Both clonidine and synthetically released NA from bulbospinal NA terminals produce similar changes in the properties of the baroreceptor-heart rate reflex. With both IV and centrally administered clonidine there is an increase in HP range (between upper and lower plateaus of the sigmoid MAP-HP curve), a rise in average gain (slope), and a fall in median blood pressure (BP50) (Fig 6).

We have found that the clonidine analog alnidine (ST 567) antagonizes the effects of IV clonidine on the baroreflex HP range and gain, but has no effect on BP50 or on the resting blood pressure (Fig 6). Alnidine alone has a direct effect on the cardiac pacemaker but has no effect on the pressure-related parameters of the baroreflex curve (Fig 6). In the guinea pig left atrium, alnidine specifically antagonizes the inhibitory effect of clonidine on the inotropic response, with a potency of 1/1,000 of that of phenolamine and about 1/100 that of yohimbine. It has no significant α1-antagonist properties assayed in the guinea pig aortic strip preparation.

The selective antagonism by alnidine on the baroreflex-mediated HP range and gain, but the absence of such antagonism for BP50 and threshold for evoking bradycardia, suggests that there may be differences in central bulbospinal α1-receptors associated with neurons controlling these variables.

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Reversal of the Central Hypotensive Effect of Clonidine by Intracisternal Curare-like Agents*

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Administration of tubocurarine, pancuronium, gallamine, or decamethonium into the cisterna magna of chloralosed dogs induced a rise in blood pressure. Clonidine (3 μg/kg) administered into the cisterna magna after tubocurarine, pancuronium, or gallamine significantly increased blood pressure; no significant change was found after decamethonium. The pressor response to clonidine after tubocurarine was antagonized by injection of the α1-adrenoceptor-blocking agents AR-C 239 or prazosin into the cisterna magna at low doses prior to injection of clonidine. Yohimbine, a preferential α1-adrenoceptor-blocking agent was ineffective. It is suggested that the pressor response to intracisternal clonidine after intracisternal tubocurarine is due to stimulation of α1-adrenoceptor stimulation.

Tubocurarine administered directly into the CNS of anesthetized cats1 or applied topically to a discrete area

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of the ventral surface of the medulla oblongata was reported to increase transiently the arterial blood pressure and to cause seizure discharges. We recently observed that clonidine, a central α-adrenoceptor-stimulating agent, injected into the cisterna magna of dogs anesthetized with α-chloralose and pretreated with tubocurarine did not induce a decrease in blood pressure, but elicited a centrally mediated pressor effect. The purpose of the present study was to examine the precise action of four curare-like agents—tubocurarine, gallamine, pancuronium, and decamethonium—and to investigate the central mechanism of clonidine-induced hypertension.

METHODS

Adult mongrel dogs, unselected as to sex and weighing 8 to 10 kg, were anesthetized with α-chloralose (100 mg/kg IV). They were intubated and ventilated with a Mark VII Bird respirator. A femoral artery and a saphenous vein were cannulated for the measurement of systemic blood pressure and for the injection of drugs, respectively. Blood pressure was recorded with a Statham P23Db transducer on a channel of a Gould-Brush 2400 recorder. Heart rate was counted from the pressure signal by means of a Gould-Brush tachograph and was recorded on a second channel of the recorder. Injections into the cisterna magna were performed by means of an 18-gauge needle introduced percutaneously. Drugs were given in saline solution in a volume no larger than 0.2 ml when injected into the cisterna magna. Groups of 4 to 7 dogs were used. All results are expressed as the mean ± SEM. The statistical significance was calculated using Student’s t test for paired comparison or for comparison between groups, according to the type of experiment.

The following drugs were used: tubocurarine hydrochloride (Abbott), gallamine triethiodhydrate (Rhône-Poulenc), pancuronium bromide (Organon), decamethonium bromide (Sigma), diazepam (Hoffmann-LaRoche), clonidine hydrochloride (C. H. Boehringer, Ingelheim), yohimbine hydrochloride (Boyer), AR-C 239 (2(2-(4-O-methoxyphenyl)-piperazin-1-yl)-4,4-dimethyl-1,3(2H,4H) isoquinoline-1-nedione hydrochloride (Karl Thomas), prazosin hydrochloride (Pfizer), and α-chloralose (Seilabo).

| Table 1—Action of Intracisternal Clonidine (3 μg/kg) in Dogs Pretreated With Some Curare-like Agents |
|---|---|---|
| Agents | Initial Mean Blood Pressure, mm Hg | Minimal Mean Blood Pressure, mm Hg | Difference, mm Hg |
| Clonidine (n = 7) | 91 ± 6 | 56 ± 9* | -35 ± 9* |
| Tubocurarine (100 μg/kg) + clonidine (n = 7) | 114 ± 9 | 144 ± 13* | 30 ± 11* |
| Pancuronium (100 μg/kg) + clonidine (n = 6) | 116 ± 6 | 136 ± 9* | 15 ± 4* |
| Gallamine (150 μg/kg) + clonidine (n = 6) | 93 ± 4 | 99 ± 4* | 6 ± 2† |
| Decamethonium (150 μg/kg) + clonidine (n = 6) | 89 ± 7 | 88 ± 8 | -1 ± 3 |

*p<0.01; †p<0.05

RESULTS

Cardiovascular Effects of the Four Curare-like Agents

Intracisternal administration of tubocurarine (100 μg/kg) induced a significant rise in mean arterial blood pressure from 114 ± 9 to 158 ± 7 mm Hg. This pressor response was associated with a small but not significant reduction in heart rate (18 ± 7 beats/min). Intracisternal administrations of pancuronium (100 μg/kg), decamethonium (150 μg/kg), or gallamine (150 μg/kg) induced rises in mean arterial blood pressure of 15 ± 2, 17 ± 4, and 17 ± 3 mm Hg, respectively, without any significant changes in heart rate.

Intravenous (IV) administration of tubocurarine (100 μg/kg) induced a decrease in blood pressure, whereas pancuronium (100 μg/kg), decamethonium (150 μg/kg), or gallamine (150 μg/kg) did not cause significant changes in blood pressure. Heart rate was not significantly changed by the four curare-like agents.

Effects of Clonidine Administered into the Cisterna Magna on Blood Pressure in Dogs Pretreated With Curare-like Agents

In control dogs, clonidine (3 μg/kg) injected into the cisterna magna induced progressive and long-lasting decrease in blood pressure associated with bradycardia. At maximal effects, mean arterial blood pressure was 56 ± 9 mm Hg compared with the value of 91 ± 6 mm Hg.

In other groups of animals, the curare-like agents were injected into the cisterna magna before the administration of clonidine. Clonidine was administered when the change in blood pressure induced by the curare-like agents disappeared or when blood pressure was stabilized.

Clonidine administered in dogs pretreated with tubocurarine no longer reduced blood pressure, but on the contrary induced an increase in mean arterial blood pressure from 114 ± 9 to 144 ± 3 mm Hg. After pancuronium, clonidine induced a pressor response from 111 ± 6 to 126 ± 9 mm Hg.

| Table 2—Effects of α₁- and α₂-Adrenoceptor-blocking Agents on the Pressor Response to Intracisternal Clonidine After Intracisternal Tubocurarine |
|---|---|---|
| Agent* | Initial Mean Blood Pressure, mm Hg | Minimal Mean Blood Pressure, mm Hg | Difference, mm Hg |
| Clonidine after tubocurarine (100 μg/kg) | 114 ± 9 | 144 ± 13† | 30 ± 11 |
| Clonidine after tubocurarine (100 μg/kg) and and intracisternal AR-C 239 (5 μg/kg) | 103 ± 4 | 98 ± 15 | -5 ± 7† |
| Clonidine after tubocurarine (100 μg/kg) and and intracisternal prazosin (5 μg/kg) | 138 ± 12 | 140 ± 12 | 2 ± 2† |
| Clonidine (3 μg/kg) after tubocurarine (100 μg/kg) and and yohimbine (75 μg/kg) | 120 ± 11 | 139 ± 17† | 19 ± 6 |

*All doses of clonidine were 3 μg/kg |

†p<0.01 Compared with initial value

Central alpha-Adrenoceptors
(p<0.01). After decamethonium, clonidine induced a small but significant hypertension (from 93 ± 4 to 99 ± 4 mm Hg, p<0.05). Clonidine did not cause a significant change in blood pressure after gallamine (89 ± 7 and 88 ± 8 mm Hg) (Table 1).

**Action of α-Adrenoceptor-blocking Drugs on the Pressor Response to Clonidine in Dogs Pretreated With Tubocurarine**

To investigate the mechanism of the pressor response to clonidine, groups of dogs (n = 6) pretreated with tubocurarine were treated by intracisternal administration of an α-adrenoceptor-blocking agent 15 minutes before the administration of clonidine by the same route. The rise in blood pressure produced by clonidine after tubocurarine was prevented by prior intracisternal administration of the α1-adrenoceptor blocking agents, prazosin or AR-C 239, but was not significantly reduced by the preferential α2-adrenoceptor-blocking agent yohimbine (Table 2).

**DISCUSSION**

The four curare-like agents, tubocurarine, pancuronium, gallamine, and decamethonium, injected into the cisterna magna of chloralose-treated dogs induced increase in blood pressure, whereas IV administration of the same doses produced a decrease in blood pressure with tubocurarine or no significant changes with the other three agents. These results indicate a central site of action for the pressor effect and fit in with results of previous investigations performed on chloralosed cats.14 The depressor effect of IV tubocurarine is well known and is usually ascribed to histamine release and to ganglionic blockade. The mechanism of pressor response to intracisternal administration is not known; however, tubocurarine has been reported to block the inhibitory effect of GABA on neurons.4 GABA has been suggested to reduced blood pressure and heart rate by centrally mediated effects;4 the mechanism of the pressor response to intracisternal administration may be a blockade of GABAergic mechanisms.

It is usually accepted that clonidine reduces blood pressure, heart rate, and sympathetic nerve activity by an action on the CNS.8 In the control dogs, intracisternal administration of clonidine reduced blood pressure and heart rate. By contrast, injection of clonidine into the cisterna magna after administration of tubocurarine, pancuronium, or gallamine produced a significant rise in blood pressure. Clonidine did not significantly change blood pressure after decamethonium. That clonidine could increase blood pressure by a centrally mediated effect was suggested by other results—eg, clonidine administered into the lateral ventricle of the brain in cats, with aqueduct of Sylvius cannulated to prevent access to the fourth ventricle, produced an increase in blood pressure;9 clonidine potentiated the pressor response to hypothalamic stimulation in cats,9 a part of the initial pressor response to clonidine in rats has been suggested to be centrally mediated, since the pressor response was smaller in decerebrate than in intact rats.10 It is therefore possible that some curare-like agents unmask this centrally mediated increase in blood pressure. The mechanism of action is unknown, but a blockade of GABAergic mechanisms is a possibility.

The pressor response to intracisternal clonidine in dogs pretreated with tubocurarine was suppressed by prior intracisternal administration of low doses of the α1-adrenoceptor blocking agents AR-C 239 or prazosin. A small but not significant reduction in the pressor response to clonidine was found with the preferential α2-adrenoceptor blocking agent yohimbine; this reduction could be due to α2-adrenoceptor blockade by yohimbine.

These results suggest that the central pressor response to clonidine after administration of tubocurarine may be due to stimulation of central α-adrenoceptors.

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