Studies on the effect of angiotensin II and of Des1-angiotensin II on blood pressure, plasma renin activity and plasma aldosterone in the dog

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Summary
1. The effects of infusions of equimolar doses of angiotensin II (AII) and of Des1-angiotensin II (heptapeptide) on plasma renin activity, blood pressure and plasma aldosterone were compared in normal anaesthetized dexamethasone-suppressed dogs.
2. Plasma renin activity was equally suppressed by both compounds. The increase in blood pressure induced by the heptapeptide averaged 43–62% of the increase during AII infusions. No significant differences in aldosterone increase were observed between AII and the heptapeptide. Plasma aldosterone, however, dropped significantly faster in heptapeptide-treated dogs after the end of the infusions.
3. Sar1-Ala8-angiotensin II (saralasin, 400 pmol min⁻¹ kg⁻¹) suppressed plasma aldosterone that was stimulated by heptapeptide (20 pmol min⁻¹ kg⁻¹) completely. The same angiotensin antagonist had only a moderate effect on plasma aldosterone stimulated by AII. After stopping the antagonist infusion, plasma aldosterone rose significantly higher in dogs infused with AII than in those receiving the heptapeptide.
4. The results demonstrate differences between the effects of AII and the heptapeptide both on blood pressure and on plasma aldosterone. They do not support the hypothesis that the heptapeptide may be the main mediator of aldosterone secretion.

Key words: aldosterone, angiotensin II, angiotensin antagonists, blood pressure, plasma renin activity.

Introduction
The renin-angiotensin system is one of the important systems in the control of aldosterone secretion and of the arterial blood pressure. Angiotensin II and the heptapeptide Des1-angiotensin II are its biologically active compounds. The relative importance of each of the two substances is still not clear since it is extremely difficult to measure them both simultaneously and separately in plasma. Studies in vivo and experiments in vitro, however, have shown that the vasopressor activity of the heptapeptide is smaller than of the octapeptide angiotensin II whereas the aldosterone-stimulating potencies of both substances seem to be almost identical (Bumpus, Khairallah, Arakawa, Page & Smeby, 1961; Blair-West, Coghlan, Denton, Funder, Scoggins & Wright, 1971).

Recently, it has been proposed that Des1-angiotensin II, called sometimes also angiotensin III, is more important than angiotensin II in the control of aldosterone secretion (Peach & Chiu, 1974; Campbell, Brooks & Pettinger, 1974; Goodfriend & Peach, 1975; Bravo, Khoshla & Bumpus, 1975). We have performed experiments which may help to elucidate further the role of angiotensin II and of its heptapeptide metabolite in the control of the blood pressure and of aldosterone secretion.

Methods
Mongrel dogs, fed with a standard laboratory diet, were used for this study. They were anaesthetized with thiopental and given 2 mg of dexamethasone intramuscularly 14 h and 1 h before the start of an experiment. Infusions were performed through a catheter placed in a femoral vein. Blood was drawn through the opposite femoral vein. A catheter was placed via the right femoral artery into the abdominal
aorta for the continuous measurement of the arterial blood pressure.

Substances for infusions were dissolved in 154 mmol/l sodium chloride (9 g/l; physiological saline) and infused in volumes approximately equal to the blood loss. A 6 ml blood sample was necessary for the measurement of plasma aldosterone and plasma renin activity.

Experiment 1

After control measurements of arterial blood pressure and collection of control blood samples either angiotensin II (Asp₁-Ile₅-angiotensin II, Schwarz-Mann) or Des-Asp₁-Ile₅-angiotensin II (heptapeptide, Schwarz-Mann) were infused in three different concentrations (5, 50 and 200 pmol min⁻¹ kg⁻¹). Each infusion lasted 45 min. Blood was drawn at the end of each infusion and 20, 40, 60 and 90 min after the end of the last infusion, when only saline was administered.

Experiment 2

Two groups of dogs were infused either with angiotensin II or with Des¹-angiotensin II (20 pmol min⁻¹ kg⁻¹). The angiotensin antagonist Sar¹-Ala⁸-angiotensin II (saralasin acetate, Norwich Pharmacal) was added after 60 min (200 or 400 pmol min⁻¹ kg⁻¹ over 60 min). The angiotensin II and heptapeptide infusions were continued after the end of infusion of Sar¹-Ala⁸-angiotensin II (400 pmol min⁻¹

![Diagram](image-url)
kg\(^{-1}\)) for 60 min. Blood was drawn at regular intervals during the experiment.

Plasma aldosterone was measured by radio-immunoassay (Vetter, Vetter & Siegenthaler, 1973) and plasma renin activity was measured by radio-immunoassay of angiotensin I (Beckerhoff, Nussberger, Vetter & Siegenthaler, 1975a).

Results

Experiment 1

Both peptides induced an increase in plasma aldosterone without a significant difference between angiotensin II and Des\(^1\)-angiotensin II (Fig. 1). Plasma aldosterone decreased, however, significantly faster after the end of the last infusion in the heptapeptide group (P<0.005). Aldosterone concentrations were almost identical in both groups at the end of the experiment.

Plasma renin activity was significantly suppressed from 3.0±0.54 ng 3 h\(^{-1}\) ml\(^{-1}\) (mean±SEM) to 0.54±0.15 ng 3 h\(^{-1}\) ml\(^{-1}\) by angiotensin II infusions and from 2.54±0.62 ng 3 h\(^{-1}\) ml\(^{-1}\) to 0.15±0.0 ng 3 h\(^{-1}\) ml\(^{-1}\) by heptapeptide infusions (P<0.005). Although the values were lower during heptapeptide infusions the differences were not significant. The differences between the two groups were insignificant also after the infusions. The arterial blood pressure rose when the peptides were administered and decreased again after the end of the last infusion. The increase induced by the heptapeptide was, however, only 43–62% of the increase induced by equimolar doses of angiotensin II.

Experiment 2

Plasma aldosterone increased in all dogs during the infusions of angiotensin II or of Des\(^1\)-angiotensin II (20 pmol min\(^{-1}\) kg\(^{-1}\)). When Sar\(^1\)-Ala\(^8\)-angiotensin II was added (200 pmol min\(^{-1}\) kg\(^{-1}\)) aldosterone increased further slightly in the angiotensin II group whereas it remained almost unchanged in heptapeptide-treated animals. Aldosterone decreased and reached or fell below the control values in all dogs infused with the heptapeptide when Sar\(^1\)-Ala\(^8\)-angiotensin II was increased to 400 pmol min\(^{-1}\) kg\(^{-1}\). Plasma aldosterone decreased also in animals infused with angiotensin II. However, the plasma concentration remained significantly higher (P<0.05) and was more than twice as high as the control values before the start of the experiment. Plasma aldosterone increased markedly in all dogs when after termination of saralasin the angiotensin II or Des\(^1\)-angiotensin II infusions were continued. The increase was lower in dogs receiving the heptapeptide. The difference between the two groups was significant at 20, 40 and 60 min after the end of saralasin (P<0.02 or less). Plasma renin activity decreased when angiotensin II or heptapeptide was infused (from 2.31±0.46 to 0.31±0.08 ng 3 h\(^{-1}\) ml\(^{-1}\) in angiotensin II-treated dogs and from 1.23±0.31 to 0.77±0.46 ng 3 h\(^{-1}\) ml\(^{-1}\) in heptapeptide-treated animals). With the addition of the antagonist, plasma renin activity increased to 2.78±1.16 ng 3 h\(^{-1}\) ml\(^{-1}\) and to 0.93±0.39 ng 3 h\(^{-1}\) ml\(^{-1}\) respectively. Renin activity fell again after termination of the antagonist infusions to 0.77±0.31 ng 3 h\(^{-1}\) ml\(^{-1}\) and 0.54±0.23 ng 3 h\(^{-1}\) ml\(^{-1}\) respectively. At no point of the experiment was there a significant difference between the two groups of dogs.

Discussion

Our experiments confirm previous observations that angiotensin II and Des\(^1\)-angiotensin II possess an almost equal aldosterone-stimulating potency (Blair-West et al., 1971; Spielman, Davis, Freeman & Johnson, 1974). Both peptides also suppress plasma renin activity significantly and to essentially the same degree (Lohmeier, Davis & Freeman, 1975), whereas the rise in arterial pressure induced by the heptapeptide is significantly lower than that produced by angiotensin II (Bumpus et al., 1961). In addition our experiments revealed the following further differences between angiotensin II and Des\(^1\)-angiotensin II. (1) Plasma aldosterone decreased significantly faster after the end of heptapeptide than of angiotensin II infusions (experiment 1). The faster decline may be explained by a longer action of angiotensin II at the adrenal cortex although its half-life after intravenous injection is only a few minutes. (2) Sar\(^1\)-Ala\(^8\)-angiotensin II (400 pmol min\(^{-1}\) kg\(^{-1}\)) blocked completely the aldosterone response to the heptapeptide (20 pmol min\(^{-1}\) kg\(^{-1}\)) and plasma aldosterone was only partly suppressed in dogs infused with equimolar doses of angiotensin II (experiment 2). This observation is in contrast to findings of Campbell et al. (1974) in the rat and of Bravo et al. (1975) in dogs. The latter investigators, however, used Sar\(^1\)-Ile\(^8\)-angiotensin II as inhibitor, which might cause confusion since it
possesses a potent intrinsic steroidogenic potency (Beckerhoff, Uhlischmid, Furrer, Nussberger, Schmied, Vetter & Siegenthaler, 1975b). The data presented here seem to indicate that Sar\(^1\)-Ala\(^8\)-angiotensin II displaces Des\(^1\)-angiotensin II more easily from its adrenal cortical receptor than angiotensin II. (3) The high increase of plasma aldosterone after the end of Sar\(^1\)-Ala\(^8\)-angiotensin II infusion in both groups of dogs was surprising. One possible explanation for this observation may be that pre-treatment with the antagonist rendered the adrenal gland more sensitive to angiotensin II and to Des\(^1\)-angiotensin II, which at the start of the experiment had in the same concentrations induced only a moderate increase in plasma aldosterone. Although plasma aldosterone increased in both groups after the end of the antagonist infusions the increase was significantly higher in angiotensin II-treated dogs. Since there were no significant differences in plasma renin activity, which was relatively low in all animals, endogenous angiotensin II cannot explain the observed changes of plasma aldosterone. The higher increase in angiotensin II-infused dogs may also be explained by a stronger affinity of this peptide to its adrenal receptors. Obviously, not only are higher doses of saralasin necessary to block the steroidogenic activity of angiotensin II; Sar\(^1\)-Ala\(^8\)-angiotensin II is also more easily displaced from the receptor by angiotensin II than by Des\(^1\)-angiotensin II.

The results of the experiments in vivo presented here do not support the hypothesis that Des\(^1\)-angiotensin II is the main agonist at the adrenal cortex. They rather suggest that the affinity of angiotensin II to the adrenal cortex is higher than that of the heptapeptide, favouring an important role of the octapeptide angiotensin II in the control of aldosterone secretion.

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References


