EFFECTS OF A AND B SERIES PROSTAGLANDINS ON cAMP, CORTISOL AND ALDOSTERONE PRODUCTION BY THE HUMAN ADRENAL

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Summary: PGA_1 and PGA_2 (10, 100 μg/ml) significantly increased human adrenal cAMP levels and cortisol output but low doses (1 μg/ml) depressed both parameters. Only 1 μg/ml PGA_1 significantly increased aldosterone output while higher doses depressed same. The low PGA_2 dose (1 μg/ml) depressed aldosterone output. The glucocorticoid and mineralocorticoid outputs appear to be inversely modulated by prostaglandins. PGB_1 and PGB_2 behaved similarly to E type prostaglandins. However, like PGA_1, 1 μg/ml of PGB_1 or PGB_2 significantly increased aldosterone output. Higher doses were ineffective. The present findings reveal an increased complexity of prostaglandin modulation of cyclic nucleotides and steroid output.

Considerable evidence supports the concept that prostaglandins may stimulate adrenal cAMP and subsequent steroidogenesis and/or release (1,2). In addition, ACTH stimulates adrenal prostaglandin biosynthesis (3) and release (4) but prostaglandins, in turn, modulate the mechanism of ACTH action in the adrenal (1). The majority of the evidence deals with E and F prostaglandins. In ACTH stimulated adrenal PGE and PGF biosynthesis (3) a third component tentatively identified as either PGA or PGB was isolated. Further, an A series prostaglandin produces a slight increase in aldosterone and cortisol production by bovine adrenals (5) and PGA markedly elevates plasma aldosterone levels in man (6,7). Therefore, the present study explores the action of A and B series prostaglandins on the human adrenal in order to further define the complex prostaglandin-cyclic nucleotide-steroid production relationship.

MATERIAL AND METHODS

Four adult human female adrenal glands obtained at surgery were bisected, demedullated, diced (2x3 mm), preincubated and incubated (37°C) in Krebs' Ringer bicarbonate buffer (KRBGA) as previously described (1,2). The dice were exposed to prostaglandins A_1, A_2, B_1 or B_2 at 1, 10, 100 μg/ml, prostaglandin vehicle (2% ethanol in KRBGA), porcine ACTH (100 mIU/ml; chromatographically pure; 150 IU/mg) or KRBGA alone. Adrenal incubates were analyzed for cAMP content by RIA (8). Cortisol and aldosterone secretion into the incubation medium was quantitated by RIA (1,2). Proteins were determined

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TABLE I

Temporal cAMP (pM/mg protein; $\bar{X}$±SEM) response of the human adrenal to PGA_1 and PGA_2

Time	PGA_1 (μg/ml)			PGA_2 (μg/ml)			Vehicle
(min)	1	10	100	1	10	100	
1	1.2±0.6	8.2±1.2	8.8±1.0	1.6±0.3	6.3±0.6	3.8±1.6	7.7±0.7
2	2.2±0.5	9.7±2.0	9.7±3.5	1.0±0.3	6.5±1.8	6.4±0.5	5.4±1.8
4	3.9±0.9	8.3±0.7	8.9±0.8	1.4±0.6	5.6±2.8	13.2±2.9	6.7±2.7
8	2.7±1.2	8.8±0.3	8.3±1.7	4.2±2.0	5.7±0.2	10.0±1.0	6.2±3.3
16	1.0±0.3	12.9±0.8	17.0±1.2	7.4±1.4	7.9±0.3	9.9±2.3	6.9±1.7
32	1.6±0.6	18.0±2.0	26.5±6.4	6.3±0.3	11.2±3.0	5.6±2.7	6.9±2.9

TABLE II

Temporal cAMP (pM/mg protein; $\bar{X}$±SEM) response of the human adrenal to PGB_1 and PGB_2

Time	PGB_1 (μg/ml)			PGB_2 (μg/ml)			Vehicle
(min)	1	10	100	1	10	100	
1	6.0±1.9	5.9±1.9	4.6±1.1	4.8±1.0	14.3±1.3	8.0±2.0	7.7±0.7
2	6.0±4.0	7.6±3.8	5.3±2.0	5.0±0.5	12.5±0.5	9.8±2.9	5.4±1.8
4	5.1±3.6	10.0±3.0	5.8±0.5	4.3±2.0	8.0±2.0	4.7_1.9	6.7±2.7
8	3.1±1.5	18.8±1.8	7.0±1.9	4.5±1.5	9.6±1.9	5.3±0.9	6.2±3.2
16	5.6±1.0	17.6±8.0	7.6±3.2	9.6±2.0	5.6±2.8	5.2±0.6	6.9±1.7
32	6.8±0.8	12.9±0.6	8.8±2.6	8.5±4.2	5.5±1.5	4.4±2.7	6.9±2.9

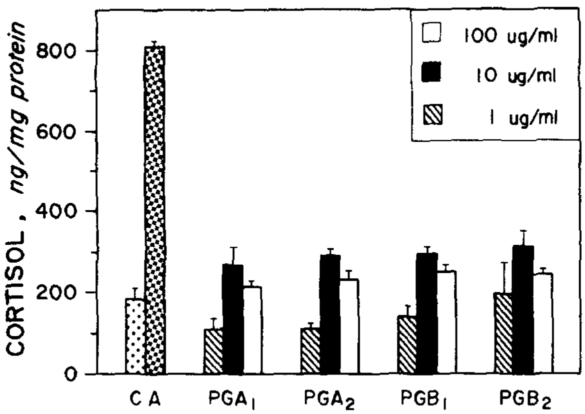

Figure 1. *In vitro* dose effects of prostaglandins A_1, A_2, B_1 and B_2 on cortisol output (32 min) relative to controls (C) and ACTH (A), 100 mIU/ml, by human adrenocortical tissue.

(9) and the data expressed as pM cAMP or ng aldosterone or cortisol/mg protein, $\bar{X}$±SEM. A minimum of three tissue replicates were used per datum point. Data were analyzed by analysis of variance and student t test. Differences were accepted as significant when $p<0.05$.

RESULTS

Prostaglandin vehicle and KRBGA control groups were not significantly different in basal cAMP, cortisol or aldosterone levels. Basal cAMP levels (Tables I and II) remained relatively constant throughout the 32 min study period ($\bar{X}$±SEM: 6.6±0.3 pM cAMP/mg protein), Figs. 1, 2.

PGA_1 (10, 100 μg/ml) significantly elevated cAMP levels above controls. The maximal response occurred at 32 min (Table I). PGA_2 (100 μg/ml) significantly elevated cAMP levels above the control group at 4 and 8 min (Table I). Although cAMP levels remained elevated 43% (16 min) above the control groups, such was not significant. 10 μg PGA_2/ml increased cAMP levels at 16 (14%) and 32 (62%) min were not significant. The lowest dose (1 μg/ml) of PGA_1 or PGA_2 significantly depressed cAMP levels below that of the control group although the temporal response differed between the two prostaglandins. The PGA_1 depression continued throughout the 32 min interval. In contrast, the depression evoked by PGA_2 was immediate (1-4 min), thereafter the cAMP levels did not differ from the control levels (Table I).

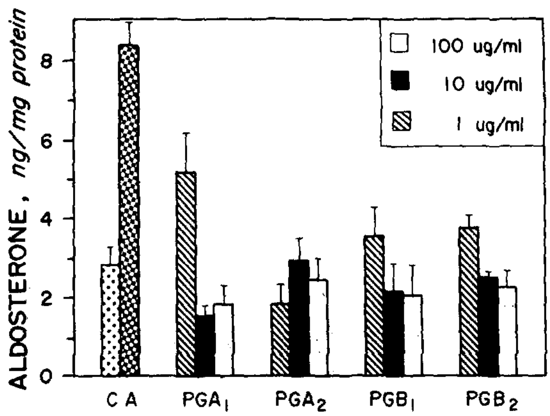

Figure 2. *In vitro* dose effects of prostaglandins A_1, A_2, B_1 and B_2 on aldosterone output (32 min) relative to controls (C) and ACTH, 100 mIU/ml, by human adrenocortical tissue.

Although PGB_1 and PGB_2 at the lowest and highest dose (1, 100 μg/ml) did not significantly alter cAMP levels from that of controls interesting trends emerged (Table II). PGB_1 and PGB_2 (100 μg/ml) elevated cAMP levels 28% (32 min) and 81% (2 min) respectively, while 1 μg/ml of PGB_1 and PGB_2 depressed cAMP levels at 8 min and 1-8 min, respectively (Table II). 10 μg PGB_1/ml significantly elevated cAMP levels at 8-32 min while 10 μg PGB_2/ml elevated cAMP levels at 1-2 min (Table II).

PGA_1 and PGA_2 (10, 100 μg/ml) significantly elevated cortisol production (Fig 1) with 10 μg/ml being more effective. In contrast, both PGA_1 and PGA_2 at 1 μg/ml significantly depressed cortisol production (Fig 1) compared to the control group. PGB_1 and PGB_2 (10, 100 μg/ml) significantly increased cortisol output (Fig 1). Again, 10 μg/ml was the most effective dose. PGB_1 (1 μg/ml) depressed cortisol output 23% below controls although such was not significant (Fig 1). PGB_2 (1 μg/ml) did not significantly alter basal cortisol output (Fig 1).

PGA_1 (10, 100 μg/ml) significantly depressed adrenocortical aldosterone output (Fig 2). These doses of PGA_2 were without effect upon aldosterone output (Fig 2). However, 1 μg/ml PGA_2 significantly depressed aldosterone output while 1 μg/ml PGA_1 significantly increased aldosterone output (Fig 2).

PGB_1 and PGB_2 (10, 100 μg/ml) did not alter aldosterone output from that of controls (Fig 2). Interestingly 1 μg/ml PGB_1 and PGB_2 significantly increased aldosterone output although not as effectively as 1 μg/ml PGA_1.

DISCUSSION

The human adrenal is stimulated by A and B series prostaglandins to increase cAMP levels and cortisol and aldosterone output. PGA_1 and PGB_1 produce the greatest cAMP increase at the higher doses used, although these are generally lower than the response to PGE_1 and PGE_2 at 100 μg/ml (1). Interestingly, PGA_1 and PGA_2 at low doses (1 μg/ml) share an effect in common with the F series prostaglandins, namely, cAMP depression (1). This interesting parallel also is observed with cortisol production. Like the E series prostaglandins, high doses (10, 100 μg/ml) of PGA_1 and PGA_2 effect a significant increase in cortisol output (1). However, similar to the F prostaglandins, low doses of PGA_1 and PGA_2 depress cortisol output (1). The increase in cortisol production by the bovine adrenal in response to an A series prostaglandin occurs at a dose of 100 μg/ml (5) whereas infusion of relatively low doses of PGA_1 into the human have produced ambivalent effects on plasma cortisol levels (7,10). Cortisol production by B series prostaglandins is qualitatively similar to PGE_1 and PGE_2 (1), *i.e.*, low doses are ineffective and higher doses stimulatory. Quantitatively, however, PGB_1 and PGB_2 are only about 50% as effective as PGE_1 and PGE_2.

The effects of low doses of PGA_1 on *in vitro* human adrenal aldosterone production support the observation of Fichman *et al.* (7) *in vivo*. However, high doses of PGA_1 depress aldosterone output. Curiously, whenever aldosterone production is depressed by PGA_1, cortisol output is increased and *vice versa*. This also relates to the dose dependent increase or depression of cAMP. Other factors in addition to cAMP may control the relative outputs of glucocorticoid or mineralocorticoid (*i.e.*, cGMP, prostaglandins). Unlike PGA_1, PGA_2 depresses aldosterone output at 32 min, however, the observed cAMP depression evoked by PGA_2 is transitory. A similar dichotomy between the effect of low doses of $PGF_{1\alpha}$ and $PGF_{2\alpha}$ on aldosterone production have been observed (2). Although high doses of B type prostaglandins tested are ineffective with regard to aldosterone output, 1 μg/ml of PGB_1 and PGB_2 effect an increase. The mechanism for such increase is unclear.

E and F series prostaglandins have been demonstrated to be antagonistic with respect to cAMP, cortisol and aldosterone production by the human adrenal (1,2). The present study indicates that A and B type prostaglandins effect human adrenal physiology, possibly by modulation of intracellular cyclic nucleotide level or via other routes.

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