passage in embryonated egg have not succeeded. 4) This demonstration of production of Type I poliovirus from nucleic acid in the embryonated egg, without subsequent multiplication, provides a system for biochemical study of genesis of whole virus from its nucleic acid. An advantage of the system is that the inciting agent (infectious RNA) can be differentiated completely, by its susceptibility to the action of RNAase, from whole virus progeny.

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Antagonism of Succinylcholine to Chlorpropamide Induced Hypoglycemia. (25006)

D. A. JAEGER, A. B. DRAKONTIDES, M. DIMITRAKIS, J. A. SCHNEIDER
Macrobiology Dept., Chas. Pfizer & Co., Brooklyn, N. Y.

Hypoglycemic activity of 1 (p-chlorobenzenesulfonyl) 3-N propylurea (chlorpropamide, Diabinese®) has been well established experimentally(1) and clinically(2). Following high doses of chlorpropamide in animals, a decrease of spontaneous motor activity and drowsiness were noted. This prompted an electroencephalographic study in the course of which cats were immobilized with succinylcholine. Surprisingly enough, severe hyperglycemia was found and normally effective doses of chlorpropamide did not lower blood glucose. This study was designed to elucidate this antagonistic action.

Methods. Forty-five cats and 100 rats were employed. Cats of both sexes ranging in weight from 2.5 to 3.5 kg were fasted 16-18 hr. Anesthesia was induced by intraperitoneal injection of pentobarbital sodium 40 mg/kg. A tracheal cannula was inserted and femoral vein was cannulated for injection of various agents and collection of blood samples. Whenever necessary, artificial respiration was maintained by Palmer Pump using 20 to 30 cc of air. Bilateral adrenalectomy was performed by lumbodorsal approach. Such animals were maintained 24 hr by subcutaneous injection of 1 mg/kg of cortisone. Male albino Wistar rats weighing 275-350 g were used necessitating artificial respiration. A tracheal cannula was inserted and attached to a Harvard Pump. For all other experiments, rats weighing 140-175 g were used. Bilateral adrenalectomy was performed 2 days prior to testing; animals were maintained by giving 1% saline in drinking water. Partial hepatectomy was performed under ether anesthesia 1 day prior to testing with removal of median and left lobes which comprise about 70% of liver tissue(3). All rats were fasted 18 hrs. The sodium salt of chlorpropamide was administered intravenously. Other agents were given as specified. Blood glucose determinations were performed with Auto Ana-

TABLE I. Effect of Chlorpropamide on Blood Glucose.

	No. of animals	Chlorpropamide dose, mg/kg I.V.	Blood glucose, mg % 0′	45′	60′	90′	120′	180′	240′	300′
Anesthetized* cats	4	25	70.0 ±7.26†		70.4 ±20.40		62.1 ±21.00	72.5 ±21.50	76.0 ±22.80	73.5 ±23.10
	3	50	84.0 ±18.16		52.0 ±9.84		34.0 ±4.18	29.0 ±3.51	30.0 ±6.00	33.0 ±4.35
	3	100	73.0 ±5.83		44.0 ±7.57		34.0 ±3.51	30.0 ±3.78	38.0 ±6.34	40.0 ±7.17
Unanesthetized cats	3	25	69.0 ±6.92		46.0 ±13.00		37.0 ±7.00	39.0 ±6.63	44.0 ±9.27	59.0 ±2.08
	3	50	60.0 ±5.56		46.0 ±6.85		41.0 ±5.78	37.0 ±8.12	31.5 ±7.87	36.0 ±6.48
	3	100	65.0 ±7.76		38.0 ±2.00		34.0 ±2.51	28.0 ±1.73	31.0 ±4.41	36.0 ±2.86
Anesthetized* rats	6	25	74.4 ±3.04	66.4 ±2.06		54.6 ±1.95			62.6 ± .89	
	6	50	81.9 ±1.93	68.0 ±1.61		44.6 ±1.33			57.5 ±2.53	
	6	100	81.4 ± .29	56.7 ±1.34		42.1 ±6.40			53.0 ± .29	
Unanesthetized rats	6	25	86.7 ± .28	82.8 ±4.01		67.6 ± .29			75.7 ±2.81	
	6	50	89.7 ±1.87	63.1 ±2.42		55.3 ±1.83			62.0 ± .60	
	6	100	79.0 ±2.18	51.0 ± .23		45.8 ±1.22			48.7 ±1.60	

* Anesthetized with pentobarbital sodium, 40 mg/kg I.P.
† ± S.E.

lyzer, employing modification of Hoffman's (4) micro method.

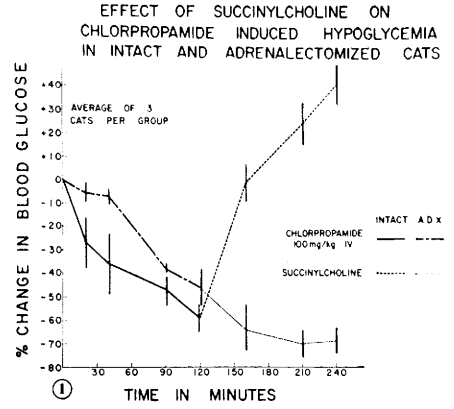
Results. Hypoglycemic activity of intravenously administered chlorpropamide in anesthetized and unanesthetized cats and rats was studied. A definite hypoglycemic response occurred in both species (Table I). To insure maximal hypoglycemic responses in anesthetized, and unanesthetized animals, chlorpropamide was used in subsequent experiments at 100 mg/kg.

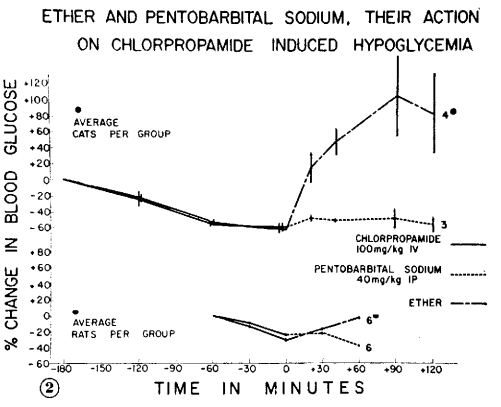
Succinylcholine at doses sufficient for complete muscular paralysis (5-8 mg/kg in rat and cat) was administered intravenously. The dose at which respiration ceases is between 1-2 mg/kg. Supplementary doses were given as necessary. Succinylcholine in the intact cat caused a complete reversal of hypoglycemic response to chlorpropamide (Fig. 1). Similar results were obtained in the rat. However, in the adrenalectomized cat, no antagonism of blood glucose was observed (Fig. 1). Because of extreme sensitivity of the adrenalectomized rat to large doses of chlorpropamide, a similar experiment was not carried out in the rat. Death from hypoglycemic shock resulted during chlorpropamide pretreatment or immediately following succinylcholine.

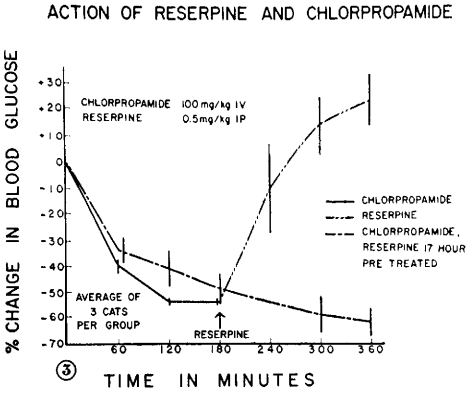
Since succinylcholine appeared to alter the hypoglycemic response obtained with chlorpropamide, another immobilizing agent was investigated. Curare, injected intravenously to cats in doses from 3-5 mg/kg, also reversed blood glucose lowering action of chlorpropamide. Following initial reversal of the hypoglycemic response with chlorpropamide, blood glucose levels gradually declined for duration of the 2 hr period.

Six rats were hepatectomized, given chlorpropamide, and after 1 hr immobilized with succinylcholine. Blood glucose values showed continuous decline in spite of administration of succinylcholine (Table II).

Since ether elevates blood glucose through liberation of adrenal medullary hormones







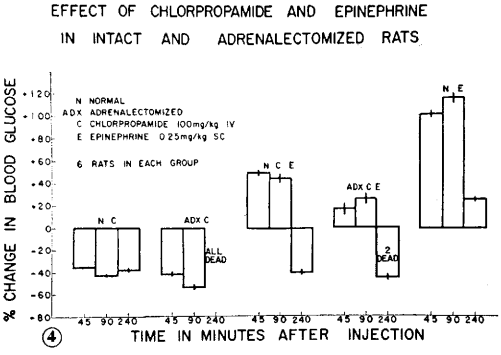


FIG. 1. There is a statistically significant difference 40 min. after succinylcholine in the intact cat ($p > .001$), and between intact and adrenalectomized groups, 40 min. after succinylcholine ($p > .001$). Vertical lines represent S.E.

FIG. 2. Difference in blood glucose values after ether and pentobarbital sodium anesthesia was significant 60 min. in the rat ($p > .01 < .02$) and 20 min. in the cat ($p > .05 < .02$). Vertical lines represent S.E.

FIG. 3. Significant difference between groups was present 60 min. after reserpine ($p > .05 < .02$). Vertical lines represent S.E.

FIG. 4. All values are statistically significant ($p < .05$) except ADX C E at 45 min. ($p > .2 < .1$). Vertical lines represent S.E.

(5) it was of interest to evaluate the effect of ether and pentobarbital sodium on drug induced hypoglycemia.

Chlorpropamide was injected to cats and rats 3 hrs and 1 hr respectively before initiating anesthesia. Hyperglycemia resulted following ether, while pentobarbital sodium administered under same conditions did not interfere with lowered blood glucose (Fig. 2).

To evaluate further the importance of adrenal medullary hormones, cats were pretreated with reserpine prior to administration

TABLE II. Effect of Succinylcholine on Chlorpropamide Induced Hypoglycemia in Normal and Hepatectomized Rats.*

		Blood glucose, mg %				
	Drug	0′	30′	60′	90′	120′
Normal	Chlorpropamide, 100 mg/kg I.V.	98.6 ± 3.94†	77.1 ± 4.35	65.9 ± 5.86	75.8 ± 7.52	95.2 ± 8.63
Hepatectomized	*Idem*	77.8 ± 4.15	76.2 ± 3.23	62.2 ± 7.52	53.7 ± 3.74	51.8 ± 1.82

Succinylcholine administered after 60 min. * 6/group. † S.E.

of chlorpropamide. According to Holzbauer and Vogt(6) reserpine depletes the adrenals of epinephrine and norepinephrine. A lowering of blood glucose after chlorpropamide was obtained, however, when reserpine was injected after inducing hypoglycemia there was an immediate rise in blood glucose presumably caused by liberation of epinephrine (Fig. 3).

Epinephrine caused hyperglycemia in normal and in adrenalectomized rats(7) therefore, epinephrine and chlorpropamide were injected simultaneously to adrenalectomized and intact rats. There was complete suppression of hypoglycemic response in intact rat until 240 min when the antagonistic effect of epinephrine was no longer evident. Sensitivity of adrenalectomized rat to chlorpropamide as evidenced by mortality at 240 min was lessened by epinephrine (Fig. 4).

Discussion. Reversal of chlorpropamide induced hypoglycemia by succinylcholine in intact and its absence in the adrenalectomized animal, indicates influence of the adrenal gland. Our experiments point to the importance of epinephrine or norepinephrine as determining factors.

Dulin(8) observed that the role of adrenal cortex and medulla was important in modifying the hypoglycemic reaction of rats to tolbutamide. He also noted that epinephrine completely counteracted the hypoglycemic effects of tolbutamide.

It is noteworthy that hyperglycemic response was most pronounced in animals immobilized with succinylcholine, where the cortex was exposed for electroencephalographic recordings. Ether, which is said to stimulate the adrenal medulla *via* the pituitary adrenal axis(5) also elevated blood glucose in animals pretreated with chlorpropamide.

Adrenalectomized chlorpropamide treated rats responded with hyperglycemia to epinephrine injections, indicating that liver glycogen content was adequate for such response. To insure presence of sufficient glycogen in the liver, adrenalectomized cats were given cortisone. If glycogen is not available, as in the hepatectomized state, administration of succinylcholine will not result in hyperglycemia even though adrenals are present. This appears to indicate that succinylcholine causes a release of adrenal medullary substances, these in turn utilizing glycogen of liver resulting in hyperglycemic blood picture.

Ward and Dance(9) reported on the effect of succinylcholine on blood sugar in nondiabetic persons undergoing minor surgery. Succinylcholine caused but slight rise in concentration of blood sugar 60 min after administration of succinylcholine when used with pentothal sodium and nitrous oxide.

Summary. 1. In cats and rats, pentobarbital anesthetized and unanesthetized, a definite hypoglycemia was evoked with intravenously administered chlorpropamide. 2. Reversal of induced hypoglycemia was obtained wtih succinylcholine in intact rat and cat, but not in adrenalectomized cat. 3. Experiments performed with ether, reserpine and epinephrine, further supported the view that this antagonism was mediated through the adrenal gland.

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