Influence of Adrenaline and Insulin on Adrenal Cortical Response to ACTH. (18392)

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(Introduced by H. Selye.)

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Previous observations have shown that the oral administration of glucose to hypophysectomized animals markedly enhances the adrenal response to exogenous ACTH(1,2). The possibility was considered that the hyperglycemic level, *per se,* was responsible for the observed effects (increased adrenal cholesterol depletion, liver-glycogen deposition and thymus involution). In order to evaluate this possibility, the adrenal cortical response to ACTH was studied in hypophysectomized animals under conditions of adrenaline-induced hyperglycemia and insulinic hypoglycemia.

Materials and Methods. 56 male piebald rats of an average weight of 180 g were equally divided into 8 groups and the following general procedure adopted. Armour's ACTH (lot No. 60-61) was used at a dose level of 2 mg, adrenaline (epinephrine HCL) of 0.1 mg, and insulin (Toronto) of 0.5 unit per 100 g. ACTH was subcutaneously injected into hypophysectomized fasted rats. Adrenaline and insulin were administered by the same route, 60 and 90 minutes respectively after ACTH administration, and the animals were killed at intervals of 3 and 6 hours following the latter injection. Hypophysectomized control rats without further treatment or receiving ACTH, adrenaline or insulin alone were killed at corresponding time intervals. In this way, the full action of ACTH on adrenal cholesterol coincided with the maximal hyper- and hypoglycemic levels and, it was possible to study all events as a function of time. The time schedule was arranged in such a way that all animals were killed 24 hours after hypophysectomy and the beginning of fasting. Samples were removed for the following determinations: blood glucose by the method of Folin(3), adrenal cholesterol by the method of Sperry(4), adrenal and plasma ascorbic acid by the method of Roe and Kuether(5), and liver glycogen according to Venning's modification of the procedure described by Good, Kramer and Somogyi(6).

Results. The results are summarized in Table I.

Blood-sugar — ACTH alone was without effect on the blood sugar and did not significantly alter the adrenaline hyperglycemia or the hypoglycemic effect of insulin.

Plasma ascorbic acid — ACTH alone caused a significant although slight and transient elevation of the plasma ascorbic acid level, while a marked drop resulted from the administration of adrenaline and insulin either alone or in association with ACTH. The observed fall is apparently related to an increased utilization. It is in contrast, in the case of adrenaline hyperglycemia, with the marked potentiation of the ACTH-induced rise in the plasma ascorbic acid concentration observed in previous experiments to follow alimentary hyperglycemia(2,7).

Liver glycogen—A slight deposition of glycogen was evidenced in both adrenaline

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TABLE I. Effects of Adrenaline and Insulin on Response of ACTH.

Chemical determinations	Blood sugar, mg/100 ml		Plasma ascorbic acid, γ/100 cc			Liver glycogen, g/100 g			Adrenal cholesterol, mg/100 mg			Adrenal ascorbic acid, γ/100 mg		
Time intervals*	0	3 hr	6 hr	0	3 hr	6 hr	0	3 hr	6 hr	0	3 hr	6 hr	0	3 hr	6 hr
Treatment															
Hypophysectomy	95.2	100.4	86.8	1383	1580	760	T.‖	T.‖	T.‖	4.58	3.17	4.24	540	417	488
+ ACTH†	±4.9	± 2.9	± 8.6	±80	±14	±60				±.18	±.43	±.36	±19	±27	±17
Hypophysectomy	95.2	157.4		1383	1000		T.‖	.033		4.58	4.15		540	565	
+ adrenaline‡	±4.9	±19.0		±80	±55			±.036		±.18	±.29		±19	±12	
Hypophysectomy	95.2	28.7		1383	967		T.‖			4.58	4.05		540	562	
+ insulin§	±4.9	± 2.4		±80	±118					±.18	±1.2		±19	±17	
Hypophysectomy	95.2	199.6	85.3	1383	780	960	T.‖	.007	T.‖	4.58	3.56	3.89	540	416	452
+ ACTH + adrenaline	±4.9	±33.2	± 18	±80	±80	±40		±.003		±.18	±.45	±.16	±19	± 5	±37
Hypophysectomy	95.2	27.0	27.0	1383	1020	900	T.‖	T.‖	T.‖	4.58	4.25	3.62	540	416	404
+ ACTH + insulin	±4.9	± 3.8	± 8.0	±80	±73					±.18	±.41	±.31	±19	±11	±49

* Time expressed in hr after ACTH administration. In groups not receiving ACTH, the animals were killed 2 hr after adrenaline and 1½ hr after insulin administration.

† ACTH, Armour, Lot No. 60.61, 2 mg/100 g.

‡ Adrenaline HCL 0.1 mg/100 g.

§ Insulin, Toronto, 0.5 U./100 g.

‖ Traces.

treated groups, while traces only were detectable in the others.

Adrenal cholesterol and ascorbic acid—30 and 20% falls were respectively observed in the concentrations of cholesterol and ascorbic acid 3 hours after the administration of ACTH. Adrenaline and insulin alone were without effect on these adrenal constituents, neither did they alter significantly, when associated with ACTH, their response to corticotrophic stimulation.

Conclusions. The above results show that adrenaline or insulin induced alterations of the blood sugar level do not modify the adrenal response to ACTH. The previously noted effect of glucose administration on the adrenal cholesterol response to ACTH is therefore attributed to an increase in the total store of carbohydrates or to an excess production of intermediary metabolites.

Summary. In order to investigate the mechanism of the previously observed enhancement of the adrenal response to ACTH following the administration of glucose, this response was studied in hypophysectomized animals under conditions of adrenaline hyperglycemia and insulin-induced hypoglycemia. Determinations were made of blood-sugar, plasma ascorbic acid, liver glycogen, adrenal cholesterol and ascorbic acid.

1. The blood sugar changes resulting from adrenaline or insulin administration were not influenced by ACTH. 2. A marked fall in plasma ascorbic acid concentration resulted from the administration of adrenaline and insulin either alone or in association with ACTH. 3. Neither adrenaline nor insulin modified the response to ACTH of liver glycogen and of adrenal cholesterol and ascorbic acid. 4. The effects of alimentary hyperglycemia are therefore attributed to an increase in the total store of carbohydrates or to an excess production of intermediary metabolites, which conditions are not duplicated by adrenaline.

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