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Pharmacological activity of ACC-7513, a selective α-adrenoceptor and 5-hydroxytryptamine receptor blocking agent

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1 The pharmacological activity of *N*- [2-(2,6-dimethoxyphenoxy) ethyl]-2-(2-methoxyphenoxy) ethanaminium chloride (ACC-7513) was determined in isolated smooth and cardiac muscle and its effect on blood pressure and heart rate assessed in the spontaneously hypertensive rat (SHR).

2 ACC-7513 was found to be a potent α-adrenoceptor blocking agent (pA_2:8.33) and a 5-hydroxytryptamine (5-HT) antagonist (pA_2:7.01), both in rabbit aortic strips. The affinity for α-adrenoceptors was about 20 times greater than that for 5-HT-receptors.

3 High concentrations of ACC-7513 did not block histamine in rabbit aortic strips, or β_1- or β_2-adrenoceptor responses induced by isoprenaline in guinea-pig right atria and trachea, respectively, but did block cholinoceptor responses induced by carbachol in rat uterus, non-competitively.

4 High concentrations of ACC-7513 also produced sino-atrial depression in guinea-pig right atria and direct relaxation of depolarized rabbit aortic strips.

5 ACC-7513 depressed blood pressure of conscious SHRs and produced a reflex increase in heart rate. The reductions in pressure were modest and of short duration.

6 It is concluded that: (a) ACC-7513 is a potent, selective α-adrenoceptor and 5-HT receptor antagonist; and (b) ACC-7513 is not likely to be useful in the treatment of hypertension.

Introduction

A number of benzodioxane compounds such as WB 4101 (Mottram & Kapur, 1975; Kapur *et al.*, 1978; 1979); dibozane, (Levy & Ahlquist, 1961); doxazosin (Timmermans *et al.*, 1980a), piperoxan (Timmermans *et al.*, 1980b); and RX 781094 (Dabiré *et al.*, 1981; Doxey *et al.*, 1983) have been shown to have α-adrenoceptor blocking activity. In a preliminary structure-action search for new α-adrenoceptor blocking agents we synthesized and explored the activity of a series of open-ring analogues of WB 4101; the most potent compound in that series, *N*-[2-(2,6-dimethoxyphenoxy) ethyl]-2-(2-methoxyphenoxy) ethanaminium chloride (ACC-7513), was nearly equipotent with WB 4101. Some preliminary data on the potency of this compound at α-adrenoceptors has been published (Melchiorre *et al.*, 1982). In the present investigation we have determined the selectivity of this agent for several receptor types and assessed its potential for the treatment of hypertension.

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Methods

Rabbit aortic strip

Aortae were removed from male rabbits (2–3 kg), cut into spiral strips approximately 3–4 mm wide and 4 cm long, and placed in 30 ml jacketed tissue baths containing Krebs medium (composition mM: NaCl 118.4, KCl 4.7, $MgSO_4 7H_2O$ 1.2, KH_2PO_4 1.2, glucose 11.7, $CaCl_2$ 2.5 and $NaHCO_3$ 25.0) at 37°C, aerated with 95% O_2 plus 5% CO_2, for measurement of isometric tension using Statham Universal Transducers (UC3) connected to a Beckman polygraph. Resting tension was set at 4 g. Tissues were washed periodically and tension was readjusted during the

initial 1 h equilibration period and as necessary before each cumulative concentration-response curve; results from the first curve were discarded and results from the second were used as control. Tissues were allowed to equilibrate for 60 min with ACC-7513 before generating the third concentration-response curve with each agonist. Results were expressed as % of the maximal control response for each agonist.

Schild plot data were calculated by least squares regression analysis (Tallarida & Murray, 1981).

Guinea-pig right atrium

Right atria were removed from male guinea-pigs and placed in 30 ml jacketed tissue baths containing Krebs medium (composition as above) at 37°C, aerated with 95% O_2 plus 5% CO_2. Each tissue was attached to a Statham Universal transducer (Model UC3) connected to a Beckman polygraph. Enough passive stretch was applied to each tissue so that regular resting rates were recorded with each cardiotachometer (Beckman 9857B) adapted to accept a signal directly from the transducer. Tissues were allowed to equilibrate for at least 60 min before beginning the experiment.

In one series of right atria cumulative concentration-response curves were produced with isoprenaline both before and after 60 min incubation with ACC-7513. Results were expressed as % of maximum isoprenaline-induced increase in heart rate in the control curve. In this series disodium EDTA, 30 μM, was added to the bathing medium to retard oxidation of isoprenaline.

In the second series of right atria progressively increasing concentrations of ACC-7513 were added at 60 min intervals and heart rates expressed as a % of control (pre-drug) rate.

Guinea-pig left atrium

Left atria from male guinea-pigs were placed in 30 ml constant temperature (30° or 37°C, see Results) chambers containing Krebs medium aerated with 95% O_2 plus 5% CO_2. Tension was recorded with Statham Universal Transducers (UC3) connected to a Beckman polygraph. Resting tension on each tissue was set at 1 g and adjusted periodically.

A pair of silver electrodes, each approximately 3 × 5 mm, was placed on opposite sides of the tissue for field stimulation using constant current (Grass Instruments constant current units connected to a Grass S44 stimulator) at 90 pulses min^{-1}, 5 ms duration, and current amplitude 20% greater than threshold. Current amplitudes generally ranged from 4 to 8 mA.

After an equilibration period of at least 60 min, tissues were exposed to progressively increasing concentrations of ACC-7513 in a cumulative manner. Results were expressed as a % of the pre-drug (i.e., control) developed tension.

Guinea-pig trachea

Tracheae from male guinea-pigs were cut into spiral strips approximately 3–4 mm wide and 4 cm long and immersed in jacketed tissue baths containing Krebs medium at 37°C, aerated with 95% O_2 plus 5% CO_2. Tension was recorded using Statham Universal transducers connected to a Beckman polygraph. Resting tension on each tissue was set at 5 g. Tracheae were allowed to equilibrate for at least 2.5 h and washed periodically. Tension was readjusted to 5 g at intervals during the equilibration period.

Cumulative concentration-response curves for isoprenaline were produced before and 60 min after addition of ACC-7513. Before beginning the concentration-response curve each tissue was exposed to tropolone (30 μM; 35 min), phentolamine HCl (12 μM; 35 min), cocaine HCl (9.8 μM; 25 min) and carbachol (0.3 μM; 15 min). Results were expressed as a % of the maximal control response to isoprenaline.

Rat uterus

Female Sprague-Dawley rats (150–180 g) were injected with diethylstilboestrol, 100 μg, s.c., 18–24 h before use. On the day of the experiment uterine horns were removed and placed in an overflow constant temperature (31°C) tissue bath containing Munsicks medium with magnesium (Munsick, 1960) (composition mM: $CaCl_2$ 0.50, $MgCl_2$ 0.50, NaCl 111.21, KCl 6.30, glucose 2.78, $NaHCO_3$ 30.00, NaH_2PO_4 1.00) and aerated with 95% O_2 plus 5% CO_2. Basal muscle tension was set at about 0.5 g and isometric tension was measured with Statham Universal Transducers (UC3) connected to a Beckman recorder. Tissues were allowed to equilibrate for a minimum of 60 min before use.

Cumulative concentration-response curves were produced with carbachol before and after 60 min incubation with ACC-7513. Results were expressed as % of maximal tension generated with carbachol in the control curve.

Spontaneously hypertensive rat (SHR)

SHRs, (252–285 g, Wistar-Okamoto, Taconic Farms, Germantown, NY), with indwelling aortic catheters were prepared in a manner similar to that described by Weeks & Jones (1960). Following closure of all incisions, rats were returned to their cages and allowed food and water *ad libitum* until approximately 24 h before use.

Two to three days after surgery rats were placed in plastic restrainers and their catheters connected to

Statham P23Db transducers wired to a Beckman polygraph for measurement of blood pressure and heart rate. These parameters were measured before and following oral administration of a single dose of ACC-7513 (in water). Results were expressed in units of blood pressure (mmHg) and heart rate (beats min^{-1}) with time.

Drugs used and their sources were as follows: ACC-7513, American Critical Care (spectral and elemental analyses were in accord with assigned structure); WB4101 Dr Wendel L. Nelson, School of Pharmacy, University of Washington, Seattle, Washington; EDTA, (±)-isoprenaline HCl, carbachol, diethylstilboestrol, phenylephrine HCl, 5-hydroxytryptamine creatinine sulphate (5-HT), mepyramine maleate, atropine sulphate, Sigma Chemical Co.; tropolone, Regis Chemical Co.; phentolamine HCl, Ciba Geigy Corp.; cocaine HCl, Mallinkrodt, Inc.

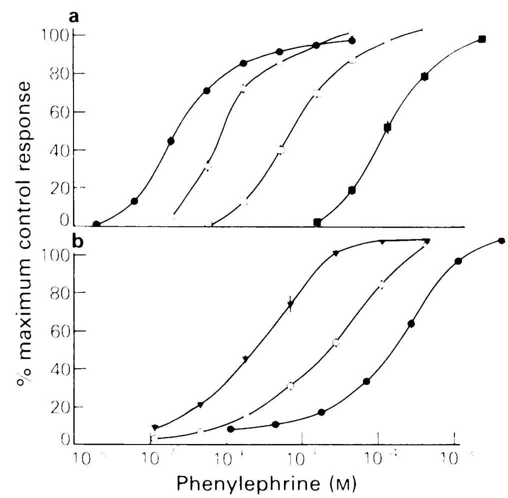


Figure 1 Cumulative concentration-response curves for phenylephrine. (a) In the absence (● $n = 18$) and presence of ACC-7513, 10 nM (○, $n = 6$), 100 nM (□, $n = 6$) and 1 μM (■, $n = 6$). (b) In the absence (●, $n = 4$) and presence of phentolamine, 50 nM (○, $n = 4$) and 0.5 μM (▲, $n = 4$). Each point shows the mean and (where larger than the symbol) s.e.mean is represented by vertical line.

Results

α-Adrenoceptor antagonism

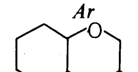
The pA_2 values were estimated for a series of structural analogues of WB 4101 in a preliminary study using a single concentration of each antagonist and the equation describing the Schild plot (Furchgott, 1967). Table 1 shows that ACC-7513 was only slightly less potent than WB 4101. ACC-7513 was selected for further evaluation.

Both ACC-7513 (Figure 1a) and phentolamine (Figure 1b) produced concentration-related parallel shifts to the right in the concentration-response curve for phenylephrine in rabbit aortic strips. Unconstrained Schild regression analysis was done on both sets of data. The pA_2 value for ACC-7513 was 8.33 (95% confidence interval: 8.21–8.46; $n = 18$) and the slope was 1.15 (95% confidence interval: 1.06–1.24). The pA_2 value for phentolamine, in comparison, was 8.07 (95% confidence interval: 8.01–8.13; $n = 8$) and the slope was 1.02 (95% confidence interval: 0.98–1.06).

ACC-7513 protected α-adrenoceptors from alkylation by the irreversible blocking agent, phenoxybenzamine (Figure 2). Phenoxybenzamine alone (30 nM) produced a non-competitive blockade, shown as a non-parallel, rightward, downward shift of the con-

Table 1 Mean pA_A values in rabbit aortic strips

$ArCH_2-NCH_2CH_2-OAr^1$
|
R

Compound	*Ar*	*Ar¹*	*R*	*pA_2*(n)†*
WB 4101		2,6-$(CH_3O)_2C_6H_3$-	H	8.9 (4)
ACC-7513	2-$CH_3OC_6H_4OCH_2$-	2,6-$(CH_3O)_2C_6H_3$-	H	8.5 (4)
I	2-$CH_3OC_6H_4OCH_2$-	2-$CH_3OC_6H_4$-	H	7.9 (3)
II	2,6-$(CH_3O)_2C_6H_3OCH_2$-	2,6-$(CH_3O)_2C_6H_3$-	H	7.0 (4)
III	2-$CH_3OC_6H_4OCH_2$-	2,6-$(CH_3O)_2C_6H_3$-	CH_3	7.8 (2)
IV	2-$CH_3OC_6H_4OCH_2$-	2,6-$(CH_3O)_2C_6H_3$-	C_2H_5	6.8 (2)

* Sixty minute equilibration time with each agent.
† Number of determinations.

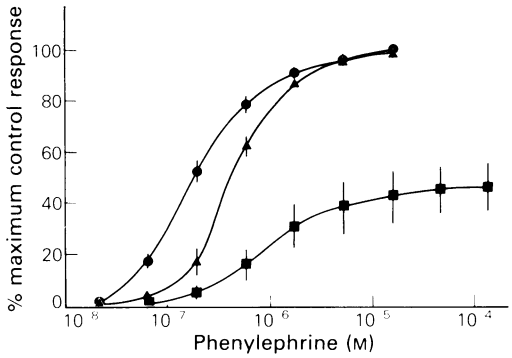


Figure 2 Protection by ACC-7513 against irreversible, non-competitive inhibition by phenoxybenzamine in rabbit aortic strips. (●) Phenylephrine control curve ($n = 7$). Tissues were subsequently exposed to either phenoxybenamine (30 nM, 5 min) (■, $n = 3$) or to both ACC-7513 (1.0 μM, 15 min) and phenoxybenzamine (30 nM, 5 min) (▲, $n = 4$) before thorough washing and subsequent generation of the concentration-response curves. Each point shows the mean and vertical lines s.e.mean.

centration-response curve. Prior addition of ACC-7513 (1.0 μM) prevented this non-competitive blockade.

5-Hydroxytryptamine antagonism

ACC-7513 produced a concentration-related parallel shift in the concentration-response curve for 5-HT (Figure 3) in rabbit aortic strips. An unconstrained Schild plot was derived from shifts in concentration-response curves in individual tissues. The pA_2 against 5-HT receptors was 7.01 (95% confidence interval: 6.85–7.17; $n = 18$) and the slope of the Schild plot was 0.95 (95% confidence interval: 0.87–1.03).

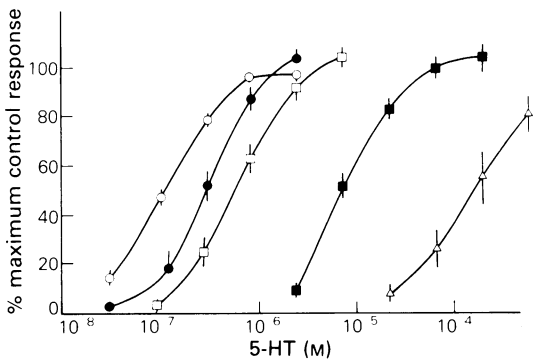


Figure 3 Cumulative concentration-response curves for 5-hydroxytryptamine (5-HT) in the absence (○, $n = 18$) and presence of ACC-7513, 0.1 μM (●, $n = 4$), 1.0 μM (□, $n = 6$), 10 μM (■, $n = 4$), and 100 μM (△, $n = 4$). Each point shows the mean and vertical lines s.e.mean.

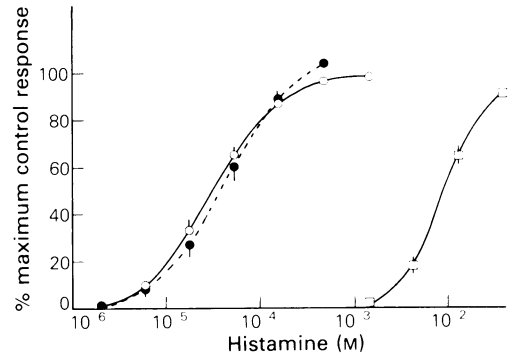


Figure 4 Cumulative concentration-response curves to histamine before (○, $n = 7$) and after either ACC-7513, 0.1 mM (●, $n = 3$) or mepyramine, 1.0 μM (□, $n = 4$) in rabbit aortic strips. Each point shows the mean and vertical lines s.e.mean.

Histamine antagonism

A high concentration of ACC-7513 (0.1 mM) did not block the increase in tension produced by histamine in rabbit aortic strips (Figure 4), while mepyramine (1.0 μM), an H_1-antagonist, produced a marked shift of the concentration-response curve to the right. The pA_2 value for mepyramine was calculated (Furchgott, 1967) to be 8.47.

Cardiodepression in vitro

ACC-7513 produced a concentration-related decrease in sinus nodal rate in isolated right atria from the guinea-pig (Figure 5a). This negative chronotropic effect was not blocked by atropine, 1.0 μM (Figure 5a).

In 8 paced left atria from the guinea-pig tested at 30°C where contractile force is substantial, there was a slight (4%) increase in developed tension with 4.1 μM ACC-7513, with no change at lower concentrations. At higher concentrations rhythms generally became very erratic and in some tissues contractile force increased. Because of the disruption in normal rhythmic activity under these conditions the drug was tested in another series of left atria at 37°C. With the higher temperature the initial developed tension was lower (718.8 ± 4.0 mg, mean ± s.e.mean, $n = 8$, at 37°C; 1575.0 ± 77.6 mg, $n = 8$, at 30°C) but the problem with automaticity was circumvented. The results at 37°C are shown in Figure 5b; under these conditions ACC-7513 produced an abrupt decrease in contractile force when the concentration exceeded 10 μM.

The concentration of ACC-7513 necessary to depress either rate or force was much higher than the concentration necessary to achieve substantial α-adrenoceptor or 5-HT-receptor blockade.

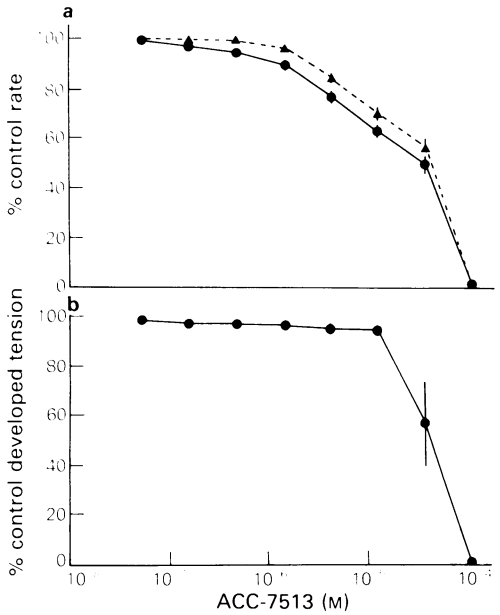


Figure 5 (a) Effect of ACC-7513 on sinus nodal rate in guinea pig right atria before (●---●) and after (▲---▲) treatment with atropine, 1.0 μM. (b) Depression of cardiac contractile force by ACC-7513. Each point represents the mean ($n = 7$, (a) and $n = 8$ (b)) and vertical lines s.e.mean (when larger than symbol).

Vascular smooth muscle relaxation

The ability to produce direct smooth muscle relaxation was assessed in rabbit aortic strips with active tension induced by depolarization with potassium (42 mM). Relaxation to resting tension, i.e. the tension level before K^+ depolarization, was taken as 100%.

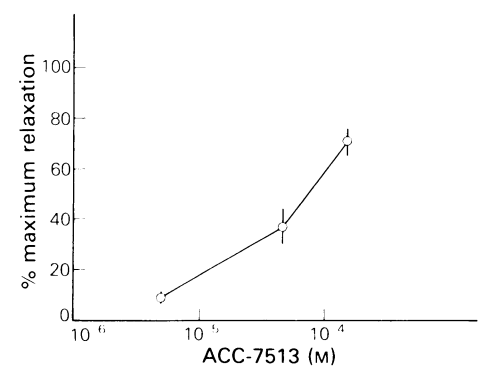


Figure 6 Direct vascular smooth muscle relaxation by ACC-7513 in rabbit aortic strips depolarized with potassium chloride (42 mM). Each point represents the mean ($n = 4$) and vertical lines s.e.mean.

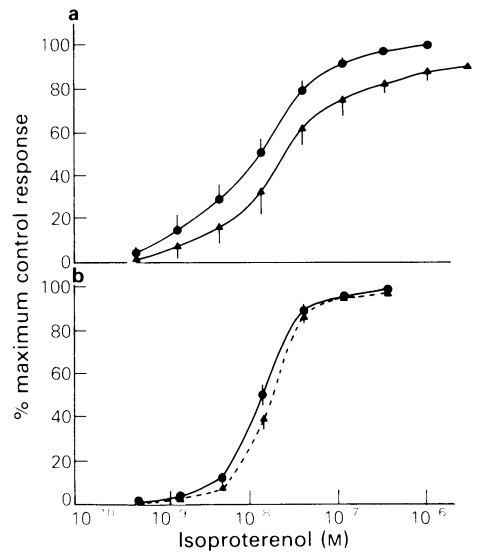


Figure 7 Cumulative concentration-response curves to isoprenaline: (a) before (●) and after (▲) ACC-7513, 2 μM, in guinea-pig right atria ($n = 5$) and (b) before (●) and after (▲) ACC-7513, 5 μM, in guinea-pig trachea ($n = 6$). Each point represents the mean and vertical lines s.e.mean.

ACC-7513 produced a concentration-related relaxation (Figure 6) at concentrations much higher than needed to produced substantial bockade of α-adrenoceptors and 5-HT-receptors.

β-Adrenoceptor blockade

At a concentration of 2.0 μM, ACC-7513 produced a slight depression of the chronotropic concentration-response curve for isoprenaline in guinea-pig right

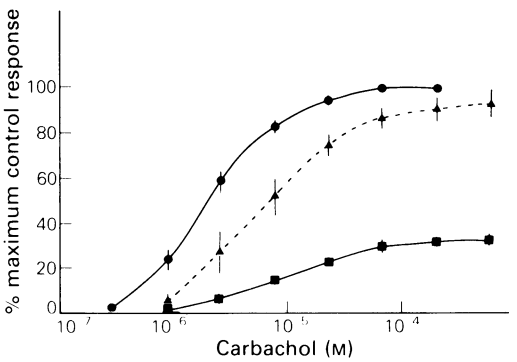


Figure 8 Cumulative concentration-response curves to carbachol in rat uterus in the absence (●, $n = 8$) and presence of ACC-7513, 10 μM (▲, $n = 4$) and 100 μM (■, $n = 4$). Each point represents the mean and vertical lines show s.e.mean (when larger than symbol).

atria (Figure 7a). Higher concentrations were not tested due to the concentration-related depression of spontaneous rate (Figure 5). In the absence of isoprenaline the concentration of ACC-7513 employed produced about a 10% decrease in sinus nodal rate which probably accounts for the slight depression of the isoprenaline concentration-response curve.

In guinea-pig trachea ACC-7513, 5 μM, had no effect on the β_2-adrenoceptor-induced relaxation in response to isoprenaline (Figure 7b). Higher concentrations were not tested due to the direct smooth muscle relaxation demonstrated in rabbit aortic strips and the presence of substantial myogenic tone in trachea.

Cholinoceptor blockade

High concentrations of ACC-7513 resulted in a non-competitive antagonism of the response of rat uterus to carbachol (Figure 8). No reduction in tone of this preparation was evident after treatment with ACC-7513.

Effect in spontaneously hypertensive rats

ACC-7513 administered orally produced dose-related decreases in both systolic and diastolic blood pressures and a decrease in pulse pressure (Figure 9). The onset of the reduction was very rapid and the duration was dose-related. At the 1 and 3 mg kg^{-1} doses both systolic and diastolic pressures returned to near control levels within 2 h. At the 10 mg kg^{-1} dose the effect persisted for more than 4 h. Heart rates increased with no clear relationship to the doses tested (Figure 10) and returned to control levels within approximately 1 h. There were no obvious changes in the appearance or behaviour of the rats.

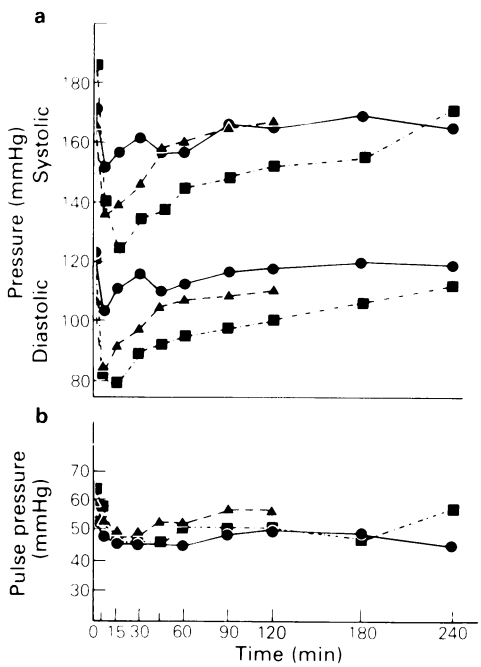


Figure 9 Effects of ACC-7513, 1 mg kg^{-1} (●---● $n = 4$); 3 mg kg^{-1} (▲---▲ $n = 4$); 10 mg kg^{-1} (■---■; $n = 4$), given orally on (a) systolic, diastolic, and (b) pulse pressures in conscious spontaneously hypertensive rats. S.e.means omitted for clarity.

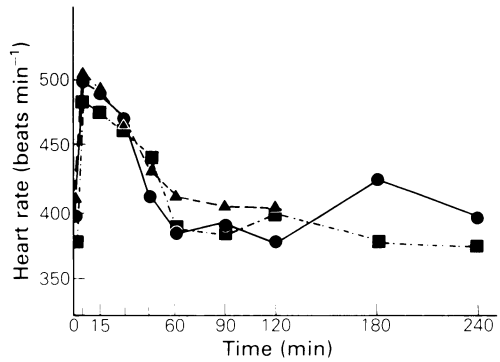


Figure 10 Effects of ACC-7513, 1 mg kg^{-1} (●---●; $n = 4$); 3 mg kg^{-1} (▲---▲; $n = 4$); 10 mg kg^{-1} (■---■; $n = 4$); given orally, on heart rate in conscious spontaneously hypertensive rats. S.e.means omitted for clarity.

Discussion

ACC-7513 was found to be a potent, competitive α-adrenoceptor and 5-HT receptor blocking agent. It blocked contractions produced by the α-adrenoceptor agonist phenylephrine, protected α-receptors against irreversible blockade by phenoxybenzamine, and blocked contractions induced by 5-HT. Apperly *et al.* (1976) and Purdy *et al.* (1981) showed that α-adrenoceptor agonists and 5-HT act on distinct receptors in rabbit aorta. The pA_2 value determined for ACC-7513 at α-receptors in aorta (8.33) agrees very well with that reported for α-adrenoceptors in rat vas deferens (8.21) (Melchiorre *et al.*, 1982). Its potency for blocking 5-HT receptors is about 20 times less than its potency for blocking α-adrenoceptors. Since the receptors involved in the vascular response to 5-HT appear to be 5-HT_2-receptors (Cohen *et al.*, 1981; 1983b), it is likely that the antagonism of responses to 5-HT in rabbit aortic strips reflects an interaction with 5-HT_2-receptors; further experiments are necessary to support this hypothesis. Since rabbit aortic strip has little if any intrinsic tone under normal ionic conditions (Furchgott, 1960), it is unlikely that the shifts in concentration-response curves to either phenylephrine or 5-HT

at the higher concentration were appreciably affected by any direct relaxant effect.

ACC-7513 also was selective for α-adrenoceptors and 5-HT receptors in smooth muscle. High concentrations did not block histamine, β_1- or β_2-receptors but did block cholinoceptors non-competitively. The rats used for the assay of ACC-7513 on cholinoceptors were pretreated with diethylstilboestrol to bring them to oestrus where uterine tone is at its lowest level (Miller, 1967). Therefore, it is likely that the shifts in the concentration-response curve to carbachol reflect cholinoceptor antagonism rather than decreased myogenic tone. The selectivity of ACC-7513 for postsynaptic α-adrenoceptors was at least 650 times greater than its selectivity for β_1-, β_2,-choline or histamine receptors. Like other α-adrenoceptor blocking agents, e.g., phentolamine and tolazoline (McDevitt, 1979), ACC-7513 produces direct smooth muscle relaxation; the separation between effective α-adrenoceptor and 5-HT receptor blocking and direct vasodepressor concentrations is very large.

The selectivity of ACC-7513 for pre- or post-synaptic α-adrenoceptors has not been determined. Some benzodioxanes such as doxazosin (Timmermans *et al.*, 1980a) and the close structural analogue of ACC-7513, WB 4101 (Butler & Jenkinson, 1978; Mottram, 1980; Drew, 1982; Ruffolo *et al.*, 1983) are selective for postsynaptic α-adrenoceptors, while others, e.g., piperoxan (Timmermans *et al.*, 1980b) and RX 781094 (Dabiré *et al.*, 1981; Doxey *et al.*, 1983) are selective for presynaptic receptors, and still others, may be relatively non-selective. In a recent binding study Timmermans *et al.* (1983) concluded that benzodioxanes other than piperoxan and its analogues are selective for α_1-adrenoceptors. If ACC-7513 should be fairly potent at presynaptic α-adrenoceptors this might account for the relatively small reductions in blood pressure observed, since reductions in blood pressure due to postsynaptic α-adrenoceptor blockade would be partially offset by the effective enhancement of sympathetic tone due to presynaptic α-adrenoceptor blockade. The presence of a reflex increase in heart rate suggests that ACC-7513 probably is not prazosin-like, i.e., highly selective for postsynaptic α-adrenoceptors.

The activity profile of ACC-7513 resembles that of the structurally dissimilar agent ketanserin in possessing both α-adrenoceptor and 5-HT receptor blocking actions (Kalkman *et al.*, 1982; Van Nueten *et al.*, 1981). Quantitatively these agents differ in that ACC-7513 is more selective for α-adrenoceptors while ketanserin shows about a 10 fold selectivity for 5-HT receptors: the pA_2 value for ketanserin antagonism of 5-HT has been found to be 8.72 in rabbit aortic strips (Humphrey, 1983) and approximately 9.0 in various canine vascular strips (Van Nueten *et al.*, 1981), while the pA_2 value against noradrenaline was found to be 7.74 in rat caudal artery strips (Van Neuten *et al.*, 1981). ACC-7513, like ketanserin and unlike other 5-HT antagonists such as methysergide (Van Nueten *et al.*, 1981), has a competitive rather than a non-competitive blocking action at 5-HT receptors.

ACC-7513 also resembles ketanserin qualitatively in its ability to reduce blood pressure in the spontaneously hypertensive rat. Dose-related reductions in both systolic and diastolic blood pressure were smaller than anticipated on the basis of the high *in vitro* α-adrenoceptor blocking potency of ACC-7513. The oral doses required to decrease blood pressure were also unexpectedly high. The onset of action was very rapid, suggesting that the activity was not limited by bioavailability. The duration of the pressure reduction was rather short. In a preliminary experiment, administration of $1.0\,\mu g\,kg^{-1}$ i.v., to conscious SHRs reduced blood pressure by $26.8 \pm 4.0/18.5 \pm 1.8$ mmHg (mean ± s.e.mean, systolic/diastolic, $n = 4$). This dose is approximately 1000 times less than that required on oral administration to achieve a similar reduction in pressure. These observations suggest that following rapid oral absorption ACC-7513 is probably metabolized by the liver, resulting in low blood levels. Additional experiments need to be done to test this hypothesis. The relatively poor antihypertensive effect in SHRs suggests that this compound is not likely to be useful in hypertension.

Indirect evidence suggests that the decrease in blood pressure in SHRs with ACC-7513 is probably due largely to α-adrenoceptor antagonism rather than 5-HT receptor blockade. Although 5-HT receptor antagonism has been suggested as an approach to the treatment of hypertension (Vanhoutte, 1983), compounds which clearly block 5-HT receptors may be ineffective as hypotensive agents. Blockade of 5-HT receptors with the highly selective, competitive antagonist, LY53857, which does not block α-adrenoceptors, did not reduce blood pressure in the SHR (Cohen *et al.*, 1983a). Similarly, methysergide, a non-competitive 5-HT antagonist, also did not decrease blood pressure in the SHR (Haeusler & Finch, 1972).

The decrease in systolic pressure with ACC-7513 exceeded the decrease in diastolic pressure. The greater decrease in systolic pressure in the presence of increased heart rate probably results from a decrease in cardiac output secondary to a decrease in myocardial contractile force and stroke volume.

Direct cardiodepression was observed with ACC-7513 *in vitro* at high concentrations. Both rate and force were reduced. Reductions in heart rate were not due to cholinoceptor stimulation since a high concentration of atropine did not block the bradycardia. Some other undefined mechanism must account for the cardiodepression observed.

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