Role of noradrenaline in the acute pressor response to angiotensin in conscious cats

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The changes in the pressor responses to angiotensin after treatment with substances known to modify sympathetic function have been compared with the changes in the responses to noradrenaline, tyramine and McN-A-343 using conscious cats. The responses to angiotensin were not reduced by blockade of adrenergic neurones, α and β-adrenoceptors, or of autonomic ganglia. In conscious cats the acute pressor response to angiotensin does not appear to be related directly to stimulation or facilitation of transmission in sympathetic ganglia or to release of catecholamines from tissue stores.

In a recent publication Day & Owen (1970) reported that the acute pressor potency of angiotensin in conscious cats was determined, in part, by the content of the neuronal noradrenaline stores. Thus, depletion of the stores with reserpine led to a reduction in the responses to angiotensin, while loading of the stores by administration of monoamine oxidase inhibitors enhanced the responses.

The purpose of the present investigation was to examine the contribution of endogenous catecholamine stores to the acute pressor response of angiotensin in conscious cats. This was done by examining the effect of drugs known to modify sympathetic function on angiotensin pressor responses. The changes in the responses to angiotensin were compared with the changes in the responses to noradrenaline, the indirect sympathomimetic amine tyramine and the sympathetic ganglion stimulant McN-A-343 (Roszkowski, 1961; Levy & Ahlquist, 1962). The latter three drugs therefore served as controls and monitored the functional state of the sympathetic nervous system.

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Methods.—The cats were prepared for measurement of aortic blood pressure and intravenous injection of substances by the method described by Day & Owen (1970) and were, in fact, the same five cats used in that study.

Adrenergic neurone blockade.—Bethanidine (3 mg/kg intravenously) lowered resting blood pressure by 15–20 mmHg (1 mmHg = 1·333 mbar), reduced the heart rate by about 50 beats/min and relaxed the nictitating membranes. The effect of bethanidine on the pressor responses to angiotensin, tyramine, noradrenaline and McN-A-343 is shown in Table 1. The responses to McN-A-343 were reduced by 80%, those to tyramine by 45%, while the effect of noradrenaline was increased by 85%. Responses to angiotensin were not significantly changed.

Adrenoceptor blockade.—Phentolamine (3·5 mg/kg intravenously) caused an immediate transient tachycardia, slightly lowered resting blood pressure and relaxed the nictitating membranes. The responses to noradrenaline and tyramine were abolished by phentolamine and the McN-

TABLE 1. *Effect of various blocking agents on the responses to angiotensin* (50 *ng/kg*), *noradrenaline* (200 *ng/kg*), *tyramine* (50 μg/kg) *and McN-A*-343 (15 μg/kg)

	Pressor responses as % of control			
Blocking drug intravenously	Angiotensin	Noradrenaline	Tyramine	McN-A-343
Bethanidine (3 mg/kg)	103±1·7	185±0	55±2·5	20±1·4
Phentolamine (3·5 mg/kg)	110±2·5	0±0	0±0	27±1·7
Propranolol (1 mg/kg)	105±2·0	94±2·4	60±0	87±1·2
Phentolamine (3·5 mg/kg) +propranolol (1 mg/kg)	109±3·5	0±0	0±0	33±4·3
Pempidine (5 mg/kg)	162±5·4	176±1·5	250±15·7	262±6·7

Each pressor agent was initially administered three times and the mean response taken as 100%. The responses were then measured again between 1 and 2 h after the blocking agent when the responses were again constant and these are expressed as % control. The figures given are the mean responses (±S.E.) for three separate experiments with each blocking agent.

A–343 responses were reduced by more than 70%. Angiotensin responses were slightly increased (Table 1).

Propranolol (1 mg/kg intravenously) caused a bradycardia of about twenty beats/minute but did not affect resting blood pressure or tone of the nictitating membranes. β-Adrenoceptor blockade reduced the responses to tyramine by 40% but did not affect significantly the responses to the other pressor substances.

Combined treatment with phentolamine and propranolol abolished the responses to noradrenaline and tyramine and markedly reduced those to McN–A–343. Angiotensin responses, however, remained essentially unaltered.

When a higher dose of angiotensin (200 ng/kg) was used it initially caused a biphasic pressor response which was converted after α and β-adrenoceptor blockade into a single monophasic response. However, as with lower angiotensin doses the overall height of the pressor response was not reduced.

Autonomic ganglion blockade.—Pempidine (5 mg/kg intravenously) caused a fall in mean blood pressure of about 40 mmHg and a complete relaxation of the nictitating membranes, but did not alter the resting heart rate. The responses to all the four pressor agents were markedly potentiated (Table 1).

Discussion.—In a previous publication (Day & Owen, 1970) results were presented which suggested that the acute pressor response to angiotensin in the conscious cat was mediated in part by release of noradrenaline from intraneuronal stores. Thus, the pressor potency was reduced by treatment with the catecholamine depleting substances, reserpine and syrosingopine, and was restored by infusions of catecholamines. Similarly, inhibition of monoamine oxidase which has been shown to increase peripheral levels of catecholamines (Goldberg & Shideman, 1962; Sanan & Vogt, 1962) increased the angiotensin responses in normal cats and hastened recovery of the responses after reserpine or syrosingopine.

The present results cast doubt on this simple concept to explain part of the angiotensin response. Blockade of adrenergic neurones with bethanidine reduced the responses to the indirectly acting amine tyramine by about 50% but left the angiotensin responses unaffected. Similarly, blockade of α and β-adrenoceptors did not reduce the responses to angiotensin even when antagonists of each type of receptor were administered simultaneously. These results suggest that no significant part of the angiotensin response is mediated via noradrenaline release from sympathetic neurones. Angiotensin stimulates release of catecholamines from the adrenal medulla of several species (Feldberg & Lewis, 1964, 1965; Vane, 1969). The present results in the conscious cat show that medullary catecholamines do not contribute significantly to the pressor action of angiotensin as evidenced by the lack of effect of combined α and β-adrenoceptor blockade. However, the secondary pressor component to large doses of angiotensin was absent after a mixture of phentolamine and propranolol and therefore probably accounted for the adrenal component of the response.

Angiotensin has been reported to have a central as well as a peripheral site of action as a pressor agent. The central pressor component has been reported to be mediated via peripheral sympathetic nerves (Bickerton & Buckley, 1961) and via central vagal inhibition (Scroop & Lowe, 1968). The failure of both pempidine and bethanidine to reduce the angiotensin pressor responses in the present experiments argues against a significant central component to the response.

Reserpine is known to have other actions in addition to depleting neuronal catecholamine stores and it may be that its anti-angiotensin action is unrelated or only indirectly related to this action.

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