaemic convulsions might help to elucidate this action.

Effect of Hexamethonium on the Insulin Convulsion Rate

Two experiments were done on each of ten rabbits. After 24 hours' starvation 0.8 i.u. insulin per kg. was given intravenously, alone on one occasion, and on the other with 5 mg. per kg. hexamethonium iodide also intravenously. Hexamethonium increased the convulsion rates from 1 in 10 to 7 in 10. Three rabbits were not convulsed in either experiment; one was convulsed in both, the convulsion in the experiment in which hexamethonium was given being very much more severe. The value of P in this experiment was <0.01; it was obtained from Mainland's fourfold contingency tables (Mainland, 1948).

Effect of Hexamethonium on the Course of Insulin Hypoglycaemia

Four human subjects and six rabbits were used. The human subjects (two were normal and two had anxiety states) had fasted for twelve hours, the rabbits for twenty-four hours; water was allowed. The blood sugar was estimated at ten-minute intervals after a small intravenous injection of insulin. The experiment was repeated on each individual on a subsequent day under the same conditions but with the additional administration of hexamethonium, intramuscularly in the human cases, intravenously in the rabbits. The time relations and dosage are indicated in Table I and Fig. 2. In the human experiments observations were made on the heart rate, blood pressure, sweating, E.E.G., and subjective sensations. "True" blood sugar was estimated by the method of King (1947), using capillary blood in man and venous blood in rabbits.

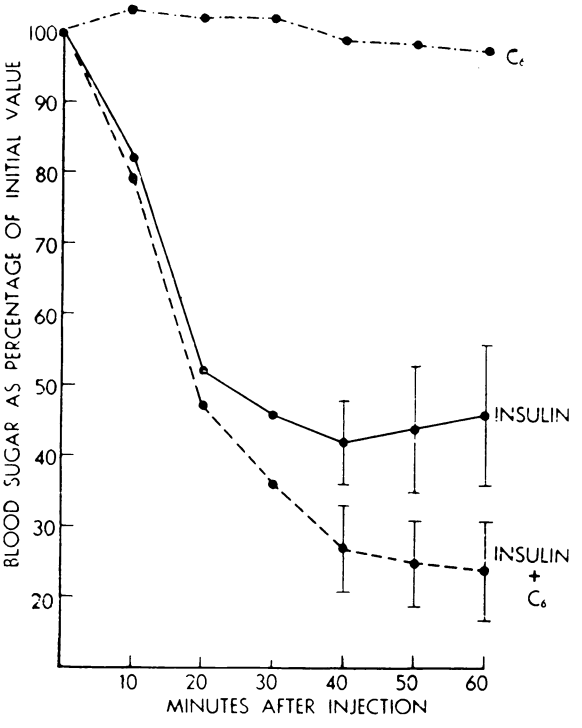

FIG. 1.—Mean blood sugar curves from six fasting rabbits. ●–.–.–● hexamethonium alone (5–10 mg./kg.). ●———● insulin alone (0.8 i.u./kg.). ●– – –● same dose of insulin with hexamethonium (for doses see Table I). Vertical lines indicate the standard deviation. All injections were intravenous.

TABLE I

Blood sugar at 10 min. intervals after insulin alone (ordinary type), and after insulin and hexamethonium iodide (italics) in six rabbits. Dose of insulin: 0.8 i.u./kg. i.v.

Rabbit	Blood sugar, mg./100 ml. blood							Hexamethonium iodide mg./kg. i.v.	Convulsions: present + absent —
	Zero hour	10′	20′	30′	40′	50′	60′		
A	125	113	75	60	58	60	60	—	—
	144	*107*	*64*	*42*	*43*	*36*	*43*	5 at 0 min.	—
B	141	121	63	49	43	45	46	—	—
	120	*96*	*48*	*37*	*24*	*22*	*27*	5 at 0 min.	+
C	93	63	43	35	37	38	41	—	—
	98	*82*	*44*	*31*	*23*	*19*	*22*	5 at 0 min.	+
D	87	88	63	50	40	40	51	—	—
	76	*60*	*38*	*29*	*18*	*17*	*17*	5 at 0 min.	+
E	86	64	36	47	40	50	47	—	—
	76	*57*	*38*	*31*	*23*	*25*	*24*	3.3 at 0′, 10′, 20′	+
F	85	61	37	35	34	35	31	—	—
	67	*54*	*35*	*28*	*25*	*21*	*9*	3.3 at 0′, 10′, 20′	+
Av.	103	85	53	46	42	45	46		
S.D.					±8.5	±9	±9.5		
Av.	*97*	*77*	*45*	*33*	*26*	*23*	*24*		
S.D.					*±8.5*	*±7.5*	*±11.5*		

Blood sugar curves

Rabbits.—The results of experiments on six rabbits are shown in Table I and Fig. 1. In every animal the fall in blood sugar was greater when hexamethonium was given with the insulin. During the first twenty minutes the differences in the blood sugar curves were insignificant, but they became more and more marked during the succeeding thirty minutes. In these experiments no rabbits were convulsed by the dose of insulin (0.8 i.u./kg. i.v.) given alone, but five out of six were convulsed when hexamethonium was given with it. Hexamethonium alone (Fig. 1) had little effect on the blood sugar.

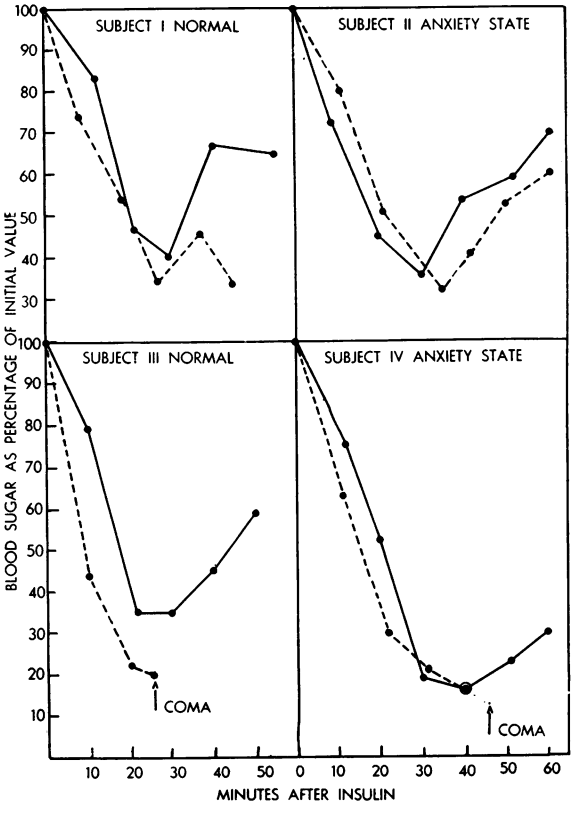

FIG. 2.—Blood sugar curves from four fasting human subjects. ●———● insulin alone (intravenously). ●- - -● same dose of insulin given 10 min. after 100 mg. hexamethonium iodide intramuscularly. Subjects I–III: 0.1 i.u. insulin/kg.; subject IV: 0.26 i.u. insulin/kg. (No blood specimen was obtained during coma from subject IV.)

Man.—Curves constructed from data obtained from four human subjects are shown in Fig. 2. Here also hexamethonium caused a more depressed blood sugar curve, though the results were less striking, probably because the dose of hexamethonium was less (1.4 mg./kg.). Nevertheless, two of the subjects became comatose when hexamethonium was given, although they did not lose consciousness with the same dose of insulin alone. Consciousness was quickly restored by intravenous glucose.

Symptoms in man

Sweating was marked in all cases when insulin was given alone, in some enough to necessitate a change of clothing. When hexamethonium was given in addition there was no sweating.

Tremor of the outstretched hand was strikingly less when hexamethonium was given.

A sharp rise in the *heart rate* occurred, just before the blood sugar reached its lowest point, when insulin was given alone. With hexamethonium the heart rate increased steadily from the beginning of the experiment and remained high without a sharp peak.

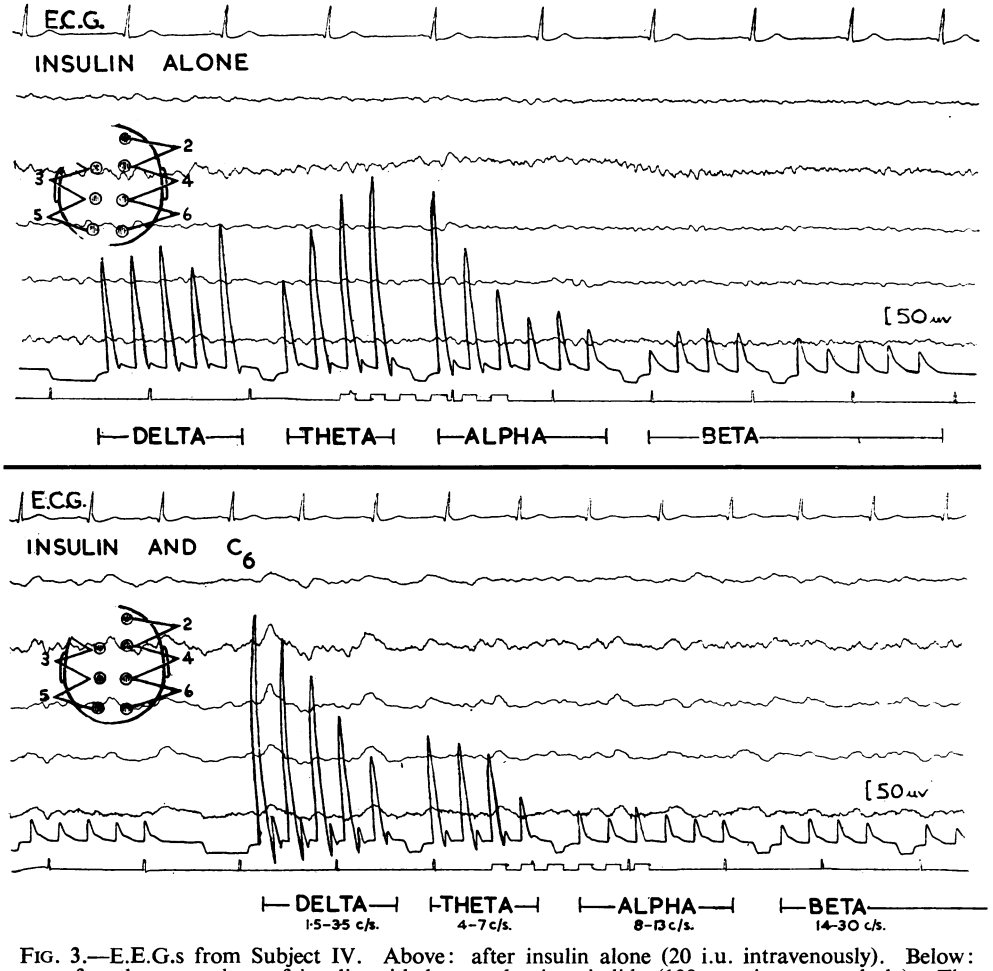

FIG. 3.—E.E.G.s from Subject IV. Above: after insulin alone (20 i.u. intravenously). Below: after the same dose of insulin with hexamethonium iodide (100 mg. intramuscularly). The blood sugar at the time these records were taken was the same, namely, 15 mg./100 ml. The bands of the analyser epoch are indicated under each tracing. Signal: 1 sec.

Hexamethonium caused a striking modification in the *subjective effects* of insulin hypoglycaemia. Restlessness and anxiety were markedly diminished in all cases, although the hypoglycaemia was greater, and two subjects passed peacefully through a stage of drowsiness to coma. One of our subjects (Subject IV) had previously received insulin treatment for his mental condition and had needed manual restraint. With hexamethonium no excitement occurred and he passed into unconsciousness without comment or movement. Subjects noticed palpitations less when hexamethonium had been given.

The *E.E.G. records* were similar whether hexamethonium had been given or not. As the blood sugar fell, *theta* activity appeared, became dominant, and was succeeded by the development and sometimes dominance of *delta* activity. *Alpha* activity diminished and sometimes disappeared. A comparison of tracings from the same subject at the same blood sugar levels showed a greater shift towards slower activity on the occasions when hexamethonium was given (Fig. 3).

Effect of Hexamethonium on the Convulsant Blood Sugar Level

Groups of 20 male mice of uniform weight were used. They had been fed on bread and milk for three days and starved for twenty-four hours. All received a subcutaneous injection of insulin and half received hexamethonium (5 mg./kg.) intraperitoneally simultaneously. They were then all placed in an incubator at 33° C. As each mouse developed convulsions a specimen of blood was taken either from the tail (Exp. 1) or by decapitation (Exps. 2 and 3) and the blood sugar estimated by King's method (1947). The results are recorded in Table II. There was no significant difference between the mean blood sugar at the development of hypoglycaemic convulsions in the two groups.

TABLE II

Effect of hexamethonium iodide (5 mg./kg. i.p.) on the mean blood sugar level at which insulin convulsions develop (mice)

Exp.	No. of mice in each group	Dose of insulin i.u./mouse	Mean blood sugar on convulsion, mg./100 ml. blood	
			Without hexamethonium	With hexamethonium
1	10	0.2 s.c.	17 ± 2	15 ± 4
2	10	0.2 s.c.	9 ± 3	10 ± 3
3	8	0.4 s.c.	14 ± 4	11 ± 6

Discussion

The experiments described indicate that hexamethonium potentiates the convulsant action of insulin by increasing the degree of hypoglycaemia. This is due to blocking of the hypoglycaemia-induced sympathetic discharge to the liver and adrenal medulla. Cannon *et al.* (1924) obtained a similar result by adrenalectomy and section of the hepatic nerves.

The other changes in the response to hypoglycaemia can also be attributed to the same action. The absence of sweating, of increased tachycardia, and of palpitations was to be expected as these symptoms occur with sympathetic stimulation.

Tremor of the hands, restlessness, and anxiety occur during intravenous infusion of adrenaline in man, and these symptoms, present when insulin was give alone, were absent when hexamethonium was given with it. Adrenaline infusion in man favours the development of fast rhythms in the E.E.G. (Gibbs and Maltby, 1943). Studies on the patients in this series showed that at the same low blood sugar levels slower rhythms were more marked with hexamethonium and insulin than with insulin alone. This may be due to the absence of adrenaline from the circulation in the former case.

Feldberg (1945) suggested that hypoglycaemic convulsions might be due to an accumulation of acetylcholine in the brain through the removal of the "glucose brake" on acetylcholine synthesis. We have shown that hexamethonium antagonizes nicotine convulsions possibly by a central action; it was of interest to see whether hexamethonium antagonized hypoglycaemic convulsions. The experiments described in the last section failed to demonstrate any such action.

A clinical application for some of these results can be suggested. A diabetic receiving a ganglionic blocking agent in the course of treatment for hypertension or any other condition would be unlikely to have any of the warning symptoms of a hypoglycaemic reaction and might slip quietly into coma as did two of the subjects in this series.

The relation of this work to the smooth induction of insulin coma in psychiatric therapy might be worthy of further investigation.

While this paper was in preparation a paper by Schachter (1951) appeared in which he showed that hexamethonium causes an increased sensitivity to insulin in unanaesthetized dogs.

SUMMARY

1. The effect of hexamethonium on insulin hypoglycaemia in man and in rabbits has been examined.

2. Hexamethonium (i) potentiates the convulsant action of insulin by increasing the degree of hypoglycaemia, (ii) abolishes or markedly alters the symptoms of insulin hypoglycaemia in man, and (iii) modifies the E.E.G. changes in hypoglycaemia.

3. The relation of these effects to sympathetic blockade is discussed.

4. The blood sugar level at which insulin convulsions develop is not affected by hexamethonium.

5. Attention is drawn to the possibility of symptomless hypoglycaemia occurring when insulin and hexamethonium are used together.

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REFERENCES

Cannon, W. B., McIver, M. A., and Bliss, S. W. (1924). *Amer. J. Physiol.*, **69**, 46.
Feldberg, W. S. (1945). *J. Physiol.*, **103**, 367.
Gibbs, F. A., and Maltby, G. L. (1943). *J. Pharmacol.*, **78**, 1.
King, E. J. (1947). *Microanalysis in Medical Biochemistry*, p. 20. London: Churchill.
Laurence, D. R., and Stacey, R. S. (1952). *Brit. J. Pharmacol.*, 7, 80.
Mainland, D. (1948). *Canad. J. Res. E.*, **26**, 1.
Schachter, M. (1951). *J. Physiol.*, **115**, 206.