Tableau 2. Surfaces nucléaires moyennes (en mm²) et pourcentages des cellules épithéliales thymiques chez les rats normaux, hypophysectomisés (HX) HX + GH, HX + ACTH, surrénalectomisés (SX), SX + ACTH

| | Témoin | Hypophysec tomisé (HX) | HX + GH | HX + ACTH | Surrénalectomisé (SX) | SX + ACTH |
|---|---|---|---|---|---|---|
| Surface nucléaire | 75,75 ± 1,00 | 72,13 + 0,77<br>$p < 0,01$* | 75,24 ± 0,81<br>NS* | 78,04 ± 0,88<br>NS* | 71,27 ± 0,88<br>$p < 0,01$* | 59,21 ± 0,80<br>$p < 0,001$* |
| % | 44 | 47<br>NS* | 53<br>NS* | 49<br>NS* | 38<br>NS* | 51<br>NS* |

*Test de significativité par rapport au témoin.

térieur de la médullaire; nous avons montré que ce paramètre était un indice de l'activité cellulaire[5]. L'hypophysectomie se traduit par une diminution significative au niveau de la surface nucléaire moyenne des cellules épithéliales (4,78%; $p < 0,01$). En revanche, aucune variation significative dans le pourcentage des cellules n'a pu être retenue. L'administration de la GH ou d'ACTH chez les animaux hypophysectomisés corrige la diminution de la surface nucléaire moyenne des cellules épithéliales. L'influence de l'ACTH en l'absence de corticostérone est étudiée chez des animaux surrénalectomisés. L'injection d'ACTH entraîne une diminution de la surface nucléaire moyenne des cellules épithéliales.

Lors d'une étude précédente nous avons pu séparer les différentes catégories de cellules réticulaires thymiques en en cellules mésenchymateuses épithéliales et hypertrophiées[2]. D'après certains auteurs, le principe actif thymique est synthétisé par les cellules à caractères épithélioides[6] et plus particulièrement par les cellules épithéliales[7] et son taux est fortement abaissé par l'hypophysectomie[8]; dans le travail que nous rapportons nous constatons que les effets de l'hypophysectomie modifient seulement l'activité des cellules épithéliales. Il semblerait donc que l'activité secrétrice du thymus se situe au niveau des cellules épithéliales dont le métabolisme est perturbé par l'hypophysectomie.

L'administration d'ACTH ou de GH à des animaux hypophysectomisés permet un effet d'opothérapie de substitution plus important avec l'ACTH. Cependant nous constatons sur des animaux surrénalectomisés chez lesquels l'ACTH provoque un effet indépendant de la corticostérone que l'hormone adrénocorticotropique a un effet propre: une diminution de la surface nucléaire des cellules épithéliales. Donc sur animal simplement hypophysectomisé l'opothérapie de substition observée n'est que la conséquence d'une hypersécrétion de corticostérone qui, dans un précédent travail[2] s'était avérée augmenter la surface nucléaire. L'hormone de croissance et l'hormone corticotropique exercent in vivo un effet antagoniste au niveau de la glande thymique. L'hypophyse jouerait un rôle sur le fonctionnement de la glande thymique par l'intervention d'un mécanisme d'équilibre entre les effets de ses hormones.

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## Temporal effects of ACTH, indomethacin and 7-oxa-13-prostynoic acid upon glucocorticoid production by the human adrenal

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*Summary.* Indomethacin or 7-oxa-13-prostynoic acid does not alter basal adrenal cortisol output. Preincubation in either, depresses subsequent ACTH-stimulated cortisol output below ACTH alone and controls. Either inhibitor following ACTH preincubation blunts normal ACTH-stimulated cortisol production.

Prostaglandins are believed to exert multiple effects on adrenocortical physiology including an allosteric effect upon ACTH-binding to adrenocortical cells[1], cAMP generation[2-4], steriodogenesis[2,3,5,6] and steroid release[7,8]. Indomethacin, an inhibitor of prostaglandin biosynthesis, and 7-oxa-13-prostynoic acid, a competitive prostaglandin antagonist, have been employed to elucidate the role of prostaglandins in ACTH-induced steroidogenesis[1,2,8], however, some aspects of these inhibitor effects are contradictory. Indomethacin has been reported both to produce no effect[2] and to augment basal steroid release[8]. Further, indomethacin may augment[8] or inhibit[1,2,8]

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ACTH-induced steroid production depending upon dosage. These effects have been reported from long term (>30 min) single time interval observations. Therefore, the present study was designed to elucidate the short term temporal effects of these prostaglandin inhibitors upon basal and ACTH-stimulated glucocorticoid production by human adrenocortical tissue.

*Materials and Methods.* 4 adult human female adrenal glands obtained at surgery were immediately placed in cold (0–4 °C) Krebs' 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 indomethacin (10 µg/ml), 7-oxa-13-prostynoic acid (50 µg/ml), porcine ACTH (100 mIU/ml; chromatographically pure; 150 IU/mg) or KRBGA alone. Further, dice were incubated initially (4 min) in ACTH, indomethacin or 7-oxa-13-prostynoic acid followed by transfer to ACTH plus the appropriate test substance. Cortisol secretion into the incubation medium was quantitated by RIA[9]. Proteins were determined[10] and the data expressed as ng cortisol/mg protein, $\bar{X} \pm$ SEM. 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 $p < 0.05$.

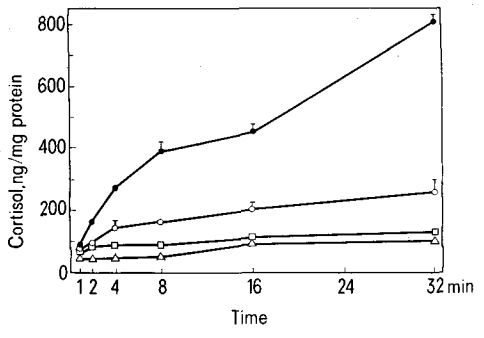


Fig. 1. Effects of preincubation (4 min) in either 7-oxa-13-prostynoic acid or indomethacin upon subsequent ACTH (100 mIU/ml) stimulated cortisol production compared to basal ACTH-stimulated cortisol production by human adrenocortical tissue. Closed circle, ACTH; open circle, KRBGA control; square, ACTH-following 7-oxa-13-prostynoic acid preincubation; triangle; ACTH-following indomethacin preincubation.

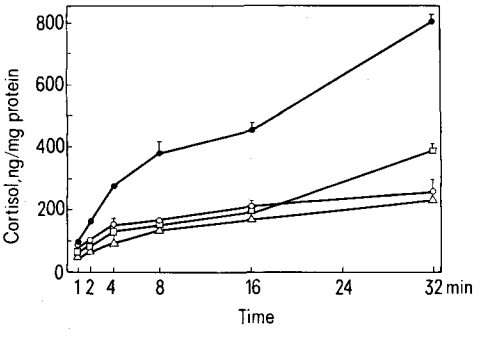


Fig. 2. Effects of 7-oxa-13-prostynoic acid or indomethacin on human adrenocortical cortisol production in response to ACTH-following preincubation (4 min) in ACTH alone (100 mIU/ml). Closed circle, ACTH; open circle, KRBGA control; square, 7-oxa-13-prostynoic acid following ACTH incubation; triangle, Indomethacin following ACTH-preincubation.

*Results and Discussion.* Indomethacin or 7-oxa-13-prostynoic acid alone do not significantly alter basal human adrenal cortisol production during the entire 32-min-interval studied. These results differ from those reported for feline adrenocortical cells incubated for a longer time interval[8]. However, the results are consistent with the observed inability of these inhibitors to alter basal human adrenocortical cAMP levels[2]. Preincubation (4 min) in either indomethacin or 7-oxa-13-prostynoic acid followed by transfer to a flask containing ACTH + test substance effectively blocks ACTH-stimulated steroid production for the entire 32-min-interval (figure 1). In fact, steroid production was significantly lower than the basal level during 4–32 min (figure 1). Interestingly, pretreatment with these inhibitors also depresses subsequent ACTH-stimulated cAMP levels during this interval[2]. Indomethacin pretreatment in vivo depresses steroid production following ACTH stimulation[1].

Preincubation (4 min) in ACTH followed by transfer to ACTH + 7-oxa-13-prostynoic acid or indomethacin significantly depressed steroid release compared to ACTH alone (figure 2), however, these levels were not depressed below basal levels as observed with preincubation in the inhibitor (figure 1). At 32 min (figure 2) the cortisol output of the indomethacin group was significantly higher than that of control or 7-oxa-13-prostynoic acid treated adrenals. Interestingly, application of these inhibitors following ACTH preincubation results in a supramaximal cAMP response compared to ACTH alone. However, this nucleotide response does not result in increased corticoid output (figure 2) suggesting that prostaglandins have effects on steroid release which are not cyclic nucleotide mediated. In addition, the present findings suggest consideration of possible temporally dissimilar prostaglandin modulation of the mechanism of ACTH action in the adrenal.

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## Increased liver calcium after calcium or milk gavage in rats[1]

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*Summary.* For 1 or 2 h following a gavage of milk or 300 mM $CaCl_2$ (2 ml/100 g b.wt), rats had an increased liver calcium content when compared to rats receiving a deionized water gavage.

Yamaguchi et al. have reported that calcitonin administration increases the calcium content of the liver of rats both in vivo[2] and in vitro[3]. In rats, calcitonin is secreted after ingestion of a meal[4] and is useful in preventing hypercalcemia after meals of milk[5] or dissolved $CaCl_2$[6]. If the increased liver calcium is of physiological significance, then there should be uptake of calcium by the liver during times of elevated secretion of calcitonin. The liver