

EFFECTS OF CLONIDINE ON CANINE CARDIAC NEUROEFFECTOR STRUCTURES CONTROLLING HEART RATE

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1 In intact dogs anaesthetized with pentobarbitone, clonidine (10 µg/kg, i.v.) produced a sustained decrease in heart rate. This effect was significantly smaller in vagotomized dogs in which the sympathetic drive to the heart was either left intact or experimentally created by continuous electrical stimulation of the decentralized cardioaccelerator nerve. In the latter preparation, the negative chronotropic action of clonidine was reversed by an intravenous injection of phentolamine, whereas in the former experimental situation it was antagonized only by an intravenous plus an intravertebral artery injection of phentolamine.

2 In dogs with denervated hearts the tachycardia produced by electrical stimulation of the cardioaccelerator nerve was accompanied by a rise in noradrenaline overflowing into the coronary sinus plasma. Clonidine inhibited both these effects and phentolamine restored them to pre-clonidine levels.

3 Clonidine decreased heart rate in dogs with an intact parasympathetically innervated heart and decentralized stellate ganglia. When the low basal heart rate of this preparation was elevated by electrical stimulation of the cardioaccelerator nerve, clonidine had a negative chronotropic effect, the degree of which was similar to that observed in intact dogs.

4 Clonidine neither modified baseline heart rates of dogs with denervated hearts nor the levels of heart rate which in this preparation were reduced by a sustained electrical stimulation of the right vagus or increased by intravenous infusions of either isoprenaline or noradrenaline.

5 These findings indicate that in the intact dog, bradycardia induced by clonidine resulted both from a reduction of sympathetic drive and from a concomitant increase in parasympathetic tone. The latter action did not occur at the level of cardiac neuroeffector structures since it was observed only in the presence of centrally connected vagal pathways. The inhibition of cardiac sympathetic tone was of both peripheral and central origin. Clonidine, in fact, diminished the quantity of noradrenaline overflowing into the coronary sinus plasma in cardiac denervated dogs with a tachycardia elicited by electrical stimulation of the decentralized cardioaccelerator nerve. This peripheral effect was probably due to an activation of α -adrenoceptors located on sympathetic nerve terminals since it was antagonized by phentolamine. However, in vagotomized dogs (intact sympathetic pathways) intravenous phentolamine failed to antagonize the heart rate effects of clonidine which were abolished by a subsequent injection of phentolamine into the vertebral artery. Thus, the clonidine-induced inhibition of both the peripheral and central sympathetic drive to the heart would appear to be mediated via α -adrenoceptors.

Introduction

The heart rate slowing induced by clonidine in man and animals is the epiphenomenon of a complex interplay involving both the sympathetic and the parasympathetic components of the autonomic ner-

vous system (see review: Schmitt, 1977). In fact, clonidine in doses exerting pronounced cardiovascular effects does not significantly affect the intrinsic firing of the sinus node in several animal species (Schmitt, 1977).

It has been proposed that the negative chronotropic action of clonidine involves a reduction of the sympathetic drive and an activation of parasympathetic tone occurring predominantly within the central

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nervous system (Schmitt, 1977). However, at present there is a considerable amount of evidence favouring an action of clonidine on sympathetic nerve terminals innervating the sino-atrial (S-A) node. Clonidine, in fact, was found to inhibit the positive chronotropic effects elicited by low frequency electrical stimulation of the cardioaccelerator nerve in dogs (Scriabine, Stavorski, Wenger, Torchiani & Stone, 1970; Scriabine & Stavorski, 1973; 1977). Many authors have shown that this compound reduces cardiac acceleration elicited by electrical stimulation of sympathetic fibres in pithed rats (Armstrong & Boura, 1973; Drew, 1976; Doxey & Everitt, 1977; Roach, Lefèvre & Cavero, 1978) and spinalized dogs (Roach *et al.*, 1978). This effect of clonidine has been demonstrated in dogs to be due to a reduction of the amount of neurotransmitter released from cardiac sympathetic nerve endings (Yamaguchi, De Champlain & Nadeau, 1977; Cavero, Dennis, Lefèvre-Borg, Perrot, Roach & Scatton, 1979a).

This investigation was specifically designed to assess the role of the peripheral autonomic nervous system in the bradycardia induced by clonidine. The experimental approach was that of mimicking the cardiac sympathetic or parasympathetic drive by continuous electrical stimulation of the cardioaccelerator or peripheral vagus nerves, respectively, in the dog anaesthetized with pentobarbitone.

Part of this work was presented to the International Symposium on Presynaptic Receptors, held in Paris in July 1978 (Cavero, Dennis, Roach & Scatton, 1979b).

Methods

Mongrel dogs of either sex weighing 12 to 18 kg were used in this study. Anaesthesia was induced with sodium pentobarbitone (35 mg/kg, *i.v.*) and maintained at surgical state with an intravenous infusion (5 to 10 mg kg⁻¹ h⁻¹) of the same anaesthetic agent. The animals were kept under artificial respiration (Bird Mark 7 respirator) throughout the experimental procedure.

The brachial vein was cannulated for intravenous drug administration. A catheter was inserted into the thoracic aorta via the brachial artery to measure blood pressure (Statham P23Db transducer connected to a Grass 7P1 preamplifier). A cardiometer (Grass 7P44E: triggered by the pressure pulse) was used to measure heart rate. Both parameters were recorded on a Grass 79B polygraph.

In several groups of dogs, the vagi were dissected free from the carotid arteries, ligated and severed. In a few animals, the right vagus was severed and the peripheral end placed on a bipolar electrode and stimu-

lated with a train of square waves (10 V, 5.0 ms, 1.0 Hz, F. Haer Pulsar 6i stimulator).

The thorax was open at the level of the second intercostal space in all animals in order to standardize experimental conditions. In some preparations both the right and the left stellate ganglia were completely decentralized. The most caudal postganglionic branch of the right stellate ganglion (cardioaccelerator nerve) was placed on a bipolar platinum electrode for electrical stimulation (10 V, 2.0 ms, 1.0 Hz).

The right vertebral artery was dissected at its branching point from the subclavian artery in 3 thoracotomized dogs and a small catheter inserted into it by means of a needle in order to avoid the interruption of blood flow.

In 4 thoracotomized dogs, the sinus node artery was dissected (Hashimoto, Tanaka, Hirata & Chiba, 1967) and after heparinization (700 u/kg, *i.v.*) a shunt was established between this artery and a femoral artery. The shunt circuit contained an extracorporeal electromagnetic flow probe (Carolina Medical Electronics) in order to survey the blood flow and a rubber connector for drug administration.

The methods for collection of blood samples from the coronary sinus and for measurement of coronary sinus plasma noradrenaline concentration have been explained in detail in a recent paper from this laboratory (Cavero *et al.*, 1979a).

Generally, the time period between the end of the surgical preparation and the start of the experimental procedure was 30 to 45 min. The intravenous dose of clonidine in each study was 10 µg/kg, given as a bolus injection. A lower dose (3 µg/kg, *i.v.*) was used in a few preliminary experiments, but did not elicit consistent heart rate effects. In a group of animals clonidine (2.0 µg total dose, equivalent to 0.11 to 0.14 µg/kg) was administered directly into the artery perfusing the S-A node area.

The design of various experimental procedures is given in the Results section.

Analysis of results

Results are given as means ± standard error of the mean. The area under the effect-time curve (AUC) was calculated for several experimental procedures (Table 1) by using the trapezoidal rule. A two-way analysis of variance or a *t* test was used to perform statistical comparisons.

Drugs

The drugs used in this study were clonidine hydrochloride (Boehringer Ingheleim), isoprenaline hydrochloride (Labaz), noradrenaline bitartrate (Sigma), phentolamine mesylate (Ciba-Geigy) and sodium pentobarbitone (Abbott).

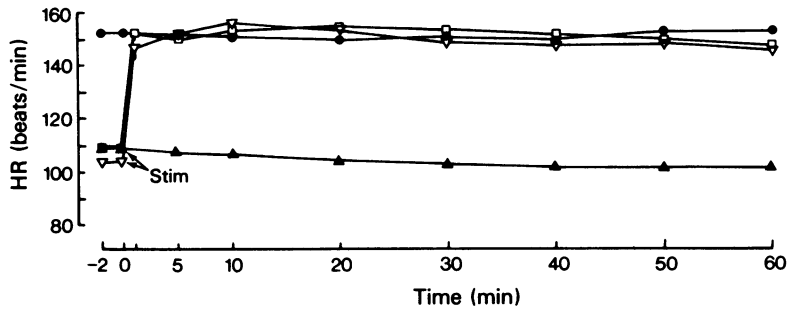


Figure 1 Heart rate (HR) levels during 1 h control period in pentobarbitone-anaesthetized dogs with an intact cardiac innervation (●; *n* = 6) or a surgically denervated heart (▲; *n* = 5). In cardiac denervated dogs (▽; *n* = 3) or in dogs with stellate ganglia decentralized (□; *n* = 3) the stability of heart rate increase produced by sustained electrical stimulation (10 V, 2 ms, 1 Hz) of the cardioaccelerator nerve over a 60 min period is shown.

The doses of each drug in the text refer to the bases of these compound.

Results

Heart rates were stable over a 60 min observation

period in thoracotomized pentobarbitone-anaesthetized dogs in which cardiac innervation was either left intact or surgically removed by bilateral vagotomy plus decentralization of both stellate ganglia (Figure 1).

Both in cardiac denervated dogs or in dogs with vagi intact and stellate ganglia decentralized, sus-

Table 1 Baseline values of heart rates (HR) of several animal preparations and the estimated number of beats (area under the time-bradycardia curves represented in Figure 2: AUC) not performed by the heart during 10, 30 and 60 min following the administration of clonidine (10 µg/kg, i.v.) to several groups of dogs in which the autonomic innervation to the heart was left intact (Intact) or surgically removed by section of vagi and/or decentralization of stellate ganglia (D); in 2 groups of dogs with decentralized stellate ganglia the sympathetic drive was experimentally created by electrical stimulation of the cardioaccelerator nerve (STC)

Preparation	<i>n</i>	Time after clonidine (min)						
		0 HR (beats/min)	10 AUC (beats)	%Δ*	30 AUC (beats)	%Δ*	60 AUC (beats)	%Δ*
Intact	6	156 ± 7	772 ± 127	-49	2186 ± 374	-49	4027 ± 673	-43
Vagotomised (V)	5	158 ± 6	218 ± 14	-14	730 ± 57	-16	1477 ± 119	-16
D	6	124 ± 5	447 ± 70	-37	1250 ± 237	-33	2662 ± 544	-32
V + D*	3	129 ± 7	15 ± 5	0	103 ± 12	0	337 ± 32	0
D + STC	6	170 ± 7	745 ± 124	-43	2054 ± 365	-38	3491 ± 672	-34
V + D + STC	7	149 ± 8	253 ± 31	-17	838 ± 107	-19	1643 ± 247	-18

n = number of dogs per group.

*Percentage changes (%Δ) in the given AUC from theoretical control AUC (= number of beats performed by the heart if no treatment was given during 10, 30 and 60 min; this value is found by multiplying the baseline heart rate by these time periods).

There was no significant difference in calculated AUC and %Δ between intact and D + STC or V and V + D + STC (analysis of variance). The responses (AUC and %Δ) in V and V + D + STC preparations were significantly smaller than in intact and D + STC dogs (*P* < 0.05; analysis of variance). Furthermore, in stellectomized (D) dogs the effects of clonidine were significantly smaller than in both intact or D + STC dogs (*P* < 0.05; analysis of variance) only if expressed as AUC, however, if they are expressed as %Δ from control there is no difference between D, Intact, D + STC preparations.

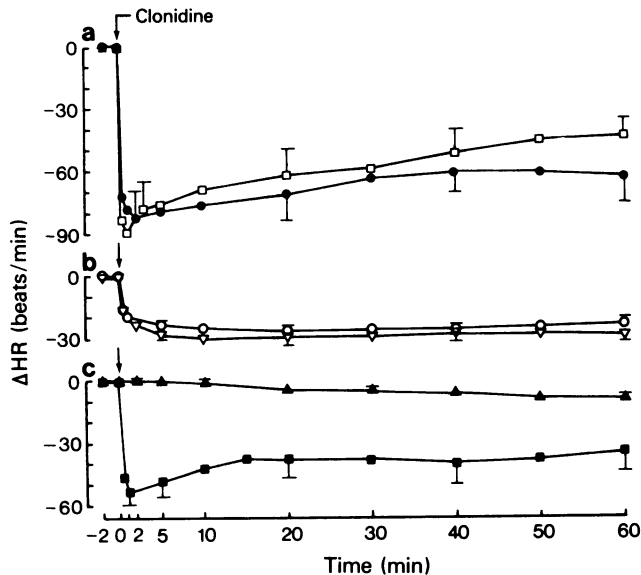


Figure 2 Changes in heart rate (Δ HR) produced by clonidine ($10 \mu\text{g}/\text{kg}$, i.v.) in pentobarbitone anaesthetized dogs under several experimental conditions. In (a) the effects on animals with an intact cardiac innervation (\bullet ; $n = 6$) or decentralized stellate ganglia plus electrical stimulation of cardioaccelerator nerve (\square ; $n = 6$) are represented. In (b) the dogs were vagotomized (\circ ; $n = 5$) or cardiac denervated with heart rate elevated by sustained electrical stimulation (10 V , 2 ms , 1 Hz) of the cardioaccelerator nerve before clonidine administration (∇ ; $n = 7$). In (c) the effects of clonidine in animals with cardiac denervation (\blacktriangle ; $n = 3$) or decentralized sympathetic ganglia plus vagi intact (\blacksquare ; $n = 6$) are shown.

tained electrical stimulation of the cardioaccelerator nerve resulted in a rapid rise in heart rate which after attaining a plateau persisted for the 1 h experimental period (Figure 1).

Table 1 shows heart rates of selected groups of dogs in which the autonomic innervation of the S-A node was either left intact or surgically removed and, then, mimicked in some preparations by continuous stimulation of the cardioaccelerator nerve. Interruption of the vagal input to the S-A node did not modify heart rate (Table 1) since pentobarbitone produces a vagolytic action resulting in a sympathetic predominance (Olmsted & Page, 1966). For this reason removal of sympathetic drive significantly decreased heart rate (Table 1).

Role of the autonomic nervous system in the bradycardia induced by clonidine

Intravenous administration of clonidine ($10 \mu\text{g}/\text{kg}$) to dogs with an intact cardiac innervation produced a fall in heart rate which attained a maximum (-82 ± 13 beats/min) within 2 min of the injection (Figure 2) and in some animals was accompanied by

dysrhythmia. The latter effect and part of the initial bradycardia were undoubtedly of vagal origin in response to the pressor action of clonidine since the negative chronotropic action of clonidine became smaller and the dysrhythmia disappeared when the raised blood pressure recovered to baseline values. Additionally, no dysrhythmia was noted in response to the greater clonidine pressor response in vagotomized dogs. During the 60 min period following the administration of clonidine the heart beat 4027 ± 673 times less than it would have done in the absence of this treatment (Table 1). In a group of animals used as control, there was no significant heart rate changes over the same period of time (Figure 1).

Surgical interruption of the autonomic innervation to the S-A node by section of the vagi and decentralization of both stellate ganglia lowered heart rate (Table 1). In this experimental situation clonidine did not significantly modify cardiac automaticity (Figure 2 and Table 1).

In vagotomized dogs, clonidine decreased heart rate. This effect was approximately 63% smaller (as estimated from the action of clonidine during a 60 min period: Table 1) than that produced by this

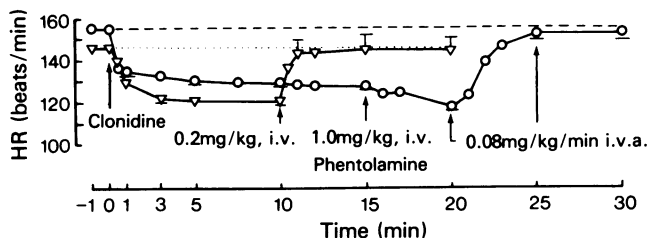


Figure 3 Heart rate (HR) effects of clonidine (10 $\mu\text{g}/\text{kg}$, i.v.) in vagotomized dogs (O; $n = 3$) and in cardiac denervated dogs (∇ ; $n = 4$) in which heart rate was increased by electrical stimulation (10 V, 2 ms, 1 Hz) of the cardioaccelerator nerve. The effects of phentolamine administered only intravenously (0.2 mg/kg) to the latter group of animals or both intravenously (0.2 + 1.0 mg/kg) and, then, into the vertebral artery (i.v.a.) (0.08 mg kg^{-1} min $^{-1}$ over 5 min) to vagotomized dogs are shown.

compound in intact dogs even though the initial heart rates of the two groups of animals were similar (Table 1).

In dogs with intact vagi and decentralized stellate ganglia (baseline heart rate significantly lower than in intact animals: Table 1), administration of clonidine induced a negative chronotropic effect which reached a peak (-53 ± 7 beats/min) in about 2 min and, then, attained a steady state (-38 ± 9 beats/min) within approximately 20 min which persisted until the end of the experiment (Figure 2). The heart rate effects of clonidine in this group of animals were 44% less (as estimated from data of Table 1) than those observed in intact animals.

In dogs with intact vagi in which the decentralized cardioaccelerator nerve was stimulated to increase heart rate to a value similar to that of intact dogs (Table 1), clonidine induced a peak heart rate decrease (-90 ± 10 beats/min) comparable to that in intact animals. This effect during the first 30 min was practically the same in both groups of animals (Figure 2 and Table 1). However, in the period 30 to 60 min it tended to become smaller in dogs with intact vagi plus a peripherally simulated sympathetic tone (Figure 2, Table 1).

In cardiac denervated dogs in which the low baseline heart rate was elevated by stimulation of the cardioaccelerator nerve (Table 1), clonidine produced a negative chronotropic effect, the peak of which was similar to that elicited by clonidine in vagotomized dogs with an intact cardiac sympathetic drive (Figure 2). This bradycardia was approx. 59% smaller than that measured in intact dogs at the end of the 1 h observation period (Table 1).

Role of baseline heart rate levels in the bradycardia induced by vagal stimulation

The greater absolute change in heart rate produced

by clonidine in dogs with decentralized stellate ganglia and heart rate increased by stimulation of the cardioaccelerator nerve, as compared to that observed in dogs with only decentralized stellate ganglia (Figure 2 and Table 1) could be interpreted as a direct evidence for a peripheral inhibition of sympathetic tone by this compound. However, if this conclusion of the paper (see Discussion) were only based on these results, it could be incorrect, as is indicated by the following experiments.

In cardiac denervated dogs, electrical stimulation of the right vagus (1 Hz, 5 ms, 10 V over 90 s) produced a bradycardia which was reproducible upon repetition of the stimulation. In three dogs this procedure was performed before and during a sustained elevation of heart rate (HR) produced by stimulation of the cardioaccelerator nerve. The respective responses to vagal stimulation were as follows: -29 ± 2 beats/min ($= -25\%$ change from baseline HR = 114 ± 2 beats/min); and -48 ± 4 beats/min ($= -30\%$ change from baseline HR = 160 ± 15 beats/min).

In an additional group of three dogs, vagal stimulation was performed before and during the tachycardia produced by an infusion of isoprenaline. The respective responses to this stimulation were: -33 ± 1 beats/min ($= -28\%$ change from baseline HR = 118 ± 8 beats/min) and -52 ± 5 beats/min ($= -31\%$ change from baseline HR = 167 ± 10 beats/min).

Therefore, the absolute changes in heart rate due to vagal activation are dependent upon the baseline heart rate. However, if the data are reported as percentage change from prestimulation heart rate, this dependency appears not to exist. This conclusion holds true also for the results obtained with clonidine in dogs with decentralized stellate ganglia in which heart rate was either unmodified or increased by electrical stimulation of the cardioaccelerator nerve (Table 1).

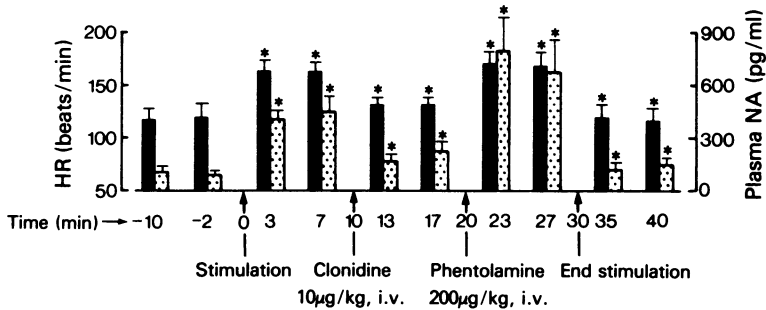


Figure 4 Effects of electrical stimulation of the cardioaccelerator nerve on heart rate (solid columns) and noradrenaline (NA) coronary sinus plasma content (stippled columns) in cardiac denervated (spinal) dogs ($n = 4$). The effects of clonidine ($10 \mu\text{g}/\text{kg}$, i.v.) and of phentolamine ($0.2 \text{ mg}/\text{kg}$, i.v.) administered 10 min after clonidine on these parameters are also given. Heart rate and coronary sinus plasma noradrenaline returned to approximately pre-stimulation levels when electrical stimulation was terminated.

An asterisk indicates that the value of the parameter is significantly different from that produced by the immediately preceding treatment ($P < 0.05$: analysis of variance). There was no difference between the values of heart rate and plasma noradrenaline measured before initiation and after termination of the stimulation.

Effects of phentolamine on the slowing of heart rate induced by clonidine

In dogs with denervated hearts in which heart rate was increased by stimulation of the cardioaccelerator nerve, the decrease in heart rate produced by clonidine was entirely inhibited by intravenous administration of $0.2 \text{ mg}/\text{kg}$ phentolamine (Figures 3 and 4). However, in vagotomized dogs (intact sympathetic pathways) this dose of phentolamine plus an additional $1.0 \text{ mg}/\text{kg}$ dose did not modify the clonidine-induced bradycardia which was abolished by a subsequent intravertebral artery infusion of the α -adrenoceptor blocking agent (Figure 3).

Effects of clonidine on heart rate and coronary sinus plasma noradrenaline content

In cardiac denervated dogs electrical stimulation of the cardioaccelerator nerve raised heart rate and the content of noradrenaline present in the coronary sinus plasma (Figure 4). Both effects were reduced by clonidine (Figure 4). Phentolamine antagonized the bradycardia induced by clonidine and restored coronary sinus noradrenaline concentration to levels higher than those measured before administration of clonidine (Figure 4). When the electrical stimulation of the cardioaccelerator nerve was stopped heart rate and coronary sinus plasma noradrenaline content returned to pre-stimulation levels (Figure 4).

Effect of clonidine on heart rate increased by isoprenaline and noradrenaline or decreased by sustained vagal stimulation

In dogs with denervated hearts, heart rate was increased (approximately 40 beats/min) by an intravenous infusion of isoprenaline (0.12 to $0.25 \mu\text{g kg}^{-1} \text{ min}^{-1}$, $n = 2$) or noradrenaline (0.3 to $0.7 \mu\text{g kg}^{-1} \text{ min}^{-1}$, $n = 3$). Clonidine did not affect this tachycardia whereas it reduced the heart rate elevated by electrical stimulation of the cardioaccelerator nerve (Figure 4).

In a group of cardiac denervated dogs, a sustained stimulation of the right vagus for 25 min reduced the baseline heart rate (118 ± 8 beats/min) by approx. 20%. Clonidine did not significantly modify this experimentally evoked vagal bradycardia.

Effects of clonidine administered into the coronary sinus artery

Clonidine ($2 \mu\text{g}$, total dose) administered directly into the artery perfusing the S-A node region produced a decrease in heart rate which after reaching a peak in about 2 min and persisting at this level for the subsequent 2 min disappeared in approx. 20 min. This effect was reproducible upon repetition of the injection of clonidine. Administration of phentolamine ($50 \mu\text{g}$, total dose) into the sinus node artery antagonized this bradycardia produced by clonidine (Figure 5).

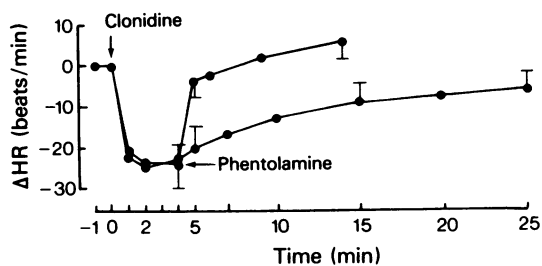


Figure 5 Changes in heart rate (Δ HR) produced by clonidine (2 μ g; total dose) injected into the artery perfusing the S-A node region in intact dogs ($n = 4$). The two curves were obtained in the same animals at a 60 min interval. Phentolamine (50 μ g; total dose) was given 4 min after the second administration of clonidine. The initial heart rate value was 148 ± 8 beats/min. Whereas the area under the heart rate decrease-time profiles (AUC) during the first 4 min following two successive administrations of clonidine were the same, the AUCs for the subsequent 10 min were significantly different ($P < 0.05$, paired t test), the heart rate effect of clonidine being significantly antagonized by phentolamine. These doses of clonidine or phentolamine did not affect mean aortic blood pressure.

Discussion

That clonidine caused a similar decrease in heart rate in both vagotomized dogs (i.e. with intact efferent sympathetic pathways) and in cardiac denervated dogs in which the sympathetic drive to the heart was experimentally simulated by continuous electrical stimulation of the cardioaccelerator nerve, clearly indicates that this compound can produce significant negative chronotropic effects by an action at the sympathetic neuroeffector level. The end organ was excluded as a possible site of action since this agent failed to modify the tachycardia to either noradrenaline or isoprenaline. Therefore, presumably clonidine reduced in some way the amount of neurotransmitter released from the sympathetic nerve terminal and reaching postsynaptic cardiac β -adrenoceptors. This suggestion was confirmed biochemically. Clonidine, in fact, decreased the quantity of noradrenaline overflowing into the coronary sinus blood in cardiac denervated dogs in which heart rate was elevated by continuous stimulation of the cardioaccelerator nerve (for a more complete discussion of these results, see Cavero *et al.*, 1979a). This peripheral mechanism of action is probably of functional significance because it was shown that in intact dogs, small doses of clo-

nidine injected into the artery perfusing the S-A node region produced a negative chronotropic effect without affecting blood pressure. This effect, previously described by Scriabine *et al.*, (1970), was antagonized by an injection of phentolamine (a classical α -adrenoceptor antagonist) into the same artery. While in this preparation Scriabine *et al.* observed heart rate reductions only after 0.1 and 0.4 μ g clonidine, our preparations needed 2.0 μ g. This difference may be explained on the basis of the method used by these authors whereby clonidine was injected into a cannulated artery in which the blood flow was stopped. However, in this investigation the S-A node area was continuously perfused.

It has been suggested that the inhibition of noradrenaline release by clonidine from sympathetic nerve endings is mediated via stimulation of presynaptic α -adrenoceptors (see reviews: Langer, 1977; Starke, 1977), since α -adrenoceptor blocking agents, such as phentolamine or phenoxybenzamine antagonize this effect (Yamaguchi *et al.*, 1977; Cavero *et al.*, 1979a; present results).

The peripheral site of action of clonidine should be considered additional and complementary to the well known reduction of the central sympathetic outflow to the heart as previously demonstrated by the fall in neural activity recorded at the level of sympathetic cardiac nerve fibres after clonidine administration (Schmitt, 1977). In this investigation phentolamine abolished the peripherally-induced heart rate slowing effect of clonidine in cardiac denervated dogs with a tachycardia experimentally produced by electrical stimulation of the cardioaccelerator nerve. However, since this antagonist failed to do so when administered intravenously to vagotomized dogs with intact efferent sympathetic nerve fibres to the heart, an action of clonidine on sympathetic drive emanating from the central nervous system was presumed. This latter mechanism became evident when an intravertebral infusion of phentolamine, after blockade of cardiac presynaptic α -adrenoceptors, abolished the clonidine-induced bradycardia. Thus, an activation of α -adrenoceptors mediates the inhibition of sympathetic tone produced by clonidine both at the peripheral and central sites.

Clonidine reduced heart rate in dogs with decentralized stellate ganglia. This effect was entirely due to a vagal activation since it did not occur in cardiac denervated dogs. No effort was made to clarify the sites of action of the clonidine-induced increase in parasympathetic efferent activity which may result from an action on peripheral (via afferent pathways) and central sites (Laubie, Schmitt & Drouillard, 1976; Schmitt, 1977). A possible effect of clonidine at the level of the cardiac vagal neuroeffector has been suggested by Duchène-Marullaz, Combre, Lapalus, Boucher & Lavarenne (1971) since clonidine poten-

tiated the bradycardia and the duration of cardiac arrest produced by electrical stimulation of the right vagus nerve. However, in cardiac denervated dogs clonidine failed to modify the bradycardia experimentally evoked by electrical stimulation of the peripheral stump of the severed right vagus nerve. This discrepancy might be due to the difference in experimental procedure or the relatively small dose of clonidine used in this investigation.

In conclusion, the inhibition of the cardiac sympathetic tone elicited by clonidine in the dog anaesthetized with pentobarbitone occurred both at the level of the central nervous system and at the level of sympathetic nerve terminals innervating the S-A node. The latter mechanism might be of importance especially in clinical situations characterized by an enhanced sympathetic drive to the S-A node since under the present experimental conditions it was

observed after the administration of a small dose of clonidine. It would appear premature to extrapolate this peripheral action of clonidine to other organs or systems since the physiological role played by presynaptic α -adrenoceptors controlling noradrenaline release from sympathetic nerve terminals may not be of equal physiological importance at the level of each sympathetically innervated structure.

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