The Effects of Propranolol on Acute Hypertension of Anesthetized Dogs and on the Carotid Sinus Reflex Responses of Anesthetized and Awake Dogs

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With the assistance of Bryant Logan and Muriel Branford

SUMMARY Experiments are presented to show the effects of (1) propranolol on the response of systolic blood pressure and diastolic blood pressure to bilateral carotid artery occlusion in chloralose-anesthetized dogs; (2) the effects of propranolol on acute hypertensive states in chloralose-anesthetized dogs; and (3) the effects of propranolol on the response of trained awake dogs to bilateral carotid artery occlusion. Acutely, propranolol in successive doses administered intravenously lowered the systolic and diastolic blood pressure response to 35% and 27%, respectively, of the original response during bilateral carotid artery occlusion. There was no significant change in the systolic and diastolic blood pressure of controls. Systolic blood pressure, diastolic blood pressure, ventricular contractile force, dp/dt, and heart rate, which were elevated by double vagotomy and carotid sinus denervation, were returned to control levels by doses of propranolol. Hypertensive blood pressures of dogs infused with angiotensin and norepinephrine were made normotensive by simultaneous infusion or bolus injection of propranolol. Administered centrally in "isolated head" experiments (dogs) and ventromedial nucleus (in cats), propranolol had no effect on acute hypertension or on carotid sinus reflex response or ventromedial nucleus stimulation. The systolic and diastolic blood pressure responses to bilateral carotid artery occlusion in awake dogs were not significantly altered after the 1st week of daily treatment with propranolol (2.5 mg/kg). The responses of both the systolic and diastolic blood pressure to bilateral carotid artery occlusion decreased, however, after 1 week of daily propranolol administration at 5.0 mg/kg and there was a further decrease in heart rate, and in systolic and diastolic blood pressure responses to bilateral carotid artery occlusion when propranolol was raised to 7.5 mg/kg in daily doses for 1 week.

FROHLICH' focused attention on the use of β-blocking agents against hypertension. The mechanism by which β-blocking agents modify elevated blood pressure seems to be unclear. In our preliminary experiments, we found that in anesthetized dogs propranolol decreases the response of both systolic and diastolic blood pressure to common carotid occlusion. Extension of our work later demonstrated that in acute hypertension, produced by bilateral vagotomy and carotid sinus denervation, blood pressure was returned to normotensive levels by successive doses of propranolol. Hyde et al.4 subsequently showed in instrumented dogs that concomitant with the decrease in systolic and diastolic blood pressure and heart rate in acutely hypertensive dogs the end-diastolic volume and the end-diastolic pressure increased, while the cardiac output decreased and maximum ejection time was lengthened. It seemed apparent that a diminution in cardiac function might be the mechanism by which propranolol acted to reduce blood pressure. Two other mechanisms, however, have attracted our attention and merit consideration: (1) Buhler et al.5 proposed that propranolol acts as an anti-renin substance to lower blood pressure in patients who have moderate to high renin secretion with their hypertension. They point to the ineffectiveness of propranolol in patients in whom the renin secretion is low and in whom, indeed, it may be contraindicated. (2) Garvey and Ram (5) very recently presented data which they believe show that propranolol acts at the hippocampus to reduce sympathetic activity and thereby to promote peripheral vasodilation and lower blood pressure. We present our recent results in an attempt to shed further light on a problem that needs clarification, if a fuller understanding of the mechanism of action of propranolol in hypertension is to be had. The problem is by no means solved; we have attempted to contribute to a better understanding by using a variety of laboratory approaches with which we are familiar.

Methods

EXPERIMENTS ON ANESTHETIZED DOGS

Bilateral Carotid Artery Occlusion

Mongrel dogs of either sex weighing 18-22 kg were pretreated with morphine, 2 mg/kg, subcutaneously (sc). The dogs were given chloralose, 80 mg/kg, intravenously (iv) 15 minutes later. A tracheotomy was performed; the carotid sheaths were opened, the vagi were loosely ligated, and the carotid sinuses were completely exposed. Loose ligatures were placed around the carotid sinus nerves. The femoral artery on one side and the femoral vein on the opposite side were exposed for cannulation. Blood pressure was monitored by a Sanborn or a Honeywell 5600...
recorder using a Statham transducer (P230c) connected to the artery via polyethylene tubing. An electrocardiogram (ECG) (lead II) was recorded. For many experiments in this group data were collected by a Honeywell magnetic tape recorder connected to an on-line catheterization computer.

Left ventricular pressure and dp/dt were recorded from open-chest preparations. A Honeywell Accu data 132 differentiator was used for dp/dt recording. A small stab wound was made in the apex of the left ventricle and a hard polyethylene catheter, connected to a Statham transducer, was quickly inserted. The heart was cradled in such a way that the Statham transducer was approximately 6 cm above it. The vagus nerves were sectioned and, after stabilization of the blood pressure, the carotid arteries were occluded for 15-30 seconds. Two to three control responses of blood pressure and the aforementioned parameters were recorded before administration of propranolol. Occlusions were performed at 5-minute intervals beginning just before injection of the drugs, and again 5 minutes after drug administration and just prior to the next dose. Doses of propranolol (0.2 mg/kg) were administered 10 minutes apart via the femoral vein through an indwelling polyethylene catheter-syringe connection. The experiment was concluded after insignificant changes in hemodynamics were observed on occlusion of the common carotid arteries. Experiments were performed on control dogs in the manner described above, except that no propranolol was administered.

**Acute Hypertension**

Dogs were prepared in the manner described above with the exception that, after bilateral vagotomy, the carotid arteries were occluded for 30 seconds to assess the carotid sinus reflex response. The carotid sinus nerves, which had been loosely ligated, were tied in order to denervate the sinuses. The carotid arteries were again occluded after stabilization of blood pressure to be certain that no neural elements remained functional. Propranolol was then administered after 10 minutes via the femoral vein in doses of 0.2 mg/kg at intervals of 10 minutes. Anesthetized control dogs, whose vagi had been sectioned and carotid sinuses denervated, received no propranolol.

**The Effects of Propranolol against Angiotension and Norepinephrine**

These experiments were designed to widen our observations regarding the action of propranolol against hypertensive states produced by mechanisms other than carotid sinus denervation and bilateral vagotomy or by bilateral carotid artery occlusion with the vagi sectioned. Angiotensin II and norepinephrine were infused in separate experiments via the femoral vein as described below.

**Angiotensin.** Dogs of either sex weighing 16-22 kg were anesthetized with pentobarbital sodium (30 mg/kg, iv). Blood pressure, heart rate, left ventricular pressure, dp/dt, and ECG were recorded as described for acute experiments. Renal artery blood flow was monitored by a Statham electromagnetic pulsed square wave flowmeter, model SP2202. The vagi were left intact.

Angiotensin II (Hypertensin, Ciba-Geigy), made freshly for each experiment from powder and prepared in aqueous solution, was infused at the rate of 0.4 μg/kg per min, using a Sigma infusion pump to produce sustained and stable hypertension. Ten minutes after the angiotensin infusion was begun, infusion of propranolol (0.1 mg/kg per min) was started. From this time both drugs were infused simultaneously until the blood pressure, elevated by angiotensin infusion, had returned to or below control levels. Control untreated dogs were infused with angiotensin II only for 30 minutes.

**Norepinephrine.** The preparations and the monitoring techniques were the same as for the angiotensin experiments, except that dp/dt and blood flow were not measured. Norepinephrine (solutions were made fresh for each experiment from powder dissolved in distilled water) was infused for 30 minutes via the femoral vein, using a Sigma infusion pump, at a rate of 1.5 μg/kg per min to produce sustained and stable hypertension. Doses of propranolol (0.2 mg/kg) were administered at 10-minute intervals after stabilization of the elevated blood pressure and during the constant norepinephrine infusion. The experiment was concluded when all hemodynamic parameters had returned to or had fallen below values for propranolol infusion. Control dogs were infused with same dose of norepinephrine as the propranolol-treated dogs, but no propranolol was administered to them.

**Effects of Central Administration of Propranolol on the Carotid Sinus Reflex Response and on the Pressor Response to Electrical Stimulation of the Ventromedial Hypothalamic Nucleus**

Cats of either sex, weighing 2.5-4 kg, were anesthetized with chloralose (80 mg/kg); a tracheotomy was performed and the vagi were sectioned. Blood pressure was recorded from the femoral artery through a Statham transducer connected by polyethylene tubing to a Physiograph recorder. The skull was trephined, and a cannula-electrode, which was a 22-gauge needle insulated (to the tip), was passed into the ventromedial nucleus of the hypothalamus by the stereotaxic procedure of Jasper and Ajmone-Marsan. 5 Electrical stimulation through the needle-electrode resulted in a prominent pressor response. The stereotaxic coordinates for the ventromedial nucleus were: anterior, 12 mm; lateral, 1-1.5 mm; and vertical, 5 mm.

**Studies on the Isolated Head**

The experimental procedure of Heymans 8 was used. The dog whose head was functionally isolated from its trunk, designated as the "receiver" dog, was pretreated with morphine (2 mg/kg, sc) and anesthetized 15 minutes later with chloralose (80 mg/kg, iv). A low tracheotomy was performed. Blood pressure was monitored via the femoral artery with a Statham transducer. The carotid arteries and external jugular veins were dissected free along their entire length. The carotid sinus nerves were loosely ligated. The vertebreal arteries and veins at the base of the neck were loosely ligated. Muscle and connective tissue on the ventral side of the neck at C 2 were carefully dissected in preparation for inserting the Semaan-Hey-
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EXPERIMENTS ON AWAKE DOGS

Carotid arteries and vagus nerves of dogs used for these experiments were surgically exteriorized in loops of skin under anesthesia. Training of the dogs for studies of blood pressure and heart rate was begun 2–3 weeks after surgery. The dogs were placed on a padded table, while a 20-gauge needle, connected by polyethylene tubing to a Sanborn or Statham transducer number P2330C, was introduced into the femoral artery. A dose of norepinephrine (2.5 μg/kg) was administered via the femoral vein to the donor dog. Blood pressure was monitored through the femoral artery. A dose of norepinephrine (2.5 μg/kg) was administered via the femoral vein to the donor dog. An increase in blood pressure in the donor dog and a simultaneous reflex decrease in pressure in the receiver dog was thought to show the completeness of the preparation (no leakage between the trunk and the head of the receiver dog). The carotid sinuses were denervated and the vagi sectioned in the head of the receiver dog. After stabilization of the elevated blood pressure, propranolol was administered via carotid arteries to the head of the receiver dog. Blood pressure was monitored through the femoral artery. A dose of norepinephrine (2.5 μg/kg) was administered via the femoral vein to the donor dog. Blood pressure was monitored through the femoral artery. A dose of norepinephrine (2.5 μg/kg) was administered via the femoral vein to the donor dog. An increase in blood pressure in the donor dog and a simultaneous reflex decrease in pressure in the receiver dog was thought to show the completeness of the preparation (no leakage between the trunk and the head of the receiver dog). The carotid sinuses were denervated and the vagi sectioned in the head of the receiver dog. After stabilization of the elevated blood pressure, propranolol was administered via carotid arteries to the head of the receiver dog in doses of 0.05, 0.075, and 0.1 mg/kg at intervals of 10 minutes.

RESULTS

ANESTHETIZED DOGS

Carotid Occlusion

Figure 1 shows a decrease in the mean response of both systolic and diastolic blood pressure to bilateral common carotid artery occlusion after repeated iv doses of propranolol. The decrement in response was dose-dependent after the first dose. After the second dose, 10 minutes after the

FIGURE 1 The mean changes in systolic and diastolic blood pressure (ΔBP, mm Hg) response to bilateral common carotid artery occlusion in propranolol-treated and control dogs. There were six dogs in each group. The first dose of 0.2 mg/kg, iv, was given immediately after the control responses, and the same dose was administered at 10-minute intervals, thereafter. Occlusions were performed immediately after the drug was given, again 5 minutes after and just prior to the successive dose. The values for pressures in the treated dogs were significantly different from the control (P < 0.05) after the first dose. Se of the mean in both untreated and treated dogs varied from point to point between ±2.0 to ±2.8 systolic and ±0.5 to ±4.0 diastolic blood pressure. Se of the mean in the untreated dogs varied from ±2.8 to ±5.2 systolic and ±3.0 to ±5.0 diastolic pressure. See text for details.
first dose, the mean systolic blood pressure response to carotid occlusion fell to 70%, and the mean diastolic blood pressure response fell to 66%, of the control. The third dose caused the response of systolic blood pressure to decrease immediately to 35% of the control response and the diastolic pressure decreased to 27% of the control response. Five minutes after the last dose, the responses of systolic and diastolic blood pressure fell 87% and 90%, respectively. Although other parameters are not shown in Figure 1, the heart rate, the peak left ventricular pressure, and the peak dp/dt decreased at a rate corresponding to the decrease in blood pressure. The mean systolic and diastolic blood pressure before occlusion were 145 ± 6.0 (SE) mm Hg and 95 ± 5.0 mm Hg, respectively. Very little (0.5 mm Hg) change in systolic or diastolic blood pressure occurred after the first dose of propranolol. The second and third doses of propranolol, however, caused decreases of 10–15 mm Hg in systolic blood pressure and 5–10 mm Hg in diastolic pressure immediately after iv injection. After 5 minutes, at the time the reflex was tested, however, the blood pressure had returned to levels that were insignificantly different from the controls. The decrease in response to carotid occlusion that was observed, therefore, did not result from the hypotensive effect of propranolol. At the end of the experimental period (25 minutes), the mean systolic blood pressure was 125 ± 8.0 (SE) mm Hg and the mean diastolic pressure was 82 ± 7.0 mm Hg, but there was less than 15% of the initial response of systolic blood pressure and only 10% of the response of diastolic blood pressure to carotid occlusion.

Acute Hypertension

Table 1 presents the effects of propranolol on the mean systolic and diastolic blood pressure, the mean peak left ventricular contractile force, the mean peak dp/dt, and the mean heart rate changes following double vagotomy and carotid sinus denervation. The mean systolic blood pressure fell from 250 mm Hg to 148 mm Hg after successive doses of propranolol. The mean systolic blood pressure in the untreated dogs fell only from 240 mm Hg to 220 mm Hg. The mean diastolic blood pressure in the dogs receiving propranolol diminished from 180 mm Hg to 95 mm Hg after the last dose of propranolol. The mean diastolic blood pressure in the untreated dogs decreased from 170 mm Hg to 155 mm Hg by the end of the experimental period. The left ventricular pressures, which were 245 mm Hg and 255 mm Hg for control groups 1 (untreated) and 2 (treated), respectively, decreased after denervation to 160 mm Hg in the treated dogs after the last dose of propranolol, but fell only to 220 mm Hg in the untreated dogs. The mean value for dp/dt decreased after propranolol administration from 2,000 to 1,000 mm Hg/sec; but in the untreated group dp/dt fell from 2,200 after denervation to 1,990 by the end of the experimental period. Heart rate decreased in the treated group to 90 beats/min and 200 beats/min in the untreated group.

Angiotensin and Norepinephrine Infusion

Table 2 shows the systolic and diastolic arterial blood pressure response, the peak left ventricular contractile force, peak dp/dt, heart rate, and renal arterial blood flow during infusion of angiotensin alone followed by simultaneous infusion of angiotensin and propranolol. The mean systolic blood pressure rose from 148 mm Hg to 250 mm Hg during the 10-minute period of angiotensin infusion, but the mean systolic blood pressure in the dogs simultaneously infused with angiotensin and propranolol rose from 150 mm Hg to only 196 mm Hg. During the 10-minute infusion of angiotensin alone the mean diastolic
blood pressure rose from 110 mm Hg to 225 mm Hg, whereas in the dogs infused simultaneously with both drugs during the 10-minute period the diastolic pressure rose only from 100 mm Hg to 165 mm Hg. The mean left ventricular pressure in the group given only angiotensin rose from 155 to 245 mm Hg; but in the group receiving both drugs simultaneously the left ventricular pressure rose only from 155 to 200 mm Hg. The value of dp/dt in the angiotensin-infused group rose only from 160 mm Hg to 225 mm Hg, whereas in the dogs infused simultaneously with both drugs during the 10-minute period the diastolic pressure increased reflexly because of the norepinephrine infusion, fall to 75 beats/min. There were no significant changes in arterial diastolic blood pressure in control group 1 rose to 240 and 245 mm Hg, respectively. The mean systolic arterial blood pressure in control group 1 101.6 ± 5.0, diastolic 141.3 ± 2.3, mean heart rate decreased to 101 beats/min in control group 1 and control group 2 rose to 240 and 245 mm Hg, respectively. The mean arterial diastolic blood pressure in control group 1 rose to 153 mm Hg and to 160 mm Hg in control group 2. The mean heart rate decreased to 101 beats/min in control group 1 and 104 in control group 2. All of these values changed during 10 minutes of continuous infusion of norepinephrine as follows: The mean arterial systolic blood pressure of control groups 1 and 2 rose to 240 and 245 mm Hg, respectively. The mean arterial diastolic blood pressure in control group 1 rose to 153 mm Hg and to 160 mm Hg in control group 2. The mean heart rate decreased to 101 beats/min in control group 1 and 104 in control group 2. All of these values decreased after successive doses of propranolol in the control group 2 dogs. The mean systolic arterial blood pressure decreased from 160 mm Hg to 90 mm Hg. Peak left ventricular pressure was decreased from 247 mm Hg to 122 mm Hg. The heart rate, which had already decreased reflexly because of the norepinephrine infusion, fell to 75 beats/min. There were no significant changes in blood pressure, contractile force, or heart rate (except reflexly) in control group 1 dogs (not treated with propranolol) during the course of the norepinephrine infusion. The above results are indeed significant and indicate the effectiveness of propranolol in lowering blood pressure that has been increased by norepinephrine.

Studies on the Isolated Head

Table 4 presents the results of studies on the isolated head in which acute hypertension was produced in the receiver dog by bilateral vagotomy and carotid sinus denervation. A test dose of norepinephrine, 2.5 μg/kg, was injected into the femoral vein of the donor dog before denervation to demonstrate the elevation of blood pressure in the donor dog and the reflex fall in blood pressure in the receiver dog. This demonstrated that there was no "leakage" of blood from the head of the receiver dog to its
TABLE 3  The Effect of Propranol on Blood Pressure, Left Ventricular Pressure, and Heart Rate in Pentobarbital-Anesthetized Dogs Infused with Norepinephrine

<table>
<thead>
<tr>
<th>Control 1 (4 dogs)</th>
<th>Control 2 (4 dogs)</th>
<th>Infusion of norepinephrine (1.52 kg/min)</th>
<th>Control 1</th>
<th>Propranolol (0.2 mg/kg)</th>
<th>Control 1</th>
<th>Propranolol (0.2 mg/kg)</th>
<th>Control 1</th>
<th>Propranolol (0.2 mg/kg)</th>
<th>Control 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
<td>Systolic</td>
<td>Diastolic</td>
<td>Systolic</td>
<td>Diastolic</td>
<td>Systolic</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td>(mm Hg)</td>
<td>(mm Hg)</td>
<td>(mm Hg)</td>
<td>(mm Hg)</td>
<td>(mm Hg)</td>
<td>(mm Hg)</td>
<td>(mm Hg)</td>
</tr>
<tr>
<td>Systolic</td>
<td>140 ± 4.0</td>
<td>150 ± 3.5</td>
<td>240 ± 4.5</td>
<td>245 ± 5.0</td>
<td>242 ± 5.0</td>
<td>227 ± 3.0*</td>
<td>180 ± 4.0t</td>
<td>235 ± 3.2</td>
<td>120 ± 5.0t</td>
</tr>
<tr>
<td>Diastolic</td>
<td>95 ± 3.0</td>
<td>98 ± 4.0</td>
<td>153 ± 2.6</td>
<td>160 ± 5.0</td>
<td>150 ± 3.5</td>
<td>150 ± 3.5*</td>
<td>120 ± 1.5t</td>
<td>146 ± 8.0</td>
<td>105 ± 3.7</td>
</tr>
<tr>
<td>Systolic</td>
<td>142.5 ± 2.6</td>
<td></td>
<td>242.1 ± 3.5</td>
<td>247.2 ± 2.6</td>
<td>240 ± 3.2</td>
<td>227 ± 3.8*</td>
<td>182 ± 4.0t</td>
<td>142 ± 2.0</td>
<td>122 ± 1.9t</td>
</tr>
<tr>
<td>Diastolic</td>
<td>151.5 ± 3.0</td>
<td></td>
<td>247 ± 3.5</td>
<td>240 ± 3.2</td>
<td>150 ± 3.5</td>
<td>148 ± 5.5</td>
<td>120 ± 1.5t</td>
<td>142 ± 2.0</td>
<td>75 ± 4.0t</td>
</tr>
<tr>
<td>Systolic</td>
<td>242.1 ± 3.5</td>
<td></td>
<td>247.2 ± 2.6</td>
<td>240 ± 3.2</td>
<td>240 ± 3.2</td>
<td>227 ± 3.8*</td>
<td>182 ± 4.0t</td>
<td>142 ± 2.0</td>
<td>122 ± 1.9t</td>
</tr>
<tr>
<td>Diastolic</td>
<td>247 ± 3.5</td>
<td></td>
<td>240 ± 3.2</td>
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<td>120 ± 1.5t</td>
<td>142 ± 2.0</td>
<td>75 ± 4.0t</td>
</tr>
</tbody>
</table>

Control dogs (control 1) were infused with norepinephrine (1.5 μg/kg per min) and were not treated with propranolol. A second group of dogs (control 2) were infused with the same dose of norepinephrine but were treated at 10-minute intervals with propranolol (0.2 mg/kg) iv. Each parameter of the propranolol-treated group was significant (P < 0.05) at the second dose of propranolol. There were four animals in each group. Results are presented as the mean ± SEM.

* Not significant.
† Significant (P < 0.05).

trunk. On the other hand, when norepinephrine was administered to the donor dog after denervation of the carotid sinuses of the receiver dogs there was an elevation of blood pressure only in the donor dog and no change in the receiver dog.

EXPERIMENTS ON ANESTHETIZED CATS

Table 5 shows the responses of blood pressure in chloralose-anesthetized cats after electrical stimulation of the ventromedial nucleus and after alternate occlusion of the common carotid arteries. It may be observed that propranolol, administered directly into the hypothalamus, did not change the response of the blood pressure after ventromedial nucleus stimulation or alternate bilateral carotid artery occlusion.

EXPERIMENTS ON AWAKE DOGS

Table 6 presents changes in blood pressure and heart rate after carotid artery occlusion both during control periods and during daily treatment with increasing doses of propranolol over a 3-week period. It may be seen that the blood pressure and the heart rate responses to bilateral carotid artery occlusion were not appreciably affected during the 1st week of daily administration of propranolol (2.5 mg/kg). The effect of propranolol during the succeeding 2 weeks, as the doses were increased, was evident from both blood pressure and heart rate response to bilateral carotid artery occlusion. Systolic blood pressure responses decreased by 16% and diastolic pressure decreased by 19% from the control values. Systolic blood pressure responses decreased by 42% and diastolic blood pressure by

TABLE 4  The Lack of Effect of Propranol on the Elevated Blood pressure in a Dog (Recipient) Whose Head Was Perfused By Blood From a Donor Dog

<table>
<thead>
<tr>
<th>Blood pressure (mm Hg)</th>
<th>Donor</th>
<th>Recipient (before denervation)</th>
<th>After denervation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
<td>Systolic</td>
</tr>
<tr>
<td>Before propranolol</td>
<td>180.0 ± 0.3</td>
<td>95.0 ± 2.0</td>
<td>91.0 ± 0.5</td>
</tr>
<tr>
<td>After propranolol</td>
<td>106.0 ± 3.0*</td>
<td>77.0 ± 3.0*</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>92.0 ± 1.7*</td>
<td>70.0 ± 1.0*</td>
<td>0.075</td>
</tr>
<tr>
<td></td>
<td>88.0 ± 1.6*</td>
<td>62.0 ± 1.4*</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Propranolol was given in stepwise doses via the anastomosed carotid arteries to the head of the recipient dog at 10-minute intervals. The blood pressure of the recipient dog was elevated by carotid sinus denervation and double vagotomy. See text for explanation of preparation. No change in blood pressure in the recipient dog, but a significant decrease in blood pressure (P < 0.05) in the donor dog. There were three dogs in these experiments.

Results are presented as mean ± SEM.
* Significant (P < 0.05).
† Not significant.
The increase in the heart rate during carotid occlusion during administration of daily doses (7.5 mg/kg) of propranolol was essentially the same as the control. Propranolol was administered via cannula in the carotid sinus before and after procaine administration to the ventromedial hypothalamus. The blood pressure changes following VMH stimulation before and after propranolol were not significant. See text.

The foregoing results show that propranolol lowers the systolic and diastolic arterial blood pressure in anesthetized, acutely hypertensive dogs and lowers the responses of these pressures to bilateral carotid artery occlusion in both anesthetized and awake dogs. It appears to us that the effect of propranolol on the heart is the essential avenue through which the drug lowers arterial blood pressure in the hypertensive animal and decreases the responses of blood pressure in elicitation of the carotid sinus reflex. Heart rate, peak left ventricular pressure, and peak dp/dt in the acute experiments seem to support this view. In 1972 we compared propranolol to other β-adrenergic blocking agents with respect to their effects on the blood pressure response to bilateral carotid artery occlusion and on the acutely hypertensive arterial blood pressure in anesthetized dogs. Practolol, sotalol, and pindolol were found to be much less effective in lowering blood pressure and they were equally less effective in decreasing heart rate, peak left ventricular pressure, and peak dp/dt. The results of experiments with angiotensin infusion agree significantly with the experiments on the other models. There was, of course, no antagonism of angiotensin by propranolol at the receptor sites of the arterial bed, where angiotensin has its major action. The blood flow data indicate that the vasoconstriction caused by angiotensin was present during the simultaneous infusion of angiotensin and propranolol. In spite of this, however, the arterial blood pressure decreased significantly and was brought approximately to the control levels after 30 minutes of simultaneous infusion of angiotensin and propranolol. The norepinephrine infusion experiments were slightly different in design. Nevertheless, the effects of propranolol against the hypertension caused by norepinephrine were not different from effects against angiotensin. One point which may tend to make clearer the interpretation of these experiments should be mentioned. The norepinephrine effect on the heart, a β-adrenergic effect, was blocked by propranolol. Hence the heart rate (although reflexly slowed to some extent) and the contractile force effect of norepinephrine are directly antagonized by propranolol. It should not be expected that propranolol would effect the action of norepinephrine on peripheral blood vessels, because norepinephrine acts at these sites on α-adrenergic receptors. This means, therefore, that in both the angiotensin and norepinephrine infusion experiments, we are dealing principally with cardiac effects of propranolol against the hypertension caused by both of the

### Table 5 Lack of Effect of Propranolol on the Blood Pressure Response to Electrical Simulation of the Ventromedial nuclei of the hypothalamus (VMH) and the Response of the Blood Pressure to Bilateral Carotid Artery Occlusion (Vagi Sectioned) in Chloralose Anesthetized Cats

<table>
<thead>
<tr>
<th>Condition</th>
<th>Blood pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td>Carotid occlusion before propranolol</td>
<td>146 ± 3</td>
<td>100 ± 1</td>
</tr>
<tr>
<td>Carotid occlusion after propranolol 0.05 mg/kg</td>
<td>220 ± 5*</td>
<td>150 ± 1*</td>
</tr>
<tr>
<td>Carotid occlusion after propranolol 0.75 mg/kg</td>
<td>246 ± 2.3*</td>
<td>152 ± 1.1*</td>
</tr>
<tr>
<td>VMH stimulation before propranolol</td>
<td>151 ± 1</td>
<td>71.0 ± 1.2</td>
</tr>
<tr>
<td>VMH stimulation after propranolol 0.05 mg/kg</td>
<td>250 ± 2*</td>
<td>148 ± 1.7*</td>
</tr>
<tr>
<td>VMH stimulation after propranolol 0.75 mg/kg</td>
<td>264 ± 2.3*</td>
<td>152 ± 1.1*</td>
</tr>
</tbody>
</table>

The data represent the mean ± SE of three experiments. Each cat was used as its own control. Propranolol was administered via cannula in the ventromedial hypothalamus. The blood pressure changes following VMH stimulation before and after propranolol were not significant. See text.

The results of experiments with angiotensin infusion agree significantly with the experiments on the other models. There was, of course, no antagonism of angiotensin by propranolol at the receptor sites of the arterial bed, where angiotensin has its major action. The blood flow data indicate that the vasoconstriction caused by angiotensin was present during the simultaneous infusion of angiotensin and propranolol. In spite of this, however, the arterial blood pressure decreased significantly and was brought approximately to the control levels after 30 minutes of simultaneous infusion of angiotensin and propranolol. The norepinephrine infusion experiments were slightly different in design. Nevertheless, the effects of propranolol against the hypertension caused by norepinephrine were not different from effects against angiotensin. One point which may tend to make clearer the interpretation of these experiments should be mentioned. The norepinephrine effect on the heart, a β-adrenergic effect, was blocked by propranolol. Hence the heart rate (although reflexly slowed to some extent) and the contractile force effect of norepinephrine are directly antagonized by propranolol. It should not be expected that propranolol would effect the action of norepinephrine on peripheral blood vessels, because norepinephrine acts at these sites on α-adrenergic receptors. This means, therefore, that in both the angiotensin and norepinephrine infusion experiments, we are dealing principally with cardiac effects of propranolol against the hypertension caused by both of the

### Table 6 Blood Pressure and Heart Rate Changes during Bilateral Carotid Artery Occlusion in Awake Dogs in Control Periods (No Drug) and during Oral Administration of Propranolol

<table>
<thead>
<tr>
<th>Condition</th>
<th>Blood pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td>Control</td>
<td>146.2 ± 2.5</td>
<td>95.0 ± 2.14</td>
</tr>
<tr>
<td>Propranolol 2.5 mg/kg</td>
<td>138.7 ± 1.5*</td>
<td>88.7 ± 1.5*</td>
</tr>
<tr>
<td>Propranolol 5.0 mg/kg</td>
<td>121.7 ± 1.2*</td>
<td>76.2 ± 1.8†</td>
</tr>
<tr>
<td>Propranolol 7.5 mg/kg</td>
<td>121.7 ± 3.3†</td>
<td>68.5 ± 3.3†</td>
</tr>
</tbody>
</table>

The mean values (± ss) for six dogs are shown for blood pressure and heart rate. Blood pressure and heart rate changes were insignificant (compared to controls) at doses of 2.5 mg/kg daily, but were significant at doses of 5.0 mg/kg and 7.5 mg/kg (P < 0.05, Student's t-test).

* Not significant.
† Significant.
vasoconstrictor agents. There is no reason to believe that the effects are exerted at other sites.

The experiments of Hyde et al., referred to above, support this view. Hypertensive blood pressure in these experiments was returned to normal levels by propranolol as heart rate was slowed, ventricular contractile force was reduced, dp/dt was diminished, and cardiac output was lowered. Also in these experiments end-diastolic pressure was increased and maximum ejection time and cycle length were increased. These observations would explain the effect of propranolol on diastolic as well as systolic blood pressure, because the combination of the above factors results in decreased "runoff time" and results in a fall in diastolic pressure.

Our experiments should not be taken to mean that in clinical hypertension propranolol does not act to antagonize renin secretion in the presence of moderate to high renin secretory activity, as a means of lowering blood pressure. There is reason to believe from our experiments, however, that other mechanisms may be involved. It is inconceivable that, in the angiotensin and norepinephrine experiments we have reported here, propranolol would act to lower the arterial systolic and diastolic blood pressure by blocking renin secretion, because in both cases renin secretion would be expected to be decreased. The infused angiotensin would block renin secretion by the negative feedback mechanism, and the elevation of the blood pressure by norepinephrine would block renin secretion.

The failure of propranolol to affect the hypertension in anesthetized cats following ventromedial nucleus stimulation makes it less likely, in our view, that propranolol may have central action at this site. The isolated head experiments, in which the receiver dog was made hypertensive, would also discount a central action of propranolol, because the blood pressure in the receiver dog of such experiments is not lowered by propranolol administered via the carotid arteries directly to the isolated head.

The experiments of Garvey and Ram refer to the work of Kawashiama et al., who showed, using radioimmunoassay technique, that $\beta$-propranolol accumulates rapidly in the heart as it concomitantly decreases in plasma concentration. The $\alpha$ form of propranolol, on the other hand, is metabolized rapidly in the blood. Thus the results keep open the question of whether the accumulation of propranolol at a given site may be of any significance in relation to its action. It is reasonable to assume, however, that accumulation of $\beta$ propranolol in the heart may have greater significance regarding its cardiac effects than the accumulation in the hippocampus. We believe this view would be more in line with our opinion that propranolol may have its major effect on the heart rather than at some site in the central nervous system.

Acknowledgments

We express our thanks to the Ayerst Company for kindly supplying the propranolol (Inderal) used in this study and to Ciba-Geigy Pharmaceutical Company for providing angiotensin II (Hypertensin).

References

The effects of propranolol on acute hypertension of anesthetized dogs and on the carotid sinus reflex responses of anesthetized and awake dogs.
W M Booker, A Hyde, A Fletcher and D Hawthorne

Circ Res. 1977;41:179-186
doi: 10.1161/01.RES.41.2.179

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