Br. J. Pharmac. (1982), **75**, 9–11

ANGIOTENSIN INHIBITS ACTION OF VAGUS NERVE AT THE HEART

ERICA K. POTTER

School of Physiology and Pharmacology, University of New South Wales, Kensington, Sydney, 2033, Australia

The effects of angiotensin II and angiotensin III (Des-Asp angiotensin II) on cardiac vagal nerve endings were studied in intact dogs and in isolated guinea-pig atria. Decreases in heart rate evoked by electrical stimulation of the peripheral end of the cut vagus were attenuated in the presence of angiotensin II and angiotensin III.

Introduction Many studies have shown that angiotensin, a potent pressor hormone, stimulates the sympathetic nervous system at many sites both peripherally and centrally (e.g. Bickerton & Buckley, 1961; Lewis & Reit, 1965; Farr & Grupp, 1967; Aiken & Reit, 1968; Hughes & Roth, 1971; Blumberg, Ackerly & Peach, 1975). However, although angiotensin has been shown to inhibit central vagal pathways (Scroop & Lowe, 1969; Lumbers, McCloskey & Potter, 1979) no peripheral action on the parasympathetic nervous system has previously been described. The two series of experiments described here demonstrate a peripheral inhibitory action of angiotensin on the cardiac vagus.

Methods Six adult mongrel dogs were anaesthetized with thiopentone and chloralose. Both vagus nerves were cut in the neck. The peripheral end of the right vagus was immersed in a pool of mineral oil and stimulated supramaximally by means of a Grass SD9, isolated, square wave stimulator. Usually four shocks, 300 ms apart, (~30 V, 1 ms duration) were delivered once every 10 s. Blood pressure and heart rate (measured beat-by-beat, with a tachograph triggered from the electrocardiogram) were recorded.

A second series of experiments was carried out on isolated, spontaneously beating atria of the guinea-pig. In these preparations the right cervical vagus was left connected to the spontaneously beating atria. Eight guinea-pigs were killed by cervical dislocation. In each the right vagus was identified in the neck and dissected free to the heart. The heart with the vagus intact was then removed and placed in cooled oxygenated (100% O_2) Krebs solution. The ventricles were dissected away and the atria then placed in an organ bath at 30 ± 1°C. Isometric tension was recorded by a force transducer and displayed on a pen recorder. Atrial rate was recorded beat-by-beat on the tachograph, triggered here from the tension recording. The vagus was stimulated after drawing it by suction into a thin pipette containing a pair of silver electrodes connected to the stimulator. Usually four supramaximal shocks, 300 ms apart, (~3V, 1 ms) were delivered every 10 s and the resultant effects on atrial rate and tension were recorded.

Results *In vivo* stimulation of the peripheral end of the vagus caused prompt and marked bradycardia. A bolus dose of angiotensin (5–10 μg i.v.) all but abolished the bradycardia evoked by vagal stimulation. This occurred at the peak of the pressor effect as can be seen in the top panel of Figure 1a. This effect of angiotensin was not altered by sympathetic blockade by propranolol (1 mg/kg). Angiotensin III (i.e. Des-Asp angiotensin II: Peninsula Laboratories, U.S.A.) was also tested and with doses 2–3 times those of angiotensin II similar results were obtained.

In vitro, electrical stimulation of the vagus in the isolated atria also evoked prompt and marked bradycardia. Again, the bradycardia was reduced by the addition of angiotensin (2–5 μg/25 ml) to the organ bath, and this inhibition was not altered by addition of propranolol (2 μg/ml) to the organ bath (see Figure 1b). This inhibition by angiotensin added to the organ bath was usually maximal about 2 min after addition of the agent to the organ bath. Presumably this delay represented the time for angiotensin to diffuse to its site of action. Typically the control response to vagal stimulation was restored within 1–2 min of washing out the angiotensin. Angiotensin III was also tested with similar results.

Acetylcholine (final concentration: 20 ng/ml) slowed the rate of beating of the atria when added to the organ bath alone (unfilled arrow at left of Figure 1b), or when added together with angiotensin, or when added after the time of maximal vagal inhibition by angiotensin (unfilled arrow at right of Figure 1b).

Discussion Both series of experiments indicate that angiotensin inhibits the action of the vagus on the heart. In addition, the failure of angiotensin to alter the effects of acetylcholine on the isolated atria sug-

0007-1188/82/010009-03 $01.00

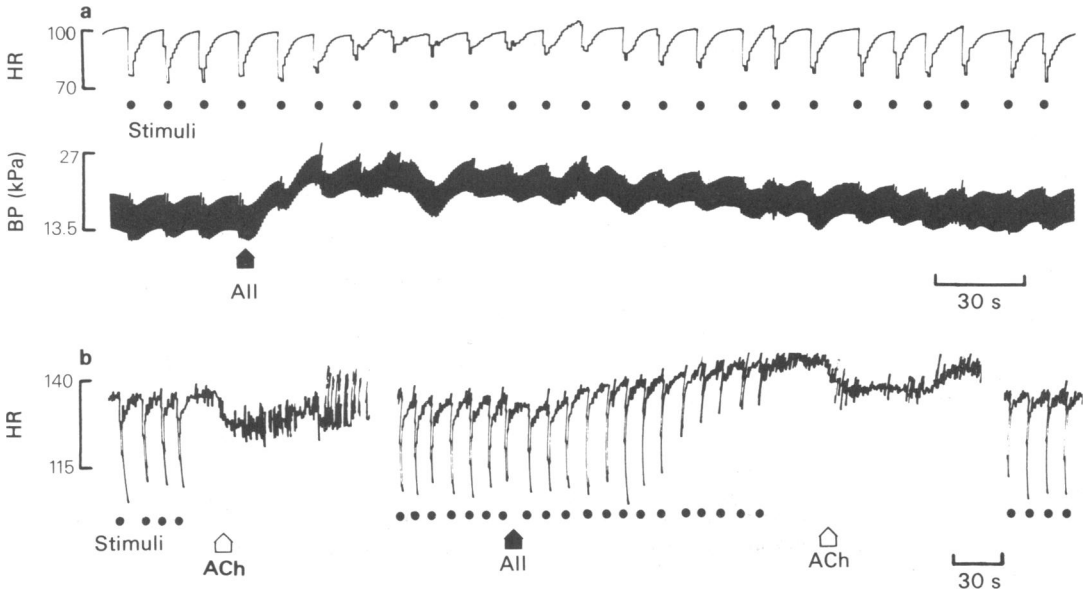

Figure 1 (a) Records of heart rate (HR) and blood pressure (BP) from an anaesthetized dog, after bilateral vagotomy and sympathetic blockade with propranolol (1 mg/kg). Markers indicate the times at which supramaximal stimuli were applied to the peripheral end of the right vagus (four shocks 300 ms apart at 30V, 1 ms). In the control conditions the stimuli elicited prompt and marked bradycardia. When angiotensin (5 μg i.v.) was given (at solid arrow), this response of heart rate was inhibited as blood pressure rose, and returned to control levels as the blood pressure response declined. (b) Record of heart rate (HR) from isolated, spontaneously beating atria of guinea-pig with the right vagus attached. Markers below the heart rate trace indicate the times at which supramaximal stimuli were delivered to the vagus (four shocks, 300 ms apart at 3V, 1 ms). In control conditions the stimuli elicited prompt and marked bradycardia. When angiotensin (5 μg) was given (at solid arrow) inhibition of this response became marked after 2 min. The full control response returned within 2–3 min of washing out the angiotensin (far right of record). Acetylcholine (ACh), whether given before the addition of angiotensin to the bath (at first unfilled arrow), or after the time angiotensin had its maximal inhibitory effect on the vagus (at second unfilled arrow) was equally effective in slowing the rate of beating of the atria (acetylcholine concentration in bath 20 ng/ml).

gests that this section is not postsynaptic to the vagal nerve endings. Whether this action of angiotensin is on the nerve endings that release acetylcholine onto the pacemaker tissue or at the intra-cardiac parasympathetic ganglion cannot be concluded from these experiments. However, it is well established that angiotensin stimulates sympathetic ganglia elsewhere (e.g. Lewis & Reit, 1965; Farr & Grupp, 1967; Aiken & Reit, 1968). This makes the intra-cardiac ganglion less likely as the site for the action described here.

The peripheral inhibitory effect of angiotensin on vagal control of heart rate is in keeping with its other pressor effects. Whether angiotensin is considered to have a role in the maintenance of blood pressure in normal man (MacGregor, Markandu, Roulston, Jones & Morton, 1981), or in the control of blood pressure only in certain circumstances (e.g. sodium depletion, pregnancy: Robertson, Wier, Düsterdieck, Fraser & Tree, 1971; Davis, Freeman, Johnson & Spielman, 1974), participation of the vagal inhibitory effect described here will require consideration.

This work was supported by a grant from the National Heart Foundation of Australia. I thank E.R. Lumbers, D.I. McCloskey and W.E. Glover for helpful comments. Miss Diane Madden provided expert technical assistance.

References

AIKEN, J.W. & REIT, E. (1968). Stimulation of the cat stellate ganglion by angiotensin. *J. Pharmac. exp. Ther.*, **159,** 107–114.

BICKERTON, R.K. & BUCKLEY, J.P. (1961). Evidence for a central mechanism in angiotensin induced hypertension. *Proc. Soc. exp. Biol. Med.*, **106,** 834–836.

BLUMBERG, A.L., ACKERLY, J.A. & PEACH, M.J. (1975). Differentiation of neurogenic and myocardial angiotensin II receptors in isolated rabbit atria. *Circulation Res.*, **36,** 719–726.

DAVIS, J.O., FREEMAN, R.H., JOHNSON, J.A. & SPIELMAN, W.S. (1974). Agents which block the action of the renin-angiotensin system. *Circulation Res.*, **34,** 279–285.

FARR, W.C. & GRUPP, G. (1967). Sympathetically mediated effects of angiotensin on the dog heart in situ. *J. Pharmac. exp. Ther.*, **156,** 528–537.

HUGHES, J. & ROTH, R.H. (1971). Evidence that angiotensin enhances transmitter release during sympathetic nerve stimulation. *Br. J. pharmac.*, **41,** 239–255.

LEWIS, G.P. & REIT, E. (1965). The action of angiotensin and bradykinin on the superior cervical ganglion of the cat. *J. Physiol.*, **179,** 538–553.

LUMBERS, E.R., McCLOSKEY, D.I. & POTTER, E.K. (1979). Inhibition by angiotensin II of baroreceptor-evoked activity in cardiac vagal efferent nerves in the dog. *J. Physiol.*, **294,** 69–80.

MACGREGOR, G.A., MARKANDU, N.D., ROULSTON, J.E., JONES, J.C. & MORTON, J.J. (1981). Maintenance of blood pressure by the renin-angiotensin system in normal man. *Nature*, **291,** 329–331.

ROBERTSON, J.I.S., WEIR, R.J., DÜSTERDIECK, G.O., FRASER, R. & TREE, M. (1971). Renin, angiotensin and aldosterone in human pregnancy and the menstrual cycle. *Scot. med. J.*, **16,** 183–196.

SCROOP, G.C. & LOWE, R.D. (1969). Afferent pathways of the cardiovascular response to vertebral artery infusions of angiotensin in the dog. *Clin. Sci.*, **37,** 605–619.

(*Received September 16, 1981.*)