Bleeding and Plasma Renin Activity in the Rat: The Role of ACTH, Glucocorticoids and the Sympathetic Nervous System[1] (36292)

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The association of increased levels of plasma renin activity (PRA) with blood loss has been demonstrated in man (1), dog (2), and rat (3). It has been postulated that the augmented PRA is caused by a diminution in renal blood flow (4) and/or reduced renal arterial pressure (1).

Previous work in this laboratory has shown that, in the rat, the administration of ACTH produces a transient increase in PRA which can be inhibited by prior administration of dexamethasone (5) or pentolinium (6).

Since ACTH and adrenal hormones are released during hemorrhage (1), it was considered of interest to examine the role of ACTH, glucocorticoids and pentolinium, as a ganglionic blocking agent, on the release of renin in the rat subjected to bleeding.

Material and Methods. Male rats (Cheek, Jones Co.) (weighing 175–225 g and fed a standard lab chow diet containing 3.8 mg of sodium/g) were utilized for the studies. The animals were divided into the following groups: control, hypophysectomized, aminoglutethimide, dexamethasone, and pentolinium treated rats. Transaural hypophysectomy was performed under general anesthesia 24 hr prior to the experiments. Aminoglutethimide (20 mg/100 g of body wt) was given subcutaneously 60 min before the bleeding; dexamethasone (1 mg) was given intraperitoneally, 2 hr before the bleeding; and pentolinium (2 mg/100 g of body wt) was given subcutaneously 30 min before the bleeding. Two milliliters of blood were drawn from the femoral vein over a period of 1 to 2 min, while the rats were under general anesthesia (Nembutal, 6 mg/100 g of body wt, ip). The measurements of PRA and corticosterone concentration were made in the blood collected from the trunk (following decapitation) at various times following bleeding. Blood from two to four rats was pooled for each sample.

PRA was measured by the method of Boucher and Genest (7) and the results were expressed in nanograms of angiotensin II (AT II) produced per 3 hr incubation/100 ml of plasma. Corticosterone concentration was measured by the method of Silber *et al.* (8) and the results were expressed in micrograms of corticosterone per 100 ml of plasma.

Results. Figure 1 demonstrates that bleeding produced a marked rise in the levels of PRA in the intact animals. Peak levels of PRA were noted during bleeding and persisted for 30 min. In the hypophysectomized rats, the levels of PRA (24 hr following hypophysectomy) were not different from those observed in the intact control rats. The rise in PRA levels in response to bleeding in the hypophysectomized rats was significantly lower than that observed in control rats ($p < .001$). In the intact animals, the levels of plasma corticosterone rose during bleeding and fell towards normal during the 120 min period of observation. In the hypophysectomized animals, there was no change in plasma corticosterone levels during the study.

In animals pretreated with aminoglutethimide (Fig. 2), bleeding produced the expected rise in PRA levels with no elevation in the plasma corticosterone concentration. The

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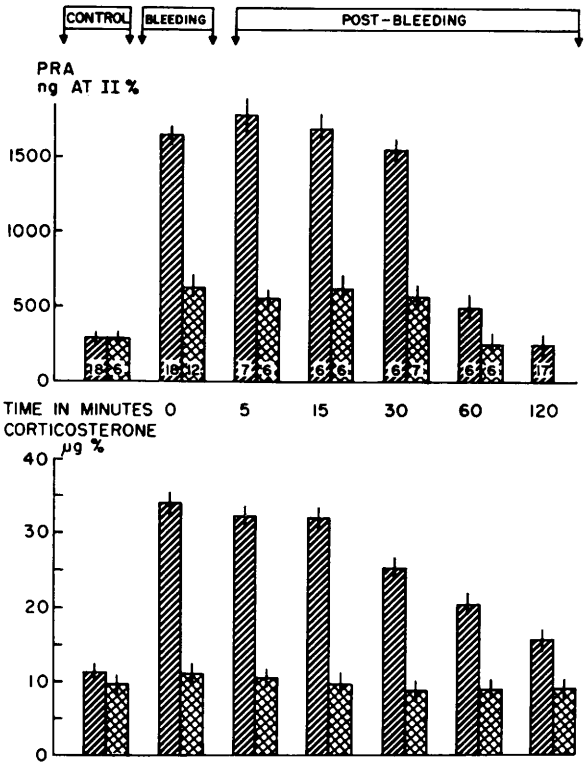

FIG. 1. Effect of bleeding on PRA and corticosterone levels in the intact (hatched bars), and hypophysectomized rats (crosshatched bars): (bars) mean values ± SEM; (values in bars) number of samples in each experiment.

mean level of PRA was significantly above that of the untreated rats 60 min after the bleeding ($p < .001$).

The effect of dexamethasone or pentolinium pretreatment on the PRA rise induced by bleeding is depicted in Fig. 3. In both of these groups, the PRA levels prior to bleeding were significantly lower than in the untreated animals ($p < .01$). With bleeding, there was no significant rise in PRA in the dexamethasone treated animals, and with pentolinium pretreatment, the PRA rise was considerably less than that in the control animals ($p < .001$).

Discussion. It is apparent that many factors are involved in the release of renin. The results of this study indicate that during bleeding the sympathetic system and the pituitary–adrenal axis participate in the release of renin.

The role of the sympathetic system in the release of renin is well documented (2, 3). Pentolinium, an adrenergic blocking agent, has been shown to impair the release of renin in response to bleeding (3). We have previously demonstrated that pentolinium also impairs the release of renin in response to ACTH administration (6), suggesting that the ACTH effect on renin release could be mediated in part by an adrenergic mechanism.

The present data demonstrated a markedly diminished response to bleeding in the hypophysectomized rat. Goodwin *et al.* (9) have also demonstrated that, in response to a sodium-free diet, plasma renin concentration did not rise in the hypophysectomized animals to the same high levels found in control rats. PRA rise in response to bleeding was immediate, while the PRA rise in response to the administration of ACTH took about 30 min (5). This finding would suggest that factors from the pituitary gland other than ACTH might be responsible for the immedi-

ate PRA response to bleeding. Since response to bleeding was diminished in the hypophysectomized rats, it is possible that some factor from the pituitary gland might stimulate the renin–aldosterone system as suggested by Palmore and Mulrow (10).

These findings are consistent with previous observations, which indicated that in the rat ACTH has a direct effect on the juxtaglomerular cells of the kidney, causing a rise in PRA levels and that the effect may be blocked by glucocorticoid administration (5). In these experiments, the levels of plasma ACTH were not measured following bleeding, but it can be assumed there was an increased secretion of ACTH because the concentration of corticosterone was significantly elevated following bleeding.

The impairment of renin release during bleeding in hypophysectomized rats lends further support to the importance of ACTH in effecting release of renin from the juxtaglomerular cells. The inhibition of renin release caused by dexamethasone treatment and its prolongation by aminoglutethimide pretreatment lends further support to the importance of the level of ACTH and glucocorticoids in

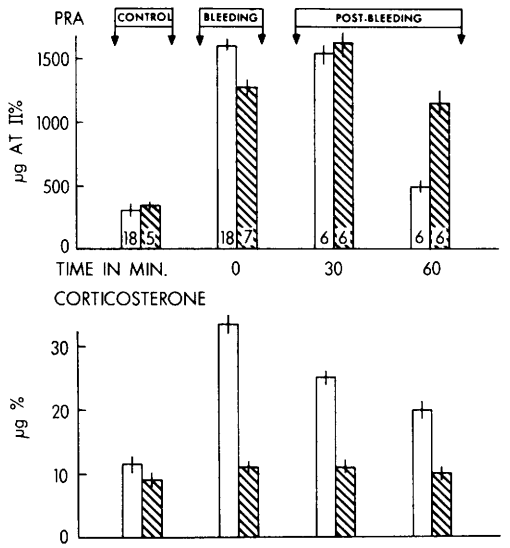

FIG. 2. Effect of bleeding on PRA and corticosterone levels in the aminoglutethimide treated rats: (hatched bars) mean value ± SEM in aminoglutethimide treated rats; (open bars) control group; (values in bars) number of samples in each assay.

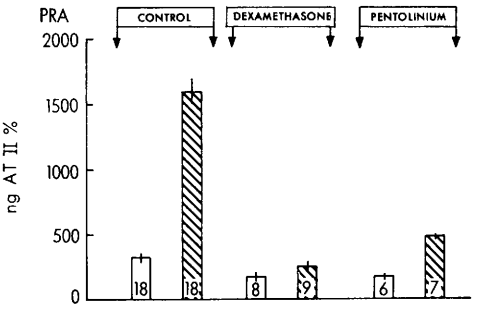

FIG. 3. Effect of bleeding on PRA in the dexamethasone and pentolinium treated rats: mean value ± SEM (open bars) intact group; (hatched bars) bled rats; (values in bars) number of samples in each group. The levels are from the blood obtained during bleeding and correspond to 0 time.

the control of the level of PRA.

It is apparent that factors other than ACTH, glucocorticoids, and the sympathetic system are important in controlling the level of PRA. Since it has been demonstrated that the transplanted kidney can respond with an increase in PRA in response to sodium deprivation or the upright posture (11), it is likely the release of renin, albeit diminished after the administration of pentolinium, is also dependent on the changes in renal blood flow occurring during bleeding.

Summary. The rise in PRA levels caused by bleeding was diminished by hypophysectomy and by the administration of dexamethasone and pentolinium. Although ACTH and the sympathetic system participate in the release of renin induced by bleeding, it is likely that the rise in PRA is also dependent on changes in renal blood flow. It is suggested that dexamethasone inhibits the release of renin induced by bleeding by a direct effect on the receptor sites within the juxtaglomerular cells.

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