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Research Article

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Adrenocortical Steroidogenesis: the Effects of Prostaglandins

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ABSTRACT Prostaglandins E₁ and E₂ significantly stimulated the synthesis of aldosterone, corticosterone, and to a lesser degree, cortisol in the outer slices of beef adrenal tissue. PGA, PGF_{1α}, and PGF_{2α} were ineffective.

PGE₁ was found to stimulate steroidogenesis in a manner similar to that of adrenocorticotropin (ACTH) in (a) needing calcium, (b) being inhibited by puromycin but not actinomycin D, (c) increasing the levels of cyclic AMP, and (d) not having an additive effect to exogenous cyclic AMP. PGE₁ did not produce an additive effect with either submaximal or maximal amounts of ACTH but did have an additive effect with angiotensin.

These results are in keeping with the hypothesis that PGE₁ shares a receptor site on the plasma membrane with ACTH.

INTRODUCTION

Prostaglandins have been found to stimulate hormonal release from various glands, including the anterior pituitary (1), the thyroid (2), the pancreas (3), and the ovary (4). Conflicting data have been published concerning their effects upon the adrenal cortex. An increase in steroidogenesis was noted both in vitro (5) and in vivo (6) in the rat but the latter study failed to show a response in the hypophysectomized animal, suggesting that prostaglandins act by stimulating adrenocorticotropin (ACTH) release and not directly upon the adrenal. Since the rat adrenal differs considerably in its response from the adrenal of most higher species (7), a study more relevant to human physiology may be one that involved sheep wherein PGE infusions into autotransplanted adrenals produced an over-all decrease in al-

dosterone secretion, though considerable variation was observed (8). Moreover, that study was done when the animals were sodium deficient, a situation wherein the responses to various stimuli may be altered (9).

We have examined the effects of prostaglandins upon steroids synthesis in beef adrenal slices, an in vitro system which we have found to respond to various stimuli—ACTH, angiotensin, potassium, and sodium—in a manner qualitatively similar to the responses of human adrenal tissue in vivo (10). These studies demonstrate a definite action of certain prostaglandins and suggest a possible role for these hormones in the control of steroidogenesis.

METHODS

Tissue preparation and incubation. As detailed in the previous paper (11), for each study the outer two slices of 15–20 fresh beef adrenal glands were combined, minced, and divided into 500-mg portions for incubation. 24–40 separate portions were incubated with at least 4 portions for each point in the experiment. After a 1 hr preincubation, the Krebs-Ringer bicarbonate medium was replaced, the various stimulatory agents being compared were added, and the tissues incubated for 2 hr.

Stimulatory agents. Prostaglandins E₁, E₂, A₁, F_{1α}, and F_{2α} were provided by Dr. James Weeks, The Upjohn Company (Kalamazoo, Mich.) and dissolved in 0.1% ethanol. Porcine ACTH and synthetic angiotensin II were the same as used in the previous experiments. Doses were at least 10-fold greater than the lowest doses previously noted to produce significant effects (10), to ensure that suppression by other agents, e.g., puromycin, would be demonstrable. Cyclic AMP was dissolved in Krebs-Ringer bicarbonate medium and brought to pH 7.4 by addition of 1 N sodium hydroxide.

Assay procedures. Portions of the media were analyzed for steroids by a double-isotope derivative assay (12), slightly modified (11). Cyclic AMP was measured by a radioimmunoassay (13). Values are expressed as micrograms of steroid or picomoles of cyclic AMP in the incubation medium/gram of tissue per total time of incubation. The mean and standard deviation of the steroid values in each group of vessels were compared with those of the

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control specimens simultaneously incubated. Statistical evaluation was by Dunnett's test for multiple comparisons with a control (14).

RESULTS

These studies were designed first to demonstrate an effect of prostaglandins upon steroid synthesis and second to examine the possible mechanism of action of these agents, in comparison to what is known about ACTH and angiotensin.

The effect of various prostaglandins. In Fig. 1, the effects of 100 μg of five prostaglandins upon the synthesis of aldosterone, corticosterone, and cortisol are shown in comparison to the effects of angiotensin, 20 μg and ACTH, 2 U/g tissue. In another experiment comparing the five prostaglandins, PGE₂ had a slightly greater effect than did PGE₁, PGA had an insignificant effect, PGF_{1 α} decreased aldosterone synthesis by 15% and corticosterone synthesis by 36%, and PGF_{2 α} was without effect. In view of its inhibitory effect, PGF_{1 α} , 50 μg , was combined with ACTH, 2 U along with separate incubations of each agent. Although in this experiment PGF_{1 α} alone decreased aldosterone synthesis by 22%, it had no effect upon the degree of stimulation of aldosterone, corticosterone, or cortisol synthesis produced by ACTH.

The effect of varying amounts of PGE₁. In the remainder of the studies, only PGE₁ was used. The results of three experiments with varying amounts of PGE₁ are shown in Fig. 2. No effect was noted with 0.01 $\mu\text{g}/\text{g}$ tissue and an insignificant effect with 0.1 $\mu\text{g}/\text{g}$ tissue. However amounts of 1.0 μg or more always increased steroidogenesis.

PGE₁ stimulated the synthesis of aldosterone, corticosterone, and cortisol in each experiment. However the effect upon aldosterone was almost always greater than upon the other two. In 13 different experiments with

PER g TISSUE	ALDOSTERONE	CORTICOSTERONE	CORTISOL
PGE ₁ 100 μg	44%	44%	44%
PGE ₂ 100 μg	49%	49%	45%
PGA 100 μg	10%	12%	0
PGF _{1α} 100 μg	-11%	-7%	-3%
PGF _{2α} 100 μg	-3%	1%	-2%
Angiotensin 20 μg	71%	67%	64%
ACTH 2 U	23%	39%	62%

FIGURE 1 The effects of five prostaglandins, angiotensin, and ACTH upon steroid synthesis in beef adrenal tissue. The percentages are the change in synthesis from control vessels.

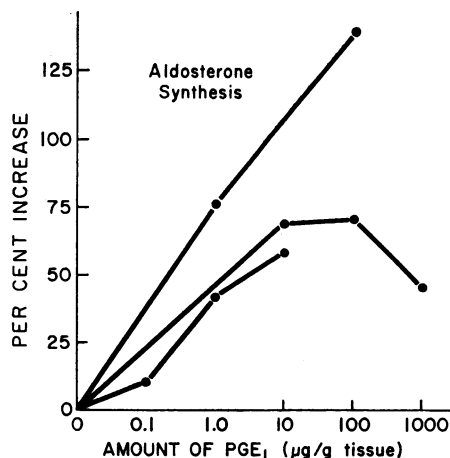


FIGURE 2 The effect of increasing amounts of PGE₁ upon aldosterone synthesis in three separate experiments.

amounts of PGE₁ varying from 1 to 100 $\mu\text{g}/\text{g}$ tissue, the mean increases in synthesis above control were: aldosterone 63%, corticosterone 37%, and cortisol 38%. In three experiments with 1.0 $\mu\text{g}/\text{g}$ tissue, aldosterone increased an average of 59% whereas cortisol increased 18%. On a molar basis, PGE₁ was about equal to angiotensin II in its effect upon aldosterone synthesis in this preparation (10).

Having demonstrated an effect of PGE₁ upon steroidogenesis, four approaches were taken to examine its mode of action: (a) combining it with other stimuli: ACTH, cyclic AMP, angiotensin, or increased concentrations of potassium, (b) examining the effect of inhibitors of protein and RNA synthesis, (c) determining the need for calcium, and (d) measuring cyclic AMP levels.

Combinations of PGE₁ and other stimuli

ACTH or cyclic AMP. As shown in Table I, PGE₁ 1 $\mu\text{g}/\text{g}$ tissue, did not produce an additive effect to that of a submaximal dose of ACTH in experiment 1 nor did PGE₁, 50 $\mu\text{g}/\text{g}$ tissue stimulate steroidogenesis beyond that noted with a presumably maximal dose of ACTH in experiment 2. Similarly, in experiment 3, PGE₁ did not potentiate the effect of exogenous cyclic AMP, 1 mM/g tissue.

Angiotensin. ACTH and cyclic AMP are thought to affect adrenal steroidogenesis in a similar manner, whereas angiotensin appears to act differently (11). Therefore PGE₁ was next combined with submaximal doses of angiotensin II (Table II). The results of experiments 4 and 5, similar to those of four other studies, indicate that PGE₁ produces an additive effect to that of angiotensin II. The levels of all three steroids achieved with the combination of PGE₁ plus angiotensin are significantly greater than those achieved with each agent

TABLE I

The Effect of PGE₁ in Combination with ACTH or Cyclic AMP

Ex- peri- ment	Stimulant		Aldosterone		Corti- costerone		Cortisol	
	Name	Dose	Mean	SD	Mean	SD	Mean	SD
			<i>per g tissue</i>		<i>µg/g tissue per 2 hr incubation</i>			
1	None		0.91	0.12	14.42	1.09	1.56	0.12
	PGE ₁	1 µg	<i>1.18</i>	<i>0.07*</i>	16.77	0.89	2.42	0.24
	ACTH	2 U	<i>1.11</i>	<i>0.09</i>	15.79	1.20	2.47	0.22
	PGE ₁	1 µg and	<i>1.14</i>	<i>0.05</i>	15.28	1.15	2.36	0.26
	ACTH	2 U						
	ACTH	4 U	1.40	0.12	17.40	2.32	2.95	0.27
2	None		0.96	0.08	10.49	1.09	1.68	0.13
	PGE ₁	50 µg	<i>1.78</i>	<i>0.24</i>	11.45	0.79	2.05	0.18
	ACTH	20 U	<i>2.01</i>	<i>0.15</i>	14.39	0.70	4.35	0.77
	ACTH	40 U	<i>2.07</i>	<i>0.18</i>	14.06	0.88	4.01	0.68
	PGE ₁	50 µg and	<i>2.02</i>	<i>0.27</i>	15.29	0.72	4.26	0.59
	ACTH	20 U						
3	None		1.56	0.15	5.49	0.58	1.58	0.16
	PGE ₁	1 µg	<i>2.47</i>	<i>0.25</i>	7.28	0.59	1.85	0.07
	Cyclic AMP	1 mM	<i>1.98</i>	<i>0.10</i>	7.59	1.47	1.96	0.24
	PGE ₁	1 µg and	<i>2.58</i>	<i>0.17</i>	8.33	0.72	2.06	0.10
	Cyclic AMP	1 mM						

* Results in italics differ statistically from the control level with *P* value less than 0.05.

individually. These differences between ACTH and angiotensin with PGE₁ are shown in Fig. 3 for submaximal doses and in Fig. 4 for maximal doses. The doses of ACTH and angiotensin depicted in Fig. 4 are considered to be maximal because no greater effect was noted with doses twice as large.

Potassium. As shown in Table III, PGE₁, 50 µg/g tissue, did not produce an additive effect on aldosterone

TABLE II

The Effect of PGE₁ in Combination with Angiotensin II

Ex- peri- ment	Stimulant		Aldosterone		Corti- costerone		Cortisol	
	Name	Dose	Mean	SD	Mean	SD	Mean	SD
			<i>per g tissue</i>		<i>µg/g tissue per 2 hr incubation</i>			
4	None		2.19	0.23	6.06	1.29	2.26	0.23
	PGE ₁	1 µg	<i>3.20</i>	<i>0.19*</i>	9.52	2.29	3.24	0.22
	Angiotensin	10 µg	<i>3.01</i>	<i>0.21</i>	8.51	1.15	3.25	0.27
	PGE ₁	1 µg and	<i>4.18</i>	<i>0.26</i>	14.20	3.14	6.02	0.80
	Angiotensin	10 µg						
	Angiotensin	100 µg	4.43	0.52	16.82	2.30	6.23	1.25
5	None		0.91	0.12	14.42	1.09	1.56	0.12
	PGE ₁	50 µg	<i>1.18</i>	<i>0.07</i>	16.77	0.89	2.42	0.24
	Angiotensin	1000 µg	<i>1.41</i>	<i>0.10</i>	18.72	1.67	2.68	0.18
	Angiotensin	2000 µg	<i>1.38</i>	<i>0.05</i>	17.46	0.88	2.38	0.24
	PGE ₁	50 µg and	<i>1.79</i>	<i>0.12</i>	20.15	1.80	3.62	0.31
	Angiotensin	1000 µg						

* Results in italics differ statistically from the control level with *P* value less than 0.05.

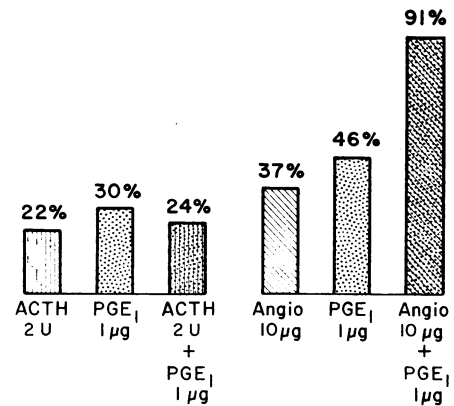


FIGURE 3 The effect of submaximal doses, individually and together, of ACTH and PGE₁, on the left, and of angiotensin II and PGE₁, on the right. Each set of three bars is a separate experiment.

synthesis to that of an increased potassium concentration of 7.6 mEq/liter. In this experiment aldosterone synthesis could be further stimulated by an even higher potassium concentration.

Inhibitors of protein and RNA synthesis

Puromycin. In a manner similar to that observed with ACTH, angiotensin and increased potassium concentration (11), puromycin 10⁻⁸ M completely inhibited the stimulation of steroid synthesis by PGE₁. The effect upon aldosterone synthesis in one experiment is shown in Fig. 5 and a similar inhibition of the stimulation of aldosterone, corticosterone, and cortisol synthesis was observed in two other studies.

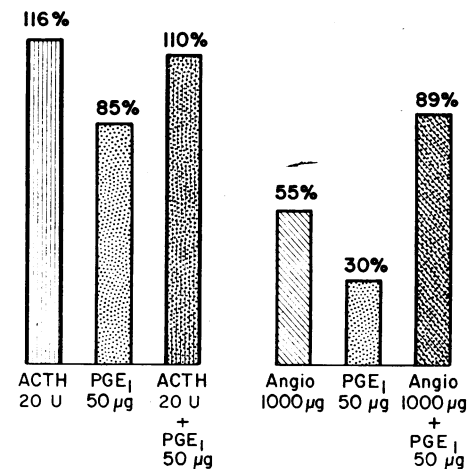


FIGURE 4 The effect of maximal doses, individually and together, of ACTH and PGE₁, on the left, and of angiotensin II and PGE₁, on the right. Each set of three bars is a separate experiment.

TABLE III
The Effect of PGE₁ in Combination with an Increased Potassium Concentration

PGE ₁ dose	Potassium concentration	Aldosterone		Corticosterone		Cortisol	
		Mean	SD	Mean	SD	Mean	SD
	<i>μg/g tissue</i>			<i>μg/g tissue per 2 hr incubation</i>			
None	5.2	1.59	0.18	8.55	0.42	2.11	0.18
50 μg	5.2	2.39	0.20*	14.65	1.12	2.88	0.16
None	7.6	2.64	0.35	14.44	1.30	2.05	0.25
50 μg	7.6	2.62	0.34	15.12	1.16	2.78	0.29
None	9.8	3.48	0.29	19.44	2.00	2.16	0.22

* Results in italics differ statistically from the control level with *P* value less than 0.05.

Actinomycin D. In three experiments, actinomycin D, 5×10^{-4} M, had little if any effect upon the steroidogenic effect of PGE₁. In one study, shown in Table IV, blunting of the stimulation of aldosterone synthesis but not of corticosterone or cortisol was observed with actinomycin D. In the other two studies, not even this partial inhibition was observed.

The need for calcium

The stimulation of steroidogenesis by PGE₁ was prevented in the absence of calcium from the incubation medium.

The effect of PGE₁ upon cyclic AMP

As shown in Table V, the levels of cyclic AMP in the incubation media increased in association with the stimulation of steroidogenesis by PGE₁. In these and two other experiments, one at each interval of incubation, the effects of PGE₁ were quite similar to those of ACTH.

DISCUSSION

These studies clearly show a stimulation of beef adrenal steroidogenesis in vitro by prostaglandins E₁ and E₂.

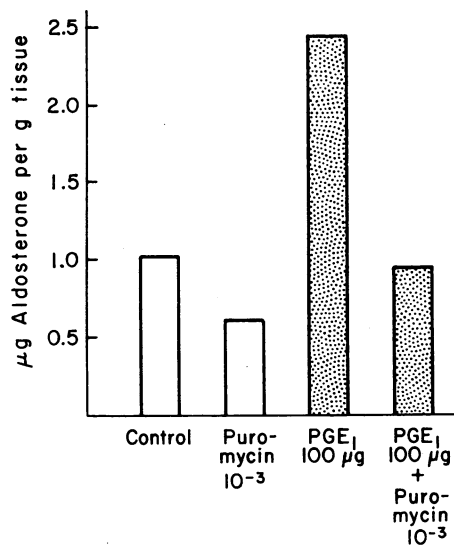


FIGURE 5 The effect of puromycin upon the stimulation of aldosterone synthesis in beef adrenal tissue by PGE₁.

Whether these findings have any relevance to human physiology is unknown since there are no published data on the effects of the prostaglandins upon adrenal steroids in man though prostaglandins have been found within human adrenal tissue (15). The results of similarly performed experiments with this in vitro model with ACTH, angiotensin and potassium have, in general, been compatible with what is known about the control of steroidogenesis in man (10).

The effect of PGE₁ upon adrenal steroidogenesis in this in vitro model requires doses of 1 μg or more/g of tissue. Whether such doses are "physiologic" is conjectural since plasma and tissue levels have not been measurable with accuracy. The availability of a radioimmunoassay (16) may make it possible to determine "physiologic" levels. It should be noted that microgram quantities of PGE₁ were needed for a steroidogenic effect in both in vitro (5) and in vivo (6) studies on the

TABLE IV
The Effects of Actinomycin D upon the Action of PGE₁

PGE ₁ dose	Agent	Aldosterone		Corticosterone		Cortisol	
		Mean	SD	Mean	SD	Mean	SD
—	—	2.08	0.20	10.24	1.05	1.89	0.17
—	Actinomycin D 5×10^{-4} M	1.90	0.15	11.74	1.29	2.05	0.48
50 μg	—	4.28	0.35*	19.73	1.75	2.81	0.18
50 μg	Actinomycin D 5×10^{-4} M	3.17	0.35	18.76	1.05	2.67	0.28

* Results in italics differ statistically from the control level with *P* value less than 0.05.

TABLE V
*The Effect of PGE₁ upon Aldosterone and Cyclic AMP Levels
in Media of Beef Adrenal Slice Incubations*

Stimulant	Aldosterone		Corticosterone		Cortisol		Cyclic AMP	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
			<i>µg/g tissue per incubation</i>				<i>pmoles/g tissue per incubation</i>	
2 hr incubation								
Control	2.08	0.20	10.24	1.05	1.89	0.17	57.5	5.2
PGE ₁ , 50 µg	<i>4.28</i>	<i>0.75*</i>	<i>19.55</i>	<i>1.46</i>	<i>3.56</i>	<i>0.28</i>	<i>83.5</i>	<i>6.4</i>
ACTH, 2 U	<i>3.21</i>	<i>0.18</i>	<i>17.38</i>	<i>1.60</i>	<i>4.08</i>	<i>0.57</i>	<i>105.6</i>	<i>12.5</i>
15 min incubation								
Control	1.02	0.08	4.44	0.40	1.10	0.06	81.2	5.9
PGE ₁ , 50 µg	<i>1.65</i>	<i>0.15</i>	<i>6.10</i>	<i>0.52</i>	<i>1.85</i>	<i>0.20</i>	<i>215.5</i>	<i>12.5</i>
ACTH, 2 U	<i>1.76</i>	<i>0.13</i>	<i>6.36</i>	<i>0.26</i>	<i>2.23</i>	<i>0.11</i>	<i>233.0</i>	<i>20.2</i>

* Results in italics differ statistically from the control level with *P* value less than 0.05.

rat. Similar amounts of prostaglandins were needed to demonstrate stimulation of other endocrine tissue in vitro, including the anterior pituitary (1), the thyroid (2), and the ovary (4). Although larger amounts of stimulatory agents are usually required in vitro, similar doses of prostaglandins were needed to demonstrate their effects in vivo, including the stimulation of growth hormone secretion in man (17).

In the studies reported here, PGE₁ and E₂ were most active in stimulating steroidogenesis, whereas PGF_{1α} and PGF_{2α} were without effect. Similar differences have been observed in studies on the thyroid (18) and anterior pituitary (1), although PGF_{2α} was effective upon the rat adrenal gland (5). More must be known about the nature and distribution of the various prostaglandins before the meaning of these differences is understood.

The studies on the possible mechanism of action of PGE₁ suggest that it may stimulate adrenal steroidogenesis in a manner similar to that proposed for ACTH which is thought to involve the following sequence: (a) binding to the plasma membrane, (b) activation of adenylyl cyclase, (c) production of cyclic AMP, (d) release of a protein phosphokinase, and (e) synthesis of a protein which regulates the conversion of cholesterol to pregnenolone within the mitochondria (19).

The similarities between the action of PGE₁ and ACTH noted in this study are: (a) PGE₁ does not produce an additive effect to either submaximal or maximal amounts of ACTH or cyclic AMP, supporting a common path or site of action. On the other hand, PGE₁ does have an additive effect with angiotensin II which appears to act in a different manner (11); (b) the action of PGE₁ requires the presence of calcium; (c) an inhibitor of protein synthesis, puromycin, blocks the effect of PGE₁ but an inhibitor of DNA synthesis, actinomycin D,

does not; (d) levels of cyclic AMP are increased when PGE₁ acts upon adrenal tissue.

Prostaglandins have been found to affect cyclic AMP in a variety of tissues (20). Early studies, primarily with fat cells, gave rise to an hypothesis that prostaglandins were released within tissues by the action of cyclic AMP, increased after hormonal stimulation (21). The prostaglandins were postulated to then exert an inhibitory action upon adenylyl cyclase, thereby limiting the action of the hormone via an "internal" negative feedback.

This hypothesis was constructed to explain the apparent paradox of the action of prostaglandin in several tissues: in fat cells, PGE₁ inhibits the effect of various lipolytic agents (20) whereas in smaller doses PGE₁ itself induces lipolysis (22); in the isolated toad bladder and rabbit renal tubule, PGE₁ inhibits the action of vasopressin upon increasing water permeability, whereas PGE₁ itself increases water permeability (23).

However a more attractive hypothesis for the action of prostaglandins upon endocrine tissue has been suggested wherein they involve the activation of adenylyl cyclase in a common pathway with the appropriate trophic hormone (23, 24). The results of the present study further suggest a sharing of the receptor site on the plasma membrane between PGE₁ and one or more other stimulatory agents. Thereby, PGE₁ could stimulate activity within the cell by activating adenylyl cyclase but at the same time competitively inhibit the binding or other necessary steps in the action of other trophic agents which also act via the adenylyl cyclase mechanisms. Within the adrenal cortex, this would be at the receptor site for ACTH. Within the thyroid, there appears to be competition between thyroid-stimulating hormone (TSH) and PGE₁ for a common adenylyl cyclase receptor site (25).

This theory would appear to explain the paradox wherein prostaglandins stimulate adenyl cyclase in almost every tissue examined but at the same time appear to inhibit the action of other trophic agents.

There are many prostaglandins some of which act differently in the same tissue. The theory supported by this study may not apply to all tissues, to all prostaglandins or to all other trophic agents. Prostaglandins may be involved in the control of steroidogenesis in other ways than the direct stimulation shown in this in vitro study. Thus ACTH may stimulate the formation or release of prostaglandins from adrenal tissue (26). Further, PGE₁ causes a release of renin which, in turn by activating angiotensin, may stimulate steroidogenesis (27).

PGE₁ appears to act primarily upon aldosterone synthesis in these in vitro studies using the outer two slices of beef adrenal cortex. This preparation contains all of the aldosterone producing tissue and only part of the cortisol producing tissue so that caution should be taken in interpretation of these data in support of a selective role of PGE₁. More pertinent studies upon steroid secretion in vivo in both man and other higher species will hopefully define the exact role of prostaglandins in steroidogenesis.

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