SUMMARY Two types of biologically active lipids have been derived from renomedullary tissue. One is neutral (ANRL) and the other polar (APRL). Upon a bolus I.V. injection, APRL causes a rapid decline of the mean arterial pressure (MAP) after a single injection and a prolonged depressor effect after either multiple injections or an infusion. APRL became evident when a reduction procedure, using the Vitride reagent, was used. Thus, APRL is likely a semisynthetic product. Multiple chemical and enzymatic manipulations suggest that APRL is a glycerophosphate with the active acyl group in Position 2. The acute and prolonged effects of APRL may be due to different components in its mixture. Hemodynamic studies indicate that both the acute and prolonged effect of APRL causes vasodilatation with minimal or no tachycardia. Visualization of the microcirculation reveals arteriolar dilatation. Larger bolus doses also cause a decrease in cardiac output (CO) that could be due to venodilatation. A negative inotropic effect has not been ruled out for APRL. This seems unlikely as indicated by minimal change in CO as MAP is lowered substantially (lower doses), no change in right atrial pressure, no direct effect on isolated atrial myocardium and no change in the index of myocardial contractility. It is suggested that the depression of CO with higher doses may be due to venodilatation. Preliminary studies fail to reveal acute toxicity. APRL is a powerful vasodilator.

KEY WORDS • vasodilator • acute depressor • antihypertensive lipid • semisynthetic • prolonged depressor • glycerophosphate

RENO MEDULLARY tissue, as well as renomedullary interstitial cells (RIC), exert an endocrine-type antihypertensive function (DuCharme, personal communication). These same tissues yield lipid substances that exert an antihypertensive action. During attempts to isolate the active principle of these lipid substances, two types of biologically active lipids have been derived (fig. 1). By chromatographic and solubility characteristics, one is neutral (designated as the antihypertensive neutral renomedullary lipid or ANRL) and the other is polar (designated as the antihypertensive polar renomedullary lipid or APRL). Upon a bolus I.V. injection of APRL into a one-kidney, one clip Goldblatt hypertensive rat (1KGH), a rapid and very sharp decline of the mean arterial pressure (MAP) occurs.

The magnitude and duration of this depressor effect is dose-dependent. When multiple doses of APRL are given to the same hypertensive animal the MAP remains depressed for 20 or more hours after the last dose. Thus, APRL evokes an acute and prolonged depressor effect, depending on the manner of its injection and the dose level. Given intravenously as a bolus dose, ANRL is attended by a lag period of 2 or more minutes and then the pressure to return to its previous level. The antihypertensive activity labeled APRL was discovered after attempts to improve the yield of ANRL. Two steps were added to the isolation procedure, namely a reduction step using the reducing agent Vitride (Na Al H₂(OCH₂OCH₃)₃, Eastman organic chemicals) followed by acetylation.

These steps were included because of hints that ANRL might have a vinyl ether side group. Vitride presumably would not attack such linkage but would break ester bonds. It was hoped that the methyl ester(s) would assist in subsequent purification steps. However, a second treatment with Vitride destroyed APRL activity (see Results and Discussion).
In view of these steps, APRL may not be a natural product, that is, an endogenous agent. Rather, it is likely a semisynthetic substance. On the other hand, ANRL is derived by extraction and chromatography only, and is a better candidate to be an endogenous substance.

In the present studies the general chemical characteristics of the mixture of lipids designated as APRL and the hemodynamic mechanisms of both its acute and prolonged effects were investigated.

Methods

Extraction and Purification of APRL

The APRL used in the present studies was extracted from fresh renal medullae of the rabbit in six steps, modified from the procedures previously described.25 These steps include total lipid extraction by the Bligh and Dyer method,26 reduction using Vitride, acetylation, silicic acid column chromatography and two thin-layer chromatographic (TLC) procedures. The polar nature of this product is indicated by its behavior on TLC and its solubility in water.

General Characterization of APRL

Attempts have been made to gain insight into the class of lipid to which APRL belongs. The following procedures were applied to the second dimension TLC product along established methods: alkaline and acid hydrolysis (acid treatment, 50-500 μg lipid/ml of 0.1 N HCl, 30 minutes at 60° and 80°C; alkaline treatment, 50 μg lipid/ml of 0.1 N NaOH, 30 minutes at 50°C); treatment with phospholipases A₄ (porcine pancreatic juice as source), C (Clostridium welchii as source) and D (cabbage as source);27 reduction with palladium (Pd) on charcoal plus H₂ (1 mg lipid in 100 mg Pd on charcoal plus bubbling H₂ for 5-10 minutes, 1 hour at room temperature with occasional swirling); treatment with mold lipase (Rhizopus delemar);28 repeat treatment with the Vitride reagent; treatment with HgCl₂-glacial acetic acid (1 mg lipid/5 ml 1% HgCl₂ in glacial acetic acid, 30 minutes at 46°C); and determination of the phosphorus:nitrogen ratio (by Galbraith Laboratories, Knoxville, TN).

The Acute Depressor Effect of APRL

Wistar rats (Bio-Lab Corp., St. Paul, MN) weighing about 250 g were used. The 1KGH was induced as previously described.29 After 3 months we used these animals to evaluate APRL. The presence of sustained hypertension was determined by the tail-cuff method by means of the E and M apparatus. Anesthesia was induced in seven 1KGH rats by 2% α-chlorolose and 10% urethane at a dose of 6 ml/kg. The left carotid artery was cannulated with PE 50 tubing at the arterial pressure with a Statham P23Gb strain gauge. The right external jugular vein was cannulated for the injection of APRL. In two animals the central venous pressure was measured with a Statham P23BB strain gauge. The trachea was cannulated and connected to a Harvard model 680 rodent respirator with the rate set at 70 breaths/min and tidal volume set at a minimum to prevent voluntary ventilation. A midline thoracotomy was performed and the pericardium was opened. A 2-mm Statham flow probe was placed on the root of the aorta to measure cardiac output (CO) using a Statham flowmeter, model SP 2202. The flowmeter and probe were precalibrated on the in situ brachial artery of a dog by withdrawing blood from the artery at constant rates with a Sage infusion/withdrawal pump. The mean blood flow, the instantaneous blood flow and the acceleration of blood flow were recorded. The peak acceleration of blood flow divided by the peak instantaneous blood flow was used as an index of myocardial contractility.30 All recordings were made on a Brush model 200 oscillograph. Doses of 0.01 to 1 μg of APRL were injected through the venous cannula after being made up in saline by 30-second sonication. The APRL was given in ascending doses followed by descending doses in 0.1 ml, or vice versa, so that every dose was given twice.

Prolonged Depressor Effect of APRL

We produced 1KGH as related above. Three months later the abdominal aorta below the renal arteries and the inferior vena cava at a parallel level were cannulated as previously described.31 Seven days later the MAP was measured to establish the existence of hypertension. The rats were divided into two groups of 10 rats each. In Group 1, five animals were given APRL intravenously as three separate doses (25 μg of material in 1 ml of saline containing 1 μg/ml of lecithin given in 20 minutes) on 2 consecutive days at hours designated as 0, 3 and 6 and 24, 27 and 30. Five paired controls received only the vehicle at the same intervals. The preinjection hypertensive MAP was derived by averaging five determinations made on separate days of the week before the experiment plus the preinjection determination. The MAP was determined before each injection and at 24, 48, 72, 96 and 120 hours. In Group 2, five animals were given an I.V. infusion of APRL over 8 hours (total dose 100 μg in 1 ml of 2% rat albumin) on 2 successive days. A 30-second sonication procedure was again used to insure that all of the lipid was dissolved. Five paired controls received only the vehicle under identical conditions. The infusions were conducted through a standardized leak-pump system previously described.32 Before the infusion and on Day 3, i.e., ~20 hours after the end of the second infusion, the MAP, CO and hematocrit values were determined. Then a cross-over procedure was initiated such that the animals receiving APRL now received the vehicle and those receiving the vehicle received APRL. Because of technical difficulties (obstruction of catheter) only three tests and two controls were satisfactory. This made a total of eight results with APRL and seven with the vehicle.

The CO was determined in unanesthetized animals by the rubidium-86 technique,33 which had been validated in our laboratory by comparison with a
Examination of the Viscera

Dom samples were fixed in neutral formalin and were sacrificed, the viscera were examined and randomized. Each atrium from three female guinea pigs (Redfern strain) was placed in a recording device in Kreb's solution at 35°C with 1 g of applied tension. First the vehicle (saline containing lecithin) was tested, then increasing doses of APRL were tested (0.01 to 4 μg/ml) for an effect on the myocardial tissue.

Effect on Spontaneously-Beating Atria

Each atrium from three female guinea pigs was placed in a recording device in Kreb's solution at 35°C with 1 g of applied tension. First the vehicle (saline containing lecithin) was tested, then increasing doses of APRL were tested (0.01 to 4 μg/ml) for an effect on the myocardial tissue.

Effect on Microcirculation

In preliminary experiments, the cremaster muscle of four- to six-week-old spontaneously hypertensive rats (Okamoto strain) was prepared for microvascular observation according to previously used techniques. The muscle was stretched over a lucite pedestal and superfused with a bicarbonate buffered Ringer's solution. Red blood cell velocity was determined by the dual-slit photometric method and vessel diameter was measured from a television monitor.

Preliminary Toxicological Studies

Hematological Studies and Blood Chemistry

Four 1 KGH rats received APRL (25 μg, I.V.) three times daily for 2 days. A prolonged depressor effect was evoked (MAP before APRL 188 ± 3 mm Hg; 24 hours after the last dose 164 ± 3 mm Hg, p < 0.005); paired controls on vehicle had a slight elevation of MAP, see also Results. At the outset and 24 hours after the last injection, blood was withdrawn from the aorta via its indwelling catheter for hematological studies (Coulter S apparatus) and blood chemistry values were measured using serum samples in a multichannel apparatus (SMAC, Autoanalyzer Co.).

Examination of the Viscera

After the blood samples were collected the animals were sacrificed, the viscera were examined and random samples were fixed in neutral formalin and prepared for light microscopy (hematoxylin-eosin stain). Samples were taken from the brain, heart, lungs, gastrointestinal tract, liver, spleen, adrenals, kidney, and skeletal muscle.

The data were statistically analyzed by the Student's t or paired t test as appropriate. The null hypothesis was rejected at p < 0.05.

Results

Lipid Class of APRL

Ultra-violet detection in a high-pressure liquid chromatography assembly indicated the presence of multiple components in the APRL studied. By utilizing the acute depressor effect as a biologic assay, it was possible to gain some insight into what seemed to be the class of lipid involved (table 1).

Alkaline and acid hydrolysis destroyed activity, indicating the presence of labile ester linkages. Phospholipase A_2 destroyed activity, suggesting the need for an acyl group in Position 2 of a phospholipid. Phospholipase C also destroyed activity, which may be taken as presumptive evidence of the need for a glycerophosphate ester. The action of phospholipase D was inconclusive. The compounds in the mixture were modified by the latter enzyme as indicated by changes in the TLC pattern but some activity remained. Reduction with palladium-charcoal/H_2 destroyed activity, indicating the need for a double bond(s). Mold lipase (Rhizopus delemar) did not seem to destroy activity. The specificity of this enzyme for a phospholipid has been challenged by Slotboom but in our hands it removes the acyl group in Position 1 of lecithin. The results, therefore, suggest that an acyl group in Position 1 is not essential for the activity. It should be noted that the original derivation of APRL was such as to likely acetylate Position 1. Repeat treatment with the Vitride reagent, i.e., repeated after the refinement procedures, destroyed activity, thus reemphasizing the presence of ester linkages. Since HgCl_2-gluconic acetic acid treatment did not destroy activity, it can be assumed that a plasmalogen was not the active substance. Finally, the phosphorus:nitrogen ratio (12.7:2.5) was compatible with a highly polar compound. Thus, these preliminary findings are consistent with an acute depressor effect due to a glycerophosphate having an R group in Position 2 that is probably unsaturated. The state of Position 1 is not certain at present but an acetate-acyl linkage seems likely.

Biological Activities of APRL

Acute Depressor Effect

Characteristics of the Acute Depressor Effect of APRL. During initiation of the acute depressor effect, the interval between the start of the bolus dose and the beginning of the sharp drop of the MAP was 3.8 ± 0.2 seconds (n = 10). The time for the sharp drop to reach its maximum depression was 10.5 ± 0.5 seconds (n = 10). A high dose is indicated in figure 1 by the floor of the MAP (~75 mm Hg) lasting about 6 minutes. Thereafter, the pressure recovered slowly and completely by 50 minutes.

The pulse rate before the injection averaged 405 ± 5 beats/min (n = 10). At maximum depression (~94 ±
8 mm Hg) it averaged 438 ± 6 beats/min (n = 10, p < 0.001). By 2 minutes after the maximum depression, the rate had decreased to 423 ± 3 beats/min (n = 10, vs before injection p < 0.01) and at 4 minutes after injection, the rate had recovered to 405 ± 5 (n = 8, vs before injection p > 0.9). Thus, despite the substantial acute depressor effect, tachycardia was at a minimum and recovered rapidly despite the persistent depression of MAP. During the time of the depressor effect the animals appeared alert, responding normally to abrupt provocation by a blunt instrument.

**Hemodynamic Features of the Acute Depressor Effect of APRL.** The prethoracotomy MAP of the anesthetized 1KGH rats was 147 ± 5.2 mm Hg, which was reduced to 121 ± 8 mm Hg after completion of the surgery. Although blood loss was minimal,
the CI seen under these conditions was reduced from the unanesthetized values shown in table 2. This is a common finding for open-chest animals. An example of the acute responses to APRL is shown in figure 2. Upon injection of APRL there was an immediate, dose-dependent fall in blood pressure and a slightly delayed fall in CO, which was very small at low doses and increased at the two highest doses. The heart rate showed a decline during the hypotensive period at the 1-μg dose, but in most of the experiments the heart rate did not change. The heart rate was 388 ± 5.9 beats/min before the injection of 1.0 μg of APRL and 384 ± 6.5 beats/min during the hypotensive period (not significant or NS). The peak acceleration of blood flow and the peak instantaneous blood flow decreased by similar proportions, thus giving no significant change in the contractility index of the myocardium (peak acceleration of blood flow/peak instantaneous blood flow). The index of contractility was 100 ± 2.4 sec⁻¹ during the control period and 96 ±
Figure 3. This figure relates a summary of changes in cardiac index (ΔCI), mean arterial pressure (ΔBP) and total peripheral vascular resistance (ΔPR) of all eight 1KGH rats following the bolus I.V. injection of APRL. All points are significantly different from the control except the one labeled NS. However, following the next lower two doses the CI changes were minimal. Control values were CI = 128 ± 6 ml/min · kg, BP = 121 ± 8 mm Hg; and PR = 0.941 ± 0.037 mm Hg · min/ml.

Figure 4. The prolonged depressor effect of APRL following three doses spaced 3 hours apart on 2 successive days is shown. Note that recovery, as compared to paired controls receiving the vehicle, did not occur until more than 60 hours after the last dose.
1.2 sec<sup>−1</sup> during the hypotensive period after the 1-µg dose of APRL (NS). The venous pressure measured near the right atrium (2.5 ± 0.5 mm Hg) did not change at all dose levels. At the higher doses of APRL, some of the lipid possibly could reach the venous side of the circulation and cause venodilation and pooling of blood.

The results from all seven animals are summarized in figure 3. At the three smallest doses of APRL the blood pressure fell almost entirely as a result of the decrease in peripheral resistance, while the fall in CI contributed a sizeable proportion at 0.5 µg and above. At the highest dose (1 µg) of APRL, the total peripheral resistance fell 35%, while CI fell 24%.

**Prolonged Depressor Effect**

*Group 1.* As shown in figure 4, in which the immediate acute depressor effects are deleted, the first two doses of APRL caused a substantial depression of the MAP (~−30 mm Hg). Twenty hours after the third dose the MAP remained depressed. The three additional doses on Day 2 caused the MAP to be lowered slightly further (to ~−38 mm Hg). Of special note was the prolonged depression 20–72 hours after the last dose. The paired controls had no change in MAP.

For this group, eventual recovery of the MAP was not evident until 60–90 hours after the last dose on Day 2.

We have reproduced this prolonged depressor effect of multiple doses of APRL in groups of animals on eight separate occasions, 41 animals received APRL and 33 received the vehicle (−28 vs −0.6 mm Hg, p < 0.001).

*Group 2.* The results of the 2-day, continuous-infusion experiments are shown graphically in figures 5 and 6 and numerically in table 1. Infusions of APRL caused a sustained decrease in the blood pressure (34 mm Hg) of these hypertensive animals that was due to a significant decrease in total peripheral resistance with no change in the cardiac index. It is to be remembered that the hemodynamic measurements shown here were taken on the day following the termination of the APRL infusion. The hematocrit did not differ from control values, which indicates that the fall in resistance is not due to a change in blood viscosity. An unchanged hematocrit is also an indication that blood volume remained the same, even though there was a slight decrease in body weight of both groups. The slight, but statistically insignificant, fall in hematocrit compared to pre-treatment levels is probably due to the infusions that contained 2% rat albumin, which would be partly retained in the plasma compartment. The insignificant fall in body weight is most likely due to the inability of the animals to eat and drink during the two 8-hour periods of infusion.

**Treatment of Spontaneously Beating Atria**

Neither the vehicle nor the ascending doses of APRL had any effect on the force or frequency of atrial contraction.
Table 3. Hematological Studies and Blood Chemistry Values after APRL

<table>
<thead>
<tr>
<th></th>
<th>APRL group (n = 4)</th>
<th>Vehicle group (n = 4)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>136 ± 0.6</td>
<td>130 ± 0.6</td>
<td>&gt;0.8</td>
</tr>
<tr>
<td>CO₂</td>
<td>22 ± 1.4</td>
<td>22 ± 0.5</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>BUN</td>
<td>29 ± 1.3</td>
<td>21 ± 3.6</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Creatine</td>
<td>0.8 ± 0.02</td>
<td>0.6 ± 0.06</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Glucose</td>
<td>125 ± 7.6</td>
<td>142 ± 32</td>
<td>&gt;0.6</td>
</tr>
<tr>
<td>Calcium</td>
<td>4.8 ± 0.07</td>
<td>3.9 ± 0.6</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>6.5 ± 0.3</td>
<td>6.7 ± 0.3</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Uric acid</td>
<td>4.4 ± 0.6</td>
<td>3.7 ± 0.3</td>
<td>&gt;0.4</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.3 ± 0.1</td>
<td>2.9 ± 0.09</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Globulin</td>
<td>2.7 ± 0.1</td>
<td>2.4 ± 0.1</td>
<td>&gt;0.3</td>
</tr>
<tr>
<td>SGOT</td>
<td>157 ± 15</td>
<td>211 ± 37</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>SGPT</td>
<td>35 ± 5.1</td>
<td>50 ± 7.9</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Alk phos</td>
<td>246 ± 19</td>
<td>209 ± 41</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>98 ± 7.8</td>
<td>67 ± 4.3</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hgb</td>
<td>121 ± 0.6</td>
<td>126 ± 0.7</td>
<td>&gt;0.7</td>
</tr>
<tr>
<td>Hct</td>
<td>32 ± 1.4</td>
<td>33.8 ± 1.9</td>
<td>&gt;0.5</td>
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<tr>
<td>RBC</td>
<td>6.45 ± 0.2</td>
<td>6.74 ± 0.4</td>
<td>&gt;0.6</td>
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<tr>
<td>MCV</td>
<td>50 ± 0.4</td>
<td>50.5 ± 1.1</td>
<td>&gt;0.7</td>
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<tr>
<td>MCH</td>
<td>18.9 ± 0.2</td>
<td>18.7 ± 0.4</td>
<td>&gt;0.8</td>
</tr>
<tr>
<td>MCHC</td>
<td>38.3 ± 0.2</td>
<td>37.4 ± 0.1</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>WBC</td>
<td>6.35 ± 0.2</td>
<td>6.13 ± 0.8</td>
<td>&gt;0.8</td>
</tr>
</tbody>
</table>

*There was no significant difference in the values between the group receiving APRL and the paired control group receiving the vehicle with the exception of the MCHC which was slightly lower for the vehicle group. The results indicate no azotemia, a slightly depressed CO₂ concentration and the combination of depressed Ca, elevated P and elevated alkaline phosphatase for both groups. Both groups also display a low-grade microcytic anemia.

By gross examination and light microscopy there were no abnormalities noted in the viscera of both groups. Thus, by these approaches, there was no evidence of toxicity due to APRL in amounts capable of inducing the prolonged depressor effect.

Discussion

The preliminary evidence presented herein is consistent with the view that the antihypertensive renomedullary lipid(s) designated as APRL is a highly polar glycerophosphate with an essential acyl group in Position 2.

The derivation of APRL remains an enigma. The reducing agent, Vitride, seems to assist in the generation of APRL when applied to the original renomedullary homogenate but destroys the activity when applied to the TLC refined product.

Tuskatani and associates derived a hypotensive lipid from brain tissue which they considered to be a lysolecithin. It is not possible, at present, to determine whether Tuskatani’s lipid and APRL are related. The derivation from different tissues is not helpful in comparing the two principles. The effect of APRL in the unanesthetized hypertensive rat differs from the biological effects described by others in the anesthetized cat. APRL exerts an acute depression in the arterial pressure of 1KGH rats as well as a prolonged depressor effect which takes several hours to run its complete course. The first effect is due to a single dose, but the second effect requires either multiple individual doses or an extended infusion amounting to a comparable total dose. Although the depression of the arterial pressure is due to a fall in the total peripheral resistance in both cases, the mechanism of action is likely different.

APRL is a mixture of a few lipids likely representing related compounds in view of the similar chromatographic and solubility properties. Because of this fact, it remains possible that the acute depressor effect is due to one compound and the prolonged effect to another. Further purification is needed to resolve this point.

The acute response is immediate and relatively short-lived, which is consistent with a direct action on...
the vascular smooth muscle and/or the sympathetic innervation of the vasculature. The time between the bolus I.V. injection and the beginning of the sharp decline of the MAP (average, 3.8 seconds) entails 20−25 heart beats and should be sufficient for the active compound to reach resistance vessels and/or the central nervous system. Recovery occurs in minutes to 1 hour or longer, depending on the dosage. The prolonged effect reaches its maximum more slowly and remains at or near maximum for hours, usually 20 or more hours after the last input of the compound. The characteristics of the prolonged effect suggests a complicated mechanism of action, possibly involving amplification through a secondary induction process, i.e., enzyme induction or the production of other substances. Both acute and prolonged effects may involve an action on the central nervous system, as supported by the minimal or absent tachycardia during the effect. Since the effects occur in unanesthetized animals, suppression of the baroreceptor reflex by the anesthetic appears to be ruled out as an explanation. An alternative hypothesis considers an effect on the peripheral nerve endings of the sympathetic nervous system.

From the results presented, the acute effect of APRL appears to result from a generalized relaxation of the vascular smooth muscle, mainly of the arterial side. The direct observations on arterioles of the cremaster muscle support this interpretation. Relaxation of the venous side when higher doses are used remains a possibility. Although a negative inotropic effect has not been ruled out, this seems unlikely for the following reasons. At the lower doses (figs. 2 and 3) there was minimal change in CO, while the MAP decreased substantially. At the higher doses, the CO fell substantially but right atrial pressure did not change. Had this been combined with a negative inotropic effect strong enough to reduce CO by 24%, right atrial pressure should have risen as blood dammed up in the venous side. The fact that the pressure near the right atrium did not rise is in keeping with a decrease in venous tone. Moreover, careful examination of figure 2 shows that the decrease in MAP always led the decrease in CO. This finding could reflect the time for APRL to reach the venous side of the circulation. There was no direct effect of APRL on the force or frequency of contractions of the isolated atrial myocardium. Finally, and possibly the strongest point against a negative inotropic effect is the indication that the index of myocardial contractility (peak acceleration of blood flow/peak aortic blood flow) did not change.

The prolonged depressor effect was attended not only by no change in cardiac index but also by no changes in the hematocrit reading or in weight. The lack of any change in the hematocrit reading and weight is a good indication that the blood volume and extracellular fluid volume did not change.

We have detected no evidence of toxicity due to APRL by clinical appearance, morphologic examination of the viscera and hematological and biochemical blood studies in the doses presently used. However, it should be pointed out that high doses of APRL when given rapidly intravenously are lethal.

In conclusion, APRL appears to be a potent vasoactive glycerophosphate. Its main effect in the acute and the prolonged responses is vasodilatation. There may be central nervous system and renal effects but these possibilities require additional studies for proper evaluation.

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