The Feedback Regulation of Angiotensinogen Production by Components of the Renin-Angiotensin System

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SUMMARY. The in vivo generation of angiotensin appears to be dependent on both plasma renin and angiotensinogen concentrations. Much less is known about the control of hepatic angiotensinogen synthesis and release, as compared to that of renin. In this study, we examined the feedback regulation of angiotensinogen synthesis and release by various components of the renin-angiotensin system, using an in vitro rat liver slice system. Livers were removed for study from rats which were subjected to various systemic infusions or physiological perturbations. Infusion of angiotensin II has been reported to increase angiotensinogen release rate. However, infusion of angiotensin I (with simultaneous suppression of plasma renin by antirenin antibody infusion and angiotensin II production by captopril administration) had no effect on the angiotensinogen release rate. Direct infusion of renin in rats treated with captopril resulted in further suppression of the angiotensinogen release rate, compared with those given captopril alone. We postulate that renin (or des-angiotensin I-angiotensinogen) inhibits the angiotensinogen release rate, whereas angiotensin II stimulates it. Angiotensin I has no effect on angiotensinogen release rate. This hypothesis was evaluated further in rats with various physiological states. Indeed, when conditions were such that the renin-angiotensin system was completely suppressed, such as binephrectomy and antirenin antibody infusion, angiotensinogen release rate was markedly stimulated. When angiotensin II production was prevented by captopril treatment, angiotensinogen release rate declined. This appeared to be the case for all states of sodium balance. Thus, angiotensinogen release rate is subject to a complex feedback control by other components of the renin-angiotensin system. (Circ Res 52:328–334, 1983)

PLASMA angiotensinogen is a α2-globulin synthesized and secreted by the liver. It is the substrate for the circulating enzyme, renin (EC 3.4.99.19) and is thus the precursor of angiotensin II (AI), the final product of the renin-angiotensin cascade. Recent interest in angiotensinogen has been prompted by the increasing evidences that it may be rate limiting in the generation of angiotensin I (AI) (Poulson 1973; Sam- bhi, 1977; Dzau and Herrmann, 1982) and, thus, important in the regulation of blood pressure. In addition, it is becoming apparent that certain conditions associated with increased generation of plasma angiotensin II, e.g., estrogen administration and Cushing’s disease, may be related to the increase in plasma angiotensinogen concentration (Saruta et al., 1970; Cain et al., 1971; Stubbs et al., 1976; Dzau and Herrmann, 1982). Since plasma angiotensinogen may contribute to the control of blood pressure, it becomes important to determine the mechanism by which angiotensinogen production is regulated.

Plasma angiotensinogen concentration (PAC) represents the balance between angiotensinogen production and metabolism. Therefore, changes in plasma angiotensinogen concentration may result from alterations in production or consumption. We studied the factors that influence the rate of angiotensinogen production, using an in vitro rat liver slice system.

We have previously shown that the liver slices release angiotensinogen linearly for 3 hours and that the rate of release can be increased by treating the rats in vivo with ethinyl estradiol, dexamethasone, thyroid hormone, and angiotensin II (Herrmann et al., 1980; Dzau and Herrmann, 1982).

The observation that in vivo angiotensin II infusion increased PAC, as well as the production and release of angiotensinogen from liver slices, stimulated investigators to propose that angiotensinogen production is subject to feedback regulation by components of the renin-angiotensin system (RAS) as, for example, renin secretion is inhibited by angiotensin II (Reid et al., 1978). We, therefore, examined the effects of the various components of the renin-angiotensin system on the hepatic production of angiotensinogen by studying groups of rats subjected to (1) sodium depletion, (2) sodium depletion plus captopril administration, (3 and 4) high sodium intake with or without captopril, (5) bilateral nephrectomy, (6) antirenin antibody infusion, (7) AI infusion plus antirenin antibody and captopril, and (8) renin infusion plus cap-topril. These groups were chosen in order to provide stimulation (sodium depletion) or suppression (nephrectomy or renin-antibody) of the entire renin-angiotensin system (RAS), as well as selective stimulation of each of the individual RAS components (AI...
or renin infusion), while simultaneously suppressing the other components. The results of these experiments demonstrate that the production of angiotensinogen is subject to feedback regulation by plasma renin and angiotensin II.

Methods

Preparation of Liver Slices

Sprague-Dawley rats (Charles River Laboratory) weighing 150–200 g were used in all experiments. Unless otherwise specified below, they had free access to rodent chow (normal diet contained 0.36% sodium) and tap water. Groups of animals underwent the experimental protocols described below and then were decapitated to allow collection of blood in chilled tubes (Vacutainer) containing EDTA. Livers were removed, rinsed in 0.9% saline, and blotted. Liver slices of about 200 mg were obtained with a Stadie-Riggs microtome, as previously described (Herrmann et al., 1980). Slices were rinsed in saline, blotted, and incubated in RPMI 1640 medium (3 ml) at 37°C for 3 hours in an atmosphere of 95% O₂-5% CO₂. Previous studies demonstrated that these liver slices produced and released angiotensinogen linearly during a 3-hour period and that the production of angiotensinogen was inhibited by actinomycin (Herrmann et al., 1980).

Assays

Angiotensin I was measured by radioimmunoassay according to the method of Haber et al. (1969): [125I]-labeled [1-Asp,S-Ile]angiotensin I tracer (Bachem) in 0.1 M Tris-HCl (pH 7.4) buffer was added to the unknown sample and then mixed with anti-angiotensin I antibody. After equilibration, free tracer was separated from tracer bound to the antibody by absorption with dextran-coated charcoal. The charcoal was removed by centrifugation and the 125I-Al remaining in the supernatant extract was determined using a Beckman gamma counter. 125I counts/min (cpm) were converted to nanograms (ng) of Al by comparison to known standards. Results are presented as ng Al (0.6856 pmol Al/ng Al).

Plasma-renin concentration (PRC) was determined as the amount of Al generated in 1 hour at 37°C in a reaction mixture (total volume of 350 µl) containing the sample (100 µl of plasma), anephric dog plasma (250 µl), dimercaptopropanol, and 8-hydroxyquinolone (0.34 mM) in 0.1 M Tris-HCL, pH 7.4. The concentration of angiotensinogen of anephric plasma was approximately 3600 ng Al equivalent/ml. These conditions represented substrate excess, since Al generation was linear up to 3 hour. Al concentration was determined as described above, and results are expressed as ng Al/ml per hr.

Angiotensinogen concentration was determined by adding 30 µl of excess dog renin [0.1 Goldblatt unit (GU) in 30 µl] to the sample (50 µl of plasma or 500 µl incubation medium) at pH 5.4 and incubating the mixture at 37°C for 1 hour. Generation was stopped by adding cold water (1.0 ml) and boiling for 2 minutes. Al was measured in the supernatant following centrifugation, and the results are expressed as ng Al equivalent/ml of plasma or ng Al equivalent/g liver per 3 hours of release time. The validity of measurement of angiotensinogen exhaustion was demonstrated by incubating plasma (100 µl) from rats nephrectomized 24 hour previously, with renin (0.1 GU). Al generation reached a plateau after 30 minutes of reaction. Beyond this point, no further generation or degradation of Al was observed up to 2 hours. Since no samples in these experiments had an angiotensinogen concentration as high as nephrectomized plasma, 1 hour incubation was performed in all samples.

For experiments in which animals were injected with antirenin IgG, excess circulating antibodies in the plasma of these animals were demonstrated by adding exogenous dog renin (3 × 10⁻⁴ GU) to the plasma (100 µl) and incubating at 37°C for 1 hour. Excess angiotensinogen (25 µl anephric dog plasma) was then added and the reaction continued for an additional hour. Residual renin activity, as measured by the generation of Al, is expressed as ng Al/ml plasma.

Experimental Treatments

Sodium Balance

So that we might study the effects of sodium depletion, rats were given furosemide (5 mg intraperitoneally) and then fed a low sodium diet containing 0.05% sodium (Purina) and tap water for 10 days. Sodium-loading was accomplished by feeding rats high sodium diet (1.6%) for 10 days. Daily 24-hour urine samples were collected, and the urinary sodium and potassium concentrations were determined by ion-selective electrode analysis (NOVA Biomedical). Results are expressed as mEq/24 hours after multiplying by the total urine volume. The potassium content of the low sodium diet was lower (0.46%) than the normal or high sodium diets (1.08%).

Captopril Administration

The orally active converting enzyme inhibitor captopril (SQ 14225 from Squibb Pharmaceutical Corp.) was administered by gavage (10 mg/100 g body weight per day) or by intraperitoneal injection (2 mg/100 g body weight per day). Both treatments resulted in similar increases in PRC after 10 days; hence, these data were pooled for analysis.

Nephrectomy

Anesthetized rats (sodium pentobarbital, 50 mg/kg) were bilaterally nephrectomized 20–24 hours prior to sacrifice. Care was taken not to disturb the adrenal glands.

Antirenin Antibody Injection

A non-uremic low renin state was induced by injecting rats with renin-specific antibody obtained from a goat immunized with purified canine renal renin (Dzau et al., 1980). The IgG fraction of the goat antiseraum (CLN 8–23) was prepared from the serum of DEAE column chromatography (Dzau et al., 1982). This IgG pool (100 µl) inhibited 50% of the activity of purified rat renin (5.6 × 10⁻⁴ GU) at a titer of 1:7500. Animals received a single intracardiac injection (300 µl) of antibody or saline control 6 hours before they were killed. Plasma was collected at the time of sacrifice and assayed for circulating antirenin antibody as described below.

Angiotensin Infusion

Angiotensin I was infused intravenously using Alzet osmotic minipumps (Alza Corp.). The pumps were implanted subcutaneously in the dorsal vertebral region of the anesthetized animal and the outflow catheters were led subcutaneously to the left jugular vein. Prior to implantation, the pumps and the outflow catheters were filled with angiotensin I (2.6 mg/ml saline), or isotonic saline. The solutions then were infused at the rate of 1 µl/hr (43 ng Al/min) for 3 days.
Renin Infusion

To examine the effect of renin on hepatic angiotensinogen production, semipurified rat renal renin (specific activity 2 Goldblatt units/mg protein), isolated as described (Dzau et al., 1982), was infused into rats via Alzet osmotic minipumps. Two pumps containing $2.2 \times 10^8$ to $7.5 \times 10^8$ ng Al/hr of renin activity per pump were implanted intraperitoneally, resulting in 4 days of renin infusion at a rate of $2.2 \times 10^8$ to $7.5 \times 10^8$ ng Al/hr (44 to 150 Goldblatt milliunits/hr). All animals received intraperitoneal captopril 6 days prior to and throughout renin infusion in order to avoid the generation of angiotensin II by the infused renin. A second parallel group of rats (control) received captopril and a continuous infusion of isotonic saline (2 µl/hr) instead of renin for the same periods.

Statistical Analysis

Results are presented as mean ± se. Statistical evaluation of differences between means within an experiment was determined by Student's t-test or by two-way analysis of variance.

Results

Sodium Balance

Sodium balance was assessed by measuring urinary sodium per 24 hours on days 4, 7, and 10 of a 10-day experiment (Table 1). All animals were in sodium balance by day 4, with no changes in sodium excretion occurring by day 10. At equilibrium, urinary sodium excretion was 0.05 ± 0.01 mEq/24 hours in sodium-restricted animals, 5.2 ± 0.2 mEq/24 hours in sodium-loaded animals, and 1.1 ± 0.2 mEq/24 hours in control animals eating regular chow ($P < 0.001$ for both groups relative to control).

In rats maintained on a low sodium diet, plasma renin concentration increased from a control level of 3.6 ± 0.7 to 22.0 ± 5.9 ng/ml per hour ($P < 0.01$) (Fig. 1). Plasma angiotensinogen concentration in the sodium–depleted rats was significantly lower than in the control animals (1.142 ± 147 vs. 753 ± 109 ng Al equivalent/ml respectively, $P < 0.05$). The rate of angiotensinogen release (ARR) by liver slices from these animals was not significantly different from that of the control group (Fig. 1). Although plasma renin concentration decreased during sodium loading to 0.6 ± 0.08 ng/ml per hour, no significant change in angiotensinogen release or PAC occurred.

Statistical Analysis

Results are presented as mean ± se. Statistical evaluation of differences between means within an experiment was determined by Student's t-test or by two-way analysis of variance.

Effect of Captopril

Captopril was administered to animals on low ($n = 8$), unrestricted ($n = 10$), and high sodium diets ($n = 6$), as described. Efficacy of converting enzyme inhibition was demonstrated by the increase in plasma renin concentration from 3.6 ± 0.7 to 29.4 ± 6.3 ng/ml per hour ($P < 0.001$) in animals on the normal sodium diet following captopril treatment. Plasma renin concentration also increased in both the sodium–depleted animals (22.0 ± 5.5 to 61.2 ± 4.8 ng/ ml per hour $P < 0.001$) and the high sodium animals (0.6 ± 0.08 to 5.2 ± 1.9 ng/ml per hour, $P < 0.05$) after captopril administration (Fig. 1).

Captopril treatment resulted in a decrease in PAC in all states of sodium balance. Rats with normal sodium intake had a PAC of 1142 ± 147 ng/ml which decreased to 646 ± 106 ng/ml after captopril treatment ($P < 0.02$). The PAC in sodium–depleted rats decreased from 753 ± 109 to 214 ± 40 ng/ml with captopril administration ($P < 0.001$). Similarly, captopril resulted in a decrease in PAC from 820 ± 81 to 372 ± 106 ng/ml ($P < 0.01$) in high sodium animals.

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tr>
<td>Urinary Electrolytes (mEq/24 hr)</td>
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<td>Day 4</td>
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<tr>
<td>Na⁺</td>
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<tr>
<td>Control</td>
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<tr>
<td>Low sodium</td>
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<td>Low sodium + CAP</td>
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<tr>
<td>High sodium</td>
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<td>High sodium + CAP</td>
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ND = not done; CAP = captopril.
* n = 6 in all groups.
† P values for day 10 relative to control, NS = not significant.
A decrease in the rate of angiotensinogen release (ARR) from 33.0 ± 2.9 to 19.5 ± 1.6 ng/g per 3 hours (P < 0.001) occurred during captopril treatment of rats on normal diet. The ARR by liver slices of sodium-depleted rats treated with captopril was also lower than from control slices (P < 0.005). In the high salt state, ARR from the liver slices also declined in the captopril-treated animals, but this decrease was not statistically significant, possibly due to the smaller number of animals studied on this diet (Fig. 1).

Effect of Nephrectomy

To study the effects of a low renin state, we performed bilateral nephrectomies in six rats 20-24 hours prior to sacrifice. PRC in these animals decreased from 1.97 ± 0.3 ng/ml per hour (after sham surgery) to barely detectable levels (P < 0.05). A large increase in both PAC and ARR was noted relative to sham-operated controls (n = 6) (Fig. 2); PAC increased 8-fold (P < 0.01), and angiotensinogen release increased more than 3-fold (P < 0.01). These results are expressed as percent of control in Figure 2.

Effect of Antirenin Antibody

To separate the effects of uremia from those of a low renin state, we performed bilateral nephrectomies in six rats 20-24 hours prior to sacrifice. PRC in these animals decreased from 1.97 ± 0.3 ng/ml per hour (after sham surgery) to barely detectable levels (P < 0.05). A large increase in both PAC and ARR was noted relative to sham-operated controls (n = 6) (Fig. 2); PAC increased 8-fold (P < 0.01), and angiotensinogen release increased more than 3-fold (P < 0.01). These results are expressed as percent of control in Figure 2.

Effect of AI Infusion

Although it was possible to dissociate the effects of AI on angiotensinogen production from those of renin or AI using captopril, renin and AI changed in the same directions with captopril. Hence, we isolated the effect of AI by its infusion into animals pretreated with both renin antibody to suppress renin and captopril to prevent the conversion of AI to All. Twelve animals received captopril for 10 days, continuous AI infusion intravenously (43 ng/min) for 3 days, and were injected with antirenin IgG 6 hours prior to sacrifice. These animals were compared with the controls (n = 14) receiving only captopril and antirenin IgG.

In the animals receiving AI infusions, although the plasma AI levels doubled (P < 0.05), the rate of angiotensinogen release and the plasma angiotensinogen concentration were not significantly altered (Fig. 2). The AI levels measured in the medium of the liver slices prior to angiotensinogen determinations were not significantly different in the two groups and were less than 10% of the value measured after incubation with renin, thereby confirming that the slices were not contaminated with infused AI.

Renin Infusion

Four days of continuous intraperitoneal renin infusion (n = 20) resulted in a 3- to 5-fold increase in plasma renin concentration relative to the saline-infusion control animals (n = 14) (P < 0.01). Five animals were excluded from the original experimental group because PRC failed to increase. Both the rate of release of angiotensinogen from liver slices and the plasma angiotensinogen concentration decreased by 52 and 44%, respectively, from control (Fig. 2). Because the data were pooled from several separate experiments, each with a small number of animals, results were analyzed by two-way analysis of variance and were highly significant (overall P < 0.002). When rates of angiotensinogen release from the liver slices of all of the 29 rats receiving captopril (and renin or saline infusion) were analyzed in relation to their plasma renin concentrations, a significant inverse correlation (r = −0.64, P < 0.001) was observed (Fig. 3). Similarly, plasma angiotensinogen concentration correlated inversely with plasma renin concentration in these rats (r = −0.68, P < 0.001).

Discussion

The factors which regulate renin release have been extensively studied. Feedback suppression of renin
secretion by the products of the RAS has been demonstrated to occur via angiotensin II (short feedback loop) and All-mediated vasoconstriction, as well as by aldosterone-mediated sodium retention (long feedback loop). In contrast, less is known about the factors that regulate angiotensinogen production. In this study, we examined the feedback control of angiotensinogen release by the various components of the renin-angiotensin system, using an in vitro system. Rats were first subjected to physiological perturbations in vivo; then, liver slices were obtained and the rate of angiotensinogen release was measured. This approach has been shown to be valid and has several advantages over previously employed systems (Herrmann et al., 1980). For example, the relative contributions of substrate production and degradation to the changes in PAC can be determined. Furthermore, alterations in and effects of other interacting hormonal systems can be studied simultaneously. This is not possible in the isolated perfused liver, which only allows studies on short-term regulation and in which certain perturbations, such as nephrectomy or antirenin antibody infusion, cannot be performed.

Previous experiments showed that angiotensin II infusion in vivo stimulated angiotensinogen production from the liver slices by 50% (Herrmann et al., 1980), as well as from an isolated liver preparation, suggesting a direct effect of All on the production of angiotensinogen by hepatocytes (Nasjletti et al., 1973). However, during sodium-depletion in which the entire RA axis is stimulated, no change in angiotensinogen production was observed. Herrmann and Reid therefore postulated that the increment of increase in plasma All during sodium depletion was insufficient to stimulate angiotensinogen production (Herrmann et al., 1980).

An alternative explanation for this observation is that elevated PRC exerted an inhibitory effect on angiotensinogen production. To examine this possibility, we treated sodium-deplete and sodium-replete rats with captopril. A decrease in plasma angiotensinogen of 40–70% was observed in all groups of animals after captopril administration, which was also associated with a decrease in angiotensinogen production in the normal and sodium-deplete animals. Although the decrease in PAC in low sodium animals can be accounted for partly by increased consumption by increased plasma renin, decreased hepatic angiotensinogen production was a significant contributing factor in the decline of PAC during sodium depletion. This decrease in hepatic angiotensinogen production may be due to a direct or indirect effect of increased plasma renin on angiotensinogen synthesis.

The mechanism of decreased substrate production with captopril may also be due to decreased circulating All, resulting in decreased hepatic stimulation either directly or by a secondary decrease in plasma corticosterone level. However, Reid and colleagues have previously demonstrated that glucocorticoids have an unimportant role in angiotensinogen production in dogs (Reid, 1977; Sernia et al., 1980). Since converting enzyme also degrades bradykinin, the observed response could also be due to increased kinins (Swartz et al., 1979). Finally, prostaglandins have been reported to increase with captopril. The contributions of kinins and prostaglandins to the results we obtained were not assessed in our present investigation.

To examine further the contribution of renin and All to the regulation of substrate production, we studied the effects of suppression of the RAS by nephrectomy and systemic anti-renin antibody administration. PAC and hepatic production of angiotensinogen both increased significantly, confirming the previous findings of Nasjletti et al. (1972) and of Freeman and Rostorfer (1972) in bilaterally nephrectomized animals. Although Freeman and Rostorfer (1972) suggested that the effect of nephrectomy was mediated by an increase in glucocorticoids occurring as part of a stress reaction, this is unlikely, since bilateral nephrectomy performed 7 days after bilateral adrenalectomy also results in an increased plasma angiotensinogen concentration (Tateishi et al., 1971; Carretero and Gross, 1967).

Thus, either renin or All appears to exert an inhibitory effect on angiotensinogen production. To address this question further, we isolated the effect of Al by infusing the decapeptide into rats in which both renin and All production were blocked by the administration of antirenin antibodies and captopril, and observed that Al failed to alter angiotensinogen production. This result differs from that of Nasjletti and Masson, who showed increased substrate production when Al was infused into the isolated perfused liver (Nasjletti et al., 1973). Since converting enzyme is present in the liver (Roth et al., 1969; Huggins and Thampi, 1968), intraphepic conversion of Al to All may have accounted for the increased angiotensinogen release in their experiments.

Direct evidence that renin suppresses hepatic angiotensinogen production was obtained in the renin infusion experiments. Indeed, angiotensinogen from liver slices appears to be affected by plasma renin concentration in a dose-related fashion (Fig. 3). The
mechanism by which renin suppressed substrate production is unclear. One mechanism could involve des-/(angiotensin I)-angiotensinogen, a product of renin-angiotensinogen reaction, whose concentration is dependent on renin activity, (Bouhnik et al., 1981) and might exert feedback control on its precursor, angiotensinogen. Alternatively, renin may have a direct inhibitory action on hepatocytes or may inactivate an endogenous circulating angiotensinogen-stimulating factor. The existence of such a factor was first postulated by Hasegawa et al. (1973), when they noted an increased rate of substrate synthesis by rat liver slices after incubation with plasma of nephrectomized animals in vitro. Indeed, those investigators subsequently isolated this factor and demonstrated that its activity was destroyed upon incubation with renin (Hasegawa et al., 1976).

Finally, it has been suggested that PAC may have a negative feedback effect on angiotensinogen production (Reid et al., 1974). However, based on our data, this effect may be relatively unimportant, since PAC and hepatic ARR were always directly related. In no circumstances did we observe an increased PAC associated with depressed hepatic ARR or vice versa.

The results obtained in this investigation demonstrate that renin decreases PAC by the consumption of plasma angiotensinogen, as well as by exerting an inhibitory effect on hepatic angiotensinogen synthesis and release. Angiotensin II, the final product of the cascade, stimulates hepatic ARR. However, angiotensin I has no effect on the synthesis or consumption of plasma angiotensinogen (Fig. 4). On the basis of these conclusions, the effect of various physiological perturbations in this study can be explained (Table 2):

1. During complete suppression of the RAS by nephrectomy or antirenin antibody, the net effect is increased hepatic ARR. This is consistent with a tonic inhibitory effect of renin on hepatic angiotensinogen synthesis and cannot be explained solely on the basis of induced changes in plasma corticosterone or ALL level.

2. In sodium-loaded animals, the RAS is less extensively suppressed, and a balanced effect between renin and ALL on hepatic angiotensinogen production is observed.

3. In sodium-deplete animals, whose RAS is stimulated, a balanced effect on hepatic angiotensinogen production is also observed. However, elevated PRC leads to increased consumption of plasma angiotensinogen, resulting in a net decrease in PAC.

4. Captopril increases PRC and decreases ALL. Elevated PRC results in decreased production and increased consumption of angiotensinogen. The decrease in ALL also leads to decreased angiotensinogen production. This appears to be the case for all states of sodium balance.

5. Steroid hormones increase hepatic angiotensinogen production and PAC. Studies of physiological perturbations of angiotensinogen production should, therefore, include the measurement of plasma corticosterone levels.

Thus, the interrelationships between components of the renin-angiotensin system are quite complex, and in this paper we have demonstrated these relationships as they influence angiotensinogen production. Further delineation of the factors which regulate angiotensinogen production may be important in blood pressure control, and continues to be an important area of research.

![Figure 4](image.png)

**Figure 4.** Schematic representation of the factors which regulate angiotensinogen production. Stimulating factors are shown by solid lines, inhibitory factors by dashed lines.

**Table 2**

<table>
<thead>
<tr>
<th>Renin infusion</th>
<th>AI infusion</th>
<th>ALL infusion</th>
<th>ARR*</th>
<th>PAC†</th>
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<tr>
<td><strong>Renin Ab infusion</strong></td>
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<td><strong>Low Na⁺</strong></td>
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* Hepatic rate of angiotensinogen release.
† Plasma angiotensinogen concentration.

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**References**

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