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 38% 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.

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.
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 Angiotensin 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 pre-norepinephrine infusion. Control dogs were infused with the 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 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 Ajmon-Marsan. 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 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 vertebral arteries and veins at the base of the neck were loosely ligated. Muscle and connective tissue on the ventral side of the neck at C2 were carefully dissected in preparation for inserting the Semaan-Hey-
mans instrument from the ventral side to the dorsal side of the neck. This is a U-shaped, stainless steel instrument, which is fitted with a smaller U-shaped structure that is used to surround the spinal cord. The dog was rotated on its ventral side and the head was supported from same side. The skin and muscle on the dorsal area of the skull and neck were dissected, down below the level of C2. The spinovertebral arteries on either side were isolated and ligated; and a laminectomy was performed at C2 to expose the spinal cord. The dog was transfused with whole blood throughout this procedure. The spinal cord was exposed and, after opening the dura mater, it was manipulated, by using a rubber dental dam, in such a way that the anterior spinal artery was made accessible for placement of a loose ligature around it. The steel Semaan-Heymans instrument was brought from the ventral side of the neck to the dorsal side at C2. The small U-shaped structure inside the Semaan-Heymans clamp was carefully manipulated to fit it around the spinal cord and a crossbar was arranged between the posts of the larger U-shaped instrument in such a way that screws could be adjusted to mildly compress the spinal sinuses on either side of the cord without compressing the cord itself. The carotid sinus nerves were loosely ligated in preparation for subsequent tying.

A second dog, the “donor” dog, was anesthetized with morphine-chloralose (2 mg/kg, sc, and 80 mg/kg, iv, respectively). The carotid arteries and the external jugular veins were freed along their entire length. The vagi were left intact. The carotid arteries and the jugular veins were anastomosed to the carotid arteries and jugular veins of the receiver dog. Blood pressure was monitored through the femoral artery. A dose of norepinephrine (2.5 /ng/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.

EXPERIMENTS ON AWEAK 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. The area of the femoral triangle previously had been anesthetized with 1% procaine.

One milliliter of a 1% procaine solution was introduced into the lumen of the carotid loops to block the aortic depressor nerves prior to carotid artery occlusion. An increase in heart rate after injection of procaine was taken to indicate vagal anesthesia. Control tests to determine the blood pressure response to carotid occlusion were performed on each dog for a period of 3-4 weeks. The dogs were started on daily doses of propranolol when control blood pressure responses to occlusion of the common carotid arteries varied insignificantly. Propranolol was administered daily to each dog orally in doses of 2.5 mg/kg for 1 week, followed in successive weeks by daily doses of 5.0 mg/kg and 7.5 mg/kg. The daily administration was designed to simulate clinical practice. The doses were increased to assess a possible dose-dependent effect. Blood pressure responses to bilateral carotid artery occlusion were observed twice each week under the same conditions described for the control period. At least three blood pressure and heart rate responses were observed at each of the weekly test periods.

Data for all experiments and experimental designs were analyzed for statistical significance with Student's t-test and the Honeywell catheterization computer.

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. sc 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. sc 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

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**Table 1** Effects of Propranolol on Systolic and Diastolic Blood Pressure, Peak Left Ventricular Pressure (LVP), Peak dp/dt, and Heart Rate, in Six Anesthetized Dogs Made Acutely Hypertensive by Double Vagotomy and Carotid Sinus Denervation

<table>
<thead>
<tr>
<th>Blood pressure (mm Hg)</th>
<th>Systolic</th>
<th>Diastolic</th>
<th>Peak LVP (mm Hg)</th>
<th>Peak dp/dt (mm Hg/sec)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 1 (not to be treated)</td>
<td>145 ± 2.2</td>
<td>100 ± 4.0</td>
<td>150 ± 5.0</td>
<td>1200 ± 4.5</td>
<td>140 ± 6.0</td>
</tr>
<tr>
<td>Control 2 (to be treated)</td>
<td>150 ± 0.6</td>
<td>96.8 ± 2.3</td>
<td>152 ± 2.0</td>
<td>1150 ± 5.0</td>
<td>135 ± 5.0</td>
</tr>
<tr>
<td>Vagi sectioned</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 1</td>
<td>170 ± 1.5</td>
<td>120 ± 4.0</td>
<td>165 ± 2.0</td>
<td>1400 ± 3.0</td>
<td>200 ± 5.0</td>
</tr>
<tr>
<td>Control 2</td>
<td>160 ± 3.0</td>
<td>110 ± 1.0</td>
<td>163 ± 4.0</td>
<td>1200 ± 4.5</td>
<td>195 ± 4.0</td>
</tr>
<tr>
<td>Sinuses denervated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 1</td>
<td>240 ± 4.0</td>
<td>170 ± 3.0</td>
<td>245 ± 5.5</td>
<td>2200 ± 5.0</td>
<td>220 ± 3.0</td>
</tr>
<tr>
<td>Control 2</td>
<td>250 ± 5.0</td>
<td>180 ± 2.9</td>
<td>255 ± 4.0</td>
<td>2000 ± 5.5</td>
<td>215 ± 4.0</td>
</tr>
<tr>
<td>Untreated (control 1)</td>
<td>235 ± 2.0</td>
<td>165 ± 3.0</td>
<td>238 ± 4.0</td>
<td>2200 ± 5.2</td>
<td>215 ± 5.0</td>
</tr>
<tr>
<td>Propranolol (0.05 mg/kg)</td>
<td>236 ± 2.4*</td>
<td>174 ± 2.8*</td>
<td>242 ± 3.5*</td>
<td>1600 ± 4.0*</td>
<td>160 ± 5.0*</td>
</tr>
<tr>
<td>Untreated (control 1)</td>
<td>230 ± 2.0</td>
<td>160 ± 3.0</td>
<td>235 ± 2.0</td>
<td>2100 ± 5.0</td>
<td>210 ± 4.5</td>
</tr>
<tr>
<td>Propranolol-treated (0.1 mg/kg)</td>
<td>189 ± 1.5†</td>
<td>145 ± 2.0†</td>
<td>190 ± 1.5†</td>
<td>1400 ± 4.0†</td>
<td>130 ± 6.0†</td>
</tr>
<tr>
<td>Untreated (control 1)</td>
<td>225 ± 3.0</td>
<td>160 ± 4.0</td>
<td>230 ± 4.5</td>
<td>1990 ± 5.5</td>
<td>208 ± 5.0</td>
</tr>
<tr>
<td>Propranolol-treated (0.15 mg/kg)</td>
<td>148 ± 3.0†</td>
<td>95 ± 2.0†</td>
<td>150 ± 3.0†</td>
<td>1000 ± 5.8†</td>
<td>90 ± 4.0†</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM.

Six control dogs (control 1) were untreated after denervation. Control 2 dogs were treated in stepwise doses at 10-minute intervals. The differences between the treated and untreated dogs were significant beginning with the dose of 0.1 mg/kg in each parameter (P < 0.050).

* Not significant.
† Significant (P < 0.050).
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 1,100 to 1,400 mm Hg/sec. The heart rate did not change significantly, decreasing from 160 to 154 beats/min in the 10-minute period of infusion. In the group receiving both drugs heart rate fell from 165 to 130 beats/min. The renal blood flow decreased from 150 to 40 ml/min in the angiotensin system during the 10-minute period of infusion. This change was not significantly different in the group receiving both drugs simultaneously. At the 30-minute period during infusion of angiotensin the systolic blood pressure was 243 mm Hg, compared to 161 mm Hg in the propranolol- plus angiotensin-infused group. The diastolic blood pressure in the angiotensin-infused group was 220 mm Hg, but in the propranolol- plus angiotensin-infused group it was 94 mm Hg. Left ventricular pressure after 30 minutes of angiotensin infusion was 247 mm Hg and dp/dt was 1,760 mm Hg/sec. Left ventricular pressure in the angiotensin-propranolol group after 30 minutes of infusion was 165 mm Hg, and dp/dt was 900 mm Hg/sec. Heart rate in the angiotensin-infused group was 154 beats/min, but heart rate in the propranolol-angiotensin group was 90 beats/min. Renal blood flow was sharply reduced in the angiotensin group from 137 to 37 ml/min in the 30-minute period. There was no significant difference from values for the angiotensin group in renal blood flow in dogs in which both drugs were infused simultaneously during the 30-minute period. In the former it fell from 135 to 51 ml/min. All of the hemodynamic parameters described above, except renal blood flow, showed the influence of propranolol on the response to angiotensin. Systolic and diastolic arterial blood pressure, ventricular contractile force, dp/dt, and heart rate all were reduced significantly while angiotensin was infused with propranolol. We regard these changes as significant.

Table 3 shows the effects of propranolol on the hemodynamic parameters in dogs infused continuously with norepinephrine. Values for mean systolic blood pressure, diastolic blood pressure, and mean heart rate were not significantly different for control group 1 and control group 2 dogs. 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></th>
<th>Systolic (mm Hg)</th>
<th>Diastolic (mm Hg)</th>
<th>Left ventricular pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 1 (4 dogs)</td>
<td>140 ± 4.0</td>
<td>95 ± 3.0</td>
<td>142.5 ± 2.6</td>
<td>145.5 ± 5.0</td>
</tr>
<tr>
<td>Control 2 (4 dogs)</td>
<td>150 ± 3.5</td>
<td>98 ± 4.0</td>
<td>151.5 ± 3.0</td>
<td>140.6 ± 4.0</td>
</tr>
<tr>
<td>Infusion of norepinephrine (1.52 kg/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 1</td>
<td>240 ± 4.5</td>
<td>153 ± 2.6</td>
<td>242.1 ± 3.5</td>
<td>101 ± 2.0</td>
</tr>
<tr>
<td>Control 2</td>
<td>245 ± 5.0</td>
<td>160 ± 5.0</td>
<td>247.2 ± 2.6</td>
<td>104 ± 3.0</td>
</tr>
<tr>
<td>Propranolol (0.2 mg/kg)</td>
<td>242 ± 5.0</td>
<td>150 ± 3.5</td>
<td>240 ± 3.2</td>
<td>100 ± 4.0</td>
</tr>
<tr>
<td>Control 1</td>
<td>227 ± 3.0*</td>
<td>150 ± 3.5*</td>
<td>227 ± 3.8*</td>
<td>90 ± 5.0*</td>
</tr>
<tr>
<td>Control 2</td>
<td>245 ± 6.0</td>
<td>148 ± 5.5</td>
<td>238.1 ± 2.0</td>
<td>105 ± 2.0</td>
</tr>
<tr>
<td>Propranolol (0.2 mg/kg)</td>
<td>180 ± 4.0†</td>
<td>120 ± 1.5†</td>
<td>182 ± 4.0†</td>
<td>85 ± 4.0†</td>
</tr>
<tr>
<td>Control 1</td>
<td>235 ± 3.2</td>
<td>146 ± 8.0</td>
<td>235 ± 5.0</td>
<td>105 ± 3.7</td>
</tr>
<tr>
<td>Propranolol (0.2 mg/kg)</td>
<td>150 ± 4.2†</td>
<td>100 ± 5.5†</td>
<td>150 ± 4.2†</td>
<td>80 ± 4.2†</td>
</tr>
<tr>
<td>Control 1</td>
<td>238 ± 6.0</td>
<td>142 ± 2.0</td>
<td>240 ± 5.0</td>
<td>108 ± 1.0</td>
</tr>
<tr>
<td>Propranolol (0.2 mg/kg)</td>
<td>120 ± 5.0†</td>
<td>90 ± 3.5†</td>
<td>122 ± 1.9†</td>
<td>75 ± 4.0†</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).

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>95.3 ± 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. Note 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 loop, which contained the vagus nerves (aortic depressor nerves). See text for details.

* Not significant.  
† Significant.

<table>
<thead>
<tr>
<th>Propranolol</th>
<th>Blood pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before occlusion</td>
<td>After occlusion</td>
</tr>
<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>2.5 mg/kg</td>
<td>138.7 ± 1.5†</td>
<td>88.7 ± 1.5†</td>
</tr>
<tr>
<td>5.0 mg/kg</td>
<td>121.7 ± 1.2†</td>
<td>76.2 ± 1.8†</td>
</tr>
<tr>
<td>7.5 mg/kg</td>
<td>121.7 ± 3.3†</td>
<td>68.5 ± 3.3†</td>
</tr>
</tbody>
</table>

Propranolol was administered in stepwise doses daily for 1 week at each dose level. Heart rate was monitored before and after procaine administration to the carotid loop, which contained the vagus nerves (aortic depressor nerves). See text for details.

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.,4 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 antago-
nize 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 decrease. The infused
angiotensin would block renin secretion by the negative
feedback mechanism, and the elevation of the blood pres-
sure by norepinephrine would block renin secretion.

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

The experiments of Garvey and Ram6 nevertheless
merit considerable attention. These authors believe they
have demonstrated that propranolol administered to rats
accumulates in the hippocampus either as the unmetabo-
lized substance or as its metabolites. They believe that this
is a primary basis for the postulation that propranolol acts
at the hippocampus to decrease sympathetic activity. They
have shown, additionally, that there is a decrease in symp-
thetic nerve volleys and in blood pressure in animals
-treated acutely with propranolol. This is indeed an attrac-
tive postulation which broadens further the possible mech-
nisms of action of propranolol. It is important to keep in
mind, however, that accumulation of a drug or its metabo-
lites at a given site is not prima facie evidence that the drug
may have its major action at that site. Seigel and Tassoni10
however, have recently described the hippocampus as hav-
ing central sympathetic efferent fibers to the hypothala-

dus. This, if substantiated functionally, would give sup-
port to the postulation of Garvey and Ram.6

In spite of this we find it difficult for our angiotensin
experiments to explain why the vasoconstriction caused by
angiotensin is not reversed on infusion of propranolol if
propranolol were acting centrally to decrease sympathetic
activity. It is also of great interest in these experiments
that heart rate, contractile force and dp/dt are returned to
or below control levels by propranolol infusion, although
blood flow is essentially unaffected. It is important to
mention at this point the work of Kawashiama et al.,11 who
showed, using radioimmunoassay technique, that l-pro-
pranolol accumulates rapidly in the heart as it concomi-
tantly decreases in plasma concentration. The d form
of propranolol, on the other hand, is metabolized rapidly in the
blood. These 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 l-
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.

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