transformation of Form I to Form II in aqueous suspension, as well as extrapolated values at 25°, are shown in Table III. The half-life value obtained by extrapolation (≃14 hr) was in fair agreement with the experimental value (≃16 hr) determined for suspensions stored at room temperature.

According to the results of the present study, it might be concluded that the preparation of physically stable aqueous suspensions of succinylsulfathiazole could best be obtained by using the water-stable Form II. If Form I is available commercially, as is frequently the case, adequate measures have to be taken to inhibit the transformation of the crystal form and its accompanying crystal growth, caking, and difficult resuspendability. A study of the effect of potential transformation retardants will be the subject of future reports.

REFERENCES

(1) T. Higuchi, *J. Amer. Pharm. Ass., Sci. Ed.*, **47**, 657(1958).

(2) K. J. Frederick, *J. Pharm. Sci.*, **50**, 531(1961).

(3) W. I. Higuchi, P. K. Lau, T. Higuchi, and J. W. Shell, *ibid.*, **52**, 150(1963).

(4) E. Shefter and T. Higuchi, *ibid.*, **52**, 781(1963).

(5) A. J. Aguiar, J. Krc, Jr., A. W. Kinkel, and J. C. Samyn, *ibid.*, **56**, 847(1967).

(6) J. Haleblian and W. McCrone, *ibid.*, **58**, 911(1969).

(7) Armour Research Foundation of Illinois Institute of Technology, *Anal. Chem.*, **21**, 1293(1949); through *Chem. Abstr.*, **44**, 13003(1950).

(8) R. J. Mesley and E. E. Houghton, *J. Pharm. Pharmacol.*, **19**, 295(1967).

(9) A. E. Steel, *Nature (London)*, **168**, 877(1951); through R. I. Block, E. L. Durrum, and G. Zweig, "A Manual of Paper Chromatography and Paper Electrophoresis," Academic, New York, N.Y., 1955, p. 241.

(10) M. A. Moustafa, S. A. Khalil, A. R. Ebian, and M. M. Motawi, *J. Pharm. Pharmacol.*, **24**, 921(1972).

(11) M. Maruyama, N. Hayashi, and M. Kishi, *Takamine Kenkyusho Nempo*, **13**, 176(1961); through *Chem. Abstr.*, **56**, 11708d(1962).

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Inhibitory Effects of Central Hypertensive Activity of Angiotensin I and II by 1-Sar-8-ala-angiotensin II (Saralasin Acetate)

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Abstract □ The cerebroventricular administration of 0.25–2.00 μg/kg of angiotensin I or II into α-chloralose-anesthetized cats produced significant increases in mean systemic pressure. These central hypertensive effects were inhibited by the intraventricular injection of 0.5 or 1.0 μg/kg of 1-sar-8-ala-angiotensin II (saralasin acetate). The response to angiotensin I was attenuated to a lesser extent than that to angiotensin II with this preparation. However, when both the agonists and antagonists were administered intravenously, there was equal inhibition of the effects of both angiotensin I and II. Saralasin acetate alone had little or no effect on mean blood pressure or heart rate when administered by either route; when injected intravenously, it did not significantly alter the bradycardia induced by vagal stimulation, the pressor responses to bilateral carotid occlusion or intravenously administered epinephrine, and the depressor effect of intravenous acetylcholine. The difference in the levels of antagonism at central and peripheral sites suggests that the receptors for the angiotensins are not identical in these two areas.

Keyphrases □ Angiotensin I and II—inhibition of central hypertensive activity by saralasin acetate, intravenous and intraventricular administration, cats □ Saralasin acetate (1-sar-8-ala-angiotensin II)—inhibitor of central hypertensive activity of angiotensin I and II, intravenous and intraventricular administration, cats □ 1-Sar-8-ala-angiotensin II (saralasin acetate)—inhibitor of central hypertensive activity of angiotensin I and II □ Hypertensive activity, central—inhibition of effects of angiotensin I and II by saralasin acetate

Bickerton and Buckley (1) presented evidence that angiotensin II (an octapeptide) could exert an effect on the central nervous system (CNS). Utilizing the dog cross-circulation technique, they showed that administration of the peptide into the vascularly isolated head of the recipient produced a pressor effect due to peripheral vascular constriction. Since these initial observations, several investigators (2–11), utilizing similar as well as other preparations, have confirmed this effect of angiotensin. This action appears to be mediated *via* an increase in sympathetic outflow from the CNS, since it may be blocked by the intravenous administration of α-adrenergic blockers (1) into the periphery and consists mainly of an increase in peripheral resistance, with cardiac activity only slightly altered (12).

This effect of angiotensin II has been postulated to play an important role in the central control of the cardiovascular system (13), and the possibility exists that the interaction of angiotensin II with central receptor sites contributes to the development of cardiovascular hypertensive disease (14). A strong cor-

Table I—Effects of Saralasin Acetate on Mean Blood Pressure, Heart Rate, and Blood Pressure Responses Induced by Bilateral Carotid Occlusion and Intravenously Administered Epinephrine and Acetylcholine in α-Chloralose-Anesthetized Cats[a]

	Route of Saralasin Administration	Dose of Saralasin, μg/kg/min		
		Control (n = 10)	1.0 (n = 6)	5.0 (n = 4)
Mean blood pressure, mm Hg	Intravenous	92.3 ± 9.9	60.4 ± 3.4[b]	87.5 ± 20.9
	Intraventricular	103.8 ± 13.4	95.6 ± 8.5	85.8 ± 14.3
Heart rate, beats/min	Intravenous	181.9 ± 15.5	178.5 ± 12.1	197.7 ± 16.2
	Intraventricular	174.5 ± 13.6	165.3 ± 11.8	159.4 ± 15.1
		Changes in Mean Blood Pressure, mm Hg		
Epinephrine, 1.0 μg/kg iv	Intravenous	55.6 ± 7.9	56.5 ± 8.3	54.2 ± 13.9
Acetylcholine, 0.5 μg/kg iv	Intravenous	−40.9 ± 4.5	−28.3 ± 9.7	−38.3 ± 7.4
Bilateral carotid occlusion	Intravenous	30.9 ± 5.6	23.2 ± 5.4	36.4 ± 4.8

[a] α-Chloralose, 70 mg/kg iv. [b] $p < 0.05$.

relation has been shown between the blood pressure of patients with essential hypertension and the concentration of a pressor peptide, possibly angiotensin I (a decapeptide), in the cerebral spinal fluid (15).

The centrally mediated pressor effects of angiotensin may be inhibited by blockade of the central sympathetic receptors, as demonstrated by the intraventricular (ivt) administration of phentolamine, an α-adrenergic blocking drug (16). It was suggested (16) that phentolamine could be a useful tool for studying the central effects of angiotensin II. However, this does not enable the investigator to elucidate further the direct interaction between angiotensin and specific receptor sites in the CNS. For this purpose, a compound that competes with the peptide for these sites would be helpful.

Recently, an angiotensin II analog, which exhibits properties characteristic of specific competitive antagonism of the vascular action of angiotensin II, was synthesized (17). The compound, 1-sar-8-ala-angiotensin II (saralasin acetate), was utilized in an attempt to counteract different models of hypertension (17). It had no effect on the blood pressure of normotensive, spontaneously hypertensive, metacorticoid hypertensive, and unilateral renal hypertensive rats. However, in the acute phase of experimental renal hypertension, there was a dose-related reduction in blood pressure with doses of the compound ranging from 0.62 to 10 μg/kg/min iv. The investigators concluded that angiotensin II played a role in the development of this type of hypertension.

A comparison of the two types of Goldblatt hypertension with reference to this inhibitor was made by Brunner *et al.* (18). In the one-kidney Goldblatt preparation (left renal artery clipped and contralateral kidney removed), saralasin acetate did not lower the blood pressure; in the two-kidney Goldblatt preparation (left renal artery clipped and the other kidney left intact), arterial blood pressure was significantly reduced. Therefore, these authors surmised that the renin–angiotensin system plays a causal role in the two-kidney type of hypertension but that a different mechanism was responsible for maintenance of one-kidney renal hypertension.

If the central action of angiotensin contributes to the development of sustained cardiovascular hypertensive disease, it would be of interest to determine whether saralasin acetate competes with angiotensin II for receptors in the CNS. The purpose of the present study was to investigate the effects of saralasin acetate on the centrally induced pressor effects of angiotensin I and II in cats.

EXPERIMENTAL

Drugs and Chemicals—1-Sar-8-ala-angiotensin[1] II (saralasin acetate), angiotensin[2] I (94% pure), and angiotensin[3] II were dissolved in artificial cerebral spinal fluid for intraventricular administration and in saline for intravenous administration.

Perfusion of Cerebroventricular System—Ten adult cats of either sex, weighing 2–3 kg, were anesthetized with α-chloralose (70 mg/kg iv). The right femoral artery was catheterized and connected to a pressure transducer[4], and blood pressure was recorded *via* a polygraph[5]. A tracheotomy was performed and a tracheal catheter was inserted for connection to a respiration pump[6]. The animal was then affixed into a stereotaxic instrument[7], and the calvarium was surgically exposed along the sagittal suture line. Then a small hole was made[8] in the skull above the right lateral ventricle. An unbeveled 22-gauge stainless steel needle, approximately 35 mm in length, was stereotaxically lowered into the ventricle according to the coordinates described by Snyder and Niemer (19). The coordinates used were: frontal, 15 mm; horizontal, 6.75 mm; and lateral, 2.5 mm.

The cannula was affixed to the skull with dental acrylic cement, and the cerebral ventricles were perfused with artificial cerebral spinal fluid (20) after the method of Bhattacharya and Feldberg (21). The cerebral spinal fluid entered the lateral ventricle; passed through the third ventricle, the aqueduct of Sylvius, and the fourth ventricle; and drained through a polyethylene catheter inserted into the cisterna magna. The perfusion rate was kept constant at 0.1 ml/min by means of a pump[9] connected by polyethylene tubing to a three-way stopcock attached to the stainless steel cannula. The artificial cerebral spinal fluid was maintained at 37° using a heated water jacket. Injections of angiotensin I and II were made through the stopcock without interruption of the perfusion. Angiotensin I and II (0.25–2.00 μg/kg) were injected into the ventricular catheter prior to and during intraventricular infusion of saralasin acetate (1.0 or 5.0 μg/kg/min). Saralasin acetate was infused for 15 min prior to administering the peptides and infusion was continued for approximately 90 min.

General Pharmacological Tests—Ten adult cats of either sex, weighing 2.2–3.5 kg, were anesthetized and catheterized in the manner previously described. A second catheter was inserted into the ipsilateral femoral vein for administration of angiotensin I

[1] Norwich Pharmacal Co.
[2] Schwarz-Mann, Orangeburg, N.Y.
[3] Hypertensin, Ciba-Geigy.
[4] Statham P23AC.
[5] Grass model 7.
[6] Model 606 Harvard.
[7] Trent H. Wells, Jr.
[8] With the aid of a dental burr and a model 2 Moto-tool (Dremel).
[9] Harvard Peti pump.

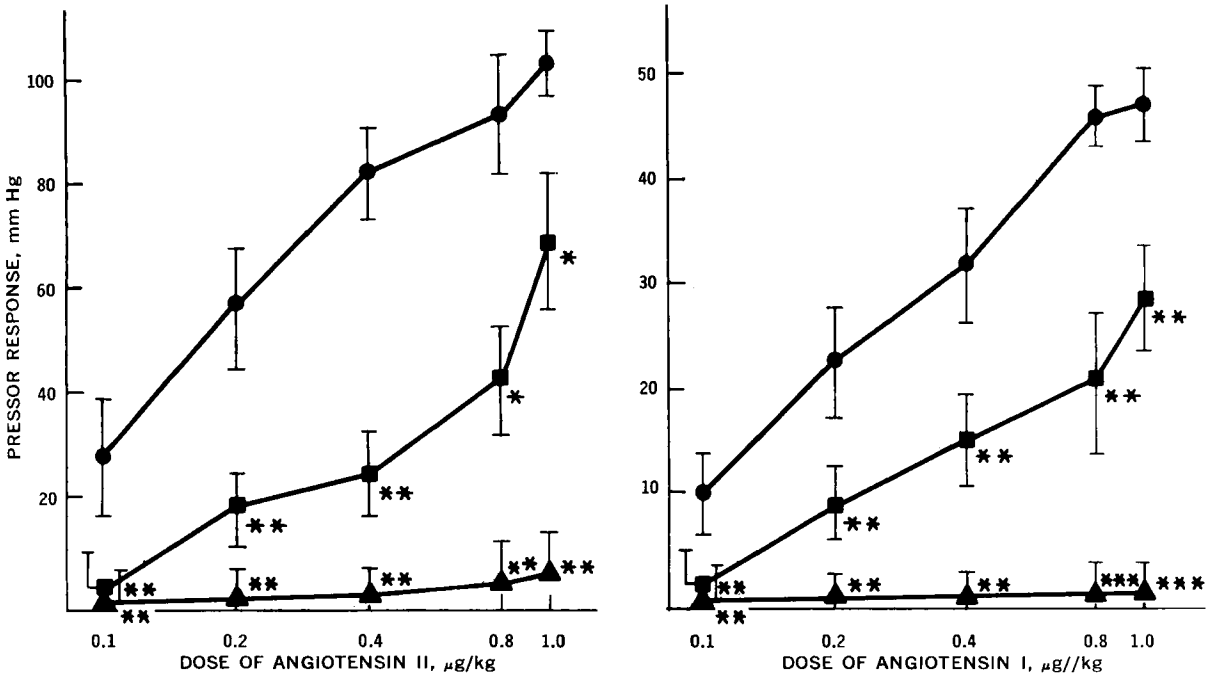

Figure 1—*Effects of intravenous saralasin acetate on the pressor response to intravenous angiotensin I and II in α-chloralose-anesthetized cats* (n = *10*). *Key:* ●, *control;* ■, *during infusion of 1.0 μg/kg/min saralasin acetate;* ▲, *during infusion of 5.0 μg/kg/min saralasin acetate;* *, $p < 0.05$; **, $p < 0.01$; *and* ***, $p < 0.005$.

and II and saralasin acetate. The left and right carotid arteries were isolated so that effects on the bilateral carotid occlusion pressor reflex could be studied. The left vagus was isolated for supramaximal stimulation (v = 3–4.5, duration = 1 msec, frequency = 1.5–12 Hz, 15 sec) by means of bipolar electrodes using a stimulator[10]. The preganglionic sympathetic trunk to the nictitating membrane was also isolated for supramaximal stimulation (v = 3–4.5, duration = 1 msec, frequency = 1.5–12 Hz, 15 sec) in the same manner. The nictitating membrane tension was measured with a force-displacement transducer[11].

Test doses of angiotensin I and II (0.1–1.0 μg/kg), epinephrine (1.0 μg/kg), and acetylcholine (0.5 μg/kg) were administered intravenously prior to and during intravenous infusion of saralasin acetate (1.0 and 5.0 μg/kg/min). Saralasin acetate was infused for 15 min prior to administering other compounds or stimulating the neurons, and perfusion was continued for approximately 110 min. The Student paired *t* test was used to determine statistical significance unless otherwise indicated.

RESULTS

Table I summarizes the effects of saralasin acetate on blood pressure and heart rate and the blood pressure changes induced by epinephrine, acetylcholine, and bilateral carotid occlusion in normotensive cats. Saralasin acetate (1.0 or 5.0 μg/kg/min) did not alter heart rate when administered *via* the intravenous or intraventricular route. Intravenous perfusion of saralasin acetate produced a nondose-related effect on blood pressure; 1.0 μg/kg/min significantly lowered blood pressure ($p < 0.05$) but 5.0 μg/kg/min did not. The intravenous perfusion of saralasin acetate in doses of 1.0 and 5.0 μg/kg/min did not significantly alter the vascular responses to bilateral carotid occlusion, 0.5 μg/kg acetylcholine, or 1.0 μg/kg epinephrine and caused no consistent alterations in the frequency–response curve to vagal stimulation (decrease in heart rate) or stimulation of the sympathetic innervation to the nictitating membrane (contraction of the membrane). There was a nonsignificant decrease in mean blood pressure when saralasin acetate was perfused *via* the lateral ventricle of the cat.

Figure 1 summarizes the inhibitory activity of saralasin acetate on the pressor responses to intravenously injected angiotensin I and II. Saralasin acetate, 1.0 and 5.0 μg/kg/min, significantly attenuated the pressor effects of both peptides at all dose levels. The percent decrease in the pressor activity of angiotensin I and II during intravenous infusion of saralasin acetate (1.0 μg/kg/min) is plotted in Fig. 2 to compare the effects on the peptides. As can be seen, the percent inhibition of the pressor responses of angiotensin I and II was similar. Figure 3 summarizes the inhibitory effects of intraventricularly perfused saralasin acetate on the pressor effects induced by the intraventricular administration of the decapeptide and the octapeptide. The responses of angiotensin I and II were markedly attenuated by both doses of saralasin acetate. Saralasin acetate, 1.0 μg/kg/min, produced an average of 48.5% inhibition of the pressor effects of intraventricularly administered angiotensin I, and 5.0 μg/kg/min produced an average of 83.5% inhibition; the pressor effects of angiotensin II were decreased by 84.9 and 98.1%, respectively. When the data were

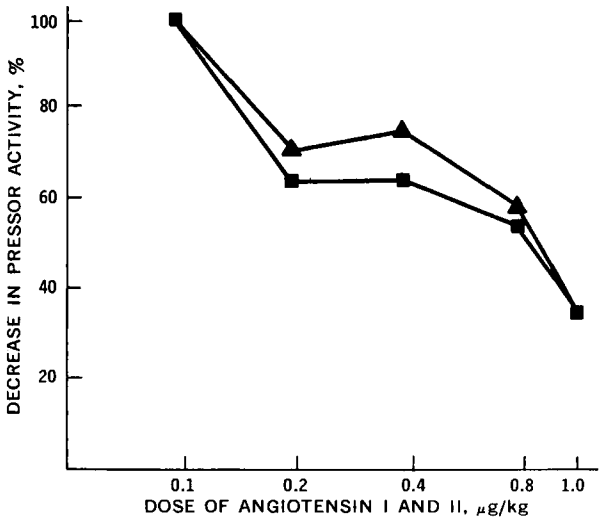

Figure 2—*Percent decrease in pressor activity of intravenous angiotensin I and II, induced by concomitant infusion of saralasin acetate, 1.0 μg/kg/min iv. Key:* ■, *angiotensin I; and* ▲, *angiotensin II.*

[10] Grass model SD5.
[11] FT03 Grass.

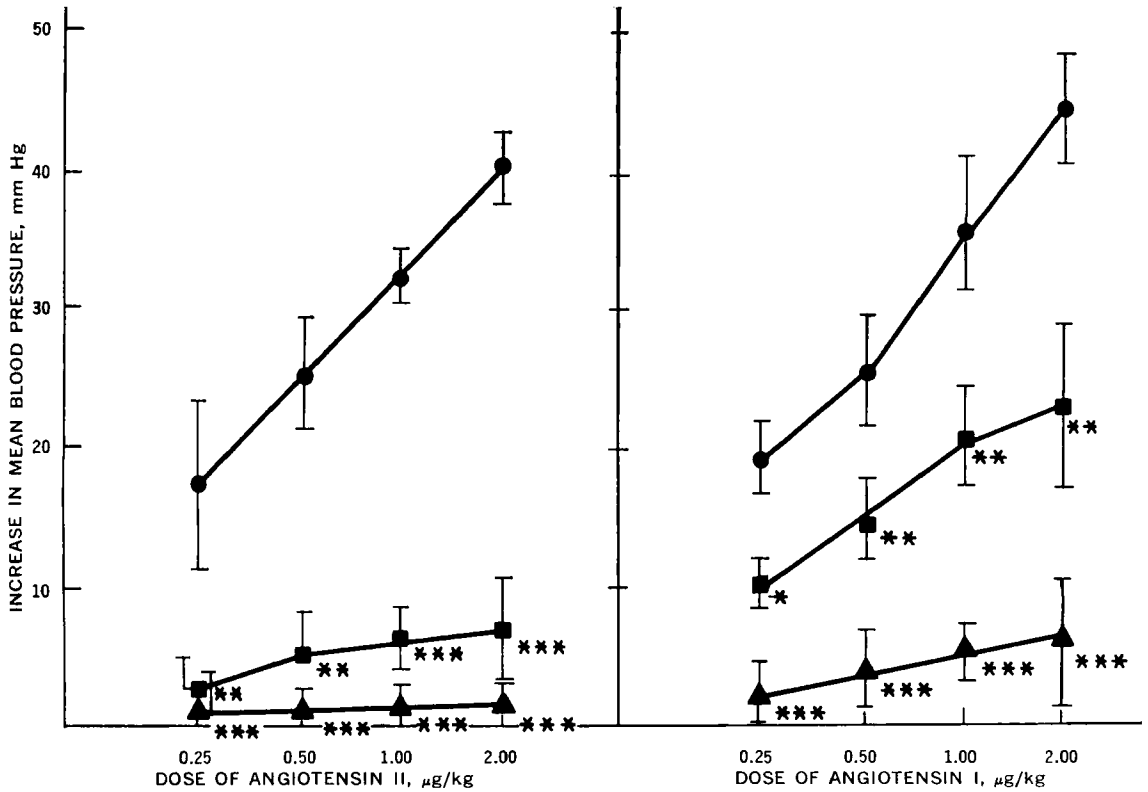

Figure 3—*Effects of intraventricular saralasin acetate on the pressor response to intraventricular angiotensin I and II in α-chloralose-anesthetized cats* (n = *10*). *Key:* ●, *control;* ■, *during infusion of 1.0 μg/kg/min saralasin acetate;* ▲, *during infusion of 5.0 μg/kg/min saralasin acetate;* *, $p < 0.05$; **, $p < 0.01$; *and* ***, $p < 0.001$.

subjected to an analysis of variance, the antagonism of angiotensin II by the low dose of saralasin acetate was significantly greater ($p < 0.01$) than that of angiotensin I. However, there was no significant difference with the higher dose of the inhibitor.

DISCUSSION

Elucidation of the involvement of the renin–angiotensin system in cardiovascular hypertensive disease is of great clinical significance. Recently, Ganten *et al.* (22) demonstrated the presence of renin in brain tissue and Finkielman *et al.* (15) showed a direct correlation between blood pressure in hypertensive patients and the concentration of an angiotensin I-like substance in the cerebral spinal fluid. In line with these reports, Ferrario *et al.* (13) stated: "The findings that angiotensin and renin are present in brain tissue suggest the possibility that angiotensin may play an important, but as yet unidentified, function in the central regulation of cardiovascular control." If the central component of activity of the renin–angiotensin system is also of importance in the development and maintenance of cardiovascular hypertensive disease, then clarification of the events occurring centrally is of even greater importance. Saralasin acetate, a specific angiotensin II antagonist, was utilized in this study to derive information that could be helpful in this clarification.

Evidence indicating that angiotensin does play a role in the development of this pathological condition is accumulating but is by no means conclusive. Whether the central or peripheral effect of these pressor substances is of more importance in this role is argumentative. Nevertheless, if alterations in the activity of angiotensin are indeed responsible for certain types of this cardiovascular disease, then one obvious pharmacological solution to this problem could be to inhibit the renin–angiotensin system at one step in this system's normal pattern of events. Formation of angiotensin II may be affected by inhibition of the synthesis and/or release of renin or by the conversion of angiotensin I to angiotensin II. Also, direct blockade of the receptor sites for angiotensin II (and possibly angiotensin I) could result in abolishing, or at least inhibiting, the pressor effects.

Since the possibility that angiotensin I may directly stimulate receptors was recently suggested (23–26), this compound was utilized along with angiotensin II in this study. The physiological events resulting from the administration of the decapeptide into the CNS were of specific importance. A comparison of how saralasin acetate affected angiotensin I and II centrally and peripherally was made to characterize the activity of angiotensin I.

Saralasin acetate failed to produce significant effects on mean blood pressure or heart rate when administered intraventricularly to normotensive cats. When infused intravenously, it had no effect on the blood pressure responses to bilateral carotid occlusion or intravenously administered epinephrine and acetylcholine. There was, however, an irregular pattern of effects on mean blood pressure upon peripheral administration. The depressor effects produced by 1.0 μg/kg/min were not in accord with the findings of other investigators (17, 18) nor with the effects seen with the higher dose (5.0 μg/kg/min) of saralasin acetate infused by this route. Saralasin acetate is reported to be a competitive antagonist of angiotensin II in the periphery (17, 18) of rats, and results obtained in cats in this study are similar to these previous findings. This can be seen by the decrease in the inhibitory effects of saralasin acetate as the dose of angiotensin I or II was increased (Fig. 2). There was no difference in activity between the peptides in this respect. Increasing doses of angiotensin I or II also override the effect of saralasin acetate in the cat lateral ventricle preparation, suggesting the possibility of competitive inhibition. However, angiotensin II is inhibited to a greater degree than angiotensin I by this route. The fact that angiotensin I retains some of its activity while that of angiotensin II is virtually abolished supports the hypothesis that angiotensin I possesses activity that is not reliant on its conversion to angiotensin II. Also, the difference in the levels of antagonism produced by central and peripheral routes of administration indicates that perhaps the receptors for the polypeptides are not identical in these two areas.

Although the activity of angiotensin I injected intravenously was significantly lower than that of angiotensin II, no significant difference between the pressor activity of the two peptides was observed upon administration into the perfused ventricular sys-

tem of cats (27). Dog cross-circulation experiments verified these results and also demonstrated that both peptides have the ability to cross the blood–brain barrier[12]. Certain observations on the central effects of angiotensin I suggest that the peptide may have activity exclusive of that mediated through conversion to angiotensin II. However, each of these points is debatable. There is a relatively small amount of converting enzyme in the brain (28), but it may be adequate for full conversion to occur. Also, angiotensin I produced a greater response than angiotensin II in some preparations, but this means little since there is a great variation in the central response to the peptides. There was no difference in the time for onset of the responses to angiotensin I and II, while a delay might be expected if conversion of angiotensin I to angiotensin II is necessary for activity. On the other hand, the rate of conversion may be such that the time required would be undetectable in this preparation.

These results with saralasin acetate are significant in that they give additional evidence to the possibility that angiotensin I is an active compound *per se*. Also, when comparing the activity of saralasin acetate centrally and peripherally, it appears that the receptive areas for angiotensin in the CNS are dissimilar in certain respects from those seen in areas exclusive of the brain.

REFERENCES

(1) R. K. Bickerton and J. P. Buckley, *Proc. Soc. Exp. Biol. Med.*, **106**, 834(1961).

(2) G. Benetato, I. Haulica, M. Uluitu, E. Bubuiana, J. Mocodean, P. Stefanescu, and G. Suhaciu, *Int. J. Neuropharmacol.*, **3**, 565(1964).

(3) R. P. Halliday and J. P. Buckley, *ibid.*, **1**, 43(1962).

(4) H. H. Smookler, W. B. Severs, W. J. Kinnard, and J. P. Buckley, *J. Pharmacol. Exp. Ther.*, **153**, 485(1966).

(5) W. B. Severs, A. E. Daniels, H. H. Smookler, W. J. Kinnard, Jr., and J. P. Buckley, *ibid.*, **153**, 530(1966).

(6) W. B. Severs, A. E. Daniels, and J. P. Buckley, *Int. J. Neuropharmacol.*, **6**, 199(1967).

(7) H. Schmitt and H. Schmitt, *Rev. Can. Biol.*, **27**, 255(1968).

(8) P. Bourdois and J. Panisset, *ibid.*, **27**, 167(1968).

(9) C. J. Dickinson and R. Yu, *Circ. Res.*, **20** and **21** (Suppl. II), 157(1967).

(10) C. M. Ferrario, C. J. Dickinson, P. L. Gildenberg, and J. W. McCubbin, *Fed. Proc.*, **28**, 394(1969).

(11) H. Ueda, Y. Uchida, K. Ueda, T. Gonodairn, and S. Katayama, *Jap. Heart J.*, **10**, 243(1969).

(12) C. M. Ferrario, C. J. Dickinson, and J. W. McCubbin, *Clin. Sci.*, **39**, 239(1970).

(13) C. M. Ferrario, P. L. Gildenberg, and J. W. McCubbin, *Circ. Res.*, **30**, 257(1972).

(14) J. P. Buckley, *Fed. Proc.*, **31**, 1332(1972).

(15) S. Finkielman, C. Fischer-Ferraro, A. Diaz, D. J. Goldstein, and V. E. Nahmod, *Proc. Nat. Acad. Sci. USA*, **69**, 3341(1972).

(16) W. B. Severs, J. Summy-Long, A. Daniels-Severs, and J. D. Connor, *Pharmacology*, **5**, 205(1971).

(17) D. T. Pals, F. D. Masucci, G. S. Denning, Jr., F. Sipos, and D. C. Fessler, *Circ. Res.*, **29**, 673(1971).

(18) H. R. Brunner, J. D. Kirshman, J. E. Sealey, and J. H. Largh, *Science*, **174**, 1344(1971).

(19) R. S. Snyder and W. T. Niemer, "A Stereotaxic Atlas of the Cat Brain," University of Chicago Press, Chicago, Ill., 1964.

(20) J. K. Merlis, *Amer. J. Physiol.*, **131**, 67(1940).

(21) B. K. Bhattacharya and M. Feldberg, *Brit. J. Pharmacol.*, **13**, 156(1958).

(22) D. Ganten, J. L. Minnich, P. Granger, K. Hayduk, H. M. Brecht, A. Barbeau, R. Boucher, and J. Genest, *Science*, **173**, 353(1971).

(23) T. C. Goodfriend and S. Lin, *Circ. Res.*, **26** and **27** (Suppl. I), 1(1970).

(24) S. Y. Lin and T. L. Goodfriend, *Amer. J. Physiol.*, **218**, 1319(1970).

(25) M. J. Peach, *Circ. Res.*, **28** and **29**(Suppl. II), 11(1971).

(26) M. J. Peach, F. M. Bumpus, and P. A. Khairallah, *J. Pharmacol. Exp. Ther.*, **176**, 366(1970).

(27) T. A. Solomon and J. P. Buckley, "Abstracts of the Proceedings of the APhA Academy of Pharmaceutical Sciences," vol. 1, 1971, p. 119.

(28) C. G. Huggins and N. S. Thampi, *Life Sci.*, **7**, 633(1968).

[12] T. A. Solomon and J. P. Buckley, unpublished data.

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