The Acute Effects of Steroid Administration on Pituitary Adrenal Secretion in the Dog *

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Prolonged steroid administration results in pituitary adrenal unresponsiveness. The mechanism appears to be decreased ACTH secretion, with resultant adrenal cortical atrophy (1). There is much controversy, however, concerning the acute effect of steroids on pituitary adrenal secretion, and there are several important unsettled problems. Evidence is conflicting about a possible direct inhibitory effect of steroids on the adrenal cortex. Some reports describe steroid inhibition of the pituitary adrenal cortical response to operative trauma (2), whereas others find no diminution of normal responsiveness with acute administration of steroids (3). There is little information available about effects of steroids on the responses to other stimuli. And, finally, there is not agreement on the central nervous system site of steroid action. Some experiments suggest a direct effect on the anterior pituitary (4), but the bulk of work indicates an effect at the hypothalamic or higher level (5, 6). The present study was designed to provide at least partial answers to these questions. The potent synthetic steroid analogue, dexamethasone, was administered to dogs in which adrenal cortical function was measured by determining adrenal venous corticosteroid secretion.

Methods

Adult mongrel dogs, ranging in weight from 15 to 30 pounds, were used in these experiments. Adrenal venous cannulations were carried out according to the technique of Hume and Nelson (7). Adrenal venous 17-hydroxycorticosteroids were measured by the method of Peterson, Karrer, and Guerra (8), utilizing hemolyzed whole blood instead of plasma. Corticosteroid secretion rate was determined by multiplying adrenal

venous blood flow by corticosteroid concentration. Hypophysectomies were performed by the transbuccal approach of Markowitz and Archibald (9). Removal of the entire brain down to the pons, leaving an isolated pituitary, or bilateral decortication was carried out according to techniques developed in our laboratories (10, 11). Dexamethasone phosphate,[1] 100 mg added to 1,000 ml of 0.9% sodium chloride solution, was infused at the rate of 50 ml per hour in the inhibition experiments. In the hemorrhage experiments, approximately 500 ml of blood was removed from the animal over a 20-minute period, and adrenal venous samples were obtained before and after completion of hemorrhage. For the endotoxin experiments, 1.0 mg of *Escherichia coli* lipopolysaccharide B [2] was rapidly administered intravenously, and adrenal venous blood samples were taken before and 20 to 40 minutes after endotoxin. The animals subjected to ether anesthesia were given a single injection of sodium pentothal, and then anesthesia was maintained with ether throughout the rest of the experiment. Heavy canvas jackets were kept on the animals between sampling periods. Approximately 1 ml of heparin was instilled into the adrenal venous catheter to prevent clotting at the end of an experimental period. We have been able to obtain adrenal venous samples in dogs under a variety of conditions for several weeks with this technique.

Results

The first group of experiments was carried out in dogs hypophysectomized 2 hours before the control period. Two and 10 mU of ACTH were administered during the control period, and adrenal 17-hydroxycorticosteroid secretion per minute was measured 5 minutes after ACTH administration. Thirty minutes was allowed between the two different doses of ACTH to permit return to base-line values of corticosteroid secretion in the animals.

The results of these experiments are shown in Table I. The mean corticosteroid response to 2 mU of ACTH administered in the control pe-

[1] Supplied through the courtesy of Merck, Sharp & Dohme Research Laboratories, West Point, Pa.

[2] Difco Laboratories, Detroit, Mich.

riod was 6.1 μg, with an increase to 10.3 μg after 10 mU of ACTH. One hour after continuous intravenous infusion of dexamethasone, the mean responses after 2 and 10 mU of ACTH were 5.3 and 1.2 μg, respectively. Statistical analysis reveals no significant difference between the responses before or during the dexamethasone infusion (p > 0.5) at either dosage. Figure 1 outlines a detailed protocol of one of these experiments. The adrenal cortical response to 2 or 10 mU of ACTH is clearly unaffected by dexamethasone infusion.

The second series of experiments involved three groups of dogs: 23 control animals in which operative response after adrenal vein cannulation and ACTH responses were observed; an experimental group of 16 animals in which adrenal vein cannulation was carried out with dexamethasone infusion for 1 hour before, and during, operation; and 18 dogs in which "resting" corticosteroid secretion was measured the day after adrenal venous cannulation and contrasted with response after 1 U of ACTH intravenously. Table II summarizes the data in these animals. The mean corticosteroid response after adrenal vein cannulation in the control series of animals was 11.2 μg, as contrasted to a value of 3.7 μg in series B in which the animals underwent the same operation but received a dexamethasone infusion. This difference is significant (p < 0.02, > 0.01) and indicates an inhibitory effect of the dexamethasone infusion on the adrenal cortical response to adrenal vein cannulation. When the cannulation response
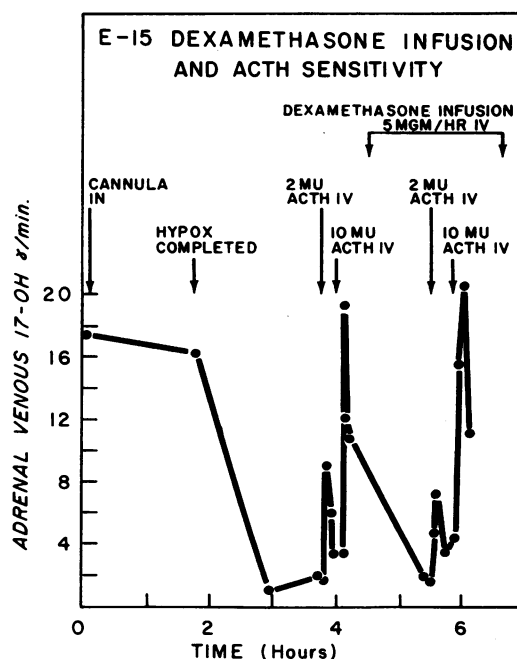

FIG. 1. ACTH SENSITIVITY OF HYPOPHYSECTOMIZED DOGS BEFORE AND DURING DEXAMETHASONE INFUSION. 17-OH = 17-hydroxycorticosteroids; hypox = hypophysectomized.

of the animals receiving dexamethasone infusion (3.7 μg) was contrasted with the resting response of animals the day after adrenal vein cannulation (1.1 μg), the difference was highly significant (p < 0.001) and indicates that the response to operative trauma in the dexamethasone-infused animals, while subnormal, was definite.

The third group of experiments was carried out

TABLE I

Effect of dexamethasone infusion on sensitivity of adrenal cortex to ACTH administration*

Experiment no.	Control period		1 hour after start of continuous infusion of dexamethasone (5 mg/hour iv)	
	2 mU ACTH	10 mU ACTH	2 mU ACTH	10 mU ACTH
	μg/minute		*μg/minute*	
E-1	7.4†		2.7	12.8
E-4	8.0	5.5	6.2	9.9
E-5	10.4	18.6	8.7	12.8
E-6	0.7	4.7	1.9	7.4
H-10	1.3	2.5	3.1	6.8
E-13	6.0	18.2	10.1	13.2
E-15	9.1	12.2	4.4	15.7
Mean	6.1 ± 1.4‡	10.3 ± 2.9	5.3 ± 1.2	11.2 ± 1.2

* Dogs were hypophysectomized 2 hours before the control period.
† Corticosteroid secretion from right adrenal gland. All samples obtained 5 minutes after ACTH administration.
‡ Standard error of the mean.

TABLE II

Effect of dexamethasone infusion on adrenal cortical response to surgical trauma of adrenal vein cannulation

A. Control series of dogs with adrenal vein cannulation			B. Series of dogs receiving continuous dexamethasone infusion, 5 mg/hour iv. Infusion started 1 hour before beginning cannulation of adrenal vein			C. Control series of dogs with values for "resting" adrenal cortical secretion 24 hours after adrenal vein cannulation		
Experiment no.	Cannulation completed	5 minutes after 1 U ACTH iv	Experiment no.	Cannulation completed	5 minutes after 1 U ACTH iv	Experiment no.	24 hrs after adrenal vein cannulation	5 minutes after 1 U ACTH iv
	$\mu g/minute$			$\mu g/minute$			$\mu g/minute$	
EII-1	10.8*	13.0	ED-10	4.1	18.4	EM-1	1.7	8.7
EI-4	10.4	10.0	B-288	1.2	20.8	EE-1	0.6	9.1
EI-5	13.2	16.0	ED-15	1.6	10.8	EE-2	0.6	11.5
EI-9	11.2	11.6	BP-60	2.2	11.4	VP-30	0.2	13.0
EI-10	12.2	13.4	ED-9	4.6	11.8	VP-28	2.0	16.4
EI-11	13.4	8.8	ED-7	4.6	9.8	VP-29	0.1	13.8
EI-13	9.2	14.8	ED-6	0.8	6.0	VP-22	0.0	10.4
B-336	10.6	19.0	ED-5	2.6	5.8	VP-24	0.8	13.2
BDJ-2	22.8	22.2	ED-4	5.8	12.4	VP-20	1.8	12.5
B-366	14.8	13.8	ED-3	0.8	6.8	VP-21	0.5	13.5
B-ACTH-5	13.0	16.2	ED-2	2.2	10.6	EN-14	0.6	21.5
B-214	12.2	12.0	ED-1	0.8	15.9	EN-12	1.9	12.6
EN-10	12.8	16.0	B1-63	9.6	26.4	EN-16	4.2	23.8
EN-9	8.2	13.8	B-245	4.6	6.8	EN-10	1.1	8.1
EN-11	11.7	12.4	ED-1-d	6.0	12.4	EN-11	1.3	17.6
EN-15	8.8	13.0	ED-12	7.0	12.0	EN-18	0.5	13.4
EN-13	7.2	12.1				EN-15	1.0	14.6
EN-6	7.2	6.6				EN-13	0.6	8.8
B-270	8.4	9.6	Mean	3.7 ± 0.6	12.4 ± 1.4			
B-272	11.2	10.8						
B-273	8.8	9.0				Mean	1.1 ± 0.2	13.5 ± 1.0
B-278	10.4	10.8						
EN-1	8.0	11.7						
Mean	11.2 ± 0.7†	12.9 ± 0.7						

* Corticosteroid secretion from right adrenal gland.
† Standard error of the mean.

in a series of dogs with "chronic" adrenal venous cannulas in which adrenal vein cannulation had been carried out the day before the experiment. A significant adrenal cortical response was observed after both hemorrhage and endotoxin administration in this group of dexamethasone-infused dogs, as shown in Table III. These responses were maximal as shown by a failure of exogenous ACTH to increase further corticosteroid secretion. These maximal adrenal cortical responses represent confirmation of the stimulatory effects of hemorrhage (7) and endotoxin (12) on adrenal cortical secretion previously described from our laboratories and those of others. In marked contrast is the complete inhibition of response to ether anesthesia that is observed when dexamethasone infusion is given before ether anesthesia. Reference to part C of Table III indicates that there is no significant difference between the mean corticosteroid secretion of 1.3 μg in the control period and that of 2.4 μg after 1 hour of continuous ether anesthesia

($p < 0.2$ and > 0.1). ACTH administration resulted in a response of 13.7 μg, which is highly significant when contrasted to the secretion observed 1 hour after ether anesthesia with dexamethasone infusion ($p < 0.005$, > 0.001). These experiments indicate that dexamethasone infusion does not alter the normal maximal response to hemorrhage or endotoxin administration but appears to prevent completely the expected maximal adrenal cortical activation after ether anesthesia in dogs (13). In addition, these experiments demonstrate that dexamethasone infusion alone does not result in increased corticosteroid content in adrenal venous blood.

The final group of experiments is divided into two parts. The first characterizes the adrenal corticosteroid response in dogs with dexamethasone infusion started before brain removal and carried on throughout the remainder of the experiment. It can be seen in Table IV that 1 hour after brain removal the corticosteroid secretion was 1.8 μg per minute, whereas 3 to 5

hours after brain removal the mean value was 7.0 µg per minute. Figure 2 illustrates a more detailed protocol of one of these animals. Despite the continuous intravenous administration of 5 mg of dexamethasone per hour, a significant operative response to adrenal vein cannulation and brain exposure was observed with depression of corticosteroid secretion levels 1 hour after removal of the brain. However, secretion increased during the next 2 hours, and administration of 1 U of ACTH approximately 3 hours after brain removal resulted in a further significant increase in corticosteroid secretion.

The second portion of these experiments revealed no decrease in the maximal corticosteroid secretion that followed bilateral decortication, de-

TABLE III

Effect of dexamethasone infusion (5 mg per hour iv) on adrenal cortical response to hemorrhage, endotoxin, and ether anesthesia*

A. Hemorrhage	µg/minute	µg/minute	µg/minute
Experiment no.	Control period	After removal of 400–500 ml blood	5 minutes after 1 U ACTH iv
NN	2.6†	10.6	
HD-9	6.2	22.0	16.4
H-D-1	0.3	9.6	7.7
HD-4	1.8	5.6	13.2
HD-7	1.8	12.9	23.6
HD-6	0.7	14.9	13.2
HD-2	0.8	8.0	12.2
HD-1	1.8	16.0	15.6
ED-1	1.0	3.2	11.4
Mean	1.9 ± 0.6‡	Mean 11.4 ± 1.9	Mean 14.2 ± 1.7

B. Endotoxin			
Experiment no.	Control period	20–40 minutes after 1 mg E. coli endotoxin iv	5 minutes after 1 U ACTH iv
EE-31		18.7	18.7
EE-30	0.5	11.7	11.2
EE-22	0.4	13.2	12.8
EE-23	0.5	10.7	10.2
EE-29	0.9	11.6	10.7
Mean	0.5 ± 0.1	Mean 1.32 ± 1.4	Mean 12.7 ± 1.4

C. Ether anesthesia			
Experiment no.	Control period	1 hour of continuous ether anesthesia	5 minutes after 1 U ACTH iv
ED-1	0.8	1.0	9.8
ED-2	1.8	2.2	17.8
ED-10	1.6	1.0	14.6
ED-7	1.0	0.9	7.9
ED-5	1.8	8.2	14.6
EE-32	0.9	1.1	17.3
Mean	1.3 ± 0.2	Mean 2.4 ± 1.2	Mean 13.7 ± 1.6

* Infusion was begun 1 hour before stimulus and carried on throughout the experiment.
† Corticosteroid secretion from right adrenal gland.
‡ Standard error of the mean.

TABLE IV

Effect of dexamethasone infusion (5 mg per hour iv) on adrenal cortical secretion in dogs with isolated pituitaries or bilateral decortication*

A. Isolated pituitaries	µg/minute	
Experiment no.	1 hour after brain removal	3–5 hours after brain removal
B-401	0.6†	4.2
B-400	1.4	6.4
B-398	2.6	11.4
B-389	0.6	10.8
B-390	0.6	0.6
B-391	0.9	11.8
B-392	5.7	6.0
B-395	1.8	6.5
B-397	2.2	4.9
Mean	1.8 ± 0.5‡	7.0 ± 1.2

B. Bilateral decortication		
Experiment no.	10–18 hours after bilateral decortication	5 minutes after 1 U ACTH iv
DD-10-A	13.2	
DD-10	38.6	34.8
DD-7	18.6	17.8
B-404	11.4	10.0
B-402	23.0	
B-403	23.9	21.8
Mean	21.5 ± 4.0†	21.1 ± 5.2

* Infusion was begun before brain removal or decortication and carried on throughout the experiment.
† Corticosteroid secretion from right adrenal gland.
‡ Standard error of the mean.

spite the constant infusion of dexamethasone throughout the experiment. The mean value of adrenal cortical secretion 10 to 18 hours after bilateral decortication was 21.5 µg per minute, with an ACTH response of 21.1 µg per minute. Dexamethasone was ineffective, therefore, in preventing the adrenal cortical hypersecretion that occurs after bilateral decortication.

Discussion

There is little specifically pertinent literature concerning a possible direct inhibitory effect of steroids on the adrenal cortical response to ACTH. Péron, Moncloa, and Dorfman (14), using very high doses of corticosterone, found less adrenal content of corticosterone in rats given ACTH than when corticosterone was not administered. Black and co-workers (15), infusing high concentrations of hydrocortisone into the isolated perfused adrenal gland of the dog, demonstrated inhibition of hydrocortisone production. Experiments in dogs with adrenal venous cannulas by Ganong (16) have failed to confirm a direct ef-
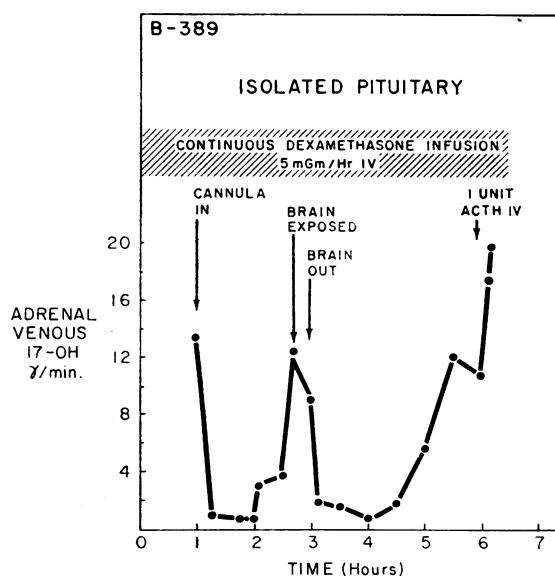
FIG. 2. CORTICOSTEROID SECRETION IN DOGS RECEIV-
ING CONSTANT INFUSION OF DEXAMETHASONE. Operative
procedures were adrenal vein cannulation and brain re-
moval, with ACTH administration at end of experiment.

pared to normal, the response is significant when
compared to resting or basal secretion. It is pos-
sible that this difference between our results and
those of Richards and Pruitt is due to more rapid
cannulation of the adrenal vein in our experiments.
We have found that the adrenal cortical response
to trauma of animals receiving dexamethasone in-
fusion may decrease rapidly after cannulation.
Estep, Island, Ney, and Liddle (3) were unable
to prevent the increase in peripheral blood cor-
ticosteroid levels that occurs after laparotomy in
patients by administering dexamethasone intra-
venously before and during operation. Myers and
colleagues (17), on the other hand, did partially
prevent the peripheral blood corticosteroid re-
sponse after operative trauma by administering
triamcinolone. The difference between our re-
sults and those of Estep and co-workers is prob-
ably based on species variation, the fact that the
patient studies involved measurements of periph-
eral blood levels of steroids and not secretion rates,
and differences in magnitude of operative trauma.
Hedner and Rerup (18) found that dexamethasone
inhibited completely the stimulating effect of ether
and inhibited partially the increase in plasma
corticosteroid levels after unilateral adrenalectomy.
Kendall (19) demonstrated maximal depression
of adrenal venous corticosteroid secretion in rats
4 to 8 hours after the administration of 2 mg of
dexamethasone. Hodges and Jones (20) were
able to block the acute release of ACTH in the
rat by pretreatment with cortisol, and Ham-
burger (21) found that dexamethasone is the
most potent inhibitor of the adrenal cortical re-
sponse to adrenalectomy in the rat. The data
of the present experiments, taken in conjunction
with these other studies, demonstrate that the
administration of steroids may modify the adrenal
cortical response to operative trauma. Because
of the widely divergent conditions of the experi-
ments in the various reported studies, particular
care must be taken in contrasting results of dif-
ferent workers. Factors that must be considered
in evaluating data in this area include steroid
dose, rate of steroid administration, species of ani-
mal, magnitude of operative trauma, and method
of assessing adrenal cortical function. Preliminary
experiments in our laboratory revealed that smaller

fect on adrenal cortical responsiveness to ACTH
after infusion of physiological concentrations of
hydrocortisone. The experiments presented in
part one of the present study are in agreement
with those of Ganong and appear to establish that
the administration of pharmacological doses of
dexamethasone does not decrease the adrenal cor-
tical responsiveness to threshold doses of ACTH
in the dog. The doses of dexamethasone utilized
in this study are considered pharmacologic be-
cause they far exceed the potential for endogenous
production of biologically active corticosteroids
by the dog. It is emphasized that the experiments
of this paper are concerned only with the acute
effects of steroid administration and do not pro-
vide any basis for speculations concerning pos-
sible long-term effects of steroid administration
on adrenal cortical responsiveness to ACTH.

Previous experimental work is also conflicting
concerning the possible inhibitory effects of steroid
administration on the adrenal cortical response
to trauma. Richards and Pruitt (2) were able
to inhibit completely the expected adrenal cortical
response of dogs to adrenal vein cannulation by in-
fusions of hydrocortisone. Although our ex-
periments demonstrate a decreased adrenal cor-
tical response to adrenal vein cannulation com-

amounts of dexamethasone give less inhibition; therefore, pharmacological doses of steroid were used.

Dexamethasone did not prevent the expected maximal adrenal cortical stimulation after hemorrhage and endotoxin administration. On the other hand, in confirmation of Kendall (19) and Hedner and Rerup (18), dexamethasone completely prevented the expected maximal response to ether anesthesia. Studies in our laboratories and those of others have revealed that maximal and sustained corticosteroid secretion is present $\frac{1}{2}$ to 1 hour after ether anesthesia (13). It appears, therefore, either that hemorrhage and endotoxin are stronger stimuli to a common mechanism of ACTH release, or that ether acts through different pathways that are blocked by steroid administration. There is nothing in the data of this or other reports that permits a choice between these two possibilities.

Our final group of experiments with brain removal and bilateral decortication indicates that dexamethasone administration does not prevent the adrenal cortical hypersecretion that these animals demonstrate and that has previously been reported in detail from our laboratories (10, 22). The previously described pattern of depressed corticosteroid secretion 1 to 2 hours after brain removal, with gradual increase to elevated but submaximal levels, was observed in dogs with isolated pituitaries receiving dexamethasone infusions. These data are in no way different from those observed in dogs not receiving steroids and appear to offer evidence for an extrapituitary site of steroid inhibition.

There are basically two possible ways to explain the findings of corticosteroid secretions that are elevated above base line but are less than maximal in dogs with isolated pituitaries. A weak stimulatory hormone or other systemic agent may be acting on the pituitary to cause ACTH release. On the other hand, if the pituitary in the intact animal is constantly bathed in a mixture of excitatory and inhibitory hormones with respect to ACTH release, it is possible that removal of the source of such hormones results in a pituitary whose intrinsic ACTH-releasing activity is revealed. Current studies in our laboratories indicate that peripheral blood from dogs with isolated pituitaries is ineffective in causing ACTH release when injected into the carotid artery of normal dogs. There is, therefore, no evidence for a systemic substance causing ACTH secretion from the isolated pituitary. Kendall, Matsuda, Duyck, and Greer (23) found that dexamethasone does suppress the moderately elevated ACTH secretion in rats with median eminence islands, and our studies taken together with his suggest a hypothalamic site for steroid inhibition of ACTH secretion. Several groups of workers (5, 6) have found that implantation of steroids into the hypothalamus, but not into the pituitary, is effective in inhibiting ACTH secretion. These findings would also appear to support a hypothalamic site for steroid action on pituitary adrenal responsiveness. If there are both excitatory and inhibitory hormones to pituitary ACTH secretion in the intact animal, steroids may act either by inhibiting release of the stimulatory hormone or enhancing release of the postulated inhibitor, or both.

The resolution of these problems awaits further work on hypothalamic and other central nervous system hormones that control ACTH secretion, understanding of the pathways for their control in the intact animal, and studies of the effect of steroids on their production and release.

Summary

1. Dexamethasone infusion did not alter the ACTH sensitivity of hypophysectomized dogs, suggesting that steroids have no direct effect on the adrenal cortex.

2. Dexamethasone administration partially prevented the increase in adrenal cortical secretion after operative trauma and completely abolished the expected stimulatory effect of ether anesthesia. On the other hand, steroid administration did not modify the expected maximal response to hemorrhage, endotoxin administration, or bilateral decortication.

3. The infusion of pharmacological doses of dexamethasone was ineffective in modifying the adrenal cortical hypersecretion of dogs with isolated pituitaries. There is evidence in favor of an extrapituitary site for steroid inhibition of ACTH secretion.

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