

# Differentiation of Neurogenic and Myocardial Angiotensin II Receptors in Isolated Rabbit Atria

By Alan L. Blumberg, John A. Ackerly, and Michael J. Peach

## ABSTRACT

The effect of angiotensin on the action of tyramine was studied in isolated rabbit left atria paced by point and field stimulation to more clearly define the interaction of angiotensin with the sympathetic nervous system. Administration of angiotensin resulted in similar increases in contractility in both point- and field-stimulated atria. In point-stimulated preparations only the muscle is stimulated to contract, whereas in field-stimulated preparations both nerve and muscle are stimulated. 1-Sar-8-Ala-angiotensin II completely blocked the direct inotropic effect of angiotensin in a molar dose ratio of 3:1 in both point- and field-stimulated preparations. However, angiotensin (0.05–10 ng/ml) potentiated the inotropic effect of tyramine in field-stimulated atria only. This facilitatory effect was not inhibited by 1-Sar-8-Ala-angiotensin II at a molar dose ratio of 3:1; indeed, a ratio of 500:1 was necessary for complete blockade of this angiotensin-induced potentiation. This antagonist in doses of 0.1–1000 ng/ml was without contractile effect in any preparation, regardless of whether tyramine was present. The data suggest the presence of (1) a presynaptic angiotensin receptor that, in the presence of sympathetic nerve stimulation, modulates the release of norepinephrine and (2) a second angiotensin receptor in cardiac tissue that directly influences myocardial contractility.

## KEY WORDS

field-stimulated atria  
myocardial contractility

## 1-Sar-8-Ala-angiotensin II

point-stimulated atria

indirectly acting sympathomimetics

## tyramine

heart

■ Angiotensin augments adrenergic nerve function in various vascular beds and isolated tissues (1–7) and has well-documented direct actions on various isolated smooth muscle preparations (8–11), blood pressure (12), the adrenal medulla (13, 14), and the heart (15–20). Recent studies using 8-Ala-angiotensin II and other related analogues of angiotensin II have indicated that these peptides are competitive inhibitors of angiotensin-induced myotropic (21–27) and pressor responses (22–24, 26, 27). The molar dose ratio of antagonist to agonist producing complete blockade of myotropic responses has been reported to be between 1:1 and 8:1 (24, 25, 27). One study indicates that 1-Sar-8-Ala-angiotensin II can

produce a comparable blockade of both the neurally mediated and the direct vasoconstrictor actions of angiotensin II in the perfused canine hind limb at a molar dose ratio of 4:1 (28).

Reports in the literature indicate that the angiotensin receptor mediating the augmentation of adrenergic nerve function may differ from the myotropic and vascular receptors. These studies have shown that angiotensin is capable of potentiating adrenergic nerve function in vascular tissue even when complete tachyphylaxis has developed to the vasoconstrictor action of the peptide (7, 29). Additional support for distinct angiotensin II receptors is the recent report that the adrenal medullary receptor for angiotensin is different from the vascular and uterine smooth muscle receptors (30).

In view of the postulated differences between receptors for angiotensin in smooth muscle and adrenal chromaffin tissue, we thought that it would be interesting to elucidate the types of angiotensin receptors in the heart. It is well documented that angiotensin has a direct effect on cardiovascular parameters (15–20) as well as a potentiating effect on cardiovascular responses to stimulation of the sympathetic nervous system (31–35). The present investigation in isolated rabbit atria was undertaken to study the antagonism by 1-Sar-8-Ala-

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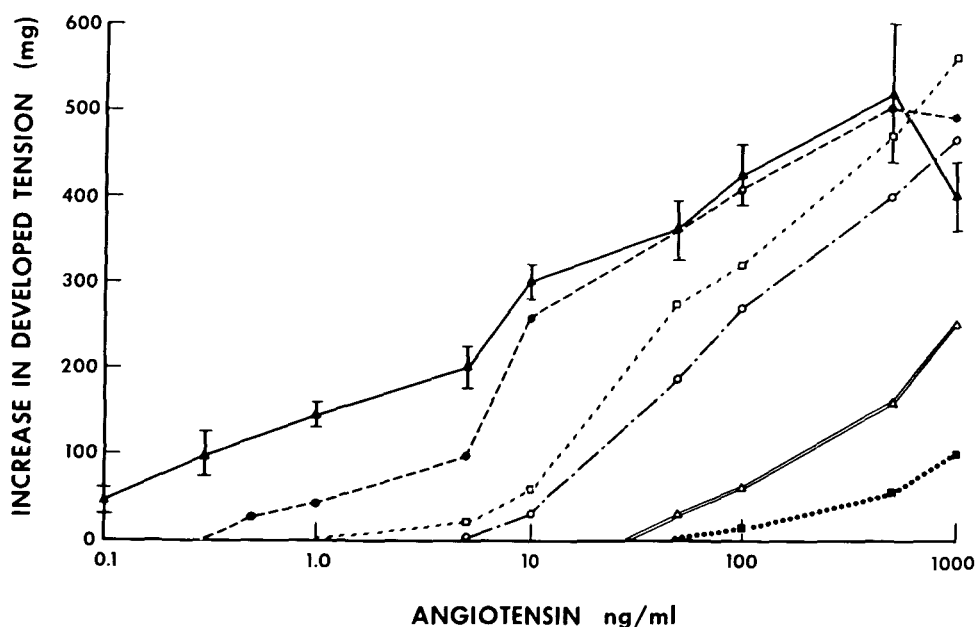


FIGURE 1

Effects of AII and AII + 1-Sar-8-Ala-AII on the contractility of isolated field-stimulated rabbit left atria. Each point represents the mean  $\pm$  SE obtained from 8-10 atria. Solid triangles = AII alone, solid circles = AII + 1 ng/ml of 1-Sar-8-Ala-AII, open squares = AII + 5 ng/ml of 1-Sar-8-Ala-AII, open circles = AII + 10 ng/ml of 1-Sar-8-Ala-AII, open triangles = AII + 50 ng/ml of 1-Sar-8-Ala-AII, and solid squares = AII + 100 ng/ml of 1-Sar-8-Ala-AII.

angiotensin II of the (1) direct inotropic action of angiotensin and (2) the potentiating action of angiotensin on sympathetic nerve function. The effect of tyramine, an indirectly acting sympathomimetic agent that causes the release of endogenous norepinephrine from adrenergic nerve terminals, was examined to more easily observe the potentiating effect of angiotensin on adrenergic nerve stimulation.

### Methods

Male New Zealand white rabbits (2-3 kg) were killed by a sharp blow to the head. The hearts were removed within 15 seconds and placed in a beaker containing oxygenated (95% O<sub>2</sub>-5% CO<sub>2</sub>) modified Kreb's solution of the following millimolar composition: NaCl 119, CaCl<sub>2</sub> 2.54, KCl 4.74, MgSO<sub>4</sub> 1.18, NaH<sub>2</sub>PO<sub>4</sub> 1.18, NaHCO<sub>3</sub> 24.9, and glucose 5.5. Isolated left atria were prepared according to the method of Levy (36). Left atria were dissected free from the ventricles, placed in the buffer at 30  $\pm$  1°C in 10-ml baths, and connected by silk threads to Grass force-displacement transducers (model FTO3C). Isometric contractions were recorded with a Grass polygraph. The atria were surrounded on both sides by coiled platinum electrodes for field stimulation or were placed in contact with two silver electrodes for point stimulation. Supramaximal (twice threshold, usually 3-6 v for field stimulation and less than 1 v for point stimulation) square-wave pulses 5 msec in duration were delivered at a rate of 96/min with a Grass model S-4 stimulator to elicit uniform atrial contractions. Length-

tension curves were established for each atrium and a resting tension of 50% maximum ( $\sim$ 2 g) was applied. The atria were equilibrated in the physiological buffer, which was changed every 10 minutes, for a total of 60 minutes. They were stimulated at threshold voltage for the initial 40 minutes of the equilibration period and at twice threshold for the remainder of the equilibration period and the duration of the experiment.

The effects of angiotensin II (AII)<sup>1</sup> (0.05-1000 ng/ml), tyramine (as the free base, 0.003-3  $\mu$ g/ml, and 1-Sar-8-Ala-angiotensin II (1-Sar-8-Ala-AII)<sup>2</sup> (1-1000 ng/ml) on atrial contractility were studied. Studies were performed to determine the effects of angiotensin (0.01-10 ng/ml) and 1-Sar-8-Ala-AII (1-1000 ng/ml) on inotropic responses of the atria to tyramine. In addition, the antagonism by 1-Sar-8-Ala-AII of angiotensin-induced inotropism and potentiation of tyramine was investigated.

Each atrium served as its own control. In experiments in which responses to tyramine were determined in the presence of angiotensin or 1-Sar-8-Ala-AII, each preparation was exposed to one of the peptides for 5 minutes prior to the administration of tyramine. When the concomitant effects of these peptides were studied, 1-Sar-8-Ala-AII was added 5 minutes prior to the administration of angiotensin. In studies in which an inotropic concentration of angiotensin (greater than 0.1 ng/ml) was investigated for potentiating effects on atrial responses to tyramine, the increase in tension resulting

<sup>1</sup>Generously supplied by Dr. A. J. Plummer, Ciba Pharmaceutical.

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TABLE 1

Effect of Angiotensin on Contractility of Point- and Field-Stimulated Isolated Rabbit Left Atria

Dose of angiotensin (ng/ml)	Increase in developed tension (mg)	
	Point stimulation	Field stimulation
0.1	31.6 ± 7	47.2 ± 18
1.0	146.0 ± 27	145.6 ± 16
10.0	237.0 ± 40	294.0 ± 24
50.0	381.4 ± 64	362.0 ± 33
100.0	415.6 ± 48	426.0 ± 43
500.0	486.0 ± 80	540.0 ± 88

All values are means ± SE obtained from 10-12 atria. No significant difference was noted between point- and field-stimulated atria as determined by Student's *t*-test.

from the administration of angiotensin was subtracted from the response to tyramine.

Cumulative dose-response curves were plotted from data obtained by administering successive doses of an agonist at the peak of the response to each preceding dose. The peak response to each dose of tyramine was attained in not less than 3 minutes and that to angiotensin in not less than 5 minutes.

Untreated control atria showed no deterioration in contractility for up to 5 hours. Atrial preparations showed less than a 5% change in their maximum responses during the course of three full cumulative tyramine dose-response schedules. In contrast, atria exposed to angiotensin usually developed tachyphylaxis after data had been obtained to plot two full curves.

Between exposures to an agonist, the preparations were washed repeatedly and allowed to stabilize (usually 30 minutes).

Analysis for significance of data was done using Student's *t*-test.

TABLE 3

Effect of Subthreshold Inotropic Concentrations of Angiotensin (0.01 and 0.05 ng/ml) on Tyramine-Induced Inotropism in Field-Stimulated Rabbit Left Atria

Dose of tyramine (μg/ml)	Increase in developed tension (mg)		
	Control	Angiotensin	
		0.01 ng/ml	0.05 ng/ml
0.003	0	0	26.3 ± 11*
0.01	0	0	71.8 ± 21*
0.03	13.1 ± 4	11.5 ± 6	109.5 ± 31*
0.1	92.1 ± 13	83.8 ± 12	159.5 ± 39*
0.3	334.2 ± 20	323.4 ± 35	445.6 ± 66*
1.0	856.0 ± 41	802.9 ± 56	1095.4 ± 87*
3.0	1192.8 ± 51	1201.0 ± 92.4	1445.3 ± 96*

All values are means ± SE obtained from 6-14 atria.

\* *P* < 0.05 compared to the control value (determined by Student's *t*-test).

Results

Angiotensin in concentrations of 0.1 ng/ml-500 ng/ml produced a dose-dependent increase in contractile force in both field- and point-stimulated rabbit left atria (Fig. 1, Table 1). The onset of the response was about 2 minutes after drug administration with a peak response at 5 minutes and a duration of not less than 20 minutes in both field- and point-stimulated preparations. As shown in Figure 1, 0.1 ng/ml was the lowest concentration of angiotensin with occasional inotropic activity. Angiotensin at concentrations of 0.05 ng/ml or less did not exhibit inotropic activity. The maximum re-

TABLE 2

Effect of Angiotensin (0.1 ng/ml) on Tyramine-Induced Inotropism in Point- and Field-Stimulated Rabbit Left Atria

Dose of tyramine (μg/ml)	Increase in developed tension (mg)			
	Point stimulation		Field stimulation	
	Control	Angiotensin	Control	Angiotensin
0.003			0	91.9 ± 15*
0.01			0	209.3 ± 45*
0.03	0	0	13.1 ± 4	242.9 ± 29*
0.1	131.3 ± 27	156.1 ± 33	92.1 ± 13	427.5 ± 106*
0.3	364.3 ± 53	386.2 ± 71	334.2 ± 20	634.4 ± 97*
1.0	685.0 ± 78	762.0 ± 122	856.0 ± 41	1209.4 ± 100*
3.0	989.5 ± 103	1005.0 ± 142	1192.8 ± 51	1706.6 ± 189*

All values are means ± SE obtained from 9-14 atria.

\* *P* < 0.01 compared to the control value for the same mode of stimulation (determined by Student's *t*-test).

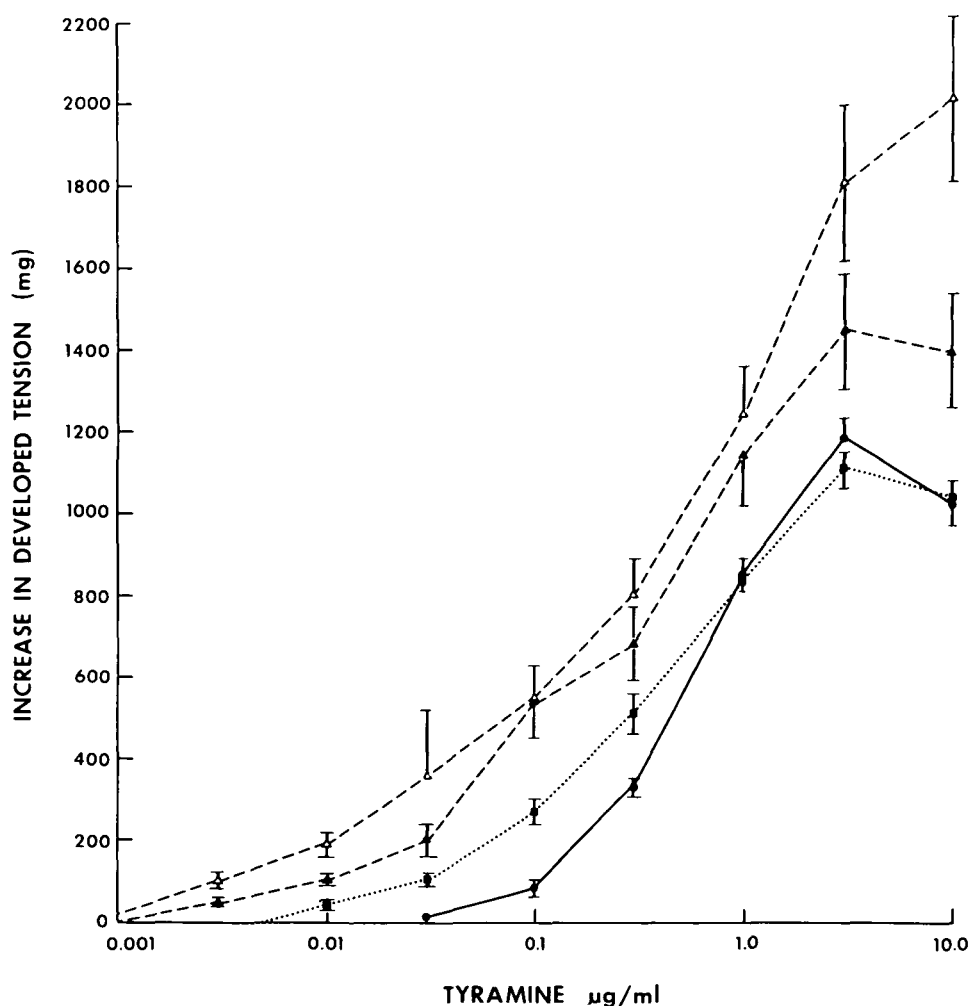


FIGURE 2

Effect of AII (0.1, 0.3, and 1.0 ng/ml) on tyramine-induced inotropism in field-stimulated rabbit left atria. Each point represents the mean  $\pm$  SE obtained from 12-14 atria. Solid circles = tyramine alone, open triangles = tyramine + 0.1 ng/ml of AII, solid triangles = tyramine + 0.3 ng/ml of AII, and solid squares = tyramine + 1.0 ng/ml of AII.

sponse to angiotensin occurred at a concentration of 500 ng/ml and resulted in increases in developed tension of  $540 \pm 88$  and  $486 \pm 80$  mg in field- and point-stimulated preparations, respectively. There was no significant difference between field- and point-stimulated atria in response to this peptide agonist.

The angiotensin antagonist, 1-Sar-8-Ala-AII, blocked the inotropic responses in field-stimulated atria to angiotensin in a dose-dependent manner and shifted the dose-response curve in a parallel manner to the right (Fig. 1). The antagonist itself exerted no inotropic effect in doses up to 1  $\mu$ g/ml. The inhibitory effect of 1-Sar-8-Ala-AII was overcome with higher concentrations of angiotensin, and maximum responses were obtained. The molar dose ratio of antagonist to agonist for complete blockade of the inotropic response to angiotensin

was about 3:1. 1-Sar-8-Ala-AII also antagonized the inotropic effect of angiotensin in point-stimulated atria at the same molar dose ratio as that required in field-stimulated preparations (data not shown).

Cumulative concentrations of tyramine evoked inotropic responses in both field- and point-stimulated atria (Table 2). The threshold inotropic concentration of tyramine was about 0.03  $\mu$ g/ml, and 3  $\mu$ g/ml produced a maximum response. The onset of tyramine-induced responses was rapid (in about 20 seconds), and the time to peak response was not less than 3 minutes.

The effect of angiotensin on tyramine-induced inotropism was studied. Potentiation of contractile responses to tyramine was observed with sub-threshold (0.05 ng/ml) (Table 3), threshold (0.1 ng/ml), and inotropic (0.3, 1.0, and 10 ng/ml)

concentrations of angiotensin in field-stimulated atria only (Table 2, Fig. 2). Angiotensin (0.05–10 ng/ml) did not alter dose-dependent atrial responses to tyramine in point-stimulated preparations.

Angiotensin in a dose of 0.1 ng/ml produced the largest potentiation of tyramine, shifted the threshold to tyramine one log unit to the left, and potentiated the contractile effects of all concentrations of tyramine assayed (Fig. 2). Angiotensin in concentrations of 0.05, 0.1, and 0.3 ng/ml caused increases in the response of the atria to tyramine at all concentrations except the higher doses of tyramine for which 0.05-ng/ml and 0.3-ng/ml concentrations of angiotensin caused a less marked but still significant potentiation. The facilitatory effect observed with 1 ng/ml and 10 ng/ml (not shown) of angiotensin was significant only at concentrations of tyramine up to and including 0.3  $\mu$ g/ml. In concentrations of 1 and 10 ng/ml, angiotensin did not potentiate the maximum response to tyramine, and the shift in the tyramine dose-response curve was significantly less than that seen with lower concentrations of angiotensin.

The ability of 1-Sar-8-Ala-AII to block angiotensin-induced potentiation of responses to tyramine was examined. This angiotensin antagonist in concentrations up to 1  $\mu$ g/ml had no statistically significant ( $P > 0.1$ ) effect on the response of the atria to tyramine. Data obtained with 100 ng/ml of 1-Sar-8-Ala-AII and tyramine are depicted in Fig-

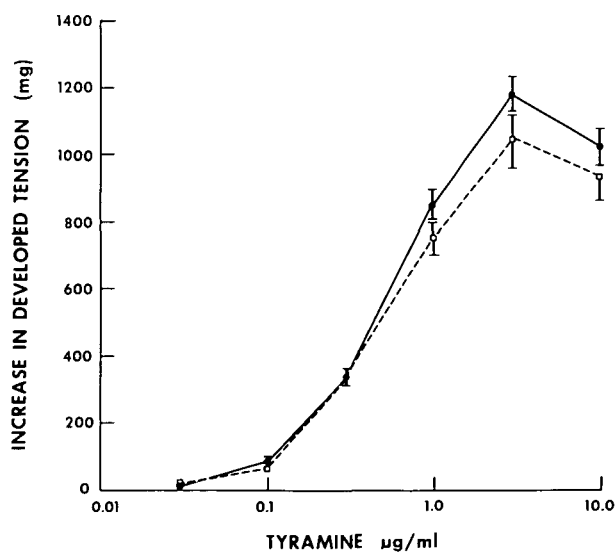


FIGURE 3  
Effect of 1-Sar-8-Ala-AII on the inotropic response to tyramine in isolated field-stimulated rabbit left atria. Each point represents the mean  $\pm$  SE obtained from 6 atria. Solid circles = tyramine alone and open squares = tyramine + 100 ng/ml of 1-Sar-8-Ala-AII.

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ure 3. A 10:1 molar dose ratio of 1-Sar-8-Ala-AII to angiotensin was used initially to ensure complete inhibition of any direct inotropic response that might result from the administration of angiotensin. 1-Sar-8-Ala-AII at 1 ng/ml (ratio 10:1) had no effect on angiotensin-induced potentiation of tyramine (Fig. 4). At a concentration of 10 ng/ml (ratio 100:1), 1-Sar-8-Ala-AII significantly decreased the angiotensin-induced facilitation of low doses of tyramine. Only at 50 ng/ml (ratio 500:1) of 1-Sar-8-Ala-AII was the angiotensin-induced potentiation completely inhibited. These molar dose ratios were then examined by varying the AII concentration (0.05 and 0.3 ng/ml); the data were identical to those presented (e.g., 25 ng/ml of 1-Sar-8-Ala-AII was required to completely inhibit the potentiation induced with 0.05 ng/ml of AII).

### Discussion

Our data, in agreement with those of other investigators (17, 18), indicated that angiotensin produced its positive inotropism by a direct effect on the strength of contraction of heart muscle. Similar increases in contractility were observed in both field- and point-stimulated left atria. In the field-stimulated atrium both the sympathetic nerves and the muscle fibers are excited, whereas in the point-stimulated atrium only the muscle fibers are stimulated (36).

1-Sar-8-Ala-AII at a molar dose ratio of antagonist to agonist of 3:1 competitively blocked the direct inotropic effect of angiotensin in both field- and point-stimulated preparations. This analogue of angiotensin as well as other 8-substituted analogues have been reported to completely block the myotropic and pressor effects of angiotensin at molar dose ratios of from 1:1 to 8:1 (24, 25, 27).

Our data showed that angiotensin potentiated tyramine-induced increases in contractility only in field-stimulated atria. The fact that sympathetic nerve stimulation was absolutely required to see the potentiating effect suggests that a neurogenic component was involved in the potentiation by angiotensin. This finding is in agreement with those of other investigators, who have reported that angiotensin potentiates the effects of sympathetic nerve stimulation in various smooth muscle preparations, isolated vascular beds, and the heart (1–7, 37, 38–40). In addition, angiotensin has been shown to increase the release of endogenous norepinephrine during nerve stimulation in certain vascular beds (3, 37) and the heart (41). We have also observed that tetrodotoxin, a selective blocker of nerve stimulation (42), blocks the potentiation of

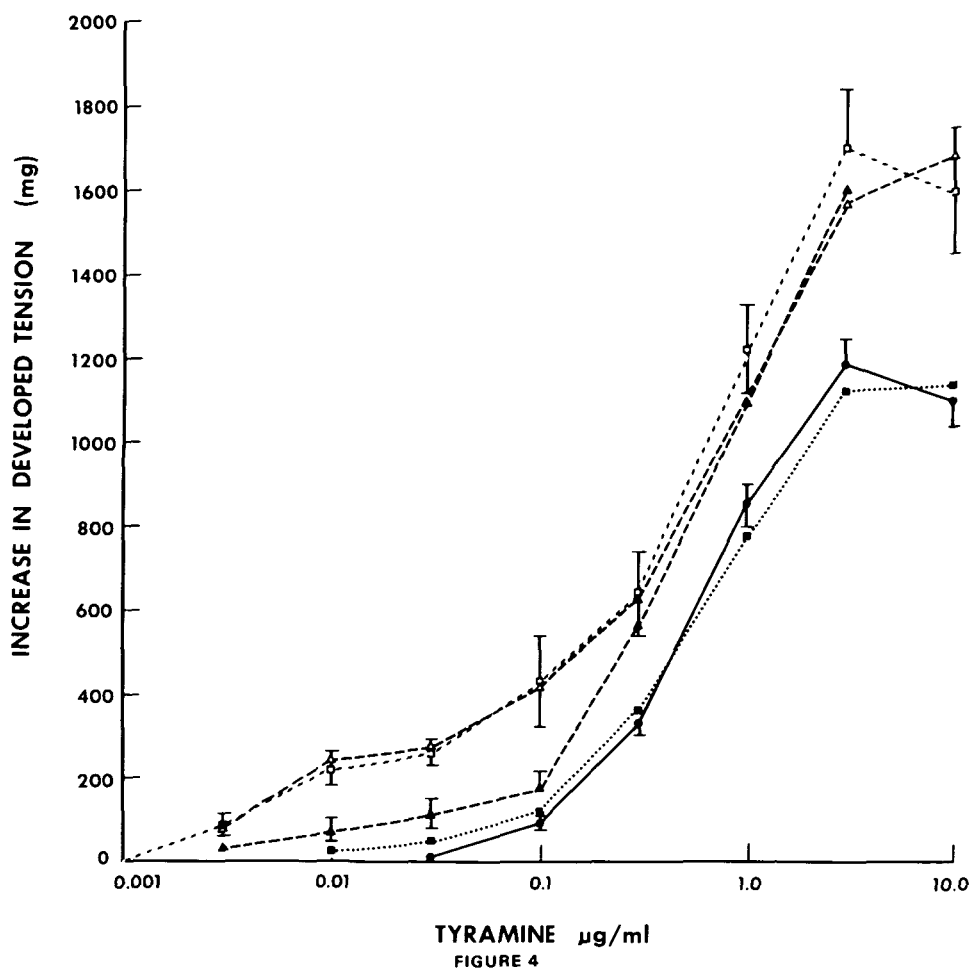


FIGURE 4  
Effect of 1-Sar-8-Ala-AII on AII (0.1 ng/ml)-induced potentiation of tyramine in isolated field-stimulated rabbit left atria. Each point represents the mean  $\pm$  SE obtained from 12-14 atria. Solid circles = tyramine alone, open triangles = tyramine + AII + 1 ng/ml of 1-Sar-8-Ala-AII, solid triangles = tyramine + AII + 10.0 ng/ml of 1-Sar-8-Ala-AII, solid squares = tyramine + AII + 50.0 ng/ml of 1-Sar-8-Ala-AII, and open squares = tyramine + AII.

tyramine-induced contractile responses by angiotensin in field-stimulated atria (unpublished observation). It seems probable that the angiotensin-induced potentiation observed during sympathetic nerve stimulation in various preparations is mediated by a facilitated release of norepinephrine by angiotensin.

The adrenergic action of angiotensin and the direct vasoconstrictor action of this peptide are blocked by 1-Sar-8-Ala-AII at a molar dose ratio of 4:1 (antagonist:agonist) in the perfused hind limb and paw of the dog (28). In the present study using the same antagonist, a molar dose ratio of 500:1 was required to inhibit the angiotensin-induced potentiation of tyramine in field-stimulated atria. This ratio of 500:1 was required to inhibit angiotensin-induced potentiation of tyramine at all potentiating concentrations of the peptide in marked

contrast to the molar dose ratio of 3:1, which completely inhibited the direct inotropic action of angiotensin. These findings together with a recent report from our laboratory (30) comparing  $pA_2$  values for various angiotensin antagonists in adrenal chromaffin tissue and smooth muscle suggest that the proposed sympathetic neuronal receptor for angiotensin may differ from the vascular and smooth muscle receptors. The aberrant dose-response curve of the potentiating action of angiotensin (increases in the concentration of angiotensin, instead of increasing the potentiation, induced smaller potentiations) may be due to the increasing direct inotropic effect of the peptide from 0.1-10 ng/ml. This direct inotropic action of angiotensin may be limiting the total inotropic capacity of the atria.

In a previous study reported by Illanes et al. (32)

the mechanism for potentiation of tyramine by angiotensin was postulated to involve the displacement of angiotensin by tyramine from inactive binding sites in point-stimulated rabbit atria. Our data are not in accord with this hypothesis. 1-Sar-8-Ala-AII that completely inhibited the direct myocardial response to angiotensin *did not* antagonize the angiotensin-induced potentiation of tyramine in field-stimulated atria. If tyramine does in fact release "bound angiotensin," the 1-Sar-8-Ala-AII present would certainly completely antagonize any angiotensin-induced direct inotropism.

In conclusion, our data suggest that angiotensin acts on a presynaptic receptor that is relatively resistant to blockade by 1-Sar-8-Ala-AII and in this regard is different from the myocardial inotropic receptor for AII.

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