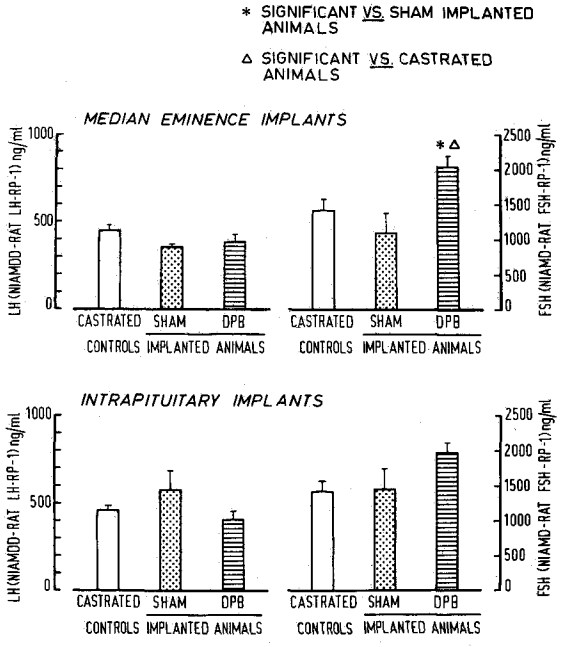

Fig. 3. Effect of median eminence and of intrapituitary implants of (+)-1,4-diphenylbutane-2,3-diol (DPB) on serum LH and FSH levels of adult ♂ rats castrated 21 days before implantation. Sacrifice 5 days after implantation.

These results, although preliminary, suggest that DPB might stimulate FSH release acting on the hypothalamus and possibly on the anterior pituitary. This effect is not accompanied by relevant changes of LH secretion. Since DPB is a natural secretory product of the testis[16–18], a physiological role of this compound in the control of FSH secretion may be postulated. The effect of DPB on the hypothalamic-pituitary axis might be explained by the antiandrogenic properties of this compound[14]. Antiandrogens have been previously reported to increase gonadotropin output, either when given systemically[21] or when placed in the median eminence of the hypothalamus[22].

The negative results obtained after systemic injections of DPB might be due to several reasons. First of all the compound has a short half-life[16]. Moreover, systemically administered DPB is rapidly conjugated with glucuronic acid[16]. It is not known at present whether the glucuronic derivative retains biological activity, and whether it is able to cross the blood-brain barrier.

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Antagonistic action of E and F series prostaglandins upon mineralocorticoid production by the human adrenal

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Summary. At long time intervals, the E and F prostaglandins exert antagonistic effects on aldosterone production in vitro. At short intervals the E prostaglandins tend to mimic the inhibitory effect of the PGF series.

The E and F prostaglandins antagonistically modulate cAMP levels and cortisol secretion by the human adrenal[1] and have antagonistic effects on ovarian steroidogenesis[2]. This antagonism appears to be basic to steroidogenic processes. Aldosterone secretion is under both stimulatory and inhibitory control[3–5], but the evidence for prostaglandin involvement is limited and contradictory[6,7]. The present study demonstrates that E and F series prostaglandins are antagonistic in the control of mineralocorticoid production.

Methods and materials. 4 adult human female adrenal glands obtained at surgery were immediately placed in cold (0–4 °C) Kreb's Ringer bicarbonate buffer, KRBGA (pH 7.4, 200 mg glucose/dl, 0.5% serum albumin fraction V). Glands were diced (2 × 3 mm) and preincubated (37 °C) in KRBGA for 45 min. These dice then were incubated (1 ml KRBGA; 37 °C; 95% O_2 + 5% CO_2) in a Dubnoff metabolic shaker for 1–32 min. The dice were exposed to prostaglandins E_1, E_2, $F_{1\alpha}$ or $F_{2\alpha}$ (1, 10, 100 µg/ml), prostaglandin vehicle (2% ethanol in KRBGA), or KRBGA alone. Aldosterone secretion into the incubation medium was quantitated by RIA[8]. Proteins were determined[9] and the data calculated as ng aldosterone/mg protein and expressed as per cent control. A minimum of 4 replicates were used per datum point. Data were analyzed by analysis of variance and Student's t-test. Differences were accepted as significant when $p < 0.05$.

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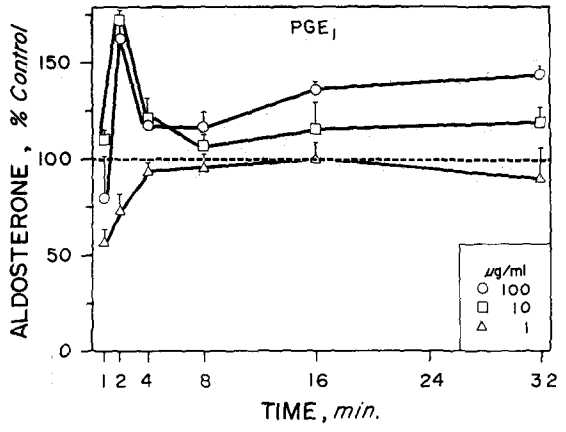

Fig. 1. Temporal release of aldosterone by human adrenocortical tissue in response to PGE_1.

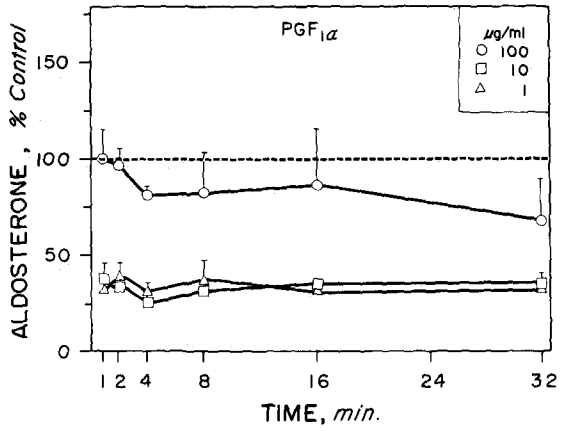

Fig. 3. Temporal inhibition of aldosterone release by human adrenocortical tissue in response to $PGF_1\alpha$.

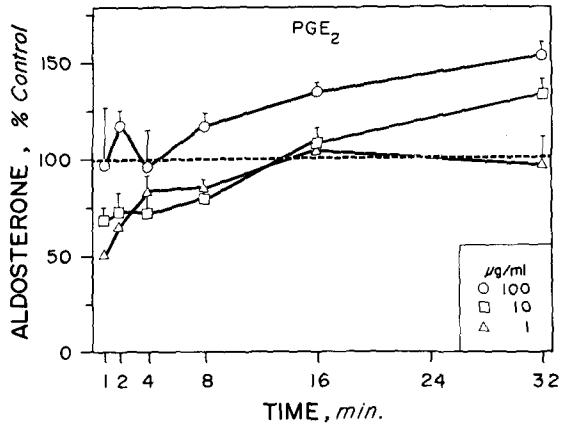

Fig. 2. Temporal release of aldosterone by human adrenocortical tissue in response to PGE_2.

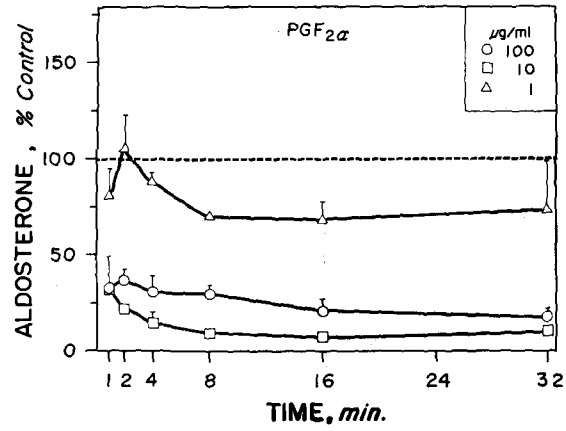

Fig. 4. Temporal inhibition of aldosterone release by human adrenocortical tissue in response to $PGF_2\alpha$.

Results and discussion. Prostaglandin and KRBGA control groups were not significantly different in basal aldosterone release during the 32 min study period. At 32 min the E series prostaglandins stimulated aldosterone release with the highest doses being equipotent. Similar results are reported for the bovine adrenal[6]. Significant increases above controls were achieved with PGE_1 (100 µg/ml) and PGE_2 (10, 100 µg/ml). The temporal aldosterone response to low doses of E series prostaglandins was an initial depression of aldosterone output by PGE_1 (1 µg/ml) during the 1–2 min incubation interval (figure 1). PGE_2 (1, 10 µg/ml) significantly depressed aldosterone release for the first 8 min (figure 2). These temporal differences may explain reported contradictions concerning E prostaglandin effects on aldosterone release[6,7]. The E prostaglandins may have other divergent actions upon aldosterone production. During the short time interval, 1–4 min, 10 and 100 µg/ml PGE_1 produced a significant burst of aldosterone output (figure 1). Although not statistically significant, 100 µg/ml PGE_2 also increased aldosterone output 18% above controls during this early interval (figure 2). The rate of aldosterone release then declined at 4–8 min relative to controls (figures 1 and 2). During this same interval (4–8 min), the initially depressed rate of aldosterone output occurring with the lower doses of PGE_1 (1 µg/ml) and PGE_2 (1, 10 µg/ml) began to rise relative to basal control output (figures 1 and 2). With time, a gradual increase in aldosterone output occurred with both PGE_1 and PGE_2 (figure 2). The initial rapid aldosterone release is interpreted as an effect of PGE_1 and possibly PGE_2 on the release of preformed aldosterone. Such, possibly by exocytosis[10], would represent a direct effect of the prostaglandin on the plasma membrane. Labeled E type prostaglandins have been localized on the adrenocortical cell plasma membrane[11] and have altered its structure allowing cytoplasmic protrusions into the sinusoidal lumen[12]. The subsequent decreased rate of release probably represents a period when de novo aldosterone synthesis has not increased sufficiently to match the rate of release. Finally (8–32 min) de novo synthesis increases, possibly due to an effect of the prostaglandins on cAMP generation[1–6].

Prostaglandins $F_{1\alpha}$ and $F_{2\alpha}$ depressed aldosterone release, however, an interesting dose response existed (figures 3 and 4). The depression with $PGF_{1\alpha}$ (1, 10 µg/ml) and $PGF_{2\alpha}$ (10, 100 µg/ml) was significant at all time intervals. However 100 µg/ml $PGF_{1\alpha}$ and 1 µg/ml $PGF_{2\alpha}$ produced only a moderate depression (figures 3 and 4). Clearly, $PGF_{1\alpha}$ most effectively inhibits aldosterone secretion at lower doses while $PGF_{2\alpha}$ is most effective at the

highest doses. The reduced inhibition of the highest $PGF_{1\alpha}$ dose may result from failure of PGE receptors to discriminate at high $PGF_{1\alpha}$ concentrations.

The E and F prostaglandins exert antagonistic effects on aldosterone production at long time intervals. However the E prostaglandins, particularly PGE_2, mimic the inhibitory effects of $PGF_{1\alpha}$ and $PGF_{2\alpha}$ at the lower doses and earlier time intervals examined. Further PGE_1 and PGE_2, although equipotent in aldosterone release at the longest time interval, produce divergent effects at the earlier intervals studied. Finally, E prostaglandin stimulation of aldosterone synthesis and release may be separate events.

Dexamethasone suppression of ovulation in PMS-treated immature rats

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Summary. A single injection of 2.0 mg/kg dexamethasone (DXM) administered at 51 h after pregnant mare serum gonadatropin (PMS) treatment inhibited both ovulation and luteinization. S.c. injection of human chorionic gonadotropin (HGG) caused ovulation ond luteinization in DXM-PMS-treated rats, whereas treatment with ACTH failed to overcome the DXM inhibitory effect. These findings are interpreted to indicate that DXM inhibits ovulation through a mechanism which might involve the central nervous system.

Dexamethasone administration in the rat usually results in inhibition of ovulation. This inhibition was suggested as a direct effect of the lack of a physiologically functioning adrenal cortex, thought to produce preovulatory progesterone which facilitates ovulation[1]. There is some supporting evidence for this: a single injection of deoxycorticosterone or corticosterone facilitates ovulation in PMS-treated immature rats[2], ovulation rate in PMS-treated rats was reduced when animals were adrenalectomized[3]. However, there are several anomalies to the hypothesis. For example, PMS-induced ovulation in the immature rat could be inhibited by the concurrent administration of ACTH[3]. Similar results were obtained in the adult rat[1]. The present experiments were designed to study further the site of dexamethasone action inhibition ovulation in PMS-treated immature rats.

Materials and methods. Sprague Dawley 22-day-old rats were housed 14:10 light-dark cycle (6.00 a.m. to 8.00 p.m. eastern time). They were injected s.c. with 25 IU of pregnant mare's serum gonadotropin (PMS, Sigma) on the 24th day of life. Dexamethasone (1,9-fluoro-16, methyl cortisol, DXM, Sigma) was given i.p. at 12.00 noon on the 26th day, 51 h following PMS administration. In 1 group of PMS-treated rats, a single injection of DXM was given. 2 mg/kg were used in 0.1 ml of a mixture of equal ratio of propylene glycol and saline. Another group of rats was treated with both human chorionic gonadotropin (10 IU HCG, Sigma) and a single injection of DXM. Corticotropic hormone (ACTH and 10 IU, Sigma) was injected in another group, i.p. along with DXM, 51 h after PMS injection. An additional control received only a s.c. injection of saline and i.p. injection of DXM vehicle.

Autopsies were performed on the 27th day of age in all animals. The occurrence of ovulation was determined by microscopic examination of the oviduct for ova with no attempt to count the ova. Ovaries were weighed prior to fixation in Bouin's Solution for histological examinations. Analysis of variance was conducted using F-test and Duncan's multiple range test.

Results. PMS injection in 24-day-old immature rats caused follicular development, ovulation and luteinization. A single injection of DXM given at 51 h after PMS-inhibited luteinization. In this group of animals, ovarian follicles, as examined microscopically, were larger than those of immature rats which did not receive PMS. These follicles contained ova at autopsy. Ovaries from PMS-treated rats which received no DXM were larger than those from animals which were injected with PMS and DXM but the difference was not significant ($p < 0.05$) (table). The presence of many corpora lutea in the ovaries of rats injected with PMS alone indicated that ovulation had occurred. The group of immature rats that received PMS, DXM and HCG showed a high ovulation rate with high ovarian weight (table). In the PMS-DXM-treated group, ACTH administration did not affect the ovulation rate nor ovarian weight when compared to the PMS-DXM group ($p < 0.05$).

Effect of dexamethasone on PMS-induced ovulation rate

Treatment	Body weight****	Ovarian weight (mg)	Uterine weight (mg)	Ovulation rate (%)
Control	52.2 ± 2.5[a]	34.8 ± 8.3[a]	27.7 ± 8.9[a]	0
PMS*	57.5 ± 3.5[a]	115.3 ± 12.3[bc]	96.8 ± 5.2[b]	82.5
PMS + DXM**	55.5 ± 4.2[a]	93.3 ± 13.5[c]	89.1 ± 5.5[b]	12.5
PMS + DXM + HCG***	56.5 ± 1.5[a]	124.9 ± 7.5[b]	98.6 ± 4.6[b]	82.5
PMS + DXM + ACTH***	48.7 ± 3.6[a]	109.1 ± 14.9[bc]	88.1 ± 19.4[b]	12.5

* PMS 25 IU was injected s.c. 72 h before sacrificing the animal.

** Dexamethasone 2 mg/kg was injected 51 h after PMS treatment.

*** HCG (10 IU) and ACTH (10 IU) were injected i.p. 51 h after PMS injection.

**** Data represent the mean ± S. E. of 8 animals in each group. Values having the same superscript are not significantly different ($p < 0.05$).