ACTH Stimulation and Glucocorticoid Inhibition of Renin Release in the Rat* (33920)

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Studies by Dougherty (1) and Marks *et al.* (2) in rats have shown that ACTH administration increases juxtaglomerular cell granularity. This occurs in intact, adrenalectomized, and hypophysectomized–adrenalectomized rats. On the other hand, several investigators have not been able to demonstrate that ACTH stimulates a rise in plasma renin levels in man (3) or the dog (4). However, an ACTH-induced rise in plasma renin activity (PRA) in individuals with hypopituitarism was reported recently (5). The inconsistencies in these studies prompted us to investigate, in the rat, the effect of supraphysiological doses of ACTH and glucocorticoids on PRA.

Materials and Methods. Male rats (Cheek Jones Co.) weighing 175–225 g and fed a standard lab chow that contained 3.8 mg of sodium/g were utilized for the studies. Blood was collected from the trunk following decapitation. Blood from 2–3 rats was pooled for each sample. The PRA was measured by the method of Boucher (6) and the results were expressed as ng of angiotensin produced per 3-hr incubation per 100 ml of plasma. Plasma corticosterone concentration was measured by the method Silber *et al.* (7).

The PRA and corticosterone concentration were measured at various times following one or more subcutaneous injections of 0.25 ml of normal saline, 1 unit of ZnACTH (Organon), 1 unit of aqueous ACTH (Parke-Davis) or 0.05 mg of β^{1-24}ACTH (Ciba).[1] Since the results from experiments utilizing the various preparations of ACTH were similar, they were analyzed together. All injections of ACTH were delivered in 0.25 ml of normal saline.

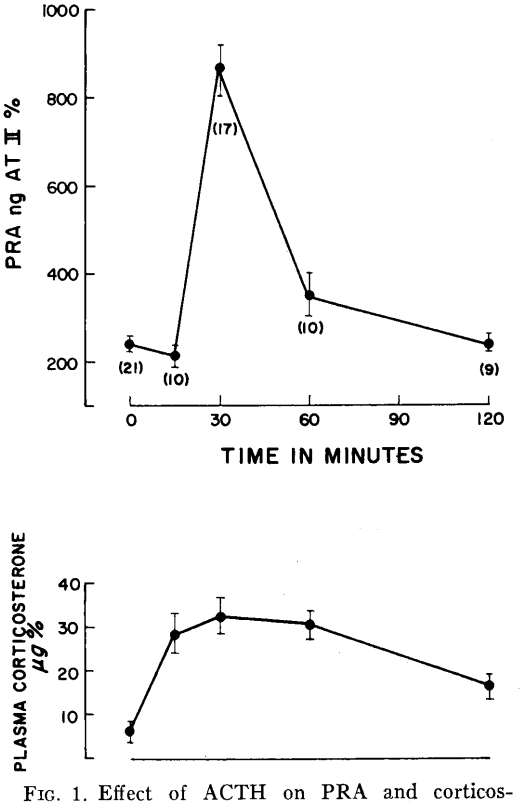

FIG. 1. Effect of ACTH on PRA and corticosterone levels in intact rats: points represent mean values ± SEM; values in parentheses indicate the number of samples in each assay.

The measurements of PRA and corticosterone concentration were made in normal rats, rats adrenalectomized 2 hr prior to injection, and rats given aminoglutethimide (20 mg/100 mg of body weight im) 30 min prior to injection.

Results. Figure 1 demonstrates that a single injection of ACTH produced a marked rise in PRA. This rise was fourfold and significant at the 0.001 level. Peak levels of renin were noted 30 min following ACTH

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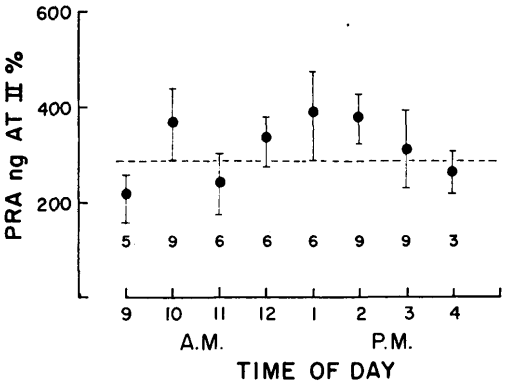

FIG. 2. Effect of normal saline injections on PRA: the mean value ± SEM of PRA levels 30 min after the administration of 0.25 ml of normal saline at the indicated times; (----), indicates the mean of the mean values; values under points indicate the number of samples in each experiment.

administration and rapidly declined to control levels by 60 min. The rise in plasma corticosterone level was apparent by 15 min and persisted until about 120 min. There was no significant change in PRA in animals receiving saline injections at different times of the day (Fig. 2).

Studies were conducted to see the effect of multiple injections of ACTH on PRA. Since peak levels of PRA were noted 30 min after a single injection of ACTH, PRA was determined 30 min after the injection of multiple doses of ACTH delivered at 30-min intervals. As shown in Fig. 3, corticosterone concentration rose progressively with multiple injections of ACTH, but PRA showed the previously demonstrated rise 30 min after the first injection but was not different from control levels in rats treated with two or three injections of ACTH.

The effect of ACTH on PRA and corticosterone levels in rats pretreated with aminoglutethimide[2] is depicted in Fig. 4. In the aminoglutethimide treated rats, there was the expected rise in the PRA of animals sacrificed 30 min after ACTH administration but no rise in the plasma corticosterone level.

[2] We wish to thank Dr. J. J. Chart, Director of Endocrinology, Ciba Pharmaceutical Company, Summit, New Jersey, for the supply of aminoglutethimide (Elipten).

Finally the relationship of the transient nature of the ACTH induced rise in PRA and ACTH induced rise in corticosterone levels was examined. Rats adrenalectomized 2 hr before were given two doses of ACTH at 30-min intervals.

Results are shown in Fig. 5; PRA was significantly higher in adrenalectomized rats than in control rats ($p < 0.01$). The administration of ACTH resulted in a significant rise in PRA ($p < 0.001$) that differed in duration from that in intact animals. Thirty min after a second injection of ACTH, PRA was still elevated in adrenalectomized rats whereas in intact animals so treated, PRA decreased to control levels (Fig. 3).

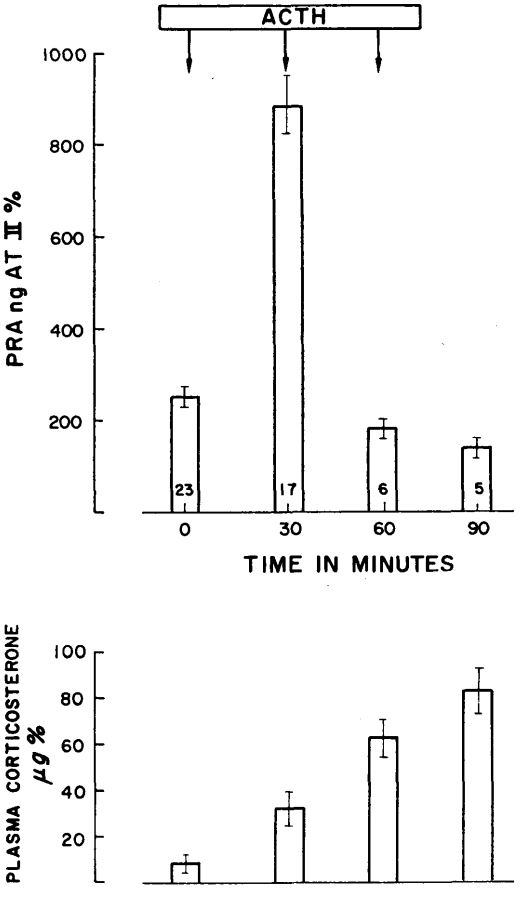

FIG. 3. Effect of multiple injections of ACTH administered at 30-min intervals on PRA and corticosterone levels in intact rats; bars indicate the mean value ± SEM; values in bars indicate the number of samples.

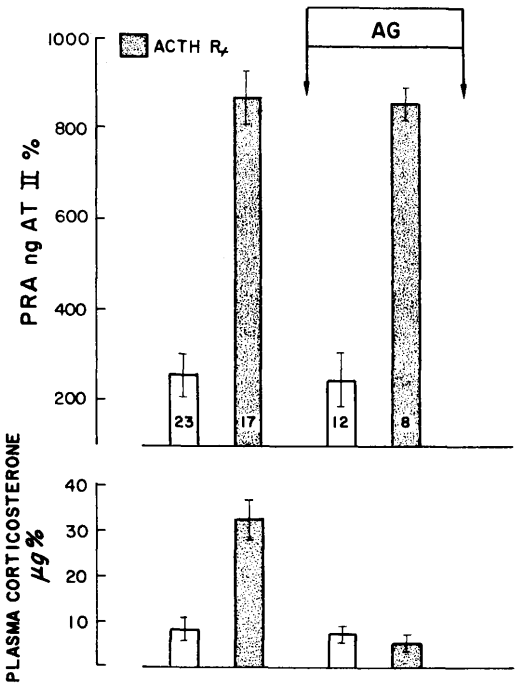

FIG. 4. Effect of ACTH on aminoglutethimide (AG)- treated rats; hatched bars indicate the mean value ± SEM in the ACTH-treated rats; white bars indicate the control group; values in bars indicate the number of samples in each assay.

Dexamethasone or cortisol (1 mg ip) was administered and the animals were sacrificed at intervals from 15 min to 5 hr after the injection. In animals pretreated with glucocorticoids there was a slight decrease in PRA levels ($p < 0.01$). The administration of ACTH to animals pretreated with glucocorticoids failed to produce a rise in PRA. The glucocorticoid inhibition of ACTH effect was seen from 15 min to as long as 5 hr after the administration of glucocorticoids (Fig. 6).

Discussion. These observations demonstrate that in the rat ACTH has a direct effect on the juxtaglomerular cells of the kidney causing a rise in PRA. This effect is independent of the action of ACTH on the adrenal and is, in fact, inhibited by the ACTH induced steroidogenesis or by glucocorticoid administration. In animals treated with aminoglutethimide, which impairs corticosterone production (8) there was a rise in PRA with no elevation of corticosterone in response to ACTH. In adrenalectomized animals, the administration of ACTH produced a higher and more prolonged rise in PRA than in intact animals.

The opposing effects of ACTH and glucocorticoids on the PRA may well explain why in normal subjects with responsive adrenals little if any discernible rise in PRA occurs following ACTH administration, especially when the sample is drawn after the ACTH has produced elevation of corticoid levels. On the other hand, in the patient with hypopituitarism whose adrenals show sluggish steroidogenesis in response to ACTH, a rise in PRA could be demonstrated.

Other workers have made observations supporting the concept of a reciprocal effect of ACTH and glucocorticoids on renin release. Marks *et al.* (2) showed that ACTH in-

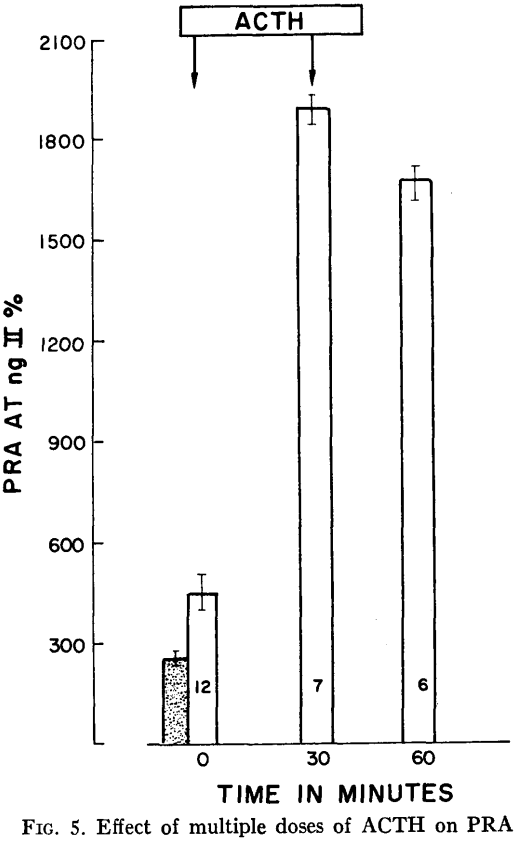

FIG. 5. Effect of multiple doses of ACTH on PRA in adrenalectomized rats; ACTH was administered at 30-min intervals; bars indicate the mean value ± SEM and values within indicate the number of samples; hatched bar represents the control PRA in intact rats.

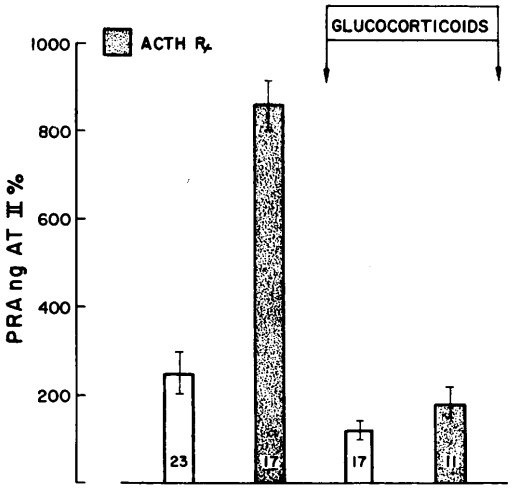

FIG. 6. Effect of ACTH on PRA in glucocorticoid treated rats. Hatched bars indicate the mean value ± SEM in the ACTH treated rats. The white bars indicate the control group. The figures within bars indicate the number of samples in each assay.

creased the granularity of the juxtaglomerular cells in intact, adrenalectomized, and hypophysectomized–adrenalectomized rats and, in fact, the hypergranularity of the juxtaglomerular cells following adrenalectomy could be prevented by prior removal of the pituitary. These observations suggested that PRA increased in the adrenalectomized rats because of low blood volume and also because of the increased secretion of ACTH. Robb *et al.* (9) found a reduction in pressor activity in the saline extract of kidneys from cortisone-treated rabbits.

The mechanism of the ACTH-induced rise or glucocorticoid suppression of PRA is unknown. Although glucocorticoids may produce sodium retention and volume expansion which may suppress PRA, the corticoid inhibition of PRA noted in our studies was too acute for sodium retention to occur.

The relevance of these observations to the effect of ACTH on aldosterone output is also not clear. There have been numerous observations showing that increased aldosterone secretion after ACTH stimulation lasts for a period of 1–2 days even with repeated administration of ACTH and under conditions where salt retention could not occur (10, 11). In our studies, the elevated PRA following ACTH administration was not seen beyond 30 min. It is likely that these phenomena will eventually be explained by changes induced in local effector sites within the juxtaglomerular apparatus.

Summary. In the rat, ACTH effected a transient rise in the level of plasma renin. Pretreatment with glucocorticoids completely inhibited the ACTH-induced renin rise. After adrenalectomy or inhibition of steroidogenesis by aminoglutethimide, ACTH produced a sustained rise in plasma renin level. Thus in the rat, ACTH has a direct effect on the juxtaglomerular apparatus causing a rise in plasma renin activity and glucocorticoids have an opposing action.

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