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Antagonism of central dipsogenic and peripheral vasoconstrictor responses to angiotensin II with Sar[1] Ala[8] angiotensin II in the conscious cat

The administration of angiotensin II directly into the brain elicits drinking in rats (Epstein, Fitzsimons & Simons, 1969), goats (Andersson & Westbye, 1970), monkeys (Setler, 1971), rabbits and doves (Fitzsimons, 1972). Recently several analogues of angiotensin II have been synthesized and those substituted in position 8 were competitive inhibitors of the vasopressor and myotropic actions of the parent compound in peripheral tissues (Needleman, Johnson, & others, 1972). Swanson, Marshall & others (1973) found in the rat that central administration of some 8-substituted analogues did not reduce the dipsogenic effect of centrally administered angiotensin II, but rather that they were potent agonists. These workers concluded that the receptors involved in the pressor response to peripherally administered angiotensin II were different from those involved in drinking behaviour caused by injection of this substance into the brain. Solomon (1972) using Sar[1] Ala[8]-angiotensin II (P113, Norwich Pharmacal Company) in the anaesthetized cat has shown that the centrally mediated and direct vasopressor responses to angiotensin II are respectively blocked by central or peripheral administration of this compound. We have recently shown that angiotensin II causes marked drinking behaviour when administered into the lateral cerebral ventricle of the cat (Cooling & Day, 1973) and have therefore used Sar[1] Ala[8]-angiotensin II as a potential antagonist of this behaviour.

The results summarizing the effects of Sar[1] Ala[8]-angiotensin II on drinking induced by centrally administered angiotensin II are shown in Fig. 1. Sodium chloride sol-

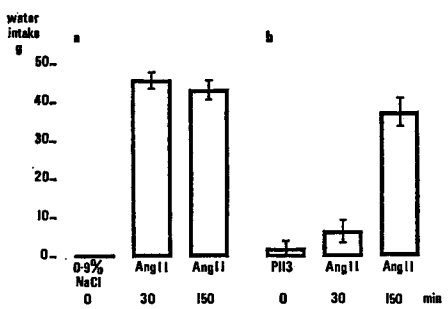

FIG. 1. In (a) water drinking induced in a group of 5 cats by intracerebroventricular (icv) injection of angiotensin II (1 μg). In (b) the same cats were used 3 days later and 5 μg Sar[1] Ala[8]-angiotensin II (P113) induced a small drinking response in one cat but significantly reduced the group response to icv angiotensin II at time 30 min. The response to icv angiotensin II recovered 150 min after the antagonist.

ution (0·9%) infused into the lateral ventricles at a rate of 25 μl min^{-1} for 4 min did not cause drinking but when 1 μg angiotensin II (Hypertensin-Ciba) was added at time 30 min and 150 min drinking responses were elicited, the means being 46·0 $\pm$ 0·2 g and 43·5 $\pm$ 2·4 g respectively. Three days later the same cats were treated with Sar^1 Ala^8-angiotensin II (5 μg) infused centrally in the same way and this induced mild drinking behaviour in one cat (9 g water taken). 30 min after the antagonist, angiotensin II induced a mean drinking response of only 6·6 $\pm$ 2·9 g which was significantly different from the control values ($P < 0·01$). However, at time 150 min the drinking response to centrally administered angiotensin II had returned to a mean of 37·6 $\pm$ 3·7 g which was not significantly different from the control response.

In this same group of conscious cats we have confirmed the observation of Solomon (1972) in anaesthetized cats, that Sar^1 Ala^8-angiotensin II infused intravenously (1 μg kg^{-1} min^{-1}) reversibly inhibited the pressor responses to intravenous angiotensin II (25 ng kg^{-1}) without affecting responses to intravenous noradrenaline (400 ng kg^{-1}).

The failure of centrally administered 8-substituted angiotensin II analogues to reduce the dipsogenic response to angiotensin II given into the brains of rats, reported by Swanson & others (1973), may be related to the observed potent agonist activity of these compounds. Swanson & others (1973) administered angiotensin II centrally only 1 min after central administration of 8-substituted analogues and the initial agonist activity of the analogues might have obscured any subsequent antagonist action. Türker, Hall, & others (1972) found that the *in vivo* antagonist activity of 8-substituted analogues was enhanced by additional substitution with sarcosine in position 1. These analogues are protected from enzymic degradation and may bind to the receptor more strongly than 8-substituted analogues. This additional substitution may explain the weak agonist and potent antagonist activity observed in our experiments. Our results suggest that the central dipsogenic and peripheral vasoconstrictor actions of angiotensin II in the cat are mediated by similar receptors.

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