*Results.* NADPH-DCPIP reductase: 3 different experiments involving gonadotrophin treatment were performed on prepuberal rats, and the results are expressed in Table I. In Table II, the results obtained with the adult animals are listed.

These results show that the activity of the so-called NADPH' diaphorase of the postmitochondrial fraction of rat testis can be modified by in vivo administration of chorionic gonadotrophin. Dichlorophenolindophenol, the acceptor used in this study, can be reduced by the NADPH diaphorase as by the NADPH cytochrome C reductase[5]. Both enzymes are flavoproteins, and both are located in microsomes. As we have not purified our system, we must say that we have a NADPH-DCPIP oxidoreductase system which is under hormonal control localized in the postmitochondrial fraction. The subcellular localization of this system renders a relationship between it and the mitochondrial electron transport system unlikely. It is known that androgen-hydroxylating enzymes are located in microsomes in rat testis[1]; therefore we may presume that the increased activity observed is related to androgen synthesis. A flavoprotein component with the property of reducing DCPIP has been described in the electron transport system of adrenal microsomes by OMURA et al.[6]. This electron transport system acts on the hydroxylation of steroids in the adrenal. Such a system has not been described in testis, but we can presume that the activity we are concerned with is related to it.

Histochemical observations[7] are against the possibility of the activation of the diaphorase system by chorionic gonadotrophin in rat testis, but qualitative observations per se cannot give a measure of activity[8].

*Resumen.* La actividad de un sistema enzimatico que oxida el NADPH usando DCPIP como aceptor, en homogenados te sticulares de ratas prepuberales y adultas tratadas con gonadotrofina corionica ha sido estudiado. Los cambios encontrados se dis cuten en relación con la sintesis de androgenos.

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## Renal and Pressor Actions of Angiotensin in Salt Loaded and Depleted Rabbits

Angiotensin is so named because it raises arterial pressure and its method of biological assay depends upon this action. In addition it has a marked effect on renal sodium excretion and may be important in the control of sodium homeostasis. The effect of infused angiotensin on renal sodium excretion is complex. Thus it may either increase or diminish sodium excretion depending on the amount infused[1-3]. Moreover, doses of angiotensin which are antinatriuretic when infused into normotensive subjects on a normal sodium intake may be natriuretic when given to salt depleted subjects[4] or to patients with cirrhosis and ascites[5]. In order to clarify its role in sodium homeostasis we have infused angiotensin in graded doses between 0.00005 and 0.5 μg/kg/min into conscious trained rabbits and determined the relative sensitivity of its pressor and renal actions and the dose range over which its natriuretic and antinatriuretic effects occur. In addition, we have infused it into the same animals when salt loaded and depleted to see the effect of changes in sodium status on the renal response to administered hormone.

The experiments were performed on 6 rabbits weighing between 2 and 2.5 kg, that had chronically implanted bladder, venous and arterial catheters. Over a period of 3–5 days the animals were either salt loaded by infusing 6 mEq sodium a day as $^1/_4$ strength Hartmann's solution, or depleted of 6–10 mEq of sodium by means of the diuretic frusemide and a salt free diet. Some animals were initially salt loaded and others depleted. During the experiment either $^1/_2$ strength Hartmann's solution in the case of salt loaded animals, or 2.5% dextrose in depleted ones was delivered at 0.75 ml/min by a constant infusion pump. When urine flow and sodium excretion were constant, synthetic angiotensin II (CIBA) was administered, dissolved in the appropriate infusate.

Infusion of angiotensin in small doses between 0.005 and 0.00005 μg/kg/min into salt loaded animals for periods ranging from 10–90 min consistently reduced urine flow and sodium excretion for the duration of the infusion. In contrast when given to salt depleted rabbits in doses of 0.0005–0.00005 μg/kg/min angiotensin had no effect on urine flow or sodium excretion, while doses of 0.005 μg/kg/min caused only an inconstant small reduction in these parameters. Table I compares the effects of identical 10 min infusions of angiotensin in 6 rabbits when salt loaded and depleted. It can be seen that sodium depletion greatly depresses both the antidiuretic and antinatriuretic response to small doses of angiotensin.

Larger doses of angiotensin caused a marked initial reduction in urine flow and sodium excretion in salt loaded animals. After an interval of 20 min however, particularly with very large doses, urine flow and especially sodium excretion were increased. In 3 animals the effects of doses of 0.05 μg/kg/min and above were com-

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pared during identical 30 min infusions in the salt loaded and depleted state (Table II). Large doses caused a less marked initial fall and a more marked secondary rise in urine flow and sodium excretion, when the animals were salt depleted. Some doses which were still antinatriuretic during the final 10 min of infusion in the salt loaded state were markedly natriuretic when the animal was salt depleted. Mean sodium excretion over the 30 min of angiotensin infusion was in all cases reduced below control levels when the animals were salt loaded, but rose above control when salt depleted. Thus sodium depletion appeared to lower the threshold to the natriuretic effect of large doses of angiotensin.

The effect of changes in salt status on the renal response to angiotensin in the same animal is illustrated in Figure 1. Low doses which were antinatriuretic when the animal was salt loaded were without effect in the depleted state and a large dose of 0.5 μg/kg/min which was antinatriuretic in the salt loaded animal was natriuretic in the depleted state.

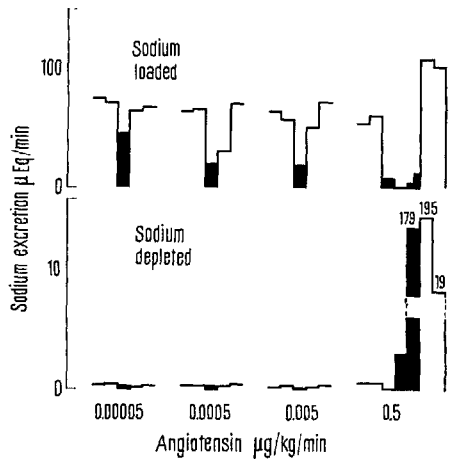


Fig. 1. The effect of angiotensin (black areas) in doses of 0.00005–0.005 μg/kg/min for 10 min and 0.5 μg/kg/min for 30 min on sodium excretion in the same animal when sodium loaded and depleted.

Table I. Effects of small doses of angiotensin in the same animals when salt loaded and depleted

| Angiotensin μg/kg/min | No. of animals | Urine flow % of control | | Urine sodium excretion % of control | |
|---|---|---|---|---|---|
| | | Salt loaded | Salt depleted | Salt loaded | Salt depleted |
| 0.00005 | 6 | 70.1 (37–85) | 96.6 (86–116) | 62.7 (40–87) | 103.6 (80–133) |
| 0.0005 | 5 | 41.2 (25–73) | 98 (65–128) | 45.4 (25–69) | 98.2 (74–131) |
| 0.005 | 5 | 27.1 (16–40) | 80.3 (40–91) | 27.6 (14–41) | 87.8 (50–119) |

Mean values are given with the ranges in brackets.

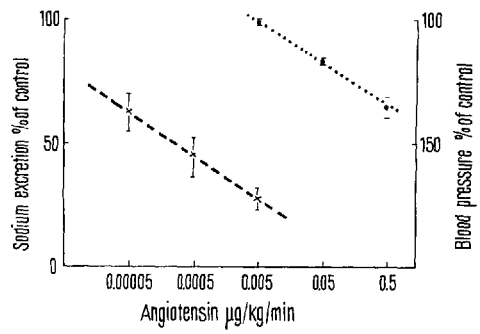


Fig. 2. The log dose response of sodium excretion ---- and arterial presure .... to infusion of angiotensin in sodium loaded animals. Mean values are given with the standard error of the means.

Table II. Urine flow and sodium excretion during infusion of large doses of angiotensin in the same animals when salt loaded (L) and depleted (D) in order of study

| Animal | Angiotensin μg/kg/min | Sodium status | Urine flow ml/min | | | | Sodium excretion μEq/min | | | | Change in [a] sodium excretion μEq/min |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | C | $A_1$ | $A_2$ | $A_3$ | C | $A_1$ | $A_2$ | $A_3$ | |
| G. | 0.025 | L | 0.79 | ← | 0.04 | → | 46.9 | ← | 2.5 | → | − 44.4 |
| | 0.025 | D | 1.52 | 0.56 | 0.74 | 0.87 | 0.46 | 0.38 | 0.70 | 0.46 | + 0.05 |
| | 0.05 | L | 0.95 | 0.47 | 0.31 | 0.54 | 68.4 | 31.8 | 25.0 | 55.2 | − 31.1 |
| | 0.05 | D | 0.99 | 0.31 | 0.22 | 0.76 | 0.26 | 0.20 | 0.25 | 2.86 | + 0.84 |
| | 0.5 | L | 1.29 | 0.10 | 0.46 | 1.35 | 91.3 | 9.5 | 59.5 | 154.2 | − 16.9 |
| | 0.5 | D | 1.17 | 0.11 | 0.40 | 0.98 | 0.16 | 0.02 | 7.91 | 33.5 | + 13.65 |
| C. | 0.125 | D | 0.72 | 0.27 | 0.13 | 1.5 | 0.76 | 0.17 | 0.12 | 50.0 | + 16.0 |
| | 0.5 | D | 0.73 | 0.20 | 0.15 | 2.20 | 0.49 | 0.12 | 3.1 | 179.5 | + 60.41 |
| | 0.5 | L | 0.87 | 0.12 | 0 | 0.14 | 56.8 | 6.9 | 0 | 8.45 | − 51.69 |
| D. | 0.5 | D | 0.88 | 0.65 | 0.30 | 1.35 | 0.33 | 0.43 | 1.21 | 15.27 | + 5.3 |
| | 0.5 | L | 1.37 | 0.03 | 0.515 | 1.53 | 81.1 | 0 | 48.1 | 158.8 | − 12.14 |

C = mean of 2 control periods. [a] Change from control in urinary sodium excretion over 30 minutes of angiotensin infusion. $A_{123}$ = Three 10 minute periods of angiotensin infusion.

In salt loaded animals, antinatriuretic doses of 0.00005 and 0.0005 μg/kg/min had no effect on mean arterial pressure and doses of 0.005 μg/kg/min caused slight increases of 3% and 6% in only 2 out of 5 animals. The log dose response of arterial pressure and sodium excretion in salt loaded animals is compared in Figure 2. It will be seen that the threshold of the antinatriuretic effect of angiotensin is less than 1% of the lowest pressor dose.

The influence of sodium status on the renal response to infused angiotensin may well be mediated by the rate of endogenous production of the hormone. In salt depletion the local renal concentration of angiotensin may be at optimal antinatriuretic levels; infusion of additional angiotensin would then be either without effect, or by summation cause the natriuresis seen with large pressor doses. Most studies of the renal action of angiotensin have used such large doses and the physiological relevance of the resulting natriuresis may be questioned. Much smaller doses, less than 1% of that required to raise arterial pressure, are shown here to reduce sodium excretion in the salt loaded animal. It is likely that angiotensin acts normally as a sodium retaining hormone, an action mediated by small amounts which have no direct pressor action.

*Résumé.* Chez les lapins auxquels on a administré du sel, l'angiotensine en doses de 0.005–0.00005 μg/kg/min a réduit l'excrétion urinaire de sodium à une quantité correspondant au logarithme de la dose, tandis que des doses inférieures à 0.005 μg/kg/min n'ont eu aucun effet sur la tension artérielle. Chez les mêmes lapins lors d'une déplétion de sel, de telles doses n'ont eu aucun effet sur l'excrétion de sodium. Des doses fortes ( > 0.05 μg/kg/min) qui élevaient toujours la pression sanguine, provoquèrent souvent une augmentation lente de l'excrétion de sodium, beaucoup plus marquée quand l'animal était exempt de sel que lors qu'il en était pourvu. On suggère que l'angiotensine agit normalement comme une hormone qui retient le sodium, action produite par de petites quantités sans effet sur la tension artérielle.

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## The Participation of Kinins in the Pathogenesis of Early Disturbances in the Skin Capillary Permeability in Local β-Ray Irradiation

Jolles and Harrison[1,2] showed that, in rabbits pretreated with soya bean trypsin inhibitor or ε-aminocaproic acid (EAC), the early increase of capillary permeability of skin locally irradiated by X-rays was abolished. Antihistamines and antiserotonin proved to have no effect on the degree of leakage of the dye. The results indicated the participation of protease system liberating substances active on capillary endothelium in early phase of X-ray inflammation and did not prove that histamine and serotonin are involved.

The experiments to be reported here were designed to investigate this problem further. Albino and pigmented rabbits of either sex weighing 2.5–4.0 kg were used in all experiments. Inflammation was evoked by β-ray ($Sr^{90}$-$Y^{90}$) irradiation of 3 areas (diameter, 1 cm) of shaved abdominal skin in doses 1660, 4750 and 9500 rad (270 rad/min). The increase in blood vessel permeability was controlled with Evans blue (20 mg/kg) and Na-fluorescein[3] (5 mg/kg) given i.v. Evans blue was administered immediately after the irradiation for the revelation of early changes of capillary permeability. Na-fluorescein was used for the evaluation of capillary permeability in various terms following the irradiation. The diffuse blueing of the skin resulting from the Evans blue administration did not prevent the visualization of the injured skin fluorescence by 360 nm.

Antihistamines. Dimedrol (Benadryl) and Dimebolin hydrochloride (the derivative of gammacarbolin series) were administered i.m. (10 mg/kg) 30 min before the irradiation. EAC was given i.v. (200 mg/kg) and Trasylol (Bayer, Leverkusen) i.p. (2000 KIE/kg) 1 h before the irradiation.

The results were evaluated according to the method of Litchfield and Wilcoxon modified by Roth[4].

The most pronounced inhibitory action was obtained with Trasylol and the least with Dimebolin. The results proved the significant role played by kinins in the development of early manifestations of the radiation-induced inflammation, in the pathogenesis of the derangement of the skin vessel permeability, in particular. This can be concluded from the protective action of Trasylol and EAC. Trasylol (proteolytic inhibitor obtained from parathyroid glands) inactivates kallikrein and hence inhibits formation of the kinins[5]. EAC, as an antifibrino-

Effect of antiproteolytic and antihistaminic preparations on the development of capillary permeability disturbances caused by β-ray irradiation of rabbits' skin

| Preparation | Doses (rad) 1660 | 4750 | 9500 |
|---|---|---|---|
| None | 5/8 | 6/8 | 7/8 |
| Dimedrol | 1/8 | 2/8 | 4/8 |
| Dimebolin | 2/8 | 2/8 | 5/8 |
| EAC | 1/8 | 1/8 | 4/8 |
| Trasylol | 0/8 | 1/8 | 2/8 |

The numerator: number of rabbits with increased skin vessel permeability, the denominator: total number of rabbits in group.

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