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HYPOTENSIVE AND SEDATIVE EFFECTS OF α-ADRENOCEPTOR AGONISTS: RELATIONSHIP TO α_1- AND α_2-ADRENOCEPTOR POTENCY

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1 The purpose of this study was to investigate whether the separation between the hypotensive and sedative effects of a new series of centrally acting antihypertensive drugs was due to differences between the relative pre-junctional (α_2) and post-junctional (α_1) adrenoceptor agonist properties of the compounds.

2 In anaesthetized rats the intravenous doses of clonidine, ICI 101187, ICI 106270, ICI 109683 and ICI 110802 required to lower blood pressure (BP) by 20 mmHg were 1.2, 5.1, 5.5, 3.3 and 5.4 μg/kg respectively.

3 In a test for sedation, ICI 101187 had at least 10 times less sedative effect than clonidine, ICI 106270 and ICI 109683 had at least 30 times less sedative effect than clonidine while ICI 110802 was not active. In a locomotor activity test the intravenous dose of clonidine required to reduce activity by 50% was 15.3 μg/kg, for ICI 101187 it was 194, for ICI 106270 it was 238 and for 110802 it was 313 μg/kg.

4 In the pithed rat the ED_{50}s of clonidine, ICI 101187, ICI 106270, ICI 109683 and ICI 110802 as α_2-agonists were 19.4, 9.3, 63.2, 43.0 and 78.5 μg/kg respectively. The α_1-adrenoceptor potencies were quite similar for the five drugs and varied between 3.2 μg/kg for ICI 110802 and 8.7 μ/kg for ICI 106720. Potency as α_2-adrenoceptor agonists was also assessed in the mouse vas deferens. Clonidine and ICI 101187 were similar in potency with IC_{50}s of 9.3×10^{-9}M and 8.9×10^{-9}M respectively. ICI 106270 and ICI 110802 were much weaker with IC_{50}s of 4.9×10^{-8}M and over 5.7×10^{-8}M respectively.

5 Since all the compounds had similar potencies as α_1-agonists, this could not explain their different sedative effects. The weakest compounds as sedatives were also weakest as α_2-agonists, although ICI 101187 which was as potent as clonidine as an α_2-agonist was still 10 times weaker as a sedative.

6 Hypotensive activity appears to be more closely related to α_1- than to α_2-potency.

7 Clonidine was more potent as both a sedative and a hypotensive agent than would be predicted from its activity at either the α_1- or the α_2-adrenoceptor.

Introduction

It is now well established that not only are there α-adrenoceptors located post-junctionally but there are also pre-junctional α-adrenoceptors, activation of which leads to a reduction of noradrenaline release from sympathetic adrenergic nerves (Langer, 1974; Starke & Endo, 1976). The post-junctional receptors have been termed α_1-adrenoceptors and the pre-junctional ones, α_2-adrenoceptors.

Drew (1976) compared the potency of various α-agonists and antagonists in a pithed rat preparation and found that the two types of α-adrenoceptors differed in their sensitivities to α-agonists and antagonists. Starke, Endo & Taube (1975) using an isolated pulmonary artery preparation came to the same conclusion. These findings raise the possibility that as well as having a central mode of action, α-agonist drugs like clonidine could also act at the α_2-adrenoceptor in the periphery to reduce noradrenaline release.

The discovery of two distinct types of α-adrenoceptors has prompted several groups of workers to investigate whether the sedative and hypotensive activities of clonidine are due to the stimulation of the same or different α-adrenoceptors. Drew, Gower & Marriot (1979) have shown that the sedative potencies of α-adrenoceptor stimulants are related to their potencies as α_2- rather than as α_1-adrenoceptor agonists. The sedative effect of clonidine was antagonized by phentolamine, yohimbine, piperoxan and tolazoline, all effective presynaptic α_2-antagonists while thymoxamine and labetolol, preferential α_1-antagonists, were without effect. Cavero & Roach (1978) showed that sedation induced by clonidine in young chicks was antagon-

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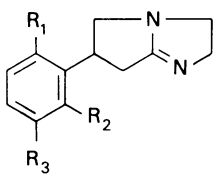
ized by phentolamine but not prazosin, the α_1-adrenoceptor antagonist (Cambridge, Davey & Massingham, 1977). However, the hypotensive action of clonidine was antagonized by prazosin. From these experiments it would seem that the α-adrenoceptors which mediate sedation are indeed different from those which mediate the fall in pressure. This evidence would favour the hypothesis that sedation is caused by α_2-adrenoceptor stimulation in the CNS and effects on the blood pressure by α_1-adrenoceptor stimulation. However, this is still a matter of controversy since the α-adrenoceptor antagonists, yohimbine and piperoxan, which are more selective for the α_2-adrenoceptor (Drew, 1976), also antagonize the hypotensive actions of clonidine (Schmitt, Schmitt & Fenard, 1971; Bolme, Corrodi, Fuxe, Hokfelt, Lidbrink & Goldstein, 1974).

We have found that a new series of α-adrenoceptor agonists show a separation between blood pressure lowering effects and sedation when compared with clonidine (Clough, Hatton, Pettinger, Samuels & Shaw, 1978). It therefore seemed important to investigate the α_1- and α_2-adrenoceptor potencies of these compounds in relation to their hypotensive and sedative properties in order to determine whether this could account for the differences seen between these compounds and clonidine. The structures of the ICI compounds investigated in this study are shown in Figure 1. An account of some of this work has been presented to the British Pharmacological Society (Birch, Clough, Hatton & Wheatley, 1980).



R_1	R_2	R_3	ICI compound No.
Cl	F	H	106 270
Cl	Cl	H	101 187
Cl	Br	H	109 683
Cl	Cl	CH_3	110 802

Figure 1 The structures of a series of new centrally acting hypertensives. These compounds were synthesized by Dr A. Shaw of the Chemistry Department, ICI Pharmaceuticals Division. ICI 101187 is a hydrochloride salt while the other three analogues are hydrobromide salts.

Methods

Blood pressure measurements in anaesthetized rats

Female rats weighing between 230 and 250 g were anaesthetized with pentobarbitone sodium (50 mg/kg i.p.). An external jugular vein was catheterized for drug administration and a carotid artery for blood pressure (BP) measurement. This cannula was connected via a Bell and Howell transducer to a Devices recorder. Heart rate (HR) was derived from the BP pulse and was displayed on the recorder. BP and HR were allowed to stabilize for at least 15 min before the drug injection. As well as the four ICI analogues (101187, 106270, 109683 and 110802), clonidine (Boehringer, Ingelheim) was also used in this study for comparison with previous literature. All the compounds were given as an injection at doses of 3, 10 and 30 μg/kg and 10 rats were used for each dose. The maximum fall in pressure produced was plotted against the log of the dose and by a linear regression analysis, the dose required to lower BP by 20 mmHg was calculated. In all experiments doses were calculated as the salts.

Potentiation of halothane-induced anaesthesia

Turnbull & Watkins (1976) have shown that potentiation of halothane-induced anaesthesia is a reliable way to assess the sedative action of drugs and has several advantages over other methods of assessing sedation. The most important of these are the rapid and smooth onset of the anaesthesia and the prompt recovery following its withdrawal. Diurnal variation has been observed in the recovery time of rats to halothane so it is important to treat rats in each group as near the same time as possible and to introduce a control rat with each treated animal.

Rats weighing between 275 and 325 g were used for this experiment. At least 2 days before the experiment, a jugular vein catheter was implanted under halothane anaesthesia. For each test, paired rats were used, one being given the compound under test and the other saline (0.9% w/v NaCl solution).

The gas flow from an anaesthetic apparatus incorporating a Fluotec Mark 2 vapouriser was passed through a perspex box (35×15×10 cm). Oxygen containing 2.5% halothane (ICI) was passed through the box for at least 5 min before the experiment to ensure an even concentration of halothane. Fifteen min after intravenous injection of either clonidine or an ICI compound, the 2 rats were placed in the box for 5 min. Anaesthesia was smooth and rapid. They were then removed from the box and placed on their backs and the time at which the righting reflex returned was measured.

The sleeping time of treated rats was expressed as a percentage of that of control rats. Ten animals were

used to assess each dose. The time for the righting reflex to return in the treated rats was plotted on a histogram as a percentage increase over control.

The effects of α-adrenoceptor antagonists on the blood pressure responses and on halothane-induced anaesthesia

The α-adrenoceptor antagonists used were yohimbine (Sigma) (1 mg/kg i.v.), piperoxan (May and Baker) (1 mg/kg i.v.) and prazosin (Pfizer) (0.1 mg/kg i.v.). To study the effects of these α-adrenoceptor antagonists on the blood pressure responses of the ICI compounds and clonidine, they were administered 15 minutes before the intravenous injection of 30 μg/kg of the ICI compound or 10 μg/kg of clonidine. Groups of 6 rats were used for each α-adrenoceptor antagonist and the effects on the blood pressure response compared with 6 rats treated only with an ICI compound or clonidine.

In order to test the effect of the α-adrenoceptor antagonists on sleeping time, they were again administered 15 min before the injection of the agonist. Control rats received the α-adrenoceptor antagonist alone. The sleeping time of treated rats was expressed as a percentage of that of control rats and 6 rats were used for each compound. Clonidine was given at 30 μg/kg, ICI 101187 at 100 μg/kg and ICI 106270 at 300 μg/kg as these doses when given alone all gave clear increases in sleeping time. In both these experiments ICI 109683 was not used due to scarcity of material. ICI 110802 was not used in the halothane-anaesthesia experiment since it did not potentiate sleeping (see results).

Measurement of locomotor activity

Rats weighing between 275 and 325 g had jugular vein catheters implanted as described above. Fifteen minutes before being placed in Animex locomotor activity cages they were injected intravenously either with one of the ICI analogues or with clonidine. The cages were linked to a computer and the activity observed during the first 10 min was compared with simultaneously treated control rats. Twelve rats were used for each dose of each compound and activity was expressed as a % of that of the control rats. A linear regression of the activity against the log of the dose was calculated and the dose required to reduce activity by 50% (ED_{50}) was estimated.

Measurement of α_1- and α_2-stimulant properties in the pithed rat

Rats weighing between 275 and 325 g were anaesthetized with halothane, their trachea were cannulated, and the animals quickly pithed via the orbit (Gillespie, McLaren & Pollock, 1970). Artificial respiration with air was then immediately started. The pithing rod was insulated throughout its length, apart from a 1 cm section 4 cm from the tip. BP was measured from a carotid artery and HR derived from the pressure pulse. Both parameters were displayed on a Devices recorder. A femoral vein was cannulated for drug administration. Atropine (1 mg/kg) and tubocurarine (1 mg/kg) were given and the vagi cut in the neck before an experiment to prevent any parasympathetic effects on the heart and to eliminate voluntary muscle activity. When the stimulator was

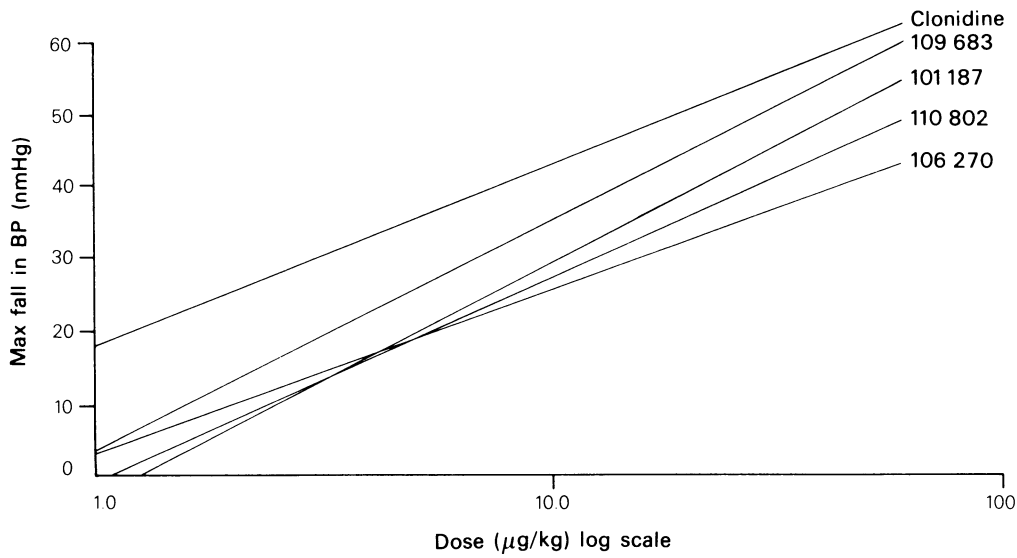


Figure 2 Dose-response regressions for the fall in diastolic blood pressure produced by clonidine, ICI 101187, ICI 106270, ICI 109683 and ICI 110802 in the anaesthetized rat.

Table 1 The potency of various α-stimulants as hypotensive and sedative agents; relation to potency at pre- and postsynaptic α-adrenoceptors

Compound ICI No.	Dose to lower BP by 20 mmHg (μg/kg i.v.)	Relative sleeping time (clonidine = 1)	Locomotor activity ED_{50}(μg/kg i.v.)	Pithed rat $ED_{50}HR$ (μg/kg i.v.)	Pithed rat $ED_{50}BP$ (μg/kg i.v.)	Vas deferens IC_{50} (M)
Clonidine	1.2 (0.6–2.3)	1	15.3 (10.1–23.3)	19.4± 4.4	8.3±2.1	$9.3\pm1.02\times10^{-9}$
101187	5.1 (4.2–6.2)	0.1	194.2 (130.6–288.7)	9.3± 1.5	5.3±1.1	$8.7\pm2.0\times10^{-9}$
106270	5.5 (4.1–7.2)	0.03	237.5 (163.6–344.9)	63.2±13.1	8.7±3.1	$4.9\pm1.18\times10^{-8}$
110802	5.4 (3.9–7.6)	0	312.5 (186.7–521.1)	78.5±18.0	3.2±0.2	$>5.7\times10^{-8}$
109683	3.3 (2.5–4.5)	0.03	—	43.0±14.5	6.1±1.5	—

Values are mean and s.e. mean.
Locomotor activity ED_{50} = dose to reduce control activity by 50%
Pithed rat ED_{50} HR = dose to reduce increment in HR due to stimulation by 50%
Pithed rat ED_{50} BP = dose to increase BP by 50mmHg
Vas deferens IC_{50} = concentration to decrease twitch response by 50%

switched on, the spinal cord between C7 and T1 was stimulated (corresponding to the uninsulated part of the pithing rod). The stimulus parameters were 1 Hz, 1 ms, supramaximal voltage (40 V) (Farnell Physiological Stimulator). The position of the rod was adjusted until a substantial tachycardia occurred with little or no change in BP and this stimulus was then maintained throughout the experiment. Prejunctional α_2-agonist activity was seen as a reduction in the tachycardia and post-junctional α_1-agonist activity as an elevation in BP (Drew, 1976).

For each compound 6 rats were used and doses 3–300 μg/kg were given. The doses that reduced the increment in HR due to stimulation by 50% (α_2 ED_{50}) and raised the diastolic BP by 50 mmHg (α_1 ED_{50}) were calculated after regression analysis of dose-response data.

Measurement of α_2 properties in the mouse vas deferens

The whole of the vas deferens from male mice weighing 30–35 g was excised, dissected free from mesenteric connections and suspended in a 10 ml organ bath between ring electrodes placed 4 cm apart.

Krebs solution free of magnesium was used since it has been shown that this enhances the responses of tissues (Hughes, Kosterlitz and Leslie, 1975). The solution was aerated with 95% O_2 and 5% CO_2. A tension of 100 mg was applied to the tissue and the tissue made to contract by field stimulation from a Farnell Physiological Stimulator (trains of 100 ms duration of 50 Hz, pulse width 1 ms, voltage 70 V, train frequency 0.1 Hz). The responses were measured isotonically with a Washington T2 lever transducer. Cumulative concentration-response curves to the compounds were contructed from at least 4 tissues and the concentrations used were from 0.1 to 100 ng/ml (final bath concentration) given cumulatively. The molar concentration to reduce contractions by 50% (IC_{50}) was calculated for each tissue.

Statistical analysis of results was by means of Student's *t* test.

Results

Blood pressure in anaesthetized rats

All five compounds produced qualitatively the same effects on BP. There was an initial brief increase in BP lasting for 1–2 min followed by a prolonged fall which reached a maximum 5–10 min after the injection and was maintained for at least 30 min. The maximum fall in BP produced by each dose was regressed against the dose (Figure 2). The correlation co-efficients of these lines were all significant ($P < 0.01$). From these regressions the dose required to lower BP by 20 mmHg for each compound was calculated and is shown in Table 1. All four ICI compounds produced similar falls in pressure, the dose ranging from 3.3 to 5.5 μg/kg i.v. while clonidine was more potent, a dose of 1.2 μg/kg lowering BP by 20 mmHg.

Potentiation of halothane-induced anaesthesia

The increase in halothane-induced sleeping time caused by clonidine was marked (Figure 3). A dose of 10 μg/kg (i.v.) increased sleeping time by 90% while a dose of 300 μg/kg (i.v.) increased sleeping time by 650%. The four ICI analogues were clearly less sedative than clonidine. ICI 101187 potentiated sleeping time by 175% at a dose of 100 μg/kg (i.v.). Increasing the dose to 1 mg/kg caused no further potentiation of halothane-induced anaesthesia indicating that ICI 101187 had a much lower maximal effect than clonidine. The least sedative compound was ICI 110802 which caused no changes in sleeping time at doses up to 1 mg/kg. ICI 106270 and

Table 2 The effect of various α-adrenoceptor antagonists on the fall in blood pressure (mmHg) induced by the intravenous injection of clonidine (10 μg/kg), ICI 101187 (30 μg/kg), ICI 106270 (30 μg/kg), and ICI 110802 (30 μg/kg)

	Control fall in BP (*Systolic* / *Diastolic*)	*Fall in BP after yohimbine (1 mg/kg)*	*Fall in BP after piperoxan (1 mg/kg)*	*Fall in BP after prazosin (0.1 mg/kg)*
Clonidine	−47 ± 6.9 / −46 ± 5.1	−14 ± 3.5 *** / −13 ± 4.4 ***	−48 ± 8.0 / −40 ± 4.4	−28 ± 3.1 * / −33 ± 3.8
ICI 101187	−65 ± 10.3 / −64 ± 10.2	−26 ± 3.7 ** / −24 ± 3.7 **	−37 ± 7.9 / −26 ± 5.7 **	−15 ± 1.3 *** / −17 ± 2.5 ***
ICI 106270	−55 ± 7.9 / −50 ± 4.8	−25 ± 2.6 ** / −22 ± 2.8 ***	−34 ± 5.1 * / −15 ± 2.6 ***	−18 ± 4.4 ** / −18 ± 4.4 **
ICI 110802	−41 ± 4.7 / −43 ± 7.4	+8 ± 3.8 *** / −4 ± 4.2 ***	−8 ± 2.1 *** / −5 ± 1.8 ***	−7 ± 2.5 *** / −7 ± 2.5 ***

Values are mean ± s.e.mean.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$: differences from the control group with no pretreatment.

ICI 109683 were intermediate between ICI 101187 and ICI 110802 and both produced some sedation at 300 μg/kg (i.v.). This experiment shows that not only are the ICI compounds less potent as sedatives than clonidine since the threshold doses required to produce sedation are higher but also that the quality of the sedation is quite different. Thus while clonidine increased sleeping time by 650% at 300 μg/kg, none of the ICI analogues increased sleeping by as much as 200%. From these data it is obviously difficult to assess relative potency of these compounds as sedatives. Using only the minimum dose required to produce sedation, these compounds are compared with clonidine as sedatives in Table 1. This may underestimate the differences between the ICI compounds and clonidine since it assumes that doses of below 10 μg/kg of clonidine would not cause sedation.

The effect of α-adrenoceptor antagonists on the blood pressure responses and on halothane-induced anaesthesia.

The falls in blood pressure produced by clonidine, ICI 101187 and ICI 106270 were clearly attenuated by α-adrenoceptor antagonists (Table 2). The selective α_2-antagonist, yohimbine, blocked the falls in BP induced by all four agonists, while prazosin, the α_1-antagonist, was only a very weak antagonist of the depressor effect of clonidine but was very potent against the three ICI analogues. Piperoxan was very potent in antagonizing the BP fall induced by ICI 106270 and ICI 110802 but was much less potent against ICI 101187 and did not antagonize the depressor response to clonidine. The effects of the same three α-adrenoceptor antagonists on halothane-induced anaesthesia are shown in Table 3. The in-

Table 3 The effect of various α-adrenoceptor antagonists on the percentage increase in halothane-induced sleeping time produced by the intravenous injection of clonidine (30 μg/kg), ICI 101187 (100 μg/kg) and ICI 106270 (300 μg/kg)

	Increase in control sleeping time	*Increase in sleeping time after 1 mg/kg yohimbine*	*Increase in sleeping time after 1 mg/kg piperoxan*	*Increase in sleeping time after 0.1 mg/kg prazosin*
Clonidine	182 ± 47	24 ± 22*	146 ± 51	90 ± 50
ICI 101187	179 ± 50	70 ± 21	−2 ± 8*	5 ± 14*
ICI 106270	98 ± 28	80 ± 45	−13 ± 12*	58 ± 19

Values are mean ± s.e.mean.
* $P < 0.05$; difference from control group without pretreatment.

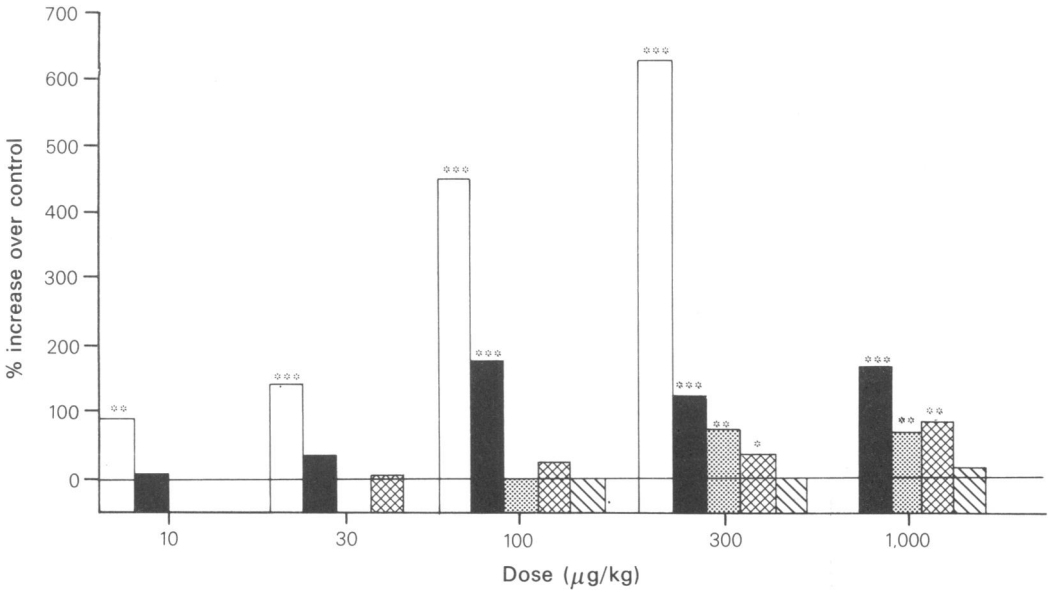


Figure 3 The effects of intravenous clonidine (open columns), ICI 101187 (solid columns), ICI 106270 (stippled columns), ICI 109683 (cross hatched columns) and ICI 110802 (hatched columns) on halothane-induced anaesthesia in rats.
$^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

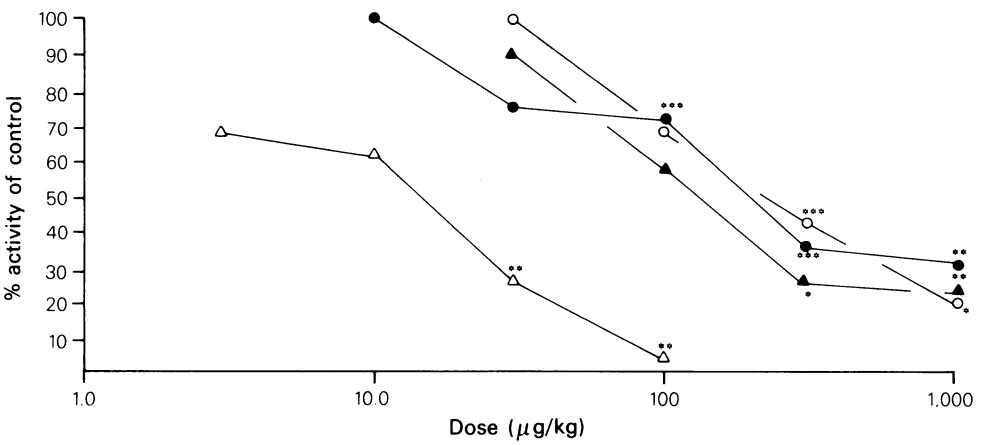


Figure 4 The effects of intravenous clonidine (△), ICI 106270 (●), ICI 110802 (○) and ICI 101187 (▲) on locomotor activity in rats.
$^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

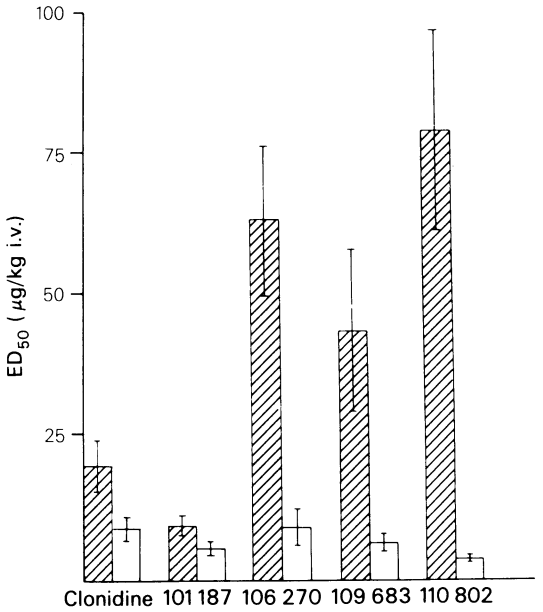


Figure 5 The potency of clonidine, ICI 101187, ICI 106270, ICI 109683 and ICI 110802 as α_1- and α_2-adrenoceptor agonists in the pithed rat. The ED_{50} heart rate (presynaptic, hatched columns) is the dose required to reduce the tachycardia induced by nerve stimulation by 50%. The ED_{50} blood pressure (post-synaptic, open columns) is the dose required to increase systolic blood pressure by 50 mmHg.
Values are mean of $n=6$; vertical lines show s.e. mean.

crease in sleeping time induced by clonidine was antagonized by yohimbine but not by prazosin or by piperoxan. The increase in sleeping time caused by both ICI analogues was however antagonized by piperoxan and not yohimbine. Surprisingly, the selective α_1-adrenoceptor antagonist, prazosin, also was an effective inhibitor of ICI 101187-induced sleeping.

Measurement of locomotor activity

The activity in treated rats as a percentage of the activity in control rats is shown in Figure 4. In this experiment clonidine and the ICI analogues all caused dose-related reductions in activity although again clonidine was more potent than the ICI analogues. These data were subjected to linear regression analysis and the dose to reduce activity by 50% (ED_{50}) was calculated (Table 1).

Clonidine had 13 times more sedative effect than ICI 101187, 16 times more than ICI 106270 and 21 times more than ICI 110802.

α_1- and α_2-Agonist activity in the pithed rat

All the compounds produced dose-related effects which were qualitatively similar on BP and HR. The ED_{50} for HR (dose to reduce the stimulation-induced increment in HR by 50%) and the ED_{50} for BP (dose to increase BP by 50 mmHg) were calculated (Figure 5). All five compounds had similar potency at the α_1-adrenoceptor while at the α_2-adrenoceptor marked differences were seen. Clonidine and ICI 101187 were both far more potent at the α_2-adrenoceptor than ICI 106270, ICI 109683 and ICI 110802. Table 1 gives the ED_{50} for these compounds at the α_1- and α_2-adrenoceptor in the pithed rat. Both the α_1 and the α_2 effects of all these compounds were antagonized by phentolamine (0.5 mg/kg i.v.).

α_2-Agonist activity in the mouse vas deferens

In this preparation it was found that ICI 106270 and ICI 110802 were less potent at inhibiting the contractions of the vas than ICI 101187 or clonidine (Figure 6). To check whether this was due to a post-junctional effect of the compounds, they were administered to the unstimulated vas and the results showed that ICI 110802 and ICI 106270 caused greater contractions than clonidine and ICI 101187 (Figure 7) and so this could account for the flattening of the dose-response curves seen in Figure 6. However, the maximal inhibition of the twitch response occurred at final bath concentrations of 10–30 ng/ml and at these concentrations little effect was observed post-junctionally. The IC_{50} (molar concentration to reduce stimulus-induced contraction by 50%) was calculated for each compound (Table 1). In this preparation, as in the pithed rat, clonidine and ICI 101187 had similar potencies pre-junctionally and both were much more potent than ICI 106270 and ICI 110802.

Discussion

The mechanism of action of clonidine as both a hypotensive and a sedative are not fully understood. Haeusler (1974) and Kobinger & Pilcher (1974) suggested that clonidine lowers blood pressure and heart rate by acting on central α-adrenoceptors which are situated post-synaptically. The selective α_2-antagonists, yohimbine and piperoxan (Drew, 1976), antagonize the hypotensive effects of clonidine (Bolme *et al.*, 1974; Finch, 1974) leading one to suppose that the central receptors involved in the cardiovascular actions of clonidine are of the α_2 type. However, recent reports that the selective α_1-antagonist prazosin, also antagonizes the hypotensive actions of clonidine (Cavero & Roach, 1978; Hamilton & Longman, 1980) make this interpreta-

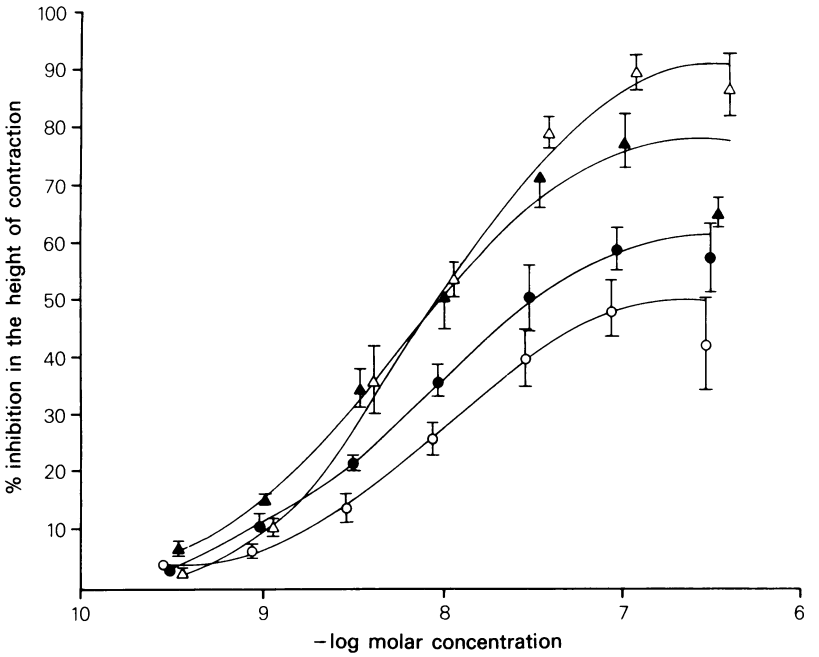


Figure 6 Concentration-response curves of clonidine (△), ICI 101187 (▲), ICI 106270 (●) and ICI 110802 (○) in the field stimulated mouse vas deferens: pre-junctional effect.

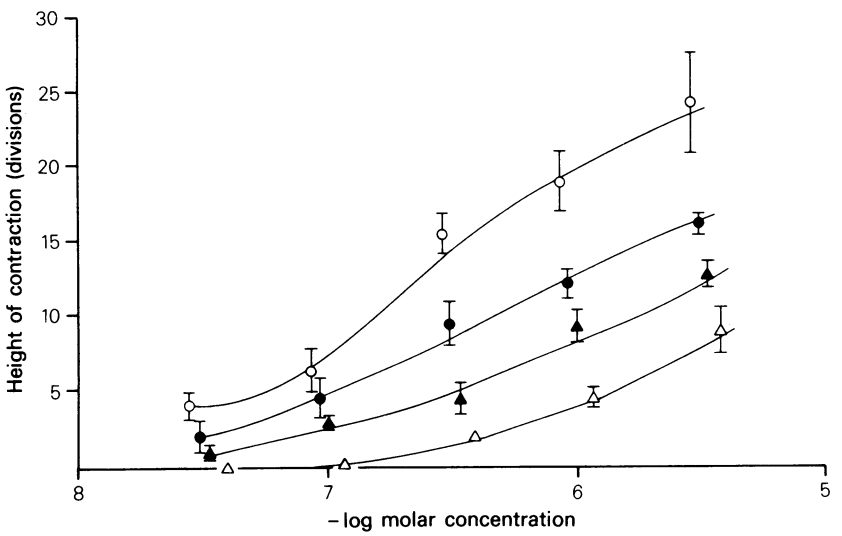


Figure 7 Concentration-response curves of clonidine (△), ICI 101187 (▲), ICI 106270 (●) and ICI 110802 (○) in the unstimulated mouse vas deferens: post-junctional effect.

tion unlikely. Previous results concerning the sedative actions of clonidine are equally confusing. The α_2-adrenoceptor antagonists piperoxan and yohimbine attenuate clonidine-induced sedation (Delbarre & Schmitt, 1971) while phentolamine, an α-adrenoceptor antagonist which is even more potent at the α_2-adrenoceptor than either piperoxan or yohimbine (Drew, 1976), fails to antagonize the sedation in some experiments (Holmann, Shillito & Vogt, 1971) but is effective in others (Drew *et al.*, 1979). The α-adrenoceptor antagonist phenoxybenzamine has also been reported to be ineffective in antagonizing clonidine-induced sedation (Delbarre & Schmitt, 1971). From the literature it is thus clear that both sedation and blood pressure lowering effects of clonidine are α-adrenoceptor mediated, although the pattern of responses obtained with α-adrenoceptor antagonists makes it difficult to ascribe these effects to either α_1- or α_2-adrenoceptors.

The results obtained in the present experiments confirm that clonidine produces both its cardiovascular and sedative actions via α-adrenoceptors although these experiments would again not allow a precise classification of which type of α-adrenoceptor is involved. From Table 2 it can be seen that yohimbine but not piperoxan antagonized the hypotensive actions of clonidine while prazosin was only weakly active. It is possible that larger doses of piperoxan would have been more effective, although this dose was very potent in antagonizing both the depressor and sedative effects of ICI 106270. With regard to the three ICI analogues, all three α-adrenoceptor antagonists attenuated the blood pressure lowering effects although piperoxan was only weakly active against ICI 101187. Yohimbine but not piperoxan antagonized the sedative actions of clonidine while piperoxan but not yohimbine antagonized the sedative effects of ICI 106270. As well as piperoxan, the α_1-antagonist, prazosin, prevented the increase in sleeping time induced by ICI 101187. Thus it appears that the hypotensive and sedative effects of the ICI analogues are mediated by α-adrenoceptors although, as with clonidine, it is far from clear from data obtained by use of α-adrenoceptor antagonists, which of these effects are mediated by α_1-receptors and which by α_2-receptors.

In the anaesthetized rat clonidine has been shown to be 3–5 times more potent in lowering blood pressure than any of the ICI analogues investigated in this study. As a sedative, clonidine is 10–13 times more active than ICI 101187 and 16–33 times more active than ICI 106270, ICI 109683 and ICI 110802. There is thus a separation between the sedative and hypotensive activity of these compounds when compared with clonidine.

In the pithed rat preparation the activity as α_1-adrenoceptor stimulants (Table 1, BP ED_{50}) was almost identical for clonidine, ICI 101187, ICI 106270 and ICI 109683, while ICI 110802 was significantly more potent as an α_1-stimulant than clonidine ($P < 0.05$). In the vas deferens, ICI 110802 also appears to be more potent than clonidine postjunctionally (Figure 7). It is unlikely therefore that the small differences in α_1-activity could account for the differences seen in sedation between these compounds. Clonidine and ICI 101187 also had similar potencies as α_2-adrenoceptor stimulants in both the pithed rat (ED_{50} HR, Table 1) and the mouse vas deferens (Table 1) so this also could not explain the difference in sedation seen between these two compounds.

However, within the ICI series of compounds, the compounds which were weakest as sedatives (ICI 106270, ICI 109683 and ICI 110802) were also the least potent as α_2-adrenoceptor agonists. ICI 110802 showed no evidence of sedation at all in the halothane sleeping time test and had least sedative effect in the locomotor activity test. It was also the most selective for the α_1-receptor and it is possible that it is not only potency for the α_2-receptor that determines degree of sedation but selectivity for the α_2-receptor.

These results thus confirm the findings of Drew *et al.* (1979) and Cavero & Roach (1978) that sedation produced by α-adrenoceptor agonists is related to pre-junctional or α_2-potency. The observation that ICI 101187, which is as potent as an α_2-adrenoceptor agonist as clonidine, has also 10 times less sedative effect than clonidine means either that clonidine has some other property which is enhancing its sedative effects or else, that measurement of α-adrenoceptor agonist potency in the periphery is not a suitable way of assessing central α-adrenoceptor potency of compounds. Alternatively it is possible that ICI 101187 has some other property which might reduce its sedative potential.

The ability of these compounds to lower BP appeared to be unrelated to α_2 activity since all four ICI analogues were equipotent at lowering BP yet had markedly different α_2-adrenoceptor potency (Table 1). Potency at the α_1-adrenoceptor seemed much more related to the fall in BP although again, clonidine was more potent in lowering BP than would be predicted from its α_1 activity.

There are several other factors that could account for the difference in the properties of these various α-agonists. If the penetration into the CNS of the ICI compounds was less than that of clonidine this could explain the reduced potency as sedatives and also possibly as hypotensive agents. The log P (octanol/water partition co-efficient) of the ICI analogues however indicates that they are at least as lipophilic as clonidine (unpublished observations) indicating that there should be no difficulty in their passing through the blood-brain barrier. In addition the relative potencies of the compounds in the differ-

ent tests would be affected if they were substrates or inhibitors of the neuronal or extra-neuronal uptake processes for noradrenaline. This information is not available for these compounds.

From these experiments it is not possible to say whether the α-adrenoceptors in the CNS responsible for the sedation or the antihypertensive effects of these compounds are of the α_1 or α_2 sub-type. However, the data presented here do confirm that the receptors responsible for these two actions are different and the results with the four ICI analogues show that it is possible to separate the anti-hypertensive effects of α-adrenoceptor stimulants from the undesirable sedative side-effects.

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