The central hypotensive action of clonidine and BAY 1470 in cats and rats

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Summary

1. Intraventricular clonidine and BAY 1470, administered in small doses to conscious renal hypertensive cats, produced a fall in mean blood pressure lasting for a period of 3 h. This fall in blood pressure was accompanied by a marked bradycardia.

2. Pretreatment with intraventricular phentolamine (0.3−6 µmol), piperoxan (0.18−0.74 µmol) or tolazoline (0.35−1 µmol) abolished the hypotensive effects of intraventricular clonidine (74 nmol), whereas pretreatment with haloperidol (2.6 µmol/kg, intraperitoneally), or desmethylimipramine (3.3 µmol/kg, intraperitoneally, or 1.7 µmol, intraventricularly) did not modify the cardiovascular responses to clonidine.

3. Emesis was observed 1 min after intraventricular administration of clonidine (18−112 nmol) or BAY 1470 (0.07−0.14 µmol), which always preceded the cardiovascular actions and was still observed after pretreatment with haloperidol, desmethylimipramine, phentolamine, piperoxan or tolazoline.

4. In conscious hypertensive rats clonidine (0.6 µmol/kg, intraperitoneally) produced a marked fall in blood pressure that was antagonized by centrally acting α-adrenoceptor blocking agents but not modified by pretreatment with either 6-hydroxydopamine (three doses of 1 µmol, intraventricularly) or 5,6-dihydroxytryptamine (0.1 µmol).

5. It is concluded that the anti-hypertensive responses to clonidine are mediated via stimulation of central α-adrenoreceptors and are independent of central dopaminergic receptors, intact central serotoninergic neurons and intact adrenergic uptake mechanisms.

Key words: blood pressure, central adrenoreceptors, clonidine.

Introduction

Clonidine and BAY 1470 are potent anti-hypertensive agents which act on central bulbar sympathetic centres leading to a reduction in peripheral sympathetic tone (Kobinger & Walland, 1967; Heise, Kroneberg & Schlossmann, 1971). The hypotensive action of clonidine is thought to be mediated via central α-adrenoreceptors since piperoxan, yohimbine and intraventricular phentolamine antagonize the actions of clonidine (Schmitt, Schmitt & Fénard, 1971, 1973; Bucher, Buckingham, Finch & Moore, 1973; Finch, 1974). However, some investigators support the hypothesis of a pre-synaptic site of action (Starke & Altmann, 1973), since the hypotensive responses to clonidine are prevented by pretreatment with desmethylimipramine or by intraventricular 6-hydroxydopamine (Reid, Brait & Dollery, 1973; Dollery & Reid, 1973).

The present studies in conscious hypertensive cats and rats support the hypothesis of a central α-adrenoreceptor-stimulating mechanism for clonidine independent of an intact central adrenergic uptake mechanism.

Materials and methods

Cats were made hypertensive by wrapping one kidney with cellophan and contralateral nephrectomy under pentobarbitone anaesthesia. Three to 6 weeks later a catheter was passed down the carotid and the tip located in the thoracic aorta. A one-way valve attached to the catheter was tied at the back of the neck, by the method described by Day & Whiting.
Lateral brain ventricular cannulae were also cemented into place by a modification of the method of Hayden, Johnson & Maickel (1966). For recordings cats were starved overnight since it was found that clonidine and BAY 1470 produced emesis (see the Results section). Blood pressures were recorded in groups of four animals continually with a Statham pressure transducer, and heart rate was counted directly from the pulse trace by increasing the chart speed of the polygraph.

Rats were made hypertensive by unilateral nephrectomy, subcutaneous implantation of deoxycorticosterone acetate (50 mg) and replacing the drinking water with 154 mmol/l sodium chloride (saline). Blood pressure was recorded directly by a cannula inserted into the abdominal aorta. Groups of eight or more animals were used for each recording.

The following drugs were made up in normal saline immediately before administration: BAY 1470, 2-(2,6-dimethylphenylamino)-4H-5,6-dihydro-1,3-thiazin (Bayer AG), clonidine HCl (Boehringer Ingelheim), desmethyliimipramine (Ciba–Geigy), haloperidol (Janssen), 6-hydroxydopamine (F. Hoffmann–La Roche, Basle), 5,6-dihydroxytryptamine creatinine sulphate (F. Hoffmann–La Roche), phentolamine (Regitine, Ciba–Geigy), piperoxan, tolazoline (Priscol, Ciba–Geigy), 5,6-Dihydroxytryptamine and 6-hydroxydopamine were dissolved in 0.1 mg/ml ascorbic acid and nitrogen-bubbled 0.01 mol/l HCl respectively.

Results

In conscious renal hypertensive cats, intraventricular clonidine (18–112 nmol) produced a dose-dependent fall in blood pressure which was also accompanied by a marked bradycardia (Fig. 1). Intraventricular administration of BAY 1470 (0.07–0.14 μmol), an analogue of clonidine, produced similar responses but was slightly less potent. These doses of clonidine and BAY 1470 caused violent emesis, 1 min after injection, and this preceded the cardiovascular responses. Administration of the vehicle solution of the same pH did not induce emesis or any significant cardiovascular responses.

When given 30 min before clonidine, phentolamine (0.3–6 μmol), piperoxan (0.18–0.74 μmol) or tolazoline (0.35–1.0 μmol) intraventricularly all produced a dose-dependent antagonism of the cardiovascular responses to intraventricular clonidine (75 nmol). Pretreatment 30 min beforehand, with either desmethyliimipramine (3.3 μmol/kg, intraperitoneally, or 1.7 μmol, intraventricularly) or haloperidol (2-6 μmol/kg, intraperitoneally) did not modify the responses to intraventricular clonidine (75 nmol). In the animals pretreated with desmethyliimipramine (3.3 μmol/kg, intraperitoneally) the pressor responses to intravenous noradrenaline were markedly potentiated and treatment with haloperidol produced catalepsy.

The emesis observed immediately after intraventricular clonidine was still seen in animals pretreated with desmethyliimipramine, haloperidol and the centrally administered α-adrenoreceptor blocking agents.

In conscious experimental hypertensive rats clonidine (0.6 μmol/kg, intraperitoneally) produced a fall in blood pressure (mean 60 mmHg), which was accompanied by a marked bradycardia (100 beats/min). Intraventricular phentolamine (6 μmol) administered 30 min beforehand completely abolished the cardiovascular response to clonidine (0.6 μmol/kg, intraperitoneally). Similar results were obtained with peripheral administration of large doses of piperoxan (30 μmol/kg, intravenously). Rats pretreated with 6-hydroxydopamine (three doses of 1 μmol intraventricularly) or 5,6-dihydroxytryptamine (0.1 μmol) still exhibited hypotensive responses to clonidine (0.6 μmol/kg, intraperitoneally).
Discussion
In conscious experimental hypertensive cats, small doses of clonidine, given intraventricularly, produced a marked fall in blood pressure, which was accompanied by a bradycardia. Similar findings have been reported with peripheral administration of clonidine in several species (Schmitt et al., 1971; Dollery & Reid, 1973; Haeusler, 1973). The antagonism of the hypotensive effect of clonidine by centrally acting a-adrenoreceptor blocking agents in conscious cats and rats confirms other studies in anaesthetized cats (Haeusler, 1973; Schmitt et al., 1973).

The cardiovascular responses induced by intraventricular clonidine were not modified by centrally or peripherally administered desmethyli mipramine, which contrasts with observations in conscious rabbits and anaesthetized cats (Reid et al., 1973; Van Spanning & Van Zweiten, 1973) but confirm the more recent study in anaesthetized rabbits (Hoe fke & Warnke-Sachs, 1974). The reason for these contrasting results may be the doses of clonidine used in the studies and it is possible that at higher doses a prejunctional action at a-adreno- receptors may take place (Starke & Allmann, 1973). This possibility is, however, not supported by the present results with intraventricular 6-hydroxy-dopamine in rats or in cats depleted of brain catecholamines by pretreatment with reserpine or a-methyl-p-tyrosine, in which the cardiovascular responses to clonidine were unchanged (Haeusler, 1974).

The anti-hypertensive responses to clonidine were not modified by pretreatment with haloperidol, a central dopaminergic receptor antagonist, or by pretreatment with intraventricular 5,6-dihydroxy-tryptamine, which is known to deplete brain 5-hydroxytryptamine neurons (Baumgarten, Lachenmayer & Schlossberer, 1972). Therefore the centrally induced cardiovascular responses to clonidine are unlikely to be mediated via central dopaminergic or serotoninergic pathways.

The emetic action of clonidine and its analogue BAY 1470 was surprising since it seems to be unrelated to its a-adrenoreceptor-stimulating action. Also it appears not to be due to dopaminergic stimulation since it was observed after haloperidol pretreatment, which is known to antagonize apomorphine-induced vomiting (Janssen, Niemegeers & Schellekens, 1965). Furthermore, since tolazoline, a close structural analogue of clonidine, and the injection of vehicle of the same pH did not induce any vomiting it would seem that the emetic action is not due to irritancy.

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